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Interventions for improving outcomes in patients with multimorbidity in primary care and community settings (Review)

Smith SM, Wallace E, O'Dowd T, Fortin M

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TABLE OF CONTENTS

[Intervention Review]

Interventions for improving outcomes in patients with multimorbidity in primary care and community settings

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ABSTRACT

Background

Many people with chronic disease have more than one chronic condition, which is referred to as multimorbidity. The term comorbidity is also used but this is now taken to mean that there is a defined index condition with other linked conditions, for example diabetes and cardiovascular disease. It is also used when there are combinations of defined conditions that commonly co-exist, for example diabetes and depression. While this is not a new phenomenon, there is greater recognition of its impact and the importance of improving outcomes for individuals affected. Research in the area to date has focused mainly on descriptive epidemiology and impact assessment. There has been limited exploration of the effectiveness of interventions to improve outcomes for people with multimorbidity.

Objectives

To determine the effectiveness of health-service or patient-oriented interventions designed to improve outcomes in people with multimorbidity in primary care and community settings. Multimorbidity was defined as two or more chronic conditions in the same individual.

Search methods

We searched MEDLINE, EMBASE, CINAHL and seven other databases to 28 September 2015. We also searched grey literature and consulted experts in the field for completed or ongoing studies.

Selection criteria

Two review authors independently screened and selected studies for inclusion. We considered randomised controlled trials (RCTs), non-randomised clinical trials (NRCTs), controlled before-after studies (CBAs), and interrupted time series analyses (ITS) evaluating interventions to improve outcomes for people with multimorbidity in primary care and community settings. Multimorbidity was defined as two or more chronic conditions in the same individual. This includes studies where participants can have combinations of any condition or have combinations of pre-specified common conditions (comorbidity), for example, hypertension and cardiovascular disease. The comparison was usual care as delivered in that setting.

Data collection and analysis

Two review authors independently extracted data from the included studies, evaluated study quality, and judged the certainty of the evidence using the GRADE approach. We conducted a meta-analysis of the results where possible and carried out a narrative synthesis for the remainder of the results. We present the results in a 'Summary of findings' table and tabular format to show effect sizes across all outcome types.

Main results

We identified 18 RCTs examining a range of complex interventions for people with multimorbidity. Nine studies focused on defined comorbid conditions with an emphasis on depression, diabetes and cardiovascular disease. The remaining studies focused on multimorbidity, generally in older people. In 12 studies, the predominant intervention element was a change to the organisation of care delivery, usually through case management or enhanced multidisciplinary team work. In six studies, the interventions were predominantly patient-oriented, for example, educational or self-management support-type interventions delivered directly to participants. Overall our confidence in the results regarding the effectiveness of interventions ranged from low to high certainty. There was little or no difference in clinical outcomes (based on moderate certainty evidence). Mental health outcomes improved (based on high certainty evidence) and there were modest reductions in mean depression scores for the comorbidity studies that targeted participants with depression (standardized mean difference (SMD) −2.23, 95% confidence interval (CI) −2.52 to −1.95). There was probably a small improvement in patient-reported outcomes (moderate certainty evidence) although two studies that specifically targeted functional difficulties in participants had positive effects on functional outcomes with one of these studies also reporting a reduction in mortality at four year follow-up (Int 6%, Con 13%, absolute difference 7%). The intervention may make little or no difference to health service use (low certainty evidence), may slightly improve medication adherence (low certainty evidence), probably slightly improves patient-related health behaviours (moderate certainty evidence), and probably improves provider behaviour in terms of prescribing behaviour and quality of care (moderate certainty evidence). Cost data were limited.

Authors' conclusions

This review identifies the emerging evidence to support policy for the management of people with multimorbidity and common comorbidities in primary care and community settings. There are remaining uncertainties about the effectiveness of interventions for people with multimorbidity in general due to the relatively small number of RCTs conducted in this area to date, with mixed findings overall. It is possible that the findings may change with the inclusion of large ongoing well-organised trials in future updates. The results suggest an improvement in health outcomes if interventions can be targeted at risk factors such as depression, or specific functional difficulties in people with multimorbidity.

PLAIN LANGUAGE SUMMARY

Improving outcomes for people with multiple chronic conditions

Background

The World Health Organization defines chronic conditions as "health problems that require ongoing management over a period of years or decades". Many people with a chronic health problem or condition, have more than one chronic health condition, which is referred to as multimorbidity. This generally means that people could have any possible combination of health conditions but in some studies the combinations of conditions are pre-specified to target common combinations such as diabetes and heart disease. We refer to these types of studies as comorbidity studies. Little is known about the effectiveness of interventions to improve outcomes for people with multimorbidity. This is an update of a previously published review.

Review question

This review aimed to identify and summarise the existing evidence on the effectiveness of interventions to improve clinical and mental health outcomes and patient-reported outcomes including health-related quality of life for people with multimorbidity in primary care and community settings.

Description of study characteristics

We searched the literature up to September 2015 and identified 18 generally well-designed randomised controlled trials meeting the eligibility criteria. Nine of these studies focused on specific combinations of health conditions (comorbidity studies), for example

diabetes and heart disease. The other nine studies included people with a broad range of conditions (multimorbidity studies) although they tended to focus on elderly people. The majority of studies examined interventions that involved changes to the organisation of care delivery although some studies had more patient-focused interventions. All studies had governmental or charitable sources of funding.

Key results

Overall the results regarding the effectiveness of interventions were mixed. There were no clear positive improvements in clinical outcomes, health service use, medication adherence, patient-related health behaviours, health professional behaviours or costs. There were modest improvements in mental health outcomes from seven studies that targeted people with depression, and in functional outcomes from two studies targeting functional difficulties in participants. Overall the results indicate that it is difficult to improve outcomes for people with multiple conditions. The review suggests that interventions that are designed to target specific risk factors (for example treatment for depression) or interventions that focus on difficulties that people experience with daily functioning (for example, physiotherapy treatment to improve capacity for physical activity) may be more effective. There is a need for further studies on this topic, particularly involving people with multimorbidity in general across the age ranges.

Quality/certainty of the evidence

All of the included studies were randomised controlled trials. The overall quality of these studies was good though many studies did not fully report on all potential sources of bias. As definitions of multimorbidity vary among studies, the potential to reasonably combine study results and draw overall conclusions is limited. Overall, we judged that the certainty or confidence we can have in the results from this review is moderate but due to small numbers of studies and mixed results we acknowledge the uncertainty remaining and the potential that future studies could change our conclusions.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Interventions aimed at improving outcomes for people with multimorbidity compared with usual care

Participant or population: Adults with multimorbidity (two or more chronic conditions)
Settings: Primary care and community settings
Intervention: Any intervention designed to improve outcomes for people with multimorbidity including professional-, organisational- and patient-oriented interventions
Comparison: Usual care

Outcomes	Impacts	Number of studies	Quality of the evidence (GRADE)
Clinical outcomes	There is no clear effect on clinical outcomes with a range of standardised effect sizes from 0.01 to 1.6 with a minority having effect sizes > 0.5; interventions aimed at improving management of risk factors in comorbid conditions were more likely to have higher effect sizes	11	⊕⊕⊕⊖ Moderate
Mental health outcomes	There are improved depression-related outcomes in studies targeting comorbid conditions that include depression with a range of standardised effect sizes from 0.09 to 2.24 with 4 of 7 studies having moderate to large effect sizes (> 0.5) . Standardised mean difference of −0.41 (95% CI, −0.63 to −0.20) was calculated from combining data from 6 studies	9	⊕⊕⊕⊕ High
Patient-reported outcome measures (PROMs)	There are mixed effects on PROMs with only half of studies that reported these outcomes showing any benefit with a range of standardised effect sizes from 0.03 to 1.7. Only 1 of 5 studies with available data on self-efficacy had a moderate effect size, 4 of 7 had a moderate effect size for HRQoL (> 0.5) and effect sizes for other psychosocial	12	⊕⊕⊕⊖ Moderate

	outcomes were generally low		
Health Service Utilisation	There were no effects on health service utilisation and changes in visits were difficult to interpret as some interventions could lead to higher numbers of visits if previous unmet need was being addressed. There was no difference in admission-related outcomes, though numbers of admissions in most of these studies were very small	5	⊕⊕⊖⊖ Low
Medication use and adherence	There are mixed effects on medication use and adherence with half the studies reporting this outcome showing benefit. Proportions adherent to medication were higher in intervention participants with ranges in absolute difference of 10% to 40% but all studies with available data had small effect sizes	4	⊕⊕⊖⊖ Low
Health-related patient behaviours	Studies measuring this outcome reported a range of effects varying from an additional 18 minutes spent walking per week to an absolute difference in kcals expenditure per week of 2516 (no studies presented data that could be used to calculate effect sizes)	7	⊕⊕⊕⊖ Moderate
Provider behaviour	The majority of studies reporting provider behaviour indicated improved provider behaviour relating to care delivery; three studies reported a range of 15%to 40%in proportions of intervention providers improving behaviours such as appropriate referral	5	⊕⊕⊕⊖ Moderate

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

We downgraded the evidence for effects on clinical and psychosocial outcomes to moderate due to lack of consistency of effect across studies and small effect sizes. We downgraded the evidence for effects on provider behaviour to moderate due to limited available data for calculation of standardised effect sizes (SES) and lack of clarity regarding the clinical importance of the results. We downgraded the evidence for effects on health service utilisation and medication use and adherence to low due to variation across studies and small effect sizes.

BACKGROUND

Many people with chronic disease have more than one chronic condition, which is referred to as multimorbidity. While this is not a new phenomenon, there is greater recognition of its impact and the importance of improving outcomes for individuals affected. Research in the area to date has focused mainly on descriptive epidemiology and impact assessment (Fortin 2007). There has been limited exploration of the effectiveness of interventions to improve outcomes for people with multimorbidity.

Description of the condition

There has been increasing focus on the enormous personal and societal burden of ill-health caused by chronic disease. The World Health Organization (WHO) has emphasised the importance of organising healthcare delivery systems to improve health outcomes and has stressed the importance of building integrated healthcare systems that can address chronic disease management (WHO 2002). This can be done by focusing on generic chronic care models, as has happened mainly in the United States of America (USA), or by developing national systems focusing on single chronic conditions as has happened with the National Service Frameworks in the UK (Lewis 2004; Satariano 2013). However, many people with chronic disease have more than one chronic condition, which is referred to as multimorbidity and formally defined as the coexistence of two or more chronic conditions (Fortin 2005). While this is not a new phenomenon, there is greater recognition of its impact and the importance of improving outcomes for individuals affected (Fortin 2007; Smith 2007).

While the accepted term for people with multiple chronic conditions is now multimorbidity, the term comorbidity has been used interchangeably in the past. It is now accepted that comorbidity should be used when there is a specified index condition or where there are defined combinations of conditions (for example hypertension and cardiovascular disease) as opposed to multimorbidity where any condition could be included (Valderas 2011). Multimorbidity is the more general term and individuals with comorbidity also have multimorbidity but the reverse does not necessarily apply. For the purposes of this review when analysing the included studies, we looked at studies based on the intervention elements but we also considered differences between studies that specifically target comorbid conditions as opposed to those targeting general multimorbidity. This is because interventions in the comorbidity studies are designed to target the specific included conditions. These distinctions are important in the context of developing and evaluating effective interventions and considering their generalisability (Fortin 2013; Smith 2013).

Individuals with multimorbidity are more likely to die prematurely (Deeg 2002; Menotti 2001; Rochon 1996), be admitted to hospital (Bähler 2015; Condelius 2008; Payne 2013), and have longer hospital stays (Bähler 2015; Librero 1999). They have poorer quality of life (Brettschneider 2013), loss of physical functioning (Bayliss 2004; Fortin 2004; Fortin 2006b), and are more likely to suffer from psychological stress (Fortin 2006a; Gunn 2012). Medicines management is often complex, resulting in polypharmacy with its attendant risks of drug interactions and adverse drug events (Duerden 2013; Gandhi 2003; Guthrie 2011). For patients, in addition to understanding and managing their conditions and drug regimes, they must also attend multiple appointments with different healthcare providers and adhere to lifestyle recommen-

dations (Gallacher 2011; Townsend 2006).

Prevalence studies of multimorbidity have been carried out in different countries indicating that, particularly in those over 60 years, the majority of people attending family primary care services had more than one chronic condition (Fortin 2005; Fortin 2006c; van den Akker 1998; Wolff 2002). A subgroup of these service users have a debilitating combination of conditions that have a high impact on their own lives but also on their utilisation of health services and related costs (Hoffman 1996; Marengoni 2011; Parmelee 1995; Smith 2008). This emerging concept may be referred to as 'complex multimorbidity' and has been defined as people with three or more chronic conditions involving three or more body systems (Harrison 2014). These individuals can pose management difficulties, resulting in frequent health care visits, frequent emergency hospital admissions, and repeated investigations with enormous cost both for the individuals and the healthcare system involved. A UK report has examined the costs associated with this group of people who are described as 'high impact users' on the basis of their frequent emergency admissions (Rowell 2006). Fragmentation of care is a significant problem for this group, resulting from the involvement of both primary care and multiple specialists who may not be communicating with each other effectively (Wallace 2015). Starfield found that people with a greater morbidity burden have a higher use of specialists even for conditions that are normally managed in primary care, and concludes that there is a need for a better understanding of the roles of generalists and specialists in managing these individuals (Starfield 2005)

Description of the intervention

Given the complexity of managing people with multiple chronic conditions, potential interventions are likely to be complex and multifaceted if they are to address the varied needs of these individuals. We anticipated that a variety of intervention types could work to improve outcomes for people with multimorbidity and could be included within the scope of this review. Cochrane Effective Practice and Organisation of Care (EPOC) has developed a taxonomy that defines intervention types (EPOC 2002). We have used this taxonomy to define health service and patient-oriented interventions that have been designed to improve outcomes of people or populations with more than one chronic condition.

1. Professional interventions: for example, education designed to change the behaviour of clinicians. Such interventions may work by altering professionals' awareness of multimorbidity or providing training or education designed to equip clinicians with skills in managing these individuals, thus improving their healthcare delivery.

2. Financial interventions: for example, financial incentives to providers to reach treatment targets. These interventions might work by incentivising health service delivery and providing resources to extend consultation length for people with multimorbidity.

3. Organisational interventions: these can be further divided into organisational changes delivered through practitioners or directly to patients. For example, any changes to care delivery such as case management or the addition of different healthcare workers such as a pharmacist to the healthcare team. These interventions may work by changing care delivery to match the needs of people with multimorbidity across a range of areas such as coordination of care, medicines management, or use of other health professionals such as physiotherapists and occupational therapists to address needs relating to physical and social functioning.

4. Patient-oriented interventions: this would include any intervention directed primarily at individuals, for example, education or support for self management. These interventions might work by improving self management, thus enabling people to manage their conditions more effectively and to seek appropriate health care.

5. Regulatory interventions: for example, changes to local or national regulations designed to alter care delivery in order to improve outcomes. Such interventions might work by introducing regulatory changes that facilitate and enable the funding of care that is directed towards those with complex health needs. An example could be the introduction of free primary care for people with multimorbidity on the basis that preventive care might prevent subsequent more costly hospital admissions. While we did not find these types of interventions, we believe they could exist and would fall within the scope of this review for future updates.

How the intervention might work

We anticipated that organisational-type interventions might predominate. We were aware that there has been a focus on case management, based mainly in health maintenance organisations in the USA (Zwarenstein 2000). Case management is defined as the explicit allocation of co-ordination of tasks to an appointed individual or group and it is postulated that the function of co-ordination is so important and specialised that responsibility for carrying it out needs to be explicitly allocated (Zwarenstein 2000). Our review included studies where case management was employed but only if it was specifically directed towards individuals identified as having multimorbidity.

The implementation of the Family Medicine Groups in the province of Québec, Canada, is another example of an organisational intervention as it involved new forms of shared responsibilities between physicians and nurses (MSSS 2001). Another example in the United Kingdom (UK) is the community matrons programme, which is being delivered through primary care trusts and is based on nurse-provided case management for people with complex care needs including those with multimorbidity (London DOH 2005). It is similar to previous programmes delivered through social services in the 1990s and there have been

concerns expressed as to the feasibility of achieving the programme targets without real integration of primary and specialist services (Murphy 2004).

The differences outlined earlier between multimorbidity in general and comorbidity where there are defined combinations of conditions also influences how interventions are designed. Interventions targeting specified comorbid conditions can be designed to address the specific challenges for people with those conditions. For example, an intervention that targets people with diabetes and depression will combine elements of diabetes-focused care with psychotherapy or escalation of antidepressant medication, or both interventions, so as to address both conditions. Interventions for people with multimorbidity in general cannot have a disease focus as there are no pre-specified conditions so the interventions might address improved coordination of care, improved medicines management or specific functional difficulties experienced by patients.

Since this review was originally planned in 2007, there has been widespread recognition of the need to address the challenge of multimorbidity across health systems with a series of articles in international medical journals highlighting the challenges involved. Two very useful resources highlighting the challenges of multimorbidity and collating research in the area are: i) the BMJ multimorbidity special collections (BMJ Multimorbidity collection) and ii) the International Research Community on Multimorbidity archive IRCMO at the University of Sherbrooke, Quèbec, Canada (IRCMO). The BMJ series includes a series of editorials, original research studies and a clinical review with a multimorbidity focus. IRCMO provides a platform for any researcher interested in multimorbidity to contribute to a regularly updated blog and also compiles a list of multimorbidity related publications.

Why it is important to do this review

This review was originally undertaken based on the clear recognition of the need for integrated care for people with multiple conditions who have complex care needs (Stange 2005). The evidence base for managing chronic conditions is based largely on trials of interventions for single conditions and individuals with multimorbidity are often excluded from such studies (Fortin 2006c; Starfield 2001; Wyatt 2014 Zulman 2011). The inadequacy of existing clinical guidelines to support clinicians in managing people with multimorbidity has been highlighted as a significant issue in delivering care (Dumbreck 2015; Wyatt 2014). Clinical guideline developers have attempted to address this issue with the consideration of certain combinations of commonly co-occurring conditions, for example, diabetes and depression (NICE 2009). However good quality evidence is essential to inform this clinical area and in recent years focus has shifted to intervention development and the need to reorientate clinical practice and healthcare systems for the people who use them most (Satariano 2013).

OBJECTIVES

To determine the effectiveness of health-service or patient-oriented interventions designed to improve outcomes in people with multimorbidity in primary care and community settings. Multimorbidity was defined as two or more chronic conditions in the same individual.

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomised controlled trials (RCTs), non-randomised clinical trials (NRCTs), controlled before-after studies (CBAs), and interrupted time series analyses (ITS), meeting EPOC quality criteria (EPOC 2013). We included NRCTs in the original protocol (Smith 2007b) as we anticipated that, given the challenges in undertaking multimorbidity research (Fortin 2007) and the likelihood that complex interventions would be tested, there would be relatively few RCTs and that non-randomised designs might be used instead.

Types of participants

We included any people or populations with multimorbidity receiving care in a primary or community care setting. We adopted the most widely used definition of multimorbidity, that is, the coexistence of multiple chronic diseases and medical conditions in the same individual, usually defined as two or more conditions (Fortin 2004; van den Akker 1998). We used the WHO definition of chronic disease, which is "health problems that require ongoing management over a period of years or decades" (WHO 2002). We included all studies that identified participants or sub-groups of participants on the basis of multimorbidity, as defined by the study authors. In some studies, additional eligibility criteria were applied (for example, history of high service utilisation) in an effort to identify more vulnerable people who might benefit more from the intervention being studied.

We excluded studies where multimorbidity was assumed to be the norm on the basis of individuals' age as the interventions were not being targeted specifically at multimorbidity and its recognised challenges. This included studies where interventions were directed at communities of people based on location or age of participants in which participants could be presumed to have multimorbidity on the basis of their age or residence in a nursing home but interventions were not designed to specifically target multimorbidity.

Types of interventions

We included any type of intervention that was specifically directed towards a group of people defined as having multimorbidity. Only interventions based in primary care and community settings were included. Interventions included care delivered by family doctors, nurses, or other primary care professionals. Primary health care was defined as providing "integrated, easy to access, health care services by clinicians who are accountable for addressing a large majority of personal health care needs, developing a sustained and continuous relationship with patients, and practicing in the context of family and community" (Vaneslow 1995). However, not all countries have clearly-defined primary care systems (Starfield 1998), so we included care delivered in community settings by individuals fulfilling the basic criteria for primary care, i.e. if they are available to treat all common conditions in all age groups and have an ongoing relationship with their patients. While some specialists may deliver components of primary care to their patients, practitioners were not included unless they fulfilled the definition of being available to treat all conditions and have an ongoing relationship with their patients.

Interventions were classified as 'simple' if they used one identifiable component or 'multifaceted' if they incorporated more than one feature.

We categorised interventions using the EPOC taxonomy presented in the Background section. Where interventions had multiple elements, we defined each element within the taxonomy and highlighted the predominant element of the intervention (see Table 1).

We excluded the following interventions:

- Professional educational interventions or research initiatives where there was no specified structured clinical care delivered to an identified group of people with multimorbidity.

- Interventions including people with comorbid conditions where the intervention was targeted solely at one condition and did not address the full extent of the multimorbidity. This commonly arises in relation to chronic disease and comorbid depression, so called 'depression plus one studies'. These are increasingly common as the link between depression and most chronic conditions has now been well established (Simon 2001). They include interventions designed to address depression in participants rather than targeting all conditions identified. We therefore excluded such studies if the intervention was only targeted at the depression and did not address the full extent of the multimorbidity.

The comparison was usual care.

Types of outcome measures

We included studies if they reported any objective, validated measure of:

- Patient clinical or mental health outcomes (e.g. blood pressure, symptom scores, depression scores).
- Patient-reported outcome measures (e.g. quality of life, well-being, measures of disability or functional status).
- Utilisation of health services (e.g. hospital admissions).
- Patient behaviour (e.g. measures of medication use and adherence, and other objective measures such as goal attainment (Cox 2002; Gordon 1999; Kiresuk 1968), if measured with a validated scale.
- Provider behaviour (e.g. chronic disease management scores).
- Acceptability of the service to recipients and providers, and treatment satisfaction were included if it was reported in a study that reported objective outcome measures behaviour.
- Economic outcomes (e.g. full economic analyses incorporating measures of efficiency or effectiveness in relation to costs or direct costs depending on what was reported in included studies). Where direct costs were reported alone, we indicated whether these costs related to society, the health service, or the recipients. We also reported, where possible, costs in relation to the specific year and currency presented; whether costs related to total costs or simple fees charged; what was included in the cost calculations; and over what time period costs were calculated.

We excluded attitude and knowledge outcomes.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases without language restrictions up to 28 September 2015:

- Cochrane Central Register of Controlled Trials (CENTRAL), *The Cochrane Library*, 2015, Issue 10, Wiley
- Database of Abstracts of Reviews of Effects (DARE), *The Cochrane Library*, 2015, Issue 3, Wiley
- MEDLINE, 1990 to September 2015, In-Process and other non-indexed citations, OvidSP
- EMBASE, 1980 to September 2015, OvidSP
- Cochrane Effective Practice and Organisation of Care (EPOC) Group Specialised Register, Reference Manager
- Cumulative Index to Nursing and Allied Health Literature (CINAHL), 1980 to September 2015, EBSCOHost
- Allied and Complementary Medicine Database (AMED), 1985 to September 2015, OvidSP
- CAB Abstracts, 1973 to September 2015, EBSCOHost
- HealthSTAR, 1999 to September 2015, OvidSP

We also searched the following trials registries:

- https://clinicaltrials.gov/
- http://apps.who.int/trialsearch/

We searched the IRCMO repository for unpublished/grey literature (IRCMO), and invited experts to inform us of other completed or ongoing studies

The search strategy was particularly challenging given the lack of a MeSH terms for multimorbidity. In addition, we were aware from existing epidemiological literature that the recognition of multimorbidity as a concept is relatively recent. Multimorbidity is sometimes used synonymously with the term comorbidity, though this tends to be used in relation to diseases that coexist with an index disease under study (de Groot 2004). However, comorbidity is a MeSH term, whereas multimorbidity is not, so we included both terms in our search. For pragmatic reasons we limited the MEDLINE search to articles indexed from 1990 onwards.

The search strategy published in the protocol (Smith 2007b) was not used; and the search strategy recorded for the 2007 search of MEDLINE was revised in 2009 to better capture the concept of multimorbidity. Results of the search were limited by filters for study design and an extensive list of intervention terms. Search strategies are provided in Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5. The MEDLINE search strategy was used in HealthSTAR and AMED; the Cochrane search strategy was used in DARE.

Searching other resources

We also:

(a) Searched the reference lists of included papers

(b) Contacted authors of relevant papers regarding any further published or unpublished work where indicated

Data collection and analysis

Selection of studies

All citations identified by the electronic searches were downloaded to reference manager software (EndNote 2013) and duplicates were removed. Potentially relevant studies were identified by review of the titles and abstracts of search results by the lead author (SS). We retrieved full text copies of all articles identified as potentially relevant. Two review authors (SS, HS, or EW)) independently screened all citations found by the electronic searches and assessed each retrieved article for inclusion. We resolved any disagreement by discussion and consensus.

Data extraction and management

Two review authors (SS, HS or EW) undertook data abstraction and cross checked data abstraction forms using a modified version of the EPOC data collection checklist (EPOC 2013a). Disagreements about data abstraction and quality were resolved by consensus between the review authors or through adjudication by the Cochrane contact editor.

We extracted the following information from the included studies: (1) Details of the intervention: a full description of the intervention was extracted as were details regarding aims; clinical protocols; use of case workers; remuneration/payment systems; providers involved; and theoretical framework on which the intervention was based; (2) Participants: patients, the nature of multimorbidity and how it was determined; providers, i.e. specialist and primary care providers, family members; (3) Clinical setting; (4) Study design; (5) Outcomes; (6) Results. Results were organised into: (i) Clinical outcomes; (ii) Mental health outcomes; (iii) Patient-reported outcomes; (iv) Health service use (v) Recipient and provider behaviours; and (vi) Recipient and provider acceptability/satisfaction.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias in all included studies using standard EPOC criteria (EPOC 2015) and included the following domains: allocation (sequence generation and concealment); baseline characteristics; incomplete outcome data; contamination; blinding; selective outcome reporting; and other potential sources of bias.

Measures of treatment effect

We reported data in natural units for each study. For RCTs, we reported results as (1) Absolute difference (mean or proportion of outcome in intervention group minus control at study completion); (2) Relative percentage difference (absolute difference divided by post-intervention score in the control group). We undertook meta-analysis where appropriate in terms of participants, interventions and outcomes using random-effects models. Analyses were undertaken for clinical outcomes (glycaemic control and blood pressure) and depression scores in the comorbidity studies. We also undertook meta-analyses for HRQoL and self-efficacy in all studies in which these were reported. All meta-analyses apart from self efficacy had significant statistical heterogeneity so we present the figures for these analyses without the pooled estimates of effect.

Standardised effect sizes (SES) are presented in tables where possible, i.e. where studies reported relevant data for their calculation. We have reported the range of effects using SES in the text of the results and used the generally accepted convention that an SES of more than 0.2 indicates a small intervention effect, an SES of more than 0.5 indicates a moderate intervention effect and an SES of more than 0.8 is a large effect size (Cohen 1988).

For ITS we had planned to report two effect sizes:

(1) The change in the outcome immediately after the introduction of the intervention.

(2) The change in the slope of the regression lines.

However, no ITS studies were identified.

Unit of analysis issues

None of the included studies had unit of analysis errors.

Dealing with missing data

If data on multimorbidity sub-groups were missing from potentially eligible studies, we contacted authors to obtain the information. Two studies provided additional data on sub-groups with multimorbidity (Coventry 2015; Eakin 2007). We did not include any studies with more than 20% missing data in meta-analyses and did not make any assumptions regarding missing data.

Assessment of heterogeneity

We assessed included studies in terms of clinical and statistical heterogeneity. Statistical heterogeneity was assessed by examining forest plots and considering the I^2 statistic (Cochrane Handbook). We planned to prepare tables and funnel plots comparing effect sizes of studies grouped according to potential effect modifiers (for example, simple versus multifaceted interventions) if sufficient studies had been identified but this was not possible.

If there had been enough studies, we had planned to use meta-regression to see whether the effect sizes could be predicted by study characteristics. These could, for example, include duration of the intervention, age groups, and simple versus multifaceted interventions (Cooper 1994). We also considered formal tests of homogeneity (Petitti 1994). None of these quantitative methods were possible for this version of the review but will be considered for future review updates.

Assessment of reporting biases

We assessed incomplete reporting of outcomes, where possible, within the 'Risk of bias' tables. This was only possible for studies that had published protocols or specifically reported different results than the outcomes mentioned in the methods sections of included papers.

Data synthesis

We expected that included studies would measure similar outcomes using different methods. These included either continuous variables (such as different depression scales) or dichotomous process measures (such as proportion of people with recovery from depression). For continuous outcomes, we reported means and standard deviations at study completion with the absolute difference and relative percentage difference. We calculated standardised effect sizes for continuous measures by dividing the difference in mean scores between the intervention and comparison group in each study, by an estimate of the pooled standard deviation. For categorical outcomes, we reported the proportions in the intervention and control groups with the absolute difference and relative percentage difference.

We undertook meta-analysis of studies that were similar in terms of settings, participants, interventions, outcome assessment and study methods. If there was a high I^2 indicating statistical heterogeneity, we used graphs to illustrate the results but did not present the combined effects as the heterogeneity indicates that combining the studies in a meta-analysis is inappropriate. Where meta-analysis was not possible we carried out a narrative synthesis of the results and presented the results based on outcome groupings. See Additional tables.

We assessed the certainty of the evidence for the main outcomes using the following GRADE (Grading of Recommendations Assessment, Development and Evaluation) criteria (Guyatt 2008); and present the main findings with our judgments in a 'Summary of findings' table

1. Study limitations (i.e. risk of bias).
2. Consistency of effect.
3. Imprecision.
4. Indirectness.
5. Publication bias.

Subgroup analysis and investigation of heterogeneity

We had planned to consider subgroup analyses based on the degree of multimorbidity of participants estimated by the number of conditions per person. These analyses were not possible due to the variation in definitions of multimorbidity and characteristics of participants across studies.

Sensitivity analysis

We planned to undertake sensitivity analyses based on intervention type or clear distinctions in studies with different risk of bias but this was not possible due to the limited number of meta-analyses undertaken with each containing relatively few studies.

RESULTS

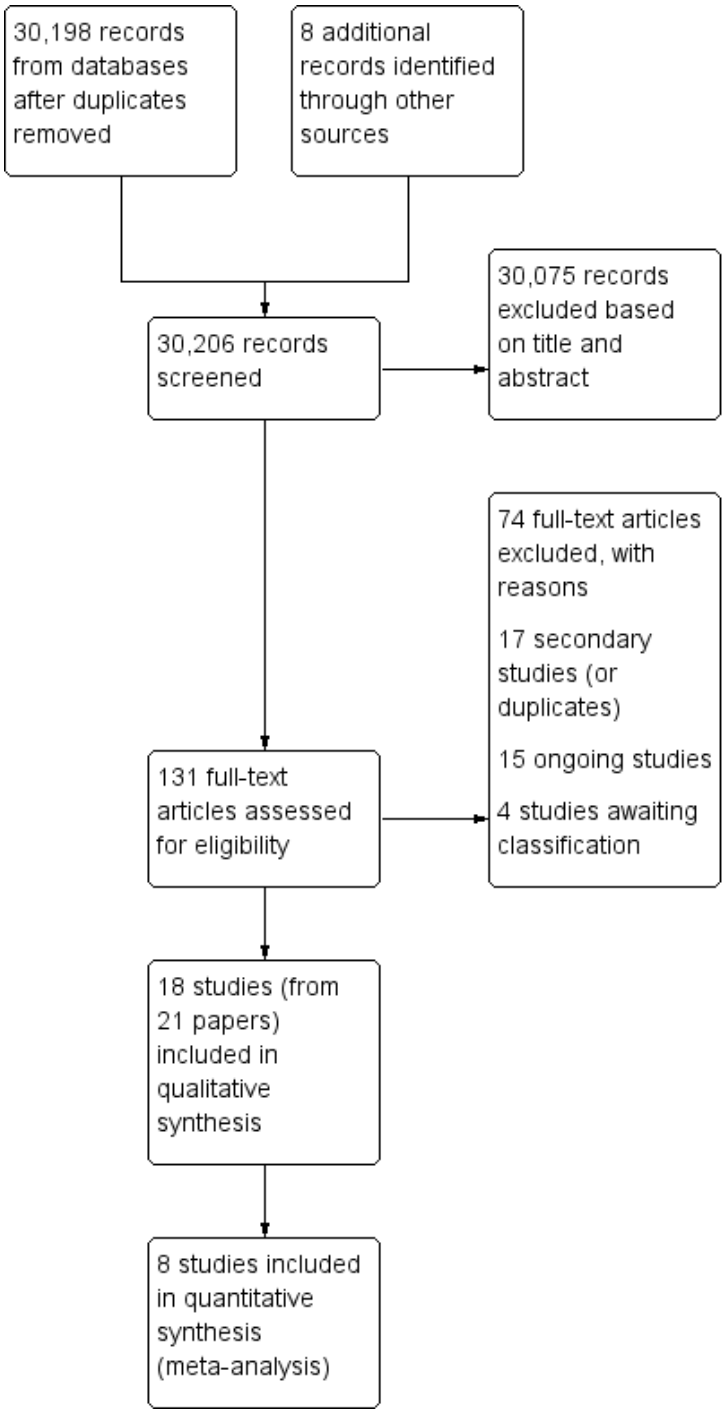
Description of studies

Results of the search

The electronic searches yielded 30,296 original citations after duplicates were removed Figure 1. Of these, 30,165 citations were irrelevant and directly excluded. Full texts were retrieved for 131 studies. Of these, 74 studies were excluded with reasons Characteristics of excluded studies. Fifteen studies are on-going (Characteristics of ongoing studies), 17 studies were duplicates or

reported secondary data analyses. Eighteen studies from 21 papers were eligible for inclusion in this review and four other studies are awaiting classification.(Characteristics of studies awaiting classification).

Figure 1. Study flow diagram.



Included studies

See Characteristics of included studies table

Study design

We identified 18 RCTs eligible for inclusion in the review, 10 from the original review (Bogner 2008; Boult 2011; Eakin 2007; Gitlin 2009; Hochhalter 2010; Hogg 2009; Katon 2010; Krska 2001; Lorig 1999; Sommers 2000;) and 8 identified in this update (Barley 2014; Coventry 2015; Garvey 2015; Kennedy 2013; Lynch 2014; Martin 2013; Morgan 2013; Wakefield 2012). No other study designs with eligible interventions were identified.

Population/participants

There were a total of 8727 participants across all studies. The interventions varied in duration from eight weeks to two years, with the majority lasting 6 to 12 months. There was also variation in post intervention follow-up, varying from immediate follow-up to follow-up 12 months post intervention cessation.

Nine of the 18 studies recruited participants with a broad range of conditions (Boult 2011; Eakin 2007; Garvey 2015; Gitlin 2009; Hochhalter 2010; Hogg 2009; Krska 2001; Lorig 1999; Sommers 2000), whereas the remaining nine focused on the following co-morbidities: depression and hypertension (Bogner 2008); depression and diabetes and/or heart disease (Barley 2014; Coventry 2015; Morgan 2013; Katon 2010); depression and headache (Martin 2013); diabetes and hypertension (Lynch 2014; Wakefield 2012); and a sub-group of people with at least two of diabetes, chronic obstructive pulmonary disease and irritable bowel syndrome (Kennedy 2013).

Settings

All studies were set in primary care or community settings in the USA, apart from Krska 2001 which was set in the UK National Health Service and Hogg 2009 which was set in Canada. Eight were funded by a government or university grant (Coventry 2015; Garvey 2015; Gitlin 2009; Hogg 2009; Katon 2010; Kennedy 2013; Krska 2001; Lorig 1999); and the remaining studies were funded by charitable foundations. None were funded directly by the pharmaceutical industry.

Comparison intervention

In the majority of included studies, the comparator was usual medical care which in some studies was supplemented by a newsletter or leaflet (Eakin 2007; Gitlin 2009), or involved a baseline assessment but no follow-on intervention (Bogner 2008; Garvey 2015; Katon 2010; Krska 2001). These minimal additions to usual care could be considered as being within the variation of usual care provided in different settings. One study invited those allocated to a control group to attend a group session based on an unrelated topic (Hochhalter 2010). This was an attempt to ensure that the intervention effect did not relate to the group setting but related to the intervention content.

Description of interventions

The interventions were all multifaceted and brief descriptions for each study are provided in the Characteristics of included studies. No study specifically reported consumer involvement in the intervention design.

As outlined in the methods, we used the EPOC taxonomy of interventions to describe and categorise the interventions tested in these studies (EPOC 2002). While the interventions identified all involved multiple components they could be divided broadly into two main groups. In 12 of 18 studies, the interventions were primarily organisational, for example case management or addition of a pharmacist to the clinical care team (Barley 2014; Bogner 2008; Boult 2011; Coventry 2015; Hogg 2009; Katon 2010; Kennedy 2013; Krska 2001; Martin 2013; Morgan 2013; Sommers 2000; Wakefield 2012). In the remaining six studies, the interventions were primarily patient-oriented, for example self-management support groups (Eakin 2007; Garvey 2015; Gitlin 2009; Hochhalter 2010; Lorig 1999; Lynch 2014). However, there were overlapping elements with some organisational-type studies including patient-oriented elements such as education provided by a case manager and vice versa. No study involving financial or regulatory type interventions were identified. We have included an additional table which outlines intervention elements and indicates which elements featured in each of the included studies (Table 1)

Excluded studies

We excluded 74 studies in total, see Characteristics of excluded studies. Thirty-four studies were excluded on the basis of ineligible participants. In some of these studies there was a potential multimorbidity sub-group but these data were not reported or not available from authors when requested. Twenty-six studies were excluded on the basis of an ineligible intervention. This was usually because it was conducted in a specialist setting or had a single-condition focus despite participants having multiple conditions. The remaining studies were excluded on the basis of study design, largely due to absence of control groups.

Risk of bias in included studies

See Characteristics of included studies table, Figure 2 and Figure 3 for a summary assessment of the risk of bias of the included studies. Overall four of the 18 studies reported all elements for the risk of bias domains. Two studies reported domains with a high risk of bias and in 13 studies there were domains classified as unclear due to lack of reporting.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

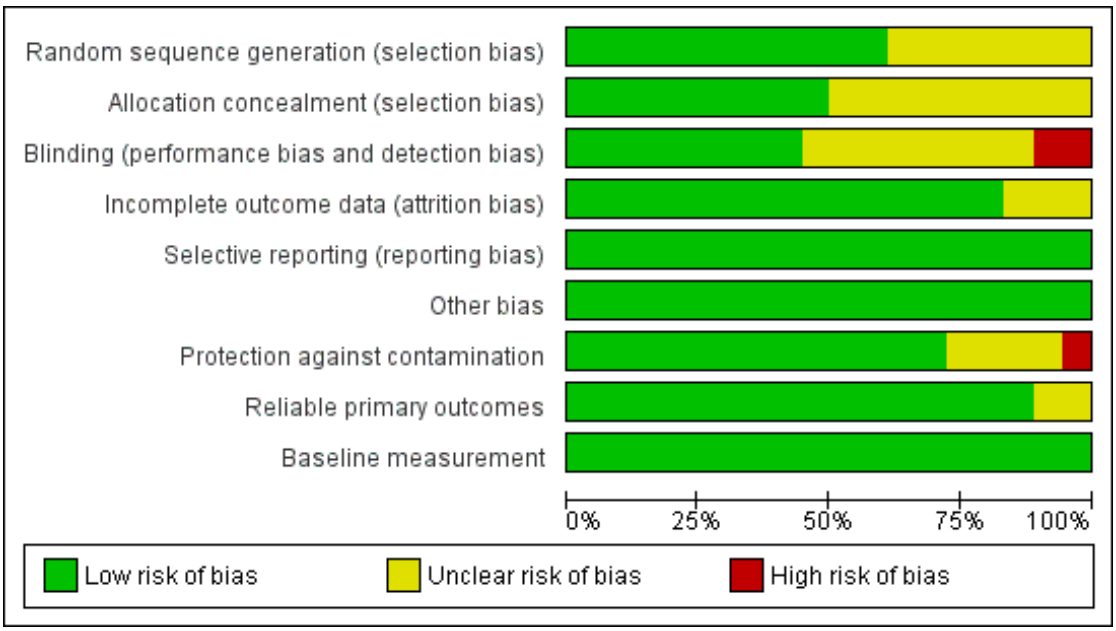
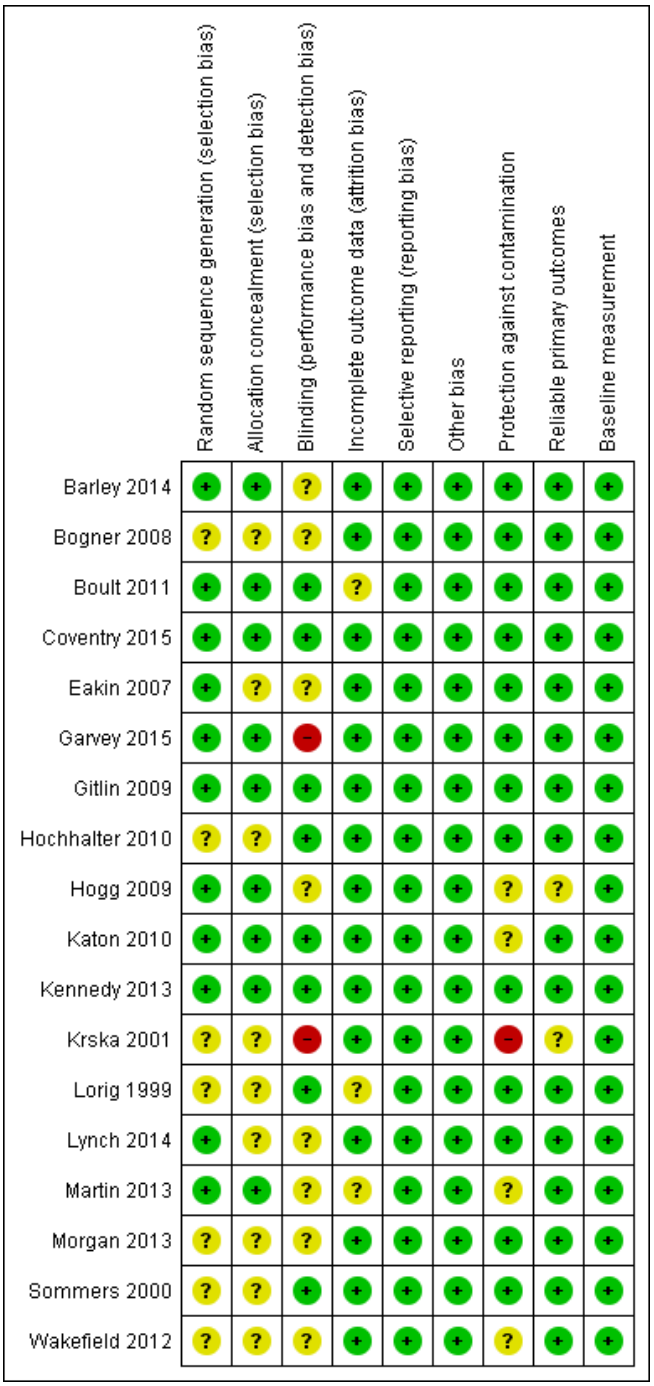


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation concealment was assessed as adequate in nine of the 18 studies (Barley 2014; Boult 2011; Coventry 2015; Garvey 2015; Gitlin 2009; Hogg 2009; Katon 2010; Krska 2001; Sommers 2000), but was assessed as unclear in the remainder. Baseline measurement of outcomes was carried out in all studies. All reported adequate follow-up of participants except Lorig 1999 and Wakefield 2012 where the risk of bias was assessed as unclear. Lorig 1999 did not provide specific details pertaining to follow-up for the multimorbidity subgroup, although follow-up for the overall study was assessed as adequate. There was high risk of bias in Martin 2013 with poorer follow-up in the intervention group (57%) compared to the control group (80%) at study completion. Objective outcomes were used in all but two studies, Krska 2001 and Hogg 2009, where this dimension was assessed as unclear. Krska 2001 used a measure detailing pharmaceutical care issues (PCIs) which was a previously developed classification system modified for the study. Hogg 2009 collected data on chronic and preventive care delivery from individuals' records but the accuracy of this process was not described. Blinding of outcome assessment was assessed as done in seven studies (Boult 2011; Coventry 2015; Gitlin 2009; Hochhalter 2010; Katon 2010; Lorig 1999; Sommers 2000). It was assessed as unclear in nine studies (Barley 2014; Bogner 2008; Eakin 2007; Hogg 2009; Lynch 2014; Martin 2013; Morgan 2013; Wakefield 2012); and assessed as not done in Garvey 2015 and Krska 2001.

Five of the 18 studies had a cluster design that ensured no contamination of control participants (Boult 2011; Coventry 2015; Kennedy 2013; Morgan 2013; Sommers 2000). Contamination of participants allocated to the control group was unlikely in a further eight studies where the intervention was directed at recipients rather than providers (Barley 2014; Bogner 2008; Garvey 2015; Eakin 2007; Gitlin 2009; Lorig 1999; Lynch 2014; Hochhalter 2010), but was possible in the remaining studies four studies (Hogg 2009; Katon 2010; Martin 2013; Wakefield 2012). However, Katon 2010 provided an appendix outlining potential contamination and indicated that it was minimal and, if it had occurred, it would have diluted rather than increased the significant effect size of their intervention. Krska 2001 stated that contamination of control participants who attended the same general practitioners (GPs) as the intervention participants could have occurred but that a cluster design would have been more problematic due to differential prescribing patterns between practices. All studies had low risk of selective outcome reporting and had no apparent other biases.

The five cluster randomised controlled trials accounted for clustering effects in their analysis so there were no unit of analysis errors (Boult 2011; Coventry 2015; Kennedy 2013; Morgan 2013; Sommers 2000).

Certainty of the evidence

See Summary of findings for the main comparison. In general, while all the included studies were RCTs the main limitation related to a lack of consistency of effect for most outcomes. Only the mental health outcomes, largely relating to depression in the comorbidity studies, were regarded as having a high GRADE ranking. We downgraded the evidence for effects on clinical and patient-reported outcomes to moderate due to lack of consistency of effect across studies and small effect sizes. We downgraded the evidence for effects on provider behaviour to moderate, due to limited available data for calculation of standardised effect sizes (SES) and lack of clarity regarding the clinical importance of the results. We downgraded the evidence for effects on health service utilisation and medication use and adherence to low, due to variation across studies and small effect sizes. We did not include economic outcomes in the Summary of findings for the main comparison due to the lack of robust economic analyses, rather we summarised this outcome in Table 2.

Effects of interventions

See: **Summary of findings for the main comparison**

Effects by type of interventions

We have presented an overview of intervention components for each study, highlighting the main intervention component in bold text and have included a brief summary of the intervention effect on the study primary outcomes in Table 1. The description of intervention components is based on reporting of intervention components in each paper and this is not consistent across studies. For example, most studies were likely to have included training of practitioners involved in interventions but not all studies reported this as an intervention component. We have also presented an overview of results based on whether the studies addressed general multimorbidity or comorbidity in Table 3.

Organisational interventions

Twelve of the 18 included studies had organisational-type interventions (Barley 2014; Bogner 2008; Boult 2011; Coventry 2015; Hogg 2009; Katon 2010; Kennedy 2013; Krska 2001; Martin 2013; Morgan 2013; Sommers 2000; Wakefield 2012). These predominantly involved case management and coordination of care or the enhancement of skill mix in multidisciplinary teams in addition to delivery of patient care.

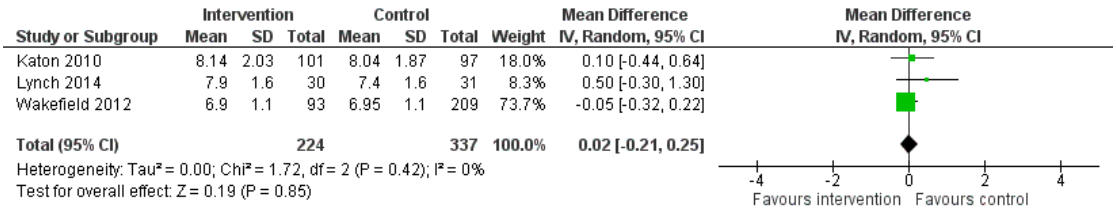
1. Clinical outcomes

Eight of the 18 organisational type studies reported clinical outcomes. These studies had a range of standardised effect sizes (SES)

varying from 0.01 to 1.6. Interventions aimed at improving management of risk factors in comorbid conditions were more likely to have larger effect sizes (e.g. Bogner 2008; Katon 2010; Morgan 2013).

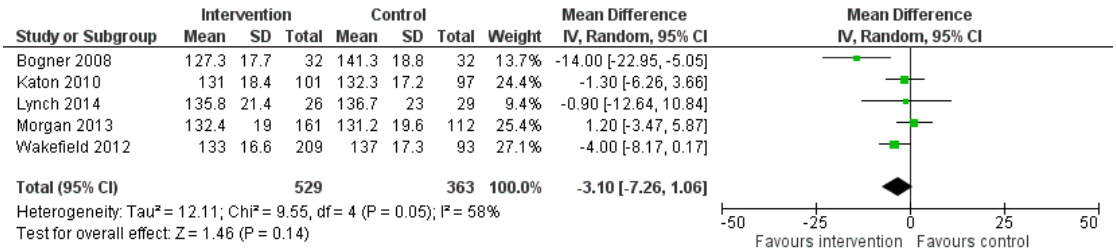
Five studies reported six measures of glycaemic control (five mean HbA1c and one study reported percentage achieving at least 0.5% reduction in HbA1c). Katon 2010 and Morgan 2013 reported improvements in mean HBA1c; however, Morgan 2013 had a substantial proportion of missing HbA1c data at study completion so these data were not included in the meta-analysis of HbA1c. Hogg 2009, Lynch 2014 and Wakefield 2012 found little or no difference in HbA1c. Lynch 2014 reported that a higher proportion of intervention participants achieved an absolute reduction in HbA1c of at least 0.5%. The SES ranged from 0.05 to 1.6 but only one of these three studies had an SES greater than 0.5. The mean difference (MD) was 0.02 (95% CI −0.21 to 0.25) as outlined in Figure 4,

Figure 4. Forest plot of comparison: 1 Glycaemic control (HbA1c) Diabetes outcome: 1.1 HbA1c.



Four studies reported on systolic blood pressure (SBP). Bogner 2008 and Katon 2010 reported improvements in blood pressure, although this was of minimal clinical significance in Katon 2010. Morgan 2013 and Wakefield 2012 reported little difference. The standardised effect sizes (SES) ranged from 0.01 to1.12 but only one of these four studies had an SES greater than 0.5. The MD was −3.10 (95% CI −7.26 to 1.06) as illustrated in Figure 5.

Figure 5. Forest plot of comparison: 2 Systolic Blood Pressure: outcome: 2.1 Systolic blood pressure.



Two studies reported on cholesterol. Katon 2010 found a reduction in LDL cholesterol, whereas Morgan 2013 found no meaningful difference (SES ranges 0.22 to 0.26). Katon 2010 reported a composite primary outcome that combined three risk factors, which showed an improvement in intervention participants compared to control (see Table 4).

Four studies reported symptom scores relating to clinical outcomes. Barley 2014, Lorig 1999 and Sommers 2000 found little or no difference whereas Martin 2013 reported improvements in mean headache rating (see Table 4).

2. Mental health outcomes

Seven studies presented data on mental health outcomes (Barley 2014; Bogner 2008; Coventry 2015; Katon 2010; Martin 2013; Morgan 2013; Sommers 2000). Five of the seven studies reported improvements in a range of depression measures whereas two showed no improvements in depression outcomes (Barley 2014; Sommers 2000). We undertook two meta-analyses: a meta-analysis of Patient Health Questionnaire, version 9 (HQ9) depression scores; and a meta-analysis of standardised mean difference (SMD) in depression scores for the studies with available data where depression was a targeted condition. This suggests a modest intervention effect. The meta-analysis for PHQ9 scores had high heterogeneity so we do not report the pooled effect (Figure 6). The SMD for other depression scores was −0.41 (95% CI −0.63 to −0.20) (Figure 7). The range in SESs for depression outcomes across these studies was from 0.09 to 2.24 with five of the nine outcomes indicating moderate to large effect sizes (i.e. SES > 0.5). These higher effect sizes were all reported in the studies in which depression was a focus of the intervention.

Figure 6. Forest plot of comparison: 3 Depression scores: 3.1 PHQ9 Depression scores.

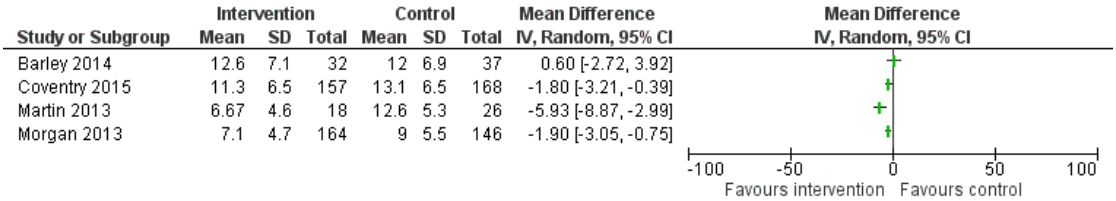
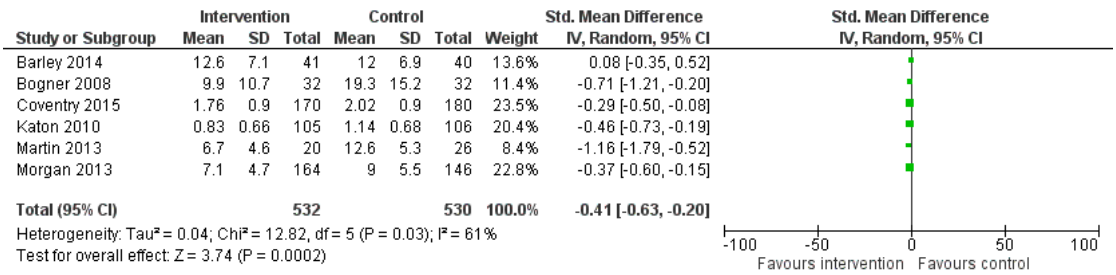


Figure 7. Forest plot of comparison: 4 Depression scores: 4.1 Depression scores.



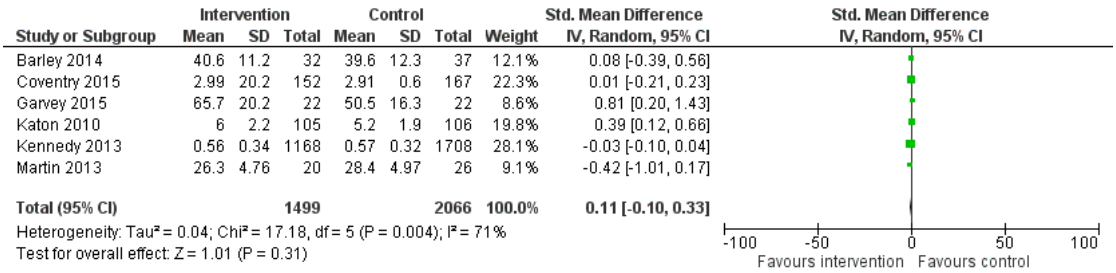
Three studies reported on anxiety measures, two showed improvements (Coventry 2015 and Martin 2013) whereas Barley 2014 reported little difference (see Table 5). There were small effect sizes in all studies (SES range 0.08 to 0.26).

3. Patient-reported outcome measures

Nine of the organisational-type studies presented patient-reported outcome measures (PROMs).

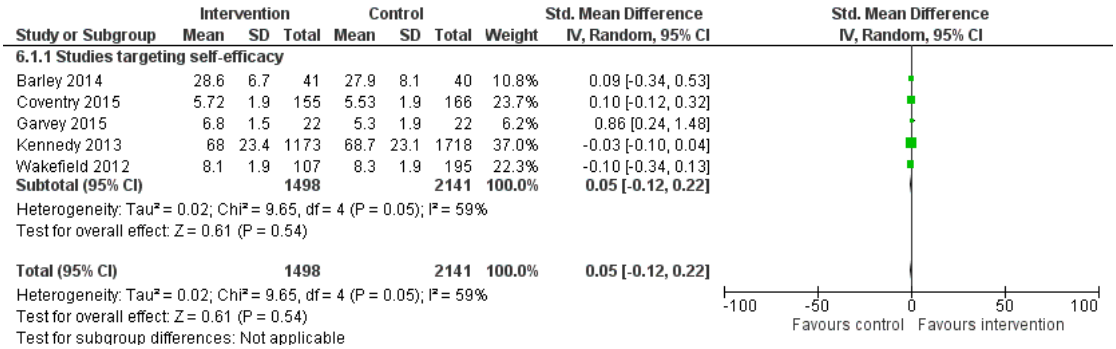
Nine of these reported a variety of HRQoL measures with a range of effects from SES of 0.03 to 1.7. Only one of the nine studies reported a large effect size (Coventry 2015). Two studies reported small effect sizes (Katon 2010; Martin 2013). The remaining six studies reported little or no effect (Barley 2014; Hogg 2009; Kennedy 2013; Krska 2001; Morgan 2013; Sommers 2000). Krska 2001 and Morgan 2013 reported that SF36 scores had been analysed across eight domains at study completion and reported little or no difference between groups, but did not present actual data. The mixed evidence regarding HRQoL is illustrated in Figure 8 which includes studies with available data only but we do not report the pooled effect due to the high heterogeneity (I^2 = 71%).

Figure 8. Forest plot of comparison: 5 Health related quality of life, outcome: 5.1 HRQoL.



Five organisational studies reported on self-efficacy with a range in SES of 0.03 to 0.11, suggesting minimal effect. (Barley 2014; Hochhalter 2010; Kennedy 2013; Wakefield 2012; Coventry 2015). We undertook a meta-analysis of standardised mean self-efficacy scores in comorbidity studies and found no effect, SMD −0.05 (95% CI −0.12 to 0.22) (Figure 9).

Figure 9. Forest plot of comparison: 6 Self-Efficacy, outcome: 6.1 Self-efficacy score.



Two of the organisational studies reported measures relating to disability or impaired activities of daily living (IADL). Hogg 2009 reported no effect of interventions on IADL, whereas Coventry 2015 reported an improvement in the Sheehan Disability score in intervention participants.

Two of the organisational studies reported measures relating to Illness perceptions and both reported no effect (Barley 2014; Coventry 2015).

A range of other PROMs were also reported with mixed effects and none had an SES greater than 0.3. These are presented in Table 6.

4. Utilisation of health services

Five organisational studies reported outcomes on health services utilisation (Boult 2011; Hogg 2009; Katon 2010; Krska 2001; Sommers 2000). Sommers 2000 reported improvements for intervention group participants across a variety of measures relating to hospital admissions, whereas Boult 2011, Hogg 2009, Katon 2010 and Krska 2001 found no difference in admission-related outcomes, although numbers of admissions in most of these studies were very small.

Three studies reported data in relation to health service visits with a range of providers none of which showed clear improvements in appropriate health service use (Boult 2011; Hogg 2009; Sommers 2000) (see Table 7). No studies that included health service utilisation reported data that could be used to calculate SESs.

5. Patient behaviour

5.1 Medication use and adherence

Four organisational studies reported measures relating to medication use and adherence. Two of these studies found an effect whereas two did not; and there was a range in SESs from 0.2 to 0.28 indicating minimal intervention effects. Bogner 2008 reported improvements in proportions of intervention participants adhering to both antidepressant and antihypertensive medication as measured using automated counting systems in the caps of medicine bottles (MEMS caps). Morgan 2013 reported a lower proportion of intervention participants were taking anti-depressant medication. Martin 2013 reported on mean daily medication use which was not significantly different between intervention and control participants. Wakefield 2012 reported two measures of medication-taking adherence both of which showed no significant difference; (see data in Table 8).

5.2 Health related behaviours

Three organisational studies provided data on a variety of outcomes relating to health behaviours by participants (Katon 2010; Morgan 2013; Sommers 2000). Katon 2010 found no difference in relation to adherence to diet and exercise. Morgan 2013 presented self-report data on three patient-behaviour outcomes with improvements in proportions of individuals exercising (Int 60% vs Con 29%) and in the proportions smoking (Int 8% vs Con 12%) and consuming alcohol (49% vs 64%). Sommers 2000 found no changes in a nutrition checklist score. No studies reporting health-related behaviours reported data that could be used to calculate SESs; (see data in Table 9).

6. Provider behaviour

6.1 Prescribing

Two organisational studies reported measures relating to practitioner prescribing or medicines management, both of which indicated significant benefits for intervention participants. Katon 2010 reported a measure examining one or more medication adjustments for five classes of drugs related to the comorbid conditions being studied and reported differences for four of these five groups. Krska 2001 reported a reduction in pharmaceutical care issues in intervention participants; (see data in Table 8)

6.2 Other provider behaviours

Provider behaviours relating to chronic disease management or preventive care were reported in four organisational studies. Boult 2011 and Coventry 2015 both presented a validated measure called the Patient Assessment of Chronic Illness Care (PACIC) score, which is a patient assessment of the quality of care received. This score includes five elements and the aggregate quality score derived was improved in the Boult 2011 Guided Care study, and a small effect reported by Coventry 2015 study (SES 0.39). Hogg 2009 reported measures relating to chronic disease management and preventive care based on chart data and both were improved in the intervention group. Morgan 2013 reported on the proportions of particpants referred to exercise and mental health programmes which was higher in intervention than control group participants; (see data in Table 10).

7. Acceptability of services

Three organisational studies reported treatment satisfaction. Katon 2010 reported the proportion of participants moderately to very satisfied with treatment for depression and diabetes and heart disease at study completion. More intervention participants were satisfied with their care at study completion compared to those experiencing usual care. Boult 2011 reported on the changes in satisfaction for providers as part of an overall examination of the effect of the intervention on providers. The measure incorporated changes in 11 domains of satisfaction with service provision; five domains relating to time spent with participants; six domains relating to provider knowledge of the participant; and four domains relating to care coordination. The only changes reported in the study were improvements in 5 of the 11 domains relating to satisfaction with service provision. Coventry 2015 reported mean Client Satisfaction Scores and reported no difference between intervention and control group participants.

8. Costs

Five organisational studies provided data on costs (Barley 2014; Boult 2011; Katon 2010; Krska 2001; Sommers 2000).

Barley 2014 undertook a parallel economic analysis of the UPBEAT intervention and found that the intervention demonstrated marginal cost effectiveness up to a quality-adjusted life-year (QALY) threshold of GBP 3035.

Leff 2009 et al provided initial cost data from Boult 2011 and indicated a saving related to Guided Care of USD 75,000 per guided care nurse (95% CI USD −244,000 to USD 150,900) or USD 1364 per individual. However, these initial results were based on small changes in outcomes with wide confidence intervals. In addition, the final study results were subsequently published and indicated no intervention effect.

Katon 2010 reported the direct mean medical costs relating to the TeamCare intervention over a 12 month period as USD 1224 per individual. A subsequent economic analysis reported that the intervention led to an additional 114 days in depression-free days and an estimated difference of 0.335 QALYs (95% CI −0.18 to 0.85) (Katon 2012). The intervention was associated with lower

OPD costs with a reduction of USD 594 per person (95% CI USD −3241 to USD 2053). There was a 99.7% probability that the intervention met the threshold of less than USD 20,000 per QALY. The authors interpreted this as a high value intervention but this must be interpreted with caution given the wide confidence intervals in the estimates with lack of statistical significance. Krska 2001 reported the mean medicine cost for the intervention and control groups at study completion and found a marginal benefit for the intervention.

Sommers 2000 reported a net saving per intervention participant of USD 90 though this did not include additional savings from fewer physician visits. It also excluded the costs of implementing the intervention, stated to be USD 118,950, mainly relating to salary costs; (see Table 2).

Patient-oriented interventions

Six of the 18 included studies had predominantly patient-oriented interventions, for example education or group-based self-management support courses (Eakin 2007; Garvey 2015; Gitlin 2009; Hochhalter 2010; Lorig 1999; Lynch 2014). All six aimed to address participant health-related behaviour and did not engage or involve individuals' current health-care providers directly. The results from these six studies were mixed and do not suggest that patient-oriented interventions are generally effective. However, there was an indication that a focus on functional capacity and activity participation may be effective (Garvey 2015; Gitlin 2009), with one study reporting a reduction in mortality at longer-term follow-up (Gitlin 2006).

1. Clinical outcomes

Three of the five patient-oriented studies reported clinical outcomes with mixed results. Gitlin 2009 published a follow-up paper looking at long-term effects of their intervention on mortality and found reduced mortality in intervention participants, which persisted up to three and a half years post intervention, (Int (n = 160): 6% mortality, Con (n = 159): 13% mortality, Absol diff 7%, Rel % diff 54% (Gitlin 2009). Lorig 1999 reported three measures relating to clinical outcomes all of which showed little or no difference between intervention and control. Lynch 2014 reported on glycaemic and blood pressure control in people with diabetes and hypertension. Mean HbA1c was no different but there was an increase in the proportion of intervention participants who achieved at least an absolute reduction in HbA1c of 0.5%. There was no or little difference in systolic blood pressure; (see Table 4). SESs for clinical outcomes in these studies ranged from 0.01 to 0.31 indicating minimal intervention effects.

2. Mental health outcomes

Two studies presented data on mental health outcomes (Garvey 2015 and Lorig 1999). Garvey 2015 reported Hospital Anxiety and Depression Scores (HADS) and found no overall difference in total HADS scores but modest improvements in the depression and anxiety scores. Lorig 1999 reported a mean difference of 0.77 points on a scale of 0 to 5, suggesting no difference in cognitive symptom management between groups at study completion; (see Table 5).

3. Patient-reported outcome measures

Five studies reported PROMs (Eakin 2007; Garvey 2015; Gitlin 2009; Hochhalter 2010; Lorig 1999). Garvey 2015's primary and secondary outcomes reflected the occupational therapy basis of the intervention. The intervention was associated with improvements in all three reported occupational participation/functional ability-type measures. Garvey 2015 also found improvements in HRQol and self-efficacy but no improvements in the Health Education Impact questionnaire overall. The results relating to HRQol and self-efficacy are included in the related meta-analyses (Figure 8; Figure 9). Results of this study have to be interpreted with caution as it is reported as an exploratory trial with immediate post-intervention follow-up. A definitive RCT is planned (Garvey 2015). Gitlin 2009 reported six PROMs by presenting difference in adjusted means between intervention and control groups at follow-up and two showed improvement (self-efficacy in relation to fear of falling and improvements in control-oriented strategies). The range in SESs across these studies, when data were available, was 0.16 to 0.86 with all higher intervention effects relating to outcomes from Garvey 2015 (see Table 6).

4. Utilisation of health services

Two studies reported outcomes on health services utilisation (Garvey 2015 and Lorig 1999). Garvey 2015 found no difference in primary care visits and hospital admissions although only examined an eight week time frame in a small sample. Lorig 1999 reported improvements for intervention group participants across a variety of measures relating to hospital admissions. Lorig 1999 also reported on primary care and emergency department visits but found no improvements (no data available to calculate SESs); (see Table 7).

5. Patient behaviour

5.1 Medication use and adherence

No study with a patient-oriented intervention reported on medication use and adherence.

5.2 Health related behaviours

Three studies provided data on a variety of outcomes relating to health behaviours by participants (Eakin 2007, Lorig 1999 and Lynch 2014). Eakin 2007 reported improvements in diet behaviour scores and in changes in minutes of walking per week. Lorig 1999 reported three measures relating to exercise and communication with doctors and while there was moderate differences in favour of the intervention groups these were unlikely to be of clinical significance; (see Table 9). Lynch 2014 reported increased exercise measured by caloric expenditure in the intervention group. There were no data presented to calculate SESs.

6. Provider behaviour

Prescribing and other provider behaviours

No study with a patient-oriented intervention reported on provider behaviour.

7. Acceptability of services

No study with a patient-oriented intervention reported on acceptability of services.

8. Costs

Two studies provided data on costs (Gitlin 2009, Lorig 1999).
Gitlin 2009 reported the direct costs associated with the intervention at USD 1222 per experimental participant. This incorporated USD 439 equipment costs and USD 783 therapy costs.
Lorig 1999 reported the mean direct cost of running the course for participants who completed it, although costs did not include the cost of accommodation as this was donated to the study. The significant reduction in hospital admissions shown by the intervention translated to a saving in healthcare costs per participant of USD 750 which the authors point out is ten times the cost of the intervention. This calculation was based on a presumed cost of USD 1000 per day if admitted to hospital (see Table 2).

DISCUSSION

Summary of main results

We have identified 18 studies eligible for inclusion in the review, 10 from the original review and 8 added in the current update. All 18 were randomised controlled trials with a generally low risk of bias. Even within this small number of studies, there was significant variation in participants and interventions. In nine of the 18 studies, the focus was on comorbid conditions, which were eligible for inclusion as their interventions had a multimorbidity focus in that they were directed at the pre-specified comorbid conditions. The commonest combinations of conditions included depression, diabetes and cardiovascular disease. In the other studies, which included people with general multimorbidity, the focus tended to be on older individuals.
The results suggest that interventions that are targeted at specific risk factor management (for example management of vascular risk factors and depression in people with comorbid vascular disease and depression) or focused on areas where people have difficulties, such as with functional ability or medicines management, are more likely to be effective. Given the importance of developing interventions for people with multimorbidity, the review provides interesting insights into the types of intervention components that are being examined. However, the majority of interventions in included studies had multiple components incorporating different elements, making comparison of intervention effects difficult. We categorised the intervention components using the EPOC taxonomy and identified the predominant intervention element for each study and then grouped studies depending on whether they had a predominantly organisational or patient focus. When examining the effectiveness of interventions by intervention type, we concluded that organisational type interventions, for example, the introduction of clinical nurse specialists to support treatment of depression or a focus on specific risk factor management in commonly co-occurring conditions such as diabetes and hypertension may be more effective. Interventions that target areas where people have particular difficulties, such as functional ability, are also more likely to be effective. The current evidence suggests that organisational interventions that have a broader focus, such as case management or changes in care delivery for all individuals with multimorbidity, seem less effective. Patient-oriented interventions that are not linked to healthcare delivery also seem less effective. Two of the three patient-oriented interventions that were delivered by professionals showed improvements in a range of outcomes including reduced mortality (Garvey 2015; Gitlin 2009) following focused and intensive interventions targeting functional difficulty, activity participation and falls prevention.
We have presented results by outcomes pre-specified in the protocol. In general these results were mixed and inconclusive, though there was a tendency for improvements in the studies that targeted common comorbid conditions that included depression. There was not a strong focus on clinical outcomes, particularly for the multimorbidity studies and this may reflect the challenge in research in multimorbidity when disease-specific measures cannot be used.
There was limited effect on patient-reported health outcomes such as HRQoL and on outcomes relating to health service utilisation and mixed effects on hospital admission rates and outcomes relating to medication use, and adherence. Five studies reported patient health behaviour outcomes with a tendency for these to be improved in the studies targeting comorbid conditions. There has

been ongoing interest in the potential for improved patient self efficacy to lead to better self management and improved health outcomes. Self efficacy represents an outcome that is not disease or condition focused and was examined in many of the included studies. However, the majority of studies including this outcome showed no effect.

Costs were presented in six studies but only two studies conducted cost-effectiveness analyses and it was not possible to compare outcomes across studies. The results relating to improved prescribing and risk factor management, in some of the comorbidity trials, indicate a potential for these interventions to reduce health service costs over longer periods of time.

Overall completeness and applicability of evidence

Most of the studies in this review are relatively recent reflecting the fact that this is a new area conceptually and that research to date has focused on description and impact rather than the evaluation of the effectives of interventions. The majority of newer studies included in this update and those studies identified as ongoing, focus on common comorbidities rather than on multimorbidity in general. In the original review (Smith 2012), only two of the ten included studies had interventions that focused on comorbid conditions whereas in this updated review, this has increased to nine of the 18 included studies. The tendency towards significant improvements in mental health outcomes in the comorbidity studies is likely related to the strong focus in these interventions on targeting the specific conditions involved, particularly depression. It is more challenging to design interventions for people with a broad range of conditions. The studies that seem more effective in the general multimorbidity group are those which had interventions targeted at specific areas of concern for participants, such as improving functional ability, which is not disease specific. One of the larger multimorbidity studies included involved a large well-designed and executed RCT, the Guided Care study, which tested a broad organisational-type intervention targeted at high risk individuals with multimorbidity, but which found no overall effect (Boult 2011). However, a pre-planned sub-group analysis indicated improvements in the use of some health services in the participants enrolled in one of the participating care plans (Kaiser-Permanente, n = 365, 43% of full sample). Boult 2011 postulated that this result may have been related to the fact that care was already more organised and structured in this system, so that the Guided Care intervention may simply have extended the existing approaches used in that setting whereas its implementation was more challenging in less organised systems. However the results of sub-group analysis, even when pre-planned, need to be interpreted with caution given the relatively small samples sizes involved. Nonetheless, the differences in these sub-groups highlight the importance of the healthcare delivery setting into which new interventions are added. Indeed, some of the patient-oriented interventions seemed to run independently of people's healthcare delivery, particularly those that recruited participants from the community rather than through healthcare providers. Most of these studies had limited effectiveness, highlighting the importance of considering the overall recipient experience and integrating interventions into the healthcare system. The results of the patient-oriented intervention studies are consistent with the Foster 2007 Cochrane review on lay-led self-management support programme, which concluded that there is no evidence that these interventions improve psychological health, symptoms or health-related quality of life, or that they significantly alter healthcare use.

The evidence from this review partially addresses the review question, i.e. what interventions can effectively improve outcomes in people with multimorbidity. It suggests that interventions such as the addition of clinical care protocols need to be targeted at populations with defined combinations of common conditions such as diabetes and depression or heart disease; or need to focus on specific problems experienced by people in multimorbidity populations, for example a multidisciplinary team intervention that addresses functional difficulties. However, even when interventions are targeted they may not be effective for appropriate use of medications. The Haynes 2008 Cochrane review of Interventions for enhancing medication adherence concludes that "current methods of improving adherence for chronic health problems are mostly complex and not very effective" and suggests further research is needed. People with multimorbidity may have more specific problems with medicines use that relate to polypharmacy and managing complex drug treatment regimens, so medicines management interventions targeting these specific difficulties may be more effective.

Most of the multimorbidity studies in this review focused on older people; however, it is important to address the needs of younger individuals as there are issues relating to employability and absenteeism. Research in Scotland has highlighted that individuals in the poorest socioeconomic groups are more likely to develop multimorbidity at a younger age and more likely to die prematurely as a result (Barnett 2012). Acting upstream for younger people with multimorbidity is preventive and has potential to bring about significant quality of life benefits for individuals as well as cost savings for healthcare systems. However, even in ageing populations, multimorbidity worsens outcomes so there is still likely to be room for improvement, at least in ambulatory care patients.

The evidence to guide intervention development for individuals with multimorbidity is increasing and evolving rapidly. A number of ongoing studies have been identified and we anticipate that future updates of the review will improve the available evidence to inform policy makers and those planning services for individuals with multimorbidity.

Quality of the evidence

All of the included studies were randomised controlled trials. Overall they were of reasonable quality with minimal risk of bias, although blinding of participants and clinicians involved in the types of interventions included in this review is often impossible. Multimorbidity is a complex area because the characteristics of participants can vary depending on definitions used. This limits the potential to reasonably combine study results for meta-analysis which is reflected in the high heterogeneity in the meta-analyses undertaken for the review update, and potentially limits the internal validity of the results of the review.

Potential biases in the review process

The review was carried out in accordance with EPOC guidelines and using the updated *Cochrane Handbook for Systematic Reviews of Interventions* (Cochrane Handbook). Potential limitations in the search process relate to the lack of a MeSH term for multimorbidity. This meant that we had to use broad search terms which led to a high yield of citations to be searched. However, the authors are active researchers in the field of multimorbidity and are unaware of any potentially eligible studies that were missed by the search. We were also unable to retrieve some missing data from authors. However, as limited meta-analyses were undertaken this did not lead to any appreciable measurement bias.

In addition, it must be noted that when we address complex interventions in primary care, there is always a context in which those interventions take place. A systematic review does not address the context that could have influenced the results in individual studies as there was limited reporting of external validity or generalisability in individual trials. The usual limitations relating to publication bias apply but we have searched the grey literature and contacted experts in the field to try and identify published and ongoing trials in this area.

Agreements and disagreements with other studies or reviews

We were unable to group sufficient numbers of studies with similar interventions in order to comment on which elements of interventions (e.g. the use of community pharmacists) seemed most effective and compare our review to other reviews of these interventions. The most consistent intervention element across all included studies was the use of case managers, but even these varied in that some were clinical case managers and others were administrative managers. The Cochrane review of the effect of case management on health care outcomes is ongoing but does plan to address differences in effectiveness between different types of case management (Zwarenstein 2000). Systematic reviews of community-based case management in general have indicated mixed effects with improvements in client and professional satisfaction with care and reductions in caregiver strain but no impact on healthcare utilisation (Challis 2014).

AUTHORS' CONCLUSIONS

Implications for practice

Multimorbidity is common in clinical practice and is an important problem in most healthcare systems. While the evidence supporting specific intervention types is limited, it does suggest that clinicians and policy makers should prioritise interventions that target specific problems experienced by people with multimorbidity or should target common comorbid conditions. However, we can only be moderately certain that this is the case and new services and interventions should be evaluated robustly to contribute to the much-needed evidence to support clinical practice. The epidemiological data on the impact of multimorbidity highlights the specific challenges for people who are socioeconomically disadvantaged (Barnett 2012); and interventions targeting this population have the potential to address health inequalities. One of the ongoing studies specifically targets multimorbidity in areas of deprivation (Mercer ongoing).

The sub-group analysis from the Guided Care study discussed above suggests that multimorbidity interventions need to be integrated into existing healthcare systems to support implementation and sustainability (Boult 2011). Independent interventions that do not integrate with existing healthcare systems will be difficult to sustain. Many of the included studies focused on integration of care between practitioners, but we also need to consider how interventions can be integrated into healthcare systems. It is likely that local adaptations will need to be made even for interventions that are effective. For example, we are confident in the review findings that interventions targeting comorbid depression are effective but these interventions require training and support for primary care clinicians which may not be available in all settings.

The literature on multimorbidity indicates that it is generally associated with poorer outcomes for patients. However, health planners and policy makers need to consider which outcomes they want to target in an intervention. This should be considered in the early stages of the development of a potential new intervention. People with multimorbidity are not only at higher risk of many adverse outcomes, but they are also more likely to experience 'treatment burden', that is that the effort needed to engage in the multiple treatments offered to them actually make their lives more difficult (May 2009). Having the individual participate in priority setting based on his/her values and preferences becomes both the rational and the ethical thing to do.

Implications for research

Definitions

There is a need for a clear conceptual definition of multimorbidity and its differentiation from other related concepts such as comorbidity, complexity, frailty, and vulnerability. The variation in definitions in the studies included in this review highlight the need for clear reporting of participant characteristics to allow consideration of external validity and generalisability. This will be particularly important given the need to account for the heterogeneity of multimorbidity; interventions could have differential effects depending on the definition or degree of multimorbidity and the socioeconomic status of participants.

Without these definitions and consideration of related concepts, the generalisability or applicability of studies for people with multimorbidity (with a broader definition than only two or three specific diseases) will be uncertain, as is the case for many of the studies in this review, particularly those with the specific comorbidity focus (Fortin 2013).

We would also advocate for including multimorbidity as a MeSH term as the search strategy for this review and for ongoing work on multimorbidity is particularly complex and time consuming, given the growing concern and interest in the issue.

Study design

While the risk of bias was generally low in this review and all studies were RCTs, we acknowledge the challenge of conducting organisational type interventions using optimal RCT designs, so pragmatic trials or quasi-experimental studies may also be appropriate while still maintaining rigour. This could include the use of stepped wedge cluster RCTs that would involve regional introduction of organisational or health system delivery change while still allowing for robust evaluation.

Future studies need to carefully consider the comparison or control group, particularly in relation to contamination of control participants. Cluster randomised designs are likely to be optimal if interventions are delivered through care providers. This needs to be taken into account both in terms of power calculations and in the analysis of results.

Interventions

This review indicates that interventions that are targeted at either specific combinations of common conditions such as comorbid depression, or at specific problems for people with multiple conditions, may be more effective. When designing interventions researchers should be clear about the theoretical assumptions underlying the intervention, consider its individual components and the evidence base behind each and then link these to outcomes as outlined below. They should also consider interventions that are likely to be reproducible and applicable within the context of primary care. The Medical Research Council Framework for the Design and Evaluation of complex interventions designed to improve health, provides useful guidance in designing and undertaking these trials (MRC Framework 2008).

A group of researchers active in the area of multimorbidity has developed a specific framework for the development of interventions for multimorbidity which is based on a series of workshops undertaken over a two-year period combined with the experience of this expert group (Smith 2013). This framework highlights the potential for other study designs such as stepped wedge designs that may be more suited to multimorbidity intervention initiatives and that can be undertaken within service/ research partnerships. The framework also stresses the importance of clearly describing all intervention components to allow replicability and generalisability to other settings.

Within this review, inter professional collaboration was embedded in all interventions. This is worth building on for future intervention development. Most of the included studies focused on changing professional care provision; it may also be worthwhile incorporating the participants' perspective. This could be achieved by adopting a participatory approach to intervention development. People with multimorbidity, their family members, and a range of professionals involved should be consulted during the modelling and exploratory phases of service and intervention planning.

The majority of the evidence for effective chronic disease management has been based on a single disease paradigm. However, it is likely that participants in these trials had some degree of multimorbidity, though sicker individuals may have been excluded. This is also the case for trials examining interventions for frail older people or for interventions seeking to improve care transitions as many participants in these studies also have multimorbidity though this is not usually clearly reported or addressed as a potential confounding variable. We should therefore seek to build on and apply the evidence regarding effective interventions for single conditions or related interventions to people with multimorbidity, rather than designing interventions with no consideration of the existing evidence base for single conditions.

In its broadest sense, multimorbidity encompasses a large variety of individuals which must be considered as it is not pragmatic to design interventions that change systems completely. For this reason, parallel economic analyses that link outcomes to costs and benefits are better than providing simple cost data alone, which make comparison across studies difficult.

Outcomes

The challenge with multimorbidity is to define a set of outcomes that can be used for different combination of diseases, so there is a need for generic outcomes measures that incorporate physical functioning, quality of life and measure of treatment burden that are responsive to change over time. Other outcomes to consider include goal attainment, self care, self efficacy, health related quality of life, distress, adherence to treatment, behavioural changes

regarding health habits, individuals' knowledge about care plans, shared decision making, and participation in care. However, unless validated measures are used, many of these outcomes will not be comparable across studies. The recent work of PROMIS (PROMIS 2011) provides validated and useful patient-reported outcomes that will be particularly relevant for those researching interventions to improve outcomes for people with multimorbidity. Work to develop a core outcome set for multimorbidity using methodology recommended by the COMET initiative (http://www.comet-initiative.org/) is ongoing.

Most of the interventions in this review used a conceptual model, particularly the Chronic Care Model. In general there needs to be clearer reporting of intervention development and outcomes chosen to reflect the theoretical underpinning as to how and why an intervention might work. It would also be helpful if authors clearly identified intervention elements and matched outcomes to these elements in an effort to clarify which components of multifaceted interventions are more effective than others.

Conclusion

This review highlights the relatively limited but growing evidence underpinning interventions to improve outcomes for people with multimorbidity with the focus to date being on comorbid conditions or multimorbidity in older individuals. The results suggest that interventions to date have had mixed effects but have shown a tendency to improve outcomes if organisational interventions can be targeted at risk factors in common comorbidities such as depression or multidisciplinary team interventions focused on specific functional difficulties in people with multimorbidity. Due to the number of studies and their low risk of bias, we can be confident that there is an effect on depression outcomes in the comorbidity studies that included treatment for depression but there are fewer studies supporting the conclusions for targeting functional difficulties in multimorbidity generally and these findings may change as new evidence becomes available. However, further research is needed and future interventions should be developed in ways that allow rigorous evaluations to be performed that will add to the evidence. There is a need for clear and broader definitions of participants, consideration of appropriate outcomes, and further pragmatic studies based in primary care settings.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Barley 2014

Methods	Randomised controlled trial (Pilot) UK
Participants	81 participants with coronary heart disease (with current chest pain) and depression (identified using two stage screening process to confirm diagnosis), mean age 64,
Interventions	UPBEAT intervention: Nurse case manager who undertook biopsychosocial assessment and developed patient-held personalised care; 3 problems prioritised with behaviour change approach aiming to increase self-efficacy. Initial face-to-face meeting then weekly telephone calls during intervention period Weekly team meetings for nurse case manager, GP and psychiatrist
Outcomes	**Primary:** Depression (HADS-D and PHQ scores) Chest pain (Rose Angina questionnaire) **Secondary:** Self-efficacy; IIlness Perceptions (BIPQ); HRQol (SF12); HADS-A; PSYCHLOPS; Well-being scores (WEMBWBS); Functional status (Specific Activity Schedule); Moriskey Adherence scale; Social Problems Questionnaire Cost effectiveness
Notes	Intervention lasted 6 months with follow-up 6 months post intervention completion Comparison: usual care

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random permuted block design
Allocation concealment (selection bias)	Low risk	Allocation by Clinical Trials Unit
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Outcome assessors and statistician blinded; not possible to blind professionals and participants due to nature of intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	85% follow-up, balanced
Selective reporting (reporting bias)	Low risk	None apparent

Barley 2014 (*Continued*)

Other bias	Low risk	None apparent
Protection against contamination	Low risk	Controls had no access to intervention
Reliable primary outcomes	Low risk	Validated measures
Baseline measurement	Low risk	Groups comparable at baseline

Bogner 2008

Methods	Randomised controlled trial USA
Participants	64 participants aged 50 years and older with hypertension and depression (defined as a diagnosis of depression or prescription of antidepressant within the past year) Integrated care manager and 12 family physicians in primary care clinic
Interventions	Integration of depression and hypertension treatment coordinated by integrated care manager; individualised program comprising three 30 minute in-person sessions with participants and two 15 minute follow-up phone calls
Outcomes	**Primary and secondary (no distinction specified):** Depression scores (Centre for Epidemiological Studies depression scale (CES-D)) Blood pressure Medication (% adherent to antidepressant medication; % adherent to antihypertensive medication (adherence measured using electronic measuring devices (MEMS caps))
Notes	Intervention lasted 6 weeks and follow-up 2 weeks later Comparison: usual care

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Paper states "patients were randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Not stated in text
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Automated measurement devices were used but authors don't specifically state that outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	100% follow-up reported
Selective reporting (reporting bias)	Low risk	None apparent

Bogner 2008 (*Continued*)

Other bias	Low risk	None apparent
Protection against contamination	Low risk	25% control consultations monitored to check for contamination
Reliable primary outcomes	Low risk	Validated measures and automated tests
Baseline measurement	Low risk	Groups comparable at baseline

Boult 2011

Methods	Cluster randomised controlled trial USA
Participants	904 participants aged 65 years or more with history of high service use and multiple medical conditions, covered by Medicare or other insurance 8 practices with 49 primary care practitioners (PCPs); 7 Guided Care nurses (GCNs) Arranged in 'pods' of 1 GCN, 2 to 5 PCPs and 50 to 60 participants
Interventions	'Guided Care' programme comprising eight clinical services including home-based assessment, individual management plan, coaching for self-management with monthly monitoring and coordination of care provision Delivered by trained GCNs
Outcomes	**Primary:** Health service use **Secondary:** PACIC (Patient assessment of chronic illness care) score Health care costs (6 months' data only available)
Notes	Intervention duration 18 months; follow-up at 6 and 18 months Controls received usual care with PCPs

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerised randomisation
Allocation concealment (selection bias)	Low risk	Carried out independently by study statistician
Blinding (performance bias and detection bias) All outcomes	Low risk	Interviewers blinded to group allocation

Boult 2011 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	> 90% follow-up, balanced
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent
Protection against contamination	Low risk	Cluster design
Reliable primary outcomes	Low risk	Validated measures
Baseline measurement	Low risk	Groups comparable at baseline

Coventry 2015

Methods	Cluster randomised controlled trial UK
Participants	387 participants with depression and diabetes and/or ischaemic heart disease, mean age 59, 62% female, mean of 6.2 chronic conditions 36 general practice teams
Interventions	COINCIDE collaborative care model Stepped care protocols with: Brief psychotherapy - up to 8 sessions Standardised treatment manual and workbook with problem statement and personalised goals At visit 2 and visit 8 had 10-minute joint consultation between participant, psychologist and practice nurse to link depression and chronic condition care with targets Drug review with GP if needed Training half-day workshop for clinicians with video and simulated patients One hour weekly supervision for Practice nurses from psychologist and monthly case meetings Telephone support from trial psychiatrist
Outcomes	**Primary:** Depression (SCL-D13 scores) **Secondary:** Depression (PHQ9 scores) Anxiety (GAD scores) Social support (ENRICHID inventory) HRQol (WHO-QOL BREF, diabetes QOL) Seattle angina questionnaire Sheehan disability index Self-efficacy Heath education (HEiQ) Ilness beliefs (multimorbidity illness perceptions scale)

Coventry 2015 (*Continued*)

	Treatment satisfaction (CSQ) Process of care (PACIC scores)
Notes	Intervention duration 3 months, follow-up at 4 months (1 month post intervention completion) 22% of intervention participants never engaged with programme, mean 4.4 sessions attended Comparison: Usual care with referral to mental health services but no access to COINCIDE psychologists

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central randomisation by Clinical Trials Unit (CTU), using minimisation
Allocation concealment (selection bias)	Low risk	Independently conducted by CTU
Blinding (performance bias and detection bias) All outcomes	Low risk	Not possible to blind clinicians and participants but cluster design. Outcome assessors blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All practices retained once participants recruited, 90% follow-up participants, balanced
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent
Protection against contamination	Low risk	Cluster design
Reliable primary outcomes	Low risk	Validated
Baseline measurement	Low risk	Comparable at baseline

Eakin 2007

Methods	Randomised controlled trial USA
Participants	Sub-group of 175 Urban Latinos with multimorbidity (defined as two or more chronic conditions) (data on sub-group directly from authors) Bilingual health educator

Eakin 2007 (*Continued*)

Interventions	Diet and physical activity intervention with self-management support delivered by a health educator; involving two face-to-face visits (60 to 90 min) 3 months apart; 3 follow-up phone calls and 3 newsletters
Outcomes	**Primary:** Physical activity (Behavioural Risk Factor Surveillance Survey Physical Activity scores) Dietary behaviour (Kristal Fat and Fiber Behaviour (FFB) questionnaire) **Secondary:** Chronic Illness Resource Survey (CIRS)
Notes	Intervention 16 weeks, follow-up 6 months post intervention Comparison: usual care plus a guide to local services and three newsletters

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated scheme
Allocation concealment (selection bias)	Unclear risk	Sequentially numbered envelopes used - unclear if were opaque
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated in text
Incomplete outcome data (attrition bias) All outcomes	Low risk	80% follow-up, balanced
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent
Protection against contamination	Low risk	Not a cluster design but authors state that providers not involved in intervention delivery and intracluster correlation coefficients low previously in this population
Reliable primary outcomes	Low risk	Validated measures used
Baseline measurement	Low risk	Groups comparable at baseline

Garvey 2015

Methods	RCT (exploratory)
Participants	50 participants with multimorbidity (at least 2 chronic conditions and 4 repeat medications), median age 66, 64% female, median 4.5 conditions
Interventions	OPTIMAL, a 6-week occupational therapy-led self-management support course, weekly meetings in local health centre Focus on goal setting and prioritisation and input from physiotherapy and pharmacist Peer support through group meetings
Outcomes	**Primary:** Activity participation (Frenchay Activities Index) **Secondary:** Occupational performance (COPM and NEADL) Self Efficacy (SSE) HRQoL (EQ5D) Mental health (HADS) Heathcare utilisation (PC visits and admissions) Health education (HEiQ)
Notes	Intervention duration: 6 weeks with 2-week post intervention follow-up Comparison: Usual care (waiting list for intervention on study completion)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerised sequence
Allocation concealment (selection bias)	Low risk	Independently done by statistician
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible due to nature of intervention and outcomes collected by research due to limited resources
Incomplete outcome data (attrition bias) All outcomes	Low risk	88% follow-up, balanced
Selective reporting (reporting bias)	Low risk	None reported
Other bias	Low risk	None reported
Protection against contamination	Low risk	Control participants had no access to the intervention
Reliable primary outcomes	Low risk	Validated measures
Baseline measurement	Low risk	

Gitlin 2009

Methods	Randomised Controlled Trial USA
Participants	319 participants aged 70 years or more with reported difficulties with at least one activity of daily living. Mean number 6.9 conditions
Interventions	Multicomponent home intervention (the ABLE programme) delivered by occupational therapist (OT) and physical therapist (PT) targeted at reducing functional difficulties; involving 5 OT contacts (4 face-to-face for 90 minutes and 1 telephone) and one PT visit (90 minutes) over 6 months followed by 6-month follow-up with 3 telephone calls and final home visit Individual priorities identified and strategies such as problem solving, balance and muscle strengthening and fall recovery techniques with use of environmental adjustments where needed
Outcomes	**Primary:** Activities of Daily living (ADLs and IADLs) Self-efficacy relating to falls (Falls Efficacy Scale), overall functional self-efficacy control-oriented strategies **Secondary:** Observed home hazards (home hazard index) Mortality (NDI records were obtained for death)
Notes	Intervention: 12 months (first 6 months intensive phase followed by second 6 months telephone contact and final closure visit); data collection at 12 months; mortality data collection 4 years later Comparison: control participants receiving a leaflet on home safety at study completion

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation done by project statistician
Allocation concealment (selection bias)	Low risk	"Randomisation lists and four sets of randomisation were prepared using double, opaque envelopes"
Blinding (performance bias and detection bias) All outcomes	Low risk	"trained interviewers who were masked to group assignment and study hypotheses and who had no role in the intervention interviewed them at 6 and 12 months."
Incomplete outcome data (attrition bias) All outcomes	Low risk	89% follow-up, balanced
Selective reporting (reporting bias)	Low risk	None reported

Gitlin 2009 (*Continued*)

Other bias	Low risk	None reported
Protection against contamination	Low risk	Control group had no access to intervention
Reliable primary outcomes	Low risk	Self-report outcomes but all validated
Baseline measurement	Low risk	Groups comparable at baseline

Hochhalter 2010

Methods	Randomised controlled trial USA
Participants	79 participants aged 65 or older with at least 2 of 7 qualifying chronic illnesses who had received treatment in previous 12 months Primary health care providers in "large Internal Medicine Clinic" in Medical School Teaching Hospital
Interventions	participant engagement intervention: "Making the most of your healthcare" comprising one 2-hour workshop and 2 follow-up phone calls before and after a subsequent routine medical appointment, delivered by 'coaches'
Outcomes	**Primary:** Patient activation measure (PAM) **Secondary:** Communication with physicians scale HRQoL (HRQOL-14); Self-Efficacy for CDM
Notes	Intervention ran during first 3 months after baseline data collection; follow-up at 6 months from baseline Comparison was 'attention control' - workshop on safety in the home Study presented as a feasibility study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Only reported as 'randomly assigned'
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	"interviews carried out by a research assistant blinded to group assignment"

Hochhalter 2010 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	81% follow-up, balanced
Selective reporting (reporting bias)	Low risk	None reported
Other bias	Low risk	None reported
Protection against contamination	Low risk	Control group had no access to patient-oriented intervention
Reliable primary outcomes	Low risk	Valid measures used
Baseline measurement	Low risk	Groups comparable at baseline

Hogg 2009

Methods	Randomised controlled trial Canada
Participants	241 participants aged 50 years or older with at least 2 chronic conditions and at risk of experiencing adverse health outcomes 8 Family Practitioners, 5 nurses and 11 administrative staff in one family-health network in rural Ontario
Interventions	APTCare Intervention: Home-based multidisciplinary team management with an initial assessment by a nurse practitioner and a medication review by pharmacist and individualised patient care plan
Outcomes	**Primary:** Chronic disease management score (CDM score) based on 12 indicators for 1 of 4 chronic diseases **Secondary:** Clinical outcomes where applicable: BP and HbA1c Quality of preventive care using 6 preventive indicators from the Canadian Task Force on Preventive Health Care (Quality of preventive care score) HRQoL (SF36 scores) Instrumental activities of daily living (IADL score) Health service use (hospitalisation, ED visits)
Notes	Intervention duration 15 months, follow-up at intervention completion Comparison: usual care

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Hogg 2009 (*Continued*)

Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Done centrally through automated telephone system
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear for primary outcome, reported as done for secondary outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	95% follow-up, balanced
Selective reporting (reporting bias)	Low risk	None reported
Other bias	Low risk	None reported
Protection against contamination	Unclear risk	Potential contamination as not cluster randomised Only intervention participants received intervention but FPs and existing nurses could have modified their behaviour with control participants based on their experience with intervention participants
Reliable primary outcomes	Unclear risk	Unclear for primary outcome Required chart review which was carried out by a physician; where the data were not clearly recorded in the chart, a nurse double-checked and they reached agreement No reporting of assessment of process
Baseline measurement	Low risk	Groups comparable at baseline

Katon 2010

Methods	Randomised controlled trial USA
Participants	214 participants with depression and diabetes and/or coronary heart disease Primary Care Practitioners (PCPs) in 14 primary care clinics and 3 trained medically supervised nurses
Interventions	TEAMcare intervention integrating a treat-to-target programme with structured visits with nurses, individualised care plans and treatment targets, support for self-care combined with pharmacotherapy, provision of self-care materials for participants, weekly meetings to discuss case progression between nurses, PCPs, psychiatrist and psychologist, electronic registry used to track participant risk factors and depression scores

Outcomes	**Primary:** Composite measure of risk factor control incorporating HbA1c; LDL cholesterol, SBP and scores on the SCL-20 depression scale **Secondary:** Depression (SCL-20 scores) participant global rating of improvement score (i.e. > 50% improvement in SCL-20 score); medication adjustments; medication adherence Adherence with diet and exercise plans HRQoL Satisfaction with care Economic analysis
Notes	Intervention duration 12 months; follow-up data collection at 12 months Comparison: "Enhanced primary care" i.e. usual care plus PCPs informed of depression diagnosis and of results at baseline, 6 and 12 months

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomly assigned by a centrally randomised process"
Allocation concealment (selection bias)	Low risk	Carried out centrally
Blinding (performance bias and detection bias) All outcomes	Low risk	"research assistants who were unaware of the intervention status implemented study procedures"
Incomplete outcome data (attrition bias) All outcomes	Low risk	12-month follow-up > 83% all measures, majority > 90%
Selective reporting (reporting bias)	Low risk	None reported
Other bias	Low risk	None reported
Protection against contamination	Unclear risk	Control group did not have access to study nurses but managed by same group of PCPs as intervention group
Reliable primary outcomes	Low risk	Automated measures or validated scales
Baseline measurement	Low risk	Comparable groups at baseline

Kennedy 2013

Methods	Cluster randomised controlled trial UK Primary outcome data from authors for multimorbidity sub-group. No secondary outcome data available for multimorbidity sub-group
Participants	Data on primary outcomes for sub-group of 4023 participants with multimorbidity, defined as at least two of Diabetes/COPD/Irritable Bowel Syndrome (IBS). 19% of full trial population (n = 5599) had 4 or more conditions, 50% 65 years or older
Interventions	WISE intervention: System-based approach to self-management support. Practice level: training; provision of resources for staff participants: guidebooks on self-management; web-based directory of local services; some IBS specific material
Outcomes	**Primary:** Shared decision making Self-efficacy HRQol (EQ5D) **Secondary:** No data available for multimorbidity sub-group
Notes	Intervention 12 months, immediate follow-up at 12 months Sub-group data on primary outcomes from authors Comparison: usual care

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"minimisation algorithm by the trial statistician".
Allocation concealment (selection bias)	Low risk	"Research staff recruiting practices are unaware of the next allocation in the sequence at the time of recruitment."
Blinding (performance bias and detection bias) All outcomes	Low risk	Postal questionnaires and "analyst blind to practice allocation to trial arms"
Incomplete outcome data (attrition bias) All outcomes	Low risk	72% follow-up at 12 months, balanced
Selective reporting (reporting bias)	Low risk	None reported
Other bias	Low risk	None reported
Protection against contamination	Low risk	Cluster design

Kennedy 2013 (*Continued*)

Reliable primary outcomes	Low risk	Validated measures
Baseline measurement	Low risk	Comparable at baseline

Krska 2001

Methods	Randomised controlled trial UK
Participants	332 participants aged over 65 years with at least 2 chronic conditions and taking at least 4 prescribed medications regularly; 6 general practices in Grampian, UK
Interventions	Pharmaceutical care plan drawn up by a pharmacist based on medical records and participant interviews, and then implemented by the practice team
Outcomes	**Primary and secondary (no distinction specified):** Pharmaceutical care issues (PCI scale) HRQoL (SF36 scores) Health service utilisation including GP and practice nurse contacts, OPD attendance, use of social services and hospital admissions Economic: direct monthly costs of prescribed medications per participant
Notes	Study duration and follow-up 3 months Comparison: controls had review of drug therapy by pharmacist but no pharmaceutical care plan implemented

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Text simply states "patients were randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Randomisation method not specified
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	87% follow-up, balanced
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Krska 2001 (*Continued*)

Protection against contamination	High risk	Authors state that contamination of control participants could have occurred but stated that a cluster design would have been more problematic due to differential prescribing patterns between practices
Reliable primary outcomes	Unclear risk	PCIs previously used but unclear whether validated as outcome measure
Baseline measurement	Low risk	Some baseline imbalance between groups for PCIs and admissions; not clinically significant

Lorig 1999

Methods	Randomised controlled trial USA
Participants	Subgroup of 536 participants over 40 years with at least 2 of the following chronic conditions: heart disease, lung disease, stroke or arthritis; recruited through mass media Volunteer lay leaders ran weekly group meetings
Interventions	Chronic Disease Self Management Programme: weekly meetings for 7 weeks delivered in community settings by trained volunteer lay leaders with professional training of lay leaders and support throughout the programme
Outcomes	**Primary and secondary (no distinction specified):** Self-rated health scale (from the National Health Interview Survey) Health Assessment Questionnaire (HAQ) Disability scale Psychological well-being (MHI-5 well-being scale) HRQoL: pain and physical discomfort scale (adaptation of the Medical Outcomes Survey (MOS) pain scale); energy and fatigue scale (MOS energy and fatigue scale) health distress scale (modified MOS health distress scale) Health behaviours including duration exercise taken, use of cognitive symptom management, communication with physicians, social and role activity limitations Health service utilisation including physician, emergency department and hospital visits and number nights as hospital inpatient Economic: direct programme costs and savings
Notes	Study duration and follow-up 6 months Comparison: waiting list controls

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Study reports "randomisation was conducted serially"

Lorig 1999 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Outcome assessors blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated specifically for multimorbidity subgroup; overall follow-up 85%
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent
Protection against contamination	Low risk	Controls on waiting list so no exposure to those delivering community-based intervention
Reliable primary outcomes	Low risk	Validated measures used
Baseline measurement	Low risk	Groups comparable at baseline

Lynch 2014

Methods	Randomised controlled trial (pilot) USA
Participants	61 African American participants with diabetes and hypertension, mean age 54 years, 47% taking insulin therapy, 32% with depression
Interventions	LIFE intervention: Diabetes self-management groups led by dietician, 18 2-hour classes, incorporating nutrition education, behaviour skills training, self-monitoring, goal-setting and problem-solving skills Social support provided by weekly telephone calls from a peer supporter
Outcomes	**Primary:** % achieving 5% weight loss at 6 months **Secondary:** HbA1c; % achieving 5% reduction in HbA1c; BP; Diabetes self care activities (SDSCA scores)
Notes	Intervention duration 6 months with immediate follow-up Comparison: usual care with two 3-hour education sessions led by a community health worker

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Lynch 2014 (*Continued*)

Random sequence generation (selection bias)	Low risk	"we used a block randomisation scheme supervised by the study statistician"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported. Outcome data collected by 'study staff'
Incomplete outcome data (attrition bias) All outcomes	Low risk	90% follow-up, balanced
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent
Protection against contamination	Low risk	Controls had no access to group-based sessions or peer support
Reliable primary outcomes	Low risk	Clinical outcomes measured using standard clinic protocols
Baseline measurement	Low risk	Groups balanced at baseline

Martin 2013

Methods	Randomised controlled trial Australia
Participants	66 people with depression and headache (migraine (66%); and tension-type headache (33%)), mean age 41, 74% female Community clinical psychologists
Interventions	Cognitive behavioural therapy programme for both depression and headache Twelve 50-minute weekly sessions incorporating pain- and lifestyle-management training Training for community psychologists Treatment manual (44 pages) Client handbook and relaxation CD
Outcomes	**Primary:** Depression (BDI and PHQ9 scores) Medication consumption **Secondary:** Anxiety (BDA scores) HRQoL (AQOL)

Martin 2013 (*Continued*)

Notes	Intervention 12 weeks with immediate follow-up. Additional follow-up at 4 months for intervention group only so data not used Comparison: usual care and GPs asked not to refer to psychology but could use other mental health services

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'Stratified randomisation procedure'
Allocation concealment (selection bias)	Low risk	Done by independent researcher
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only analysed those who completed the programme and excluded those who dropped out early
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent
Protection against contamination	Unclear risk	Unlikely as control participants had no access to programme but were treated by same GPs
Reliable primary outcomes	Low risk	Validated scores
Baseline measurement	Low risk	Done

Morgan 2013

Methods	Cluster randomised controlled trial Australia
Participants	400 people with depression and diabetes and/or ischaemic heart disease, mean age 68, 40% IHD, 44% diabetes and 17% both, mean HbA1c at baseline 7.1%, mean SBP at baseline 134 mmHg 11 general practices
Interventions	TrueBlue collaborative care model Practice nurse case manager Reviews: 3 monthly 45-minute reviews with practice nurse covering lifestyle risk factors, review of results and support for self-management and goal setting; followed by 15-minute review with GP who stepped up treatment if needed

	Indivudal care plans, copy held by participant Educational resources and fact sheets Practice nurse training, 2-day workshop
Outcomes	**Primary:** Depression (PHQ9 scores) **Secondary:** Clinical outcomes: HbA1c, SBP, Cholesterol, BMI, 10-year CVD risk HRQoL: SF36 scores Medication: on anti-depressant medication participant behaviours: smoking, alcohol, exercise (30 min/day on 5 days/week, attending exercise programme, attending mental health programme Provider behaviour: referrals to mental health and to exercise programme
Notes	Intervention duration 6 months with immediate follow-up and additional follow-up at 12 months for intervention group only (12 month data not included) Comparison: usual care and offered intervention after 6 months

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	'Random number generation' but no report on who undertook it
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not possible to blind participants and clinicians due to nature of intervention Outcome assessors: data collected from care plans
Incomplete outcome data (attrition bias) All outcomes	Low risk	72% follow-up, balanced
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent
Protection against contamination	Low risk	Cluster design
Reliable primary outcomes	Low risk	
Baseline measurement	Low risk	Validated measures, balanced

Sommers 2000

Methods	Cluster randomised controlled trial USA
Participants	543 participants older than 65 years with at least 2 chronic conditions and living independently, attending 18 private office practices of primary care physicians
Interventions	Senior Care Connections (SCC) intervention delivered by a team including the primary care physician, a nurse with geriatric medicine training and a social worker Home visit assessment followed by team discussion and development of a risk reduction plan and treatment targets
Outcomes	**Primary and secondary (no distinction specified):** Physical functioning (Health activities questionnaire (HAQ)) Emotional functioning (short form geriatric depression scale (GDS)) HRQoL (SF36 scores) Social activities count Symptom scale Medication count Nutrition checklist Health service utilisation including office, emergency room and home care visits, hospital admissions, skilled nursing facility admissions, length of hospital stay and nursing home placements Economic: direct costs of the intervention
Notes	Study duration 2 years, 12-month follow-up post completion intervention Comparison: usual care from their primary care physician

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study reports "physicians randomised"
Allocation concealment (selection bias)	Unclear risk	Unclear at cluster level but no bias at participant level as recruited through clusters
Blinding (performance bias and detection bias) All outcomes	Low risk	Healthcare utilisation measured from automated data.
Incomplete outcome data (attrition bias) All outcomes	Low risk	86% follow-up for service use measures; 74% follow-up questionnaire data, balanced
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent
Protection against contamination	Low risk	Cluster randomisation

Sommers 2000 (*Continued*)

Reliable primary outcomes	Low risk	Automated data used and validated measures used
Baseline measurement	Low risk	Groups comparable at baseline

Wakefield 2012

Methods	Randomised controlled trial USA
Participants	302 adults with diabetes and hypertension, mean age 68, 96% male (VA system setting) , 95% white, baseline mean HbA1c 7.2%, baseline mean SBP 136 mmHg
Interventions	Intervention 1: home telehealth with nurse case manager using high intensity treatment algorithms Intervention 2: home telehealth with nurse case manager using low intensity treatment algorithms Comparison: usual care in primary care clinic with access to PCP, endocrinologist, diabetes education and nurse manager (different to study nurse case manager)
Outcomes	**Primary:** HbA1c and blood pressure **Secondary:** Medication adherence Knowledge scores Self-efficacy participant perception of the intervention
Notes	Intervention duration 6 months, follow-up 6 months post intervention completion Comparison: usual care in primary care clinic with access to PCP, endocrinologist, diabetes education and nurse manager (different to study nurse case manager)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Study nurse used 'sequentially numbered envelopes'
Allocation concealment (selection bias)	Unclear risk	Study nurse used opaque envelopes, prepared in advance by project director
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported but primary outcomes automated
Incomplete outcome data (attrition bias) All outcomes	Low risk	81% follow-up, balanced

Wakefield 2012 (*Continued*)

Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent
Protection against contamination	Unclear risk	Unlikely as controls had no access to intervention but treated in same centres
Reliable primary outcomes	Low risk	Automated
Baseline measurement	Low risk	Balanced at baseline

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Addolorato 2004	Specialist setting
Agarwal 2015	Participants not defined as having multimorbidity as per review protocol
Balaban 2014	Participants not defined as having multimorbidity as per review protocol
Beck 1997	Participants not defined as having multimorbidity as per review protocol
Beretta 2014	Intervention directed at one condition only (epilepsy)
Bove 2015	Participants not defined as having multimorbidity as per review protocol
Brand 2004	Specialist setting
Chow 2014	Specialist in-patient setting for first stage of intervention delivery
Coburn 2012	Participants not defined as having multimorbidity as per review protocol
Dorr 2008	No appropriate data for sub-group with multimorbidity
Dougados 2015	Specialist setting
Drake 1998	Specialist setting
Dwinger 2013	Participants not defined as having multimorbidity as per review protocol
Eklund 2013	Participants not defined as having multimorbidity as per review protocol
Essock 2006	Specialist setting

(*Continued*)

Fischer 2015	Specialist setting
Freund 2011	Participants not defined as having multimorbidity as per review protocol
Ganz 2010	Participants not defined as having multimorbidity as per review protocol
Harpole 2005	Intervention not based on multimorbidity: the study presents an analysis of whether co-morbidity alters response to a depression intervention
Hermanns 2015	Intervention directed at one condition only
Hien 2004	Specialist setting
Hinrichs 2013	Not multimorbidity
Hutchings 2013	Not multimorbidity
Katon 2004	Intervention directed at one condition only (depression)
Leveille 1998	Participants not defined as having multimorbidity as per review protocol
Lin 2003	Intervention directed at one condition only
Liss 2013	Participants not defined as having multimorbidity as per review protocol
Lyles 2003	Participants had medically unexplained symptoms, not multimorbidity
Martinez 2013	Participants not defined as having multimorbidity as per review protocol
McCall 2011	Participants not defined as having multimorbidity as per review protocol
McCusker 2015	Participants not defined as having multimorbidity as per review protocol
Meeuwissen 2011	Intervention directed at one condition only
Morey 2006	Participants defined as having a range of chronic conditions (from 0-15) with no sub-group eligible for inclusion in this review
Morris 2012	Intervention directed at one condition only
Park 2014	Study setting - residential care
Petersen 2014	Intervention directed at one condition only
Plant 2013	Study setting: inpatients
Reuben 2012	Participants not defined as having multimorbidity as per review protocol

(*Continued*)

Rodriguez-Pascual 2013	Intervention directed at one condition (heart failure).
Rosenman 2006	No multimorbidity sub-group data
Ruikes 2012	Participants not defined as having multimorbidity as per review protocol
Schraeder 2005	No multimorbidity subgroup
Sharpe 2012	Intervention directed at one condition only (protocol)
Shaw 2014	Participants not defined as having multimorbidity as per review protocol
Srinivasan 2014	Specialist setting
Takahashi 2012	Participants not defined as having multimorbidity as per review protocol
Taveira 2011	Intervention directed at one condition only
van der Weegen 2013	Participants not defined as having multimorbidity as per review protocol
van Mourik 2012	Intervention around detection and screening
Venter 2012	Participants not defined as having multimorbidity as per review protocol, had either CCF or COPD
Via-Sosa 2013	Participants not defined as having multimorbidity as per review protocol
Von Korff 2012	Participants not defined as having multimorbidity as per review protocol
Weber 2012	Setting: specialist multidisciplinary clinics with no primary care involvement. An alternative model of specialist care
Wilhelmson 2011	Participants not defined as having multimorbidity as per review protocol
Willard-Grace 2013	Participants not defined as having multimorbidity as per review protocol
Williams 2012	Participants not defined as having multimorbidity as per review protocol
Williams 2013	Participants not defined as having multimorbidity as per review protocol
Wrede 2013	Participants not defined as having multimorbidity as per review protocol
Wu 2013	Specialist setting

Characteristics of studies awaiting assessment *[ordered by study ID]*

Alexopoulos 2014

Methods	RCT
Participants	138 participants with COPD and Depression
Interventions	A personalised intervention for depressed participants with COPD (PID-C) aimed to mobilise participants to participate in the care of both conditions
Outcomes	Primary outcome measures were the 17-item Hamilton Depression Rating Scale and the Pulmonary Functional Status and Dyspnea Questionnaire-Modified. Other measures were adherence to rehabilitation exercise (> 2 hours per week) and adherence to adequate antidepressant prescriptions
Notes	

Buhrman 2015

Methods	RCT
Participants	52 participants with chronic pain and comorbid depression and anxiety
Interventions	An individualized cognitive-behavioural treatment delivered through the Internet
Outcomes	Depressive symptoms and pain disability
Notes	

Ekdahl 2014

Methods	RCT
Participants	383 participants > 75 years, hospitalised at least 3 times during the past 12 months, with at least 3 conditions
Interventions	Comprehensive Geriatric Assessment
Outcomes	Hospitalisations, mortality, health-related quality of life (HRQoL) and costs of care
Notes	

Katz 2015

Methods	RCT
Participants	40 participants with Diabetes and Hypertension
Interventions	mHealth group with smartphone and the WellDoc™ Diabetes Manager application providing real time feedback on glucose and blood pressure (BP) entries. Case managers viewed glucose and BP via a web portal. A monthly report

	was entered into EMR
Outcomes	Primary outcome was change in the Patient Activation Measure (PAM) at 6 months. Secondary outcomes included A1c, BP, HEDIS measures, hospitalisations, and ER visits
Notes	

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12609000726257

Trial name or title	Reed 2011
Methods	RCT
Participants	n = 252 aged 60 years or older with two or more chronic conditions
Interventions	Flinders programme which is a chronic disease self-management support programme. Clinician-led generic self-management intervention. Usual care group to receive health information only
Outcomes	Primary outcome: self-rated health, multiple secondary outcomes including health status measures, health behaviours and healthcare utilisation
Starting date	Not recorded, protocol published in 2011
Contact information	Richard.Reed@flinders.edu.au
Notes	See usual care to receive health information

Crowley ongoing

Trial name or title	Tailored case management for diabetes and hypertension (TEAM-DM)
Methods	Multicentre RCT involving 9 community practices
Participants	n = 377, adults (aged over 21 years), enrolled in a participating clinic for at least 1 year, have type 2 diabetes mellitus requiring medication, have hypertension requiring medication and poor diabetes control (most recent HbA1C in past year over 7.5%
Interventions	Telephone-delivered behavioural intervention. Targets three areas: 1) cultivation of healthy behaviours for diabetes and hypertension; 2) provision of fundamentals to support attainment of healthy behaviours; and 3) identification and correction of patient-specific barriers to adopting healthy behaviours
Outcomes	**Primary**: HbA1C and blood pressure measured at 6, 12 and 24 months **Secondary**: Self-efficacy, self-reported medication adherence, exercise and cost-effectiveness
Starting date	Recruitment began on 11 June 2009 and concluded 27 July 2011

Crowley ongoing (*Continued*)

Contact information	matthew.crowley@dm.duke.edu
Notes	

ISRCTN 83908315

Trial name or title	Practice network-based care management for people with type 2 diabetes and multiple comorbidities (GEDIMAplus)
Methods	Multicentre RCT involving 30 study centres
Participants	n = 582 adults with type 2 diabetes mellitus and enrolled in the DMP Diabetes programme and at least 2 severe chronic conditions and 1 informal caregiver per participant
Interventions	Three main elements: 1) 3 home visits including structured assessment of medical and social needs; 2) 24 structured telephone monitoring contacts; and 3) self-monitoring of blood glucose levels at 3-monthly intervals. Delivered by trained healthcare assistants as an add-on to usual care
Outcomes	**Primary**: between-group differences in changes of diabetes-related self care behaviours using the revised Summary of Diabetes Self-Care Activities (SDSCA-G) **Secondary**: between-group differences in the SDSCA-G subscales, glycosylated haemoglobin A level, health-related quality of life, self-efficacy, differences in severe symptomatic hypoglycaemia, cost-effectiveness, and financial family burden
Starting date	participant recruitment started on 1 February 2014
Contact information	kayvan.bozorgmehr@med.uni-heidelberg.de
Notes	

ISRCTN24874457

Trial name or title	Web-based cognitive behavioural therapy (W-CBT) for people with diabetes and co-morbid depression
Methods	RCT
Participants	N = 286
Interventions	8-week, moderated self-help course tailored to the needs of persons living with diabetes and offered on an individual basis. Participants receive feedback on their homework assignments by email from their coach
Outcomes	**Primary**: depressive symptoms and diabetes-specific emotional distress **Secondary**: satisfaction with the course, perceived health status, self-care behaviours, glycaemic control, and days in bed/absence from work
Starting date	Protocol published in 2008

ISRCTN24874457 (*Continued*)

Contact information	k.vanbastelaar@vumc.nl
Notes	Additional publication in 2011; van Bastellar et al Patient Education and Counselling 2011;84(1):49-55. Further details on intervention development and recruitment

Lassere 2015

Trial name or title	Improving quality of care and long-term health outcomes through continuity of care with the use of an electronic or paper patient-held portable health file (COMMUNICATE):
Methods	RCT
Participants	792 participants aged 60 years or older living independently in the community, but who have 2 or more chronic medical conditions that require prescription medication and regular care by at least 3 medical practitioners (general and specialist care)
Interventions	An electronic and paper patient-held Portable Health File (PHF)
Outcomes	The primary outcome is a combined endpoint of deaths, overnight hospitalizations and blindly adjudicated serious out-of-hospital events
Starting date	March 2010 with recruitment due to complete in September 2015
Contact information	Marissa N Lassere M.Lassere@unsw.edu.au
Notes	

Mercer ongoing

Trial name or title	Care Plus Study
Methods	Exploratory/Pilot RCT
Participants	Multimorbidity and socioeconomic deprivation
Interventions	System level organisational type intervention
Outcomes	
Starting date	2012
Contact information	Prof Stewart Mercer, University of Glasgow, Scotland
Notes	

NCT01328639

Trial name or title	Trial Registration number NCT01572389
Methods	Controlled on-off time series (monthly basis)
Participants	Aged 18 years or older, diagnosis of type 2 diabetes and under the care of a primary care network family physician, score ≥ 10 on the Patient Health Questionnaire-9, speak English and have adequate hearing to complete telephone interviews, aim to recruit n = 168 participants
Interventions	Nurse care manager guides patient-centred care with family physicians and consultant physicians to monitor progress and develop tailored plans. Three phases: 1) Improving depressive symptoms; 2) improving blood glucose, blood pressure and cholesterol; and 3) improving lifestyle behaviours
Outcomes	**Primary**: change in depressive symptoms and a multivariable, scaled marginal model for the combined outcome of global disease control (i.e. haemoglobin A1C, systolic blood pressure, LDL cholesterol) **Secondary**; healthcare utilisation, costs
Starting date	Not recorded, protocol published August 2012
Contact information	jeff.johnson@ualberta.ca
Notes	

NCT01572389

Trial name or title	Healthy outcomes through patient empowerment (HOPE)
Methods	RCT
Participants	n = 242 veterans with Patient Health Questionnaire (PHQ)-9 score > 10 and haemoglobin A1C > 7.5%
Interventions	Blended diabetes/depression behavioural health coaching for 6 months (active intervention), followed by 6 months without coaching (maintenance period) vs enhanced usual care (provision of educational materials)
Outcomes	**Primary**: PHQ-9 score and haemoglobin A1C values at 6- and 12-month follow-up **Secondary**: 1) Problem area in diabetes questionnaire to assess diabetes-related distress; 2) Penn State worry questionnaire to assess changes in worry/anxiety; 3) Goal-setting evaluation tool for diabetes
Starting date	Not recorded, protocol published March 2014
Contact information	jcully@bcm.edu
Notes	

NCT01719991

Trial name or title	Trial Registration number NCT01719991
Methods	Controlled before-after study; randomised participants, delayed intervention for control group, before and after intervention analysis
Participants	n = 400, 25 participants per nurse case manager group, 8 nurse case managers
Interventions	First component is nurse-led case management including 4 elements: 1) evaluation of participant needs and resources; 2) establishment and maintenance of a patient-centred individualised service plan; 3) co-ordination of services among partners; and 4) self-management support for participants and families. Second component includes group meetings (10 to 12 participants) for self-management support in accordance with the Stanford programme
Outcomes	Personal self-efficacy, self-management practices, health habits, patient activation, psychological distress, patient satisfaction, patient empowerment, quality of life, health services utilisation, health professional satisfaction, services integration, long-term morbidity, and mortality
Starting date	Not recorded, protocol published in February 2013
Contact information	mcchouin@uqca.ca
Notes	

NTR1847

Trial name or title	The effectiveness of case management for people with comorbid diabetes type 2; the CasCo study
Methods	RCT
Participants	People with type 2 diabetes mellitus who participate in the diabetes care system and have at least one additional chronic condition from a condition list. Aim to recruit 230 participants
Interventions	Case-management programme in addition to diabetes-management programme. Based on Guided Care Model with six elements
Outcomes	**Primary**: quality of care perceived by participants **Secondary:** quality of care perceived by GP, health status of the participant, diabetes control, and healthcare utilisation
Starting date	Recruitment started February 2011
Contact information	n.versnel@nivel.nl
Notes	Usual care is the primary care-based diabetes management programme

NTR2626

Trial name or title	Trial Registration number NTR2626
Methods	Multicentre RCT
Participants	Aged 18 years or older enrolled in a disease-management programme for asthma and/or COPD and elevated score on depression/anxiety screening instruments. Aim to screen n = 1142 for participation in this trial
Interventions	Stepped care disease management programme for comorbid anxiety and depression
Outcomes	**Primary**: Depression score on PHQ-9 Anxiety scores on Generalized Anxiety disorder-7 scale Mini international neuropsychiatric interview Quality of life measures (clinical COPD questionnaire, asthma control questionnaire, health survey (SF-12))
Starting date	Not recorded, protocol published in January 2012
Contact information	F.Pouwer@uvt.nl
Notes	

NTR3715

Trial name or title	
Methods	Cluster RCT
Participants	Aged 18 years or older, treated for type 2 diabetes mellitus and/or coronary heart disease in primary care and have subthreshold depressive symptoms (score $\geq$ 6 on PHQ-9) without fulfilling the criteria for major depression. Aim to include n = 236
Interventions	Nurse-led stepped care intervention with four components: 1) watchful waiting; 2) guided self-help treatment; 3) problem solving treatment; and 4) referral to the GP
Outcomes	**Primary**: cumulative incidence of major depressive disorder as measured by the mini international neuropsychiatric interview **Secondary**: include severity of depressive symptoms, quality of life, anxiety, and clinical outcomes
Starting date	Not recorded, state first results expected early 2015
Contact information	s.e.m.van.dijk@vu.nl
Notes	

Pr1MaC ongoing

Trial name or title	Pr1MaC
Methods	RCT (sub-group)
Participants	270 participants with combinations of diabetes, COPD, Astma, CVD and other risk factors such as obesity
Interventions	Integration of chronic disease management and prevention
Outcomes	SF12, HeiQ, nutrition and physical activity
Starting date	2011
Contact information	Prof Martin Fortin, University of Sherbrooke, Canada
Notes	

Salisbury ongoing

Trial name or title	3D Study
Methods	Cluster RCT
Participants	Multimorbidity
Interventions	Organisational-type general practice-based intervention
Outcomes	HRQoL, treatment burden, self-efficacy, healthcare utilisation
Starting date	2014
Contact information	Prof Chris Salisbury, University of Bristol, UK
Notes	

Schneider ongoing

Trial name or title	
Methods	pilot RCT
Participants	Women with type 2 diabetes mellitus with the following additional criteria: 1) inadequately controlled type 2 diabetes as defined by HbA1C $\geq$ 7 and $\leq$ 10; 2) meeting criteria for major depressive disorder as defined by the structured clinical interview for DSM-IV disorders; 3) not physically active, defined as engaging in moderate intensity exercise less than 3 times per week for 20 min; 4) BMI 18.5 to 45 kg/m^2; and 5) aged 21 to 65 years

Schneider ongoing (*Continued*)

Interventions	Exercise intervention involving 38 behavioural activation-enhanced group exercise classes over 24 weeks in addition to usual care. Usual care receive depression treatment referrals and print information on diabetes management via diet and physical activity
Outcomes	HbA1C, Depression scores on Beck's depression inventory, fitness measure, BMI, waist circumference, blood pressure, self efficacy for exercise, quality of life and several process measures
Starting date	Not recorded, protocol published in June 2011
Contact information	Kirstin.Schneider@umassmed.edu
Notes	Pilot RCT, usual care group receive depression referral treatment and written information re diabetes management

DATA AND ANALYSES

Comparison 1. Glycaemic control (HbA1c) studies targeting diabetes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HBA1c	3	561	Mean Difference (IV, Random, 95% CI)	0.02 [-0.21, 0.25]

Comparison 2. Systolic Blood Pressure: studies targeting hypertension

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Systolic blood pressure	5	892	Mean Difference (IV, Random, 95% CI)	-3.10 [-7.26, 1.06]

Comparison 3. PHQ9 depression scores: studies targeting depression

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PHQ9 Depression scores	4		Mean Difference (IV, Random, 95% CI)	Totals not selected

Comparison 4. Depression scores: studies targeting depression

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Depression scores	6	1062	Std. Mean Difference (IV, Random, 95% CI)	-0.41 [-0.63, -0.20]

Comparison 5. Health related quality of life

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HRQoL	6	3565	Std. Mean Difference (IV, Random, 95% CI)	0.11 [-0.10, 0.33]

Comparison 6. Self-Efficacy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Self-efficacy score	5	3639	Std. Mean Difference (IV, Random, 95% CI)	0.05 [-0.12, 0.22]
1.1 Studies targeting self-efficacy	5	3639	Std. Mean Difference (IV, Random, 95% CI)	0.05 [-0.12, 0.22]

Analysis 1.1. Comparison 1 Glycaemic control (HbA1c) studies targeting diabetes, Outcome 1 HBA1c.

Review: Interventions for improving outcomes in patients with multimorbidity in primary care and community settings

Comparison: 1 Glycaemic control (HbA1c) studies targeting diabetes

Outcome: 1 HBA1c

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Katon 2010	101	8.14 (2.03)	97	8.04 (1.87)		18.0 %	0.10 [-0.44, 0.64]
Lynch 2014	30	7.9 (1.6)	31	7.4 (1.6)		8.3 %	0.50 [-0.30, 1.30]
Wakefield 2012	93	6.9 (1.1)	209	6.95 (1.1)		73.7 %	-0.05 [-0.32, 0.22]
Total (95% CI)	**224**		**337**			**100.0 %**	**0.02 [-0.21, 0.25]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.72$, df = 2 (P = 0.42); $I^2 = 0.0\%$

Test for overall effect: Z = 0.19 (P = 0.85)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Systolic Blood Pressure: studies targeting hypertension, Outcome 1 Systolic blood pressure.

Review: Interventions for improving outcomes in patients with multimorbidity in primary care and community settings

Comparison: 2 Systolic Blood Pressure: studies targeting hypertension

Outcome: 1 Systolic blood pressure

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Bogner 2008	32	127.3 (17.7)	32	141.3 (18.8)		13.7 %	-14.00 [-22.95, -5.05]
Katon 2010	101	131 (18.4)	97	132.3 (17.2)		24.4 %	-1.30 [-6.26, 3.66]
Lynch 2014	26	135.8 (21.4)	29	136.7 (23)		9.4 %	-0.90 [-12.64, 10.84]
Morgan 2013	161	132.4 (19)	112	131.2 (19.6)		25.4 %	1.20 [-3.47, 5.87]
Wakefield 2012	209	133 (16.6)	93	137 (17.3)		27.1 %	-4.00 [-8.17, 0.17]
Total (95% CI)	**529**		**363**			**100.0 %**	**-3.10 [-7.26, 1.06]**

Heterogeneity: $Tau^2 = 12.11$; $Chi^2 = 9.55$, df = 4 (P = 0.05); $I^2 = 58\%$

Test for overall effect: Z = 1.46 (P = 0.14)

Test for subgroup differences: Not applicable

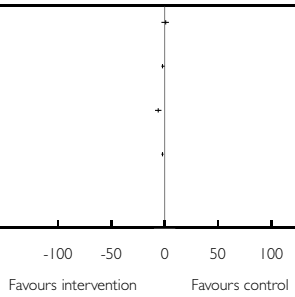
Analysis 3.1. Comparison 3 PHQ9 depression scores: studies targeting depression, Outcome 1 PHQ9 Depression scores.

Review: Interventions for improving outcomes in patients with multimorbidity in primary care and community settings

Comparison: 3 PHQ9 depression scores: studies targeting depression

Outcome: 1 PHQ9 Depression scores

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Barley 2014	32	12.6 (7.1)	37	12 (6.9)		0.60 [-2.72, 3.92]
Coventry 2015	157	11.3 (6.5)	168	13.1 (6.5)		-1.80 [-3.21, -0.39]
Martin 2013	18	6.67 (4.6)	26	12.6 (5.3)		-5.93 [-8.87, -2.99]
Morgan 2013	164	7.1 (4.7)	146	9 (5.5)		-1.90 [-3.05, -0.75]



Analysis 4.1. Comparison 4 Depression scores: studies targeting depression, Outcome 1 Depression scores.

Review: Interventions for improving outcomes in patients with multimorbidity in primary care and community settings

Comparison: 4 Depression scores: studies targeting depression

Outcome: 1 Depression scores

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Barley 2014	41	12.6 (7.1)	40	12 (6.9)		13.6 %	0.08 [-0.35, 0.52]
Bogner 2008	32	9.9 (10.7)	32	19.3 (15.2)		11.4 %	-0.71 [-1.21, -0.20]
Coventry 2015	170	1.76 (0.9)	180	2.02 (0.9)		23.5 %	-0.29 [-0.50, -0.08]
Katon 2010	105	0.83 (0.66)	106	1.14 (0.68)		20.4 %	-0.46 [-0.73, -0.19]
Martin 2013	20	6.7 (4.6)	26	12.6 (5.3)		8.4 %	-1.16 [-1.79, -0.52]
Morgan 2013	164	7.1 (4.7)	146	9 (5.5)		22.8 %	-0.37 [-0.60, -0.15]
Total (95% CI)	**532**		**530**			**100.0 %**	**-0.41 [-0.63, -0.20]**

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 12.82$, df = 5 (P = 0.03); $I^2 = 61\%$

Test for overall effect: Z = 3.74 (P = 0.00018)

Test for subgroup differences: Not applicable

Analysis 5.1. Comparison 5 Health related quality of life, Outcome 1 HRQoL.

Review: Interventions for improving outcomes in patients with multimorbidity in primary care and community settings

Comparison: 5 Health related quality of life

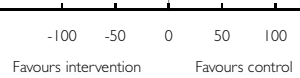
Outcome: 1 HRQoL

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Barley 2014	32	40.6 (11.2)	37	39.6 (12.3)		12.1 %	0.08 [-0.39, 0.56]
Coventry 2015	152	2.99 (20.2)	167	2.91 (0.6)		22.3 %	0.01 [-0.21, 0.23]
Garvey 2015	22	65.7 (20.2)	22	50.5 (16.3)		8.6 %	0.81 [0.20, 1.43]
Katon 2010	105	6 (2.2)	106	5.2 (1.9)		19.8 %	0.39 [0.12, 0.66]
Kennedy 2013	1168	0.56 (0.34)	1708	0.57 (0.32)		28.1 %	-0.03 [-0.10, 0.04]
Martin 2013	20	26.3 (4.76)	26	28.4 (4.97)		9.1 %	-0.42 [-1.01, 0.17]
Total (95% CI)	**1499**		**2066**			**100.0 %**	**0.11 [-0.10, 0.33]**

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 17.18$, df = 5 (P = 0.004); $I^2 = 71\%$

Test for overall effect: Z = 1.01 (P = 0.31)

Test for subgroup differences: Not applicable

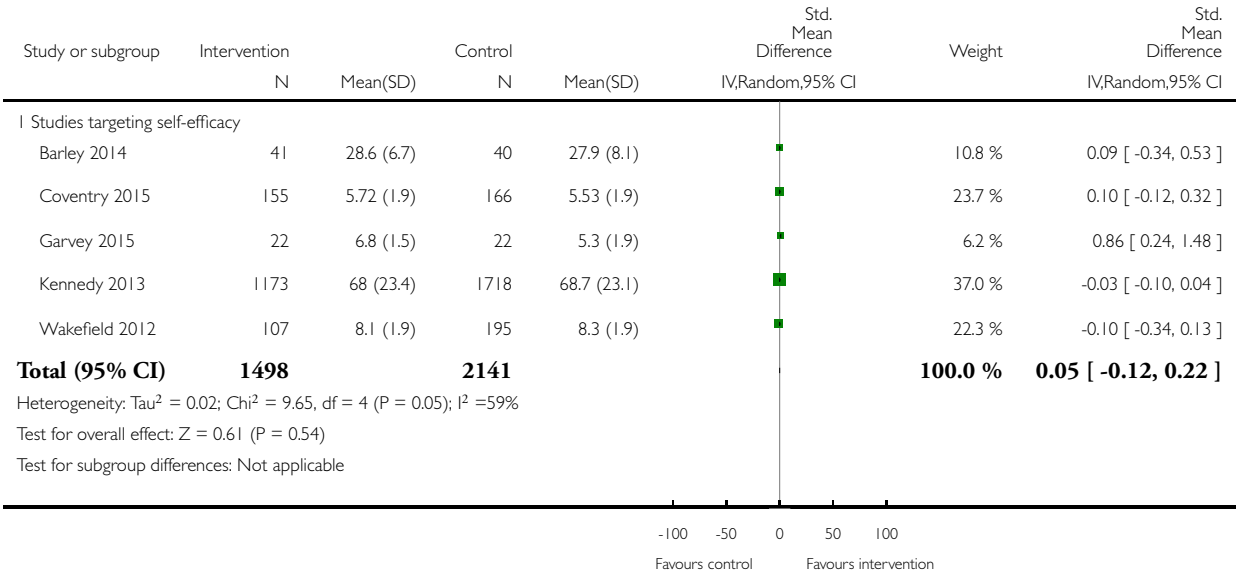


Analysis 6.1. Comparison 6 Self-Efficacy, Outcome 1 Self-efficacy score.

Review: Interventions for improving outcomes in patients with multimorbidity in primary care and community settings

Comparison: 6 Self-Efficacy

Outcome: 1 Self-efficacy score



ADDITIONAL TABLES

Table 1. Multimorbidity intervention components

Author Year	Professional	Participant	Organisational			Effect of intervention on primary outcome
			Case management or coordination of care	Reorganisation of care/team working	New team member	
Predominantly organisational						
Barley 2014	Nurse training	Participant information Prioritisation to create goals and health plan	**Case manager** provided personalised care	Regular planned participant visits Weekly team meetings	Nurse case manager	Pilot study and primary outcome was feasibility and deemed successful

Table 1. Multimorbidity intervention components (*Continued*)

Bogner 2008		Individualised programme	**Case manager**	Regular planned participant visits		Improved blood pressure control and depression scores
Boult 2011	Nurse training	Individual management plans Support for self-management	Guided care nurses coordinated care	**Guided care 'pods'** consisting of nurse and PCP Monthly monitoring of participants		No impact on healthcare utilisation
Coventry 2015	Practice team training	Personalised goals and participant workbooks		**Collaborative care using stepped care protocols** Joint consultation between participant, psychologist and practice nurse	Psychologist Supervision and input from team psychiatrist	Modest reduction in depression scores
Hogg 2009		Individualised care plans		**Multidisciplinary team-based management** with home based assessment Medication review	Pharmacist	Modest improvements in quality of chronic care delivery
Katon 2010		Individualised management plans and targets Support for self-management		**Team-based care** **Stepped care treatment protocols** Weekly team meeting	Psychologist and psychiatrist supported depression care	Improvements in composite outcome of glycaemic control, blood pressure, lipids and depression scores
Kennedy 2013	Practice training	Support for self-management Participant guidebooks		**Systems-based approach to self-management support** with practice supports and links made with related local services		No intervention effect noted

Table 1. Multimorbidity intervention components (*Continued*)

Krska 2001		Individualised pharmaceutical care plans		Practice team-implemented care plans	Pharmacist undertook medication review and devised **pharmaceutical care plans**	Reduction in pharmaceutical care issues
Martin 2013	Training for community psychologists	Cognitive behavioural therapy sessions		**Psychological care programme designed for headache and depression**	Community psychologists	Reduced headaches and improved depression scores
Morgan 2013	Practice nurse training	Support for self-management Goal setting Individualised care plans	**Nurse case manager**	Quarterly reviews with practice nurse with GP stepping up care as needed		Improved depression scores
Sommers 2000		Risk reduction plan		**Team based care** with home assessment followed by team discussion, treatment plan and targets	Social worker	Reduced hospitalisation
Wakefield 2012		Participation in home telehealth monitoring	**Nurse case manager using telehealth monitoring** and treatment algorithms			Improved blood pressure, no effect on glycaemic control
Predominantly Patient-oriented interventions						
Eakin 2007		**Support for self-management with focus on diet and physical activity**		Regular visits and follow-up telephone calls	Health educator	Improvements in diet but not in physical activity
Garvey 2015	Occupational therapist (OT) training	**OT-led, group-based support for self-management programme (6**		GP and primary care team referral	OT with input from physiotherapist and pharmacist	Improvements in activity participation

Table 1. Multimorbidity intervention components (*Continued*)

		weeks) Goal setting and peer support				
Gitlin 2006		**Home-based programme targeting functional difficulties** with individualised plans and focus on falls prevention		Home visits and regular follow-up calls	Occupational therapist and physiotherapist	Improvements in function (reduced mortality at 4 year follow-up)
Hochhalter 2010	Training for coaches running intervention	**Patient Engagement workshop** (x1)		Two follow-up phone calls	Coach who delivered workshop	No effect on outcomes
Lorig 1999	Training for volunteer lay group leaders	**Chronic Disease Self Management Support Programme** (six sessions) Peer support			Volunteer lay group leaders supported by study team	No primary outcome specified. Multiple outcomes reported with mixed effects
Lynch 2014		**Diabetes self management support groups** (18 sessions) Peer support Goal setting and behaviour skills training			Dietician led groups	No effect on primary outcome of weight reduction

The predominant intervention component is highlighted in bold text for each study
No study contained a financial-type intervention element

Table 2. Costs

Study	Study type	Outcome	Result	Notes
Barley	RCT	Cost-effectiveness	The intervention demonstrated marginal cost effectiveness up to a QALY threshold of GBP 3035	

Table 2. Costs (*Continued*)

Boult	RCT	Total healthcare cost	Saving of USD 75,000 per GCN and USD 1364 per participant	USD in 2007 Initial result only ns
Katon	RCT	Cost-effectiveness	Mean reduction of 114 days in depression free days and an estimated difference of 0.335 QALYs (95% CI −0.18 to 0.85). The intervention was associated with lower OPD costs with a reduction of USD 594 per participant (95% CI USD −3241 to USD 2053)	Non-significant but 99.7% probability that the intervention met the threshold of < USD 20,000 per QALY
Krska	RCT	Mean cost of medicines	Int: 38.83 Con: 42.61 Absol diff 3.78 Rel %diff 9%	GBP in 2000 ns SES = 0.13
Lorig	RCT	Intervention cost per completed participant	USD 70	USD in 1998 See text for assumptions made
Lorig	RCT	Cost savings per individual	USD 750	USD in 1998 See text for assumptions made
Sommers	RCT	Savings per individual	USD 90	USD in 1994 See text for assumptions made

* refers to whether original study reported statistically significant improvement in this outcome

Table 3. Overview of outcomes

Outcome category	Outcome	No. studies with this outcome	No. studies with p< 0.05 for this outcome
Physical Health	Hb1Ac	5	2
	BP	6	2
	Cholesterol	2	1
	Other symptom score	4	1
	Mortality	1	1
Mental Health	Depression scores	8	6
	% improved depression	1	1

Table 3. Overview of outcomes (*Continued*)

	Anxiety scores	4	3
	Cognitive symptom management	1	0
Psychosocial	QoL/general health	10	4
	Functional impairment & disability	6	2
	Social (activity/support)	4	1
	Self efficacy	7	3
	Home hazards	1	0
Health service use	Visits/use service	5	0
	Hospital admission related	6	2
Patient health related behaviours	Exercise/diet	6	2
Medication adherence		5	2
Provider behaviour	Prescribing	3	2
	Disease management	3	3
Costs	Direct costs	5	Not applicable

* Multimorbidity is defined as two or more independent conditions within the same individual whereas comorbidity refers to linked conditions. In this review comorbidity studies included depression and diabetes or depression and hypertension

** The scales or measurements used in each study for the outcomes are described in the Table of included studies

Table 4. Clinical Outcomes

Study	Study type	Outcomes	Results	Notes
Barley	RCT	% with angina (Rose Angina score)	Int 22/31 Con 30/37 Absol diff 8, Rel % diff 27%	ns
Bognor	RCT	Systolic BP	Int 127.3 (SD 17.7) Con 141.3 (SD 18.8) Absol diff 14, Rel % diff 10%	* SES = 1.12

Table 4. Clinical Outcomes (*Continued*)

Bognor	RCT	Diastolic BP	Int 83 (SD 10.7) Con 81.4 (SD 11.1) Absol diff 9.2, Rel % diff 11%	* SES = 0.8
Gitlin	RCT	Mortality	Int 9/160 (0.06) Con: 21/159 (0.13) Absol diff 7, Rel % diff 54%	*
Hogg	RCT	Systolic BP	Int 124.3 Con 124.2 Absol diff 0.1, Rel % diff < 0.1%	ns (No SDs reported)
Hogg	RCT	HbA1c	Int 7.01 Con 6.78 Absol diff 0.23, Rel % diff 3%	ns
Katon	RCT	Systolic BP	Int 131 (SD 18.4) Con 132.3 (SD 17.2) Absol diff 1.3, Rel % diff 1%	* SES = 0.07
Katon	RCT	HbA1c	Int 8.14 (SD 2.03) Con 8.04 (SD 1.87) Absol diff 0.1, Rel % diff 13%	* SES = 0.32
Katon	RCT	Cholesterol	Int 91.9 (SD 36.7) Con 101.4 (SD 36.6) Absol diff 9.5, Rel % diff 9%	* SES = 0.26
Katon	RCT	Composite: all three risk factors (BP, HbA1c and cholesterol) below guidelines	Int 36/97 (0.37) Con: 19/87 (0.22) Absol diff 15, Rel % diff 68%	*
Lorig	RCT	Pain/ physical discomfort	Int 59.8 (SD 20.1) Con 60.6 (SD 17.1) Absol diff 0.8, Rel % diff 1%	SES = 0.04 ns
Lorig	RCT	Energy/fatigue	Int 2.18 (SD 0.73) Con 2.02 (SD 0.75) Absol diff 0.16, Rel % diff 8%	ns
Lorig	RCT	Shortness of breath	Int 1.34 (SD 0.91) Con 1.58 (SD 0.83) Absol diff 0.24, Rel % diff 15%	ns
Lynch	RCT	HbA1C	Int 7.9 (SD 1.6) Con 7.4 (SD 1.6) Absol diff 0.5, Rel % diff 6.7%	ns SES = 0.31
Lynch	RCT	% with at least 0.5 absolute reduction in HbA1c	Int 15/30 (0.05) 7/31 Con (0.21) Absol diff 29, Rel % diff 138%	*

Table 4. Clinical Outcomes (*Continued*)

Lynch	RCT	Mean SBP	Int 135.8 (SD 21.4) Con 136.7 (SD 23) Absol diff 0.9, Rel % diff 0.6%	ns SES = 0.01
Morgan	RCT	HbA1C	Int 6.9 (SD 0.26) Con 7.4 (SD 0.36) Absol diff 0.5, Rel % diff 6.7%	* SES = 1.6
Morgan	RCT	Systolic BP	Int 134.2 (SD 3.0) Con 133.5 (SD 3.8) Absol diff 0.7, Rel % diff 0.5%	ns SES = 0.2
Morgan	RCT	Cholesterol	Int 4.22 (SD 0.14) Con 4.44 (SD 0.2) Absol diff 0.22, Rel % diff 5%	ns SES = 0.22
Morgan	RCT	Mean BMI	Int 31.2 (SD 1.0) Con 31.0 (SD 1.0) Absol diff 0.2, Rel % diff 0.6%	ns SES = 0.2
Sommers	RCT	Symptom scores	Int 17.2 Con 18.9 Absol diff 1.7, Rel % diff 9%	ns
Wakefield	RCT	HbA1c	Int 6.9 (1.1) Con 6.95 (1.1) Absol diff 0.05, Rel % diff 0.7%	ns SES = 0.05
Wakefield	RCT	Systolic BP	Int 133 (16.6) Con 137 (17.3) Absol diff 4, Rel % diff 3%	ns SES = 0.24
Martin	RCT	Mean headache rating	Int 0.63 (SD 0.5) Con 1.01 (SD 0.83) Absol diff 0.38, Rel % diff 38%	* SES = 0.58

* refers to whether original study reported statistically significant improvement in this outcome
** Total number with final data collected was 384. No final numbers of intervention and control participants presented.

Table 5. Mental Health Outcomes

Study	Study type	Outcome	Result	Notes
Barley	RCT	PHQ9 depression score	Int 12.6 (SD 7.1) Con 12 (SD 6.9) Absol diff 0.6, Rel % diff 8%	ns SES = 0.09
Barley	RCT	HADS depression score	Int 9.5 (SD 4.6) Con 8.8 (SD 4.8) Absol diff 0.7, Rel % diff 8%	ns SES = 0.15

Table 5. Mental Health Outcomes (*Continued*)

Barley	RCT	HADS anxiety score	Int 9.9 (SD 7.1) Con 9.5 (SD 5.4) Absol diff 0.4, Rel % diff 4%	ns SES = 0.08
Bognor	RCT	CES depression score	Int 9.9 (SD 10.7) Con 19.3 (SD 15.2) Absol diff 9.4, Rel % diff 49%	* SES = 0.75
Coventry	RCT	SCL-D13 depression score	Int 1.76 (SD 0.9) Con 2.02 (SD 0.9) Absol diff 2.6, Rel % diff 13%	* SES = 0.28
Coventry	RCT	PHQ9 depression score	Int 11.3 (SD 6.5) Con 13.1 (SD 6.5) Absol diff 1.8, Rel % diff 14%	* SES = 0.28
Coventry	RCT	GAD-7 anxiety score	Int 8.2 (SD 5.8) Con 9.7 (SD 5.9) Absol diff 1.5, Rel % diff 15%	* SES = 0.26
Garvey	RCT	HADS total score	Int 15.6 (SD 8.3) Con 16.7 (SD 8.2) Absol diff 1.1, Rel % diff 6.5%	ns SES = 0.13
Katon	RCT	SCL 20 depression score	Int 0.83 (SD 0.66) Con 1.14 (SD 0.68) Absol diff 0.31, Rel % diff 27%	* SES = 0.46
Katon	RCT	Patient global improvement in depression	Int 41/92 Con 16/91 Absol diff 27, Rel % diff 150%	*
Lorig	RCT	Cognitive symptom management score	Int 1.75 Con 0.98 Absol diff 0.77, Rel % diff 79%	ns
Martin	RCT	PHQ9 depression score	Int 6.7 (SD 4.6) Con 12.6 (SD 5.3) Absol diff 5.9, Rel % diff 47%	* SES = 1.18
Martin	RCT	BDI -Depression score	Int 13.1 (SD 8.6) Con 28.7 (SD 9.5) Absol diff 15.6, Rel % diff 54%	* SES = 1.73
Martin	RCT	BAI Anxiety score	Int 10.5 (SD 10.8) Con 16.4 (SD 9.3) Absol diff 5.9, Rel % diff 36%	* SES = 0.1
Morgan	RCT	PHQ9 depression score	Int 7.1 (SD 0.8) Con 9.0 (SD 0.9) Absol diff 1.9, Rel % diff 21%	* SES = 2.24

Table 5. Mental Health Outcomes (*Continued*)

Sommers	RCT	GDS score (depression)	Int 4.1 Con 4.1 Absol diff 0, Rel % diff 0%	ns

* refers to whether original study reported statistically significant improvement in this outcome

Table 6. Patient-reported outcome measures

Study	Study type	Outcome	Result	Notes
Health Related Quality of Life				
Barley	RCT	SF12 PCS	Int 32.4 (SD 10.7) Con 33.3 (SD 9.2) Absol diff 0.7, Rel % diff 2%	ns SES = 0.07
Barley	RCT	SF12 MCS	Int 34.5 (SD 11.6) Con 33.6 (SD 12.5) Absol diff 0.9 , Rel % diff 3%	ns SES = 0.08
Barley	RCT	HRQoL (WEMWBS)	Int 40.6 (SD 11.2) Con 39.6(SD 12.3) Absol diff 1, Rel % diff 2.5%	ns SES = 0.08
Coventry	RCT	HRQoL (WHOQOL)	Int 2.99 (SD 0.6) Con 2.91 (SD 0.6) Absol diff 0.08, Rel % diff 3%	* SES = 1.7
Garvey	RCT	HRQoL (EQ5D VAS)	Int 65.7 (SD 20.2) Con 50.5 (SD 16.3) Absol diff 15.2, Rel % diff 30%	* SES = 0.84
Hogg	RCT	SF 36 Mental Health	Int 52.4 Con 52.2 Absol diff 0.2, Rel % diff 0.3%	ns
Hogg	RCT	SF 36 Physical Health	Int 44.3 Con 41.5 Absol diff 2.8, Rel % diff 6.7%	ns
Katon	RCT	QoL score	Int 6.0 (SD 2.2) Con 5.2 (SD 1. 9) Absol diff 0.8, Rel % diff 15%	* SES = 0.44
Kennedy	RCT	HRQoL (EQ5D)	Int 0.56 (SD 0.34) Con 0.57 (SD 0.32) Absol diff 0.01, Rel % diff 1%	ns SES = 0.03
Lorig	RCT	Psychological well-being	Int 3.47 Con 3.33 Absol diff 0.04, Rel % diff 4%	ns SES = 0.21

Table 6. Patient-reported outcome measures (*Continued*)

Martin	RCT	HRQol (AQOL)	Int 26.3 (SD 4.76) Con 28.4 (SD 4.97) Absol diff 2.1, Rel % diff 7 %	* SES = 0.4
Sommers	RCT	SF36 score	Int 2.2 Con 3.3 Absol diff 1.1, Rel % diff 33%	ns
Self-efficacy				
Barley	RCT	Self-efficacy score	Int 28.6 (SD 6.7) Con 27.9 (SD 8.1) Absol diff 0.11, Rel % diff 2.5%	ns SES = 0.09
Coventry	RCT	Self-efficacy score	Int 5.72 (SD 1.9) Con 5.53 (SD 1.9) Absol diff 0.18, Rel % diff 3.2%	ns * SES = 0.09
Garvey	RCT	Self efficacy score	Int 6.8 (SD 1.5) Con 5.3 (SD 1.9) Absol diff 1.47, Rel % diff 28%	* SES = 0.86
Hochhalter	RCT	Self-efficacy	Int 7.4 Con 8.0 Absol diff 0.6, Rel % diff 7.5%	ns
Kennedy	RCT	Self-efficacy	Int 68 (SD 23.4) Con 68.7 (SD 23.1) Absol diff 0.7, Rel % diff 1%	ns SES = 0.03
Wakefield	RCT	Self-efficacy	Int 8.1 (SD 1.9) Con 8.3 (SD 1.9) Absol diff 0.2, Rel % diff 2.4%	ns SES = 0.11
Daily function and disability				
Coventry	RCT	Sheehan Disability Score	Int 5.73 (SD 2.8) Con 5.83 (SD 2.8) Absol diff 0.1, Rel % diff 2%	* SES = 0.04
Garvey	RCT	Frenchay Activities Index	Int 21.3 (SD 7.9) Con 18.9 (SD 7.2) Absol diff 2.4, Rel % diff 13%	* SES = 0.32
Garvey	RCT	Activities daily living: NEADL (total)	Int 47.2 (SD 11.9) Con 40.7 (SD 10.7) Absol diff 6.5, Rel % diff 16%	* SES = 0.58
Hogg	RCT	IADL	Int 10.6 Con 10.9 Absol diff 0.3, Rel % diff 2.7%	ns

Table 6. Patient-reported outcome measures (*Continued*)

Lorig	RCT	Disability	Int 0.86 Con 0.96 Absol diff 0.1, Rel % diff 10%	ns
Lorig	RCT	Social role/activity limitation	Int 1.91, Con 1.98 Absol diff 0.07, Rel % diff 4%	ns
Illness perceptions				
Coventry	RCT	Multimorbidity illness perception scale	Int 2.1 (SD 0.9) Con 2.28 (SD 0.9) Absol diff 0.18, Rel % diff 8%	ns SES = 0.2
Barley	RCT	Illness perceptions (BIPQ)	Int 40 (SD 14.8) Con 43(SD 31.1) Absol diff 3, Rel % diff 7%	ns SES = 0.22
Social support				
Coventry	RCT	Social support (ESSI)	Int 3.29 (SD 1.1) Con 3.4 (SD 1.0) Absol diff 0.11, Rel % diff 3%	ns SES = 0.11
Eakin	RCT	Multilevel support for healthy lifestyle	Int 2.7 Con 2.59 Absol diff 0.11, Rel % diff 4%	ns
Other PROMs				
Barley	RCT	Patient-reported needs (PSYCHLOPS)	Int 13.6 (SD 5.1) Con 13.4 (SD 5.4) Absol diff 0.2, Rel % diff 1.5%	ns SES = 0.04
Hochhalter	RCT	Total unhealthy days	Int 15.3 Con 14.1 Absol diff 1.2, Rel % diff 9%	ns
Hogg	RCT	Total unhealthy days	Int 7.6 Con 9.9 Absol diff 2.3, Rel % diff 23%	ns
Kennedy	RCT	Shared decision making (HCCQ)	Int 67.7 (SD 28) Con 69.3 (SD 26.1) Absol diff 1.6, Rel % diff 2%	ns SES = 0.06
Lorig	RCT	Self-rated health	Int 3.42 Con 3.44 Absol diff 0.02, Rel % diff 0.6%	ns
Lorig	RCT	Health distress	Int 1.97 Con: 2.13 Absol diff 0.16, Rel % diff 7.5%	ns SES = 0.16
Sommers	RCT	Social activities count	Int 8.7 Con:8.6 Absol diff 0.1, Rel % diff 1%	* (when adjusted for baseline diff)

Table 6. Patient-reported outcome measures (*Continued*)

Sommers	RCT	HAQ score	Int 0.44 Con 0.5 Absol diff 0.06, Rel % diff 12%	ns

* refers to whether original study reported statistically significant improvement in this outcome

Table 7. Health service use

Study	Study type	Outcome	Result	Notes
Boult	RCT	No. hospital admissions	Int 0.7 Con 0.72 Absol diff 0.02, Rel % diff 3%	ns
Boult	RCT	No. days in hospital	Int 4.26 Con 4.49 Absol diff 0.23, Rel % diff 5%	ns
Boult	RCT	No. ED visits	Int 0.44 Con 0.44 Absol diff 0, Rel % diff 0	ns
Boult	RCT	No. PC visits	Int 9.98 Con 9.88 Absol diff 0.1, Rel % diff 1%	ns
Boult	RCT	No. specialist visits	Int 9.04 Con 8.49 Absol diff 0.55, Rel % diff 6%	ns
Boult	RCT	No. home healthcare episodes	Int 0.99 Con 1.3 Absol diff 0.31, Rel % diff 24%	*
Hogg	RCT	No. hospital admissions	Int 0.4 Con 0.46 Absol diff 0.06, Rel % diff 13%	ns
Hogg	RCT	Proportion hospitalised	Int 0.26, Con 0.26 Absol diff 0, Rel % diff 0%	ns
Hogg	RCT	No. ED visits	Int 0.63 Con 0.73 Absol diff 0.01, Rel % diff 14%	ns
Hogg	RCT	Proportion with ED visit	Int 0.38 Con 0.42 Absol diff 0.04, Rel % diff 9%	ns
Katon	RCT	Proportion hospitalised	Int 0.26 Con 0.22 Absol diff 0.04, Rel % diff 18%	ns
Lorig	RCT	No. doctor and ED visits	Int 6.51 Con 7.08 Absol diff 0.57, Rel % diff 8%	ns
Lorig	RCT	No. hospital stays in past 6 months	Int 0.26 Con 0.31 Absol diff 0.05, Rel % diff 6%	*

Table 7. Health service use (*Continued*)

Lorig	RCT	No. nights in hospital in last 6 months	Int 1.3 Con 1 Absol diff 0.3 Rel % diff 30%	*
Sommers	RCT	No. hospital admissions per individual per year	Int 0.36 Con 0.52 Absol diff 0.16, Rel % diff 31%	*
Sommers	RCT	≥1 60 day readmission	Int 3.6 Con 9.4 Absol diff 5.8, Rel % diff 62%	*
Sommers	RCT	≥ 1 hospital admission	Int 8.8 Con 7.7 Absol diff 1.1, Rel % diff 14%	*
Sommers	RCT	No. PCP visits	Int 6.0 Con 6.1 Absol diff 0.1, Rel % diff 2%	ns
Sommers	RCT	No. office visits	Int 11 Con 12.5 Absol diff 1.5, Rel % diff 12%	*
Sommers	RCT	≥ 1 home care visit	Int 19.5 Con 18.8 Absol diff 0.7, Rel % diff 4%	ns
Sommers	RCT	No. medical specialist visits	Int 1.4 Con 1.7 Absol diff 0.3, Rel % diff 18%	ns
Sommers	RCT	No. other visits	Int 3.9 Con 4.3 Absol diff 0.4, Rel % diff 9%	*
Sommers	RCT	≥ 1 ED visit	Int 21.4 Con 16.7 Absol diff 4.7, Rel % diff	ns

* refers to whether original study reported statistically significant improvement in this outcome

Table 8. Medication use and adherence and prescribing

Study	Study type	Outcome	Results	Notes
Bognor	RCT	≥80% adherence to antidepressant medication (MEMS caps)	Int 23/32 Con 10/32 Absol diff 0.41, Rel % diff 132%	*
Bognor	RCT	≥80% adherence to antihypertensive medication (MEMS caps)	Int 25/32 Con 10/32 Absol diff 0.47, Rel % diff 152%	*
Martin	RCT	Mean daily medication use	Int 2.4 (SD 3.2) Con 3.0 (SD 2.8) Absol diff 0.6, Rel % diff 20%	ns SES = 0.2

Table 8. Medication use and adherence and prescribing (*Continued*)

Morgan	RCT	% taking antidepressant medication	Int 34/62 Con 36/113 Absol diff 0.11, Rel % diff 34%	*
Wakefield	RCT	Adherence (Edward's scale)	Int 3.4 (SD 0.5) Con 3.3 (SD 0.5) Absol diff 0.1, Rel % diff 3%	ns SES = 0.2
Wakefield	RCT	Medication Taking Adherence Score	Int 100 (SD 1.4) Con 98.9 (SD 6.0) Absol diff 1.1, Rel % diff 1%	ns SES = 0.28

* refers to whether original study reported statistically significant improvement in this outcome

Table 9. Health-related participant behaviours

Study	Study type	Outcome	Results	Notes
Hochhalter	RCT	PAM (patient activation measure)	Int 66.8 Con 66.2 Absol diff 0.6, Rel % diff 1%	ns
Eakin	RCT	Diet behaviour scores	Int 2.2 Con 2.41 Absol diff 0.21, Rel % diff 9%	*
Eakin	RCT	Change minutes of walking/week	Int +8 Con −10 Absol diff 18, Rel % diff 180%	*
Katon	RCT	General adherence to diet score	Int 0.86 Con 0.81 Absol diff 0.05, Rel % diff 6%	ns
Katon	RCT	General adherence to exercise score	Int 0.54 Con 0.44 Absol diff 0.1, Rel % diff 23%	ns
Lorig	RCT	Exercise: stretching and strengthening (mins/week)	Int 53.1 Con 40.4 Absol diff 12.7,Rel % diff 31%	ns
Lorig	RCT	Exercise: aerobic (mins/week)	Int 101.8 Con 88 Absol diff 13.8, Rel % diff 157%	ns
Lorig	RCT	Communication with doctor (score 1-5)	Int 3.34 Con 3.2 Absol diff 0.14, Rel % diff 4%	ns
Lynch	RCT	Physical activity (kcal expenditure per week, CHAMPS)	Int 1913.6 Con −603 Absol diff 2516, Rel % diff 417%	*
Morgan	RCT	Smoking	Int 13/162 Con 13/110 Absol diff 0.04, Rel % diff 33%	ns

Table 9. Health-related participant behaviours (*Continued*)

Morgan	RCT	Alcohol	Int 51/104 Con 27/42 Absol diff 0.15, Rel % diff 23%	ns
Morgan	RCT	Exercise (30 minutes/day for 5 days/ week)	Int 97/162 Con 22/75 Absol diff 0.31, Rel % diff 106%	*
Sommers	RCT	Nutrition checklist score	Int 2.0 Con1.9 Absol diff 0.1, Rel % diff 5%	ns

* refers to whether original study reported statistically significant improvement in this outcome

Table 10. Provider behaviour

Study	Study type	Outcome	Result	Notes
Boult	RCT	PACIC score (patient measure of quality of care received)	Int 3.14 Con 2.85 Absol diff 0.29, Rel % diff 10%	*
Coventry	RCT	PACIC score	Int 2.37 (SD 1.1) Con 1.98 (SD 1.0) Absol diff 0.39, Rel % diff 20%	ns SES = 0.39
Hogg	RCT	Chronic Disease Mangement Score	Int 0.84 Con 0.77 Absol diff 0.07, Rel % diff 9%	*
Hogg	RCT	Preventive Care Score	Int 0.89 Con 0.7 Absol diff 0.19, Rel % diff 27%	*
Krska	RCT	% Pharmaceutical care issues resolved from baseline	Int 950/1206 Con 542/1380 Absol diff 0.4, Rel % diff 102%	*
Morgan	RCT	% Referred to mental health	Int 58/162 Con 10/111 Absol diff 0.27, Rel % diff 300%	*
Morgan	RCT	% Referred to exercise programme	Int 58/162 Con 24/114 Absol diff 0.15, Rel % diff 71%	*

* refers to whether original study reported statistically significant improvement in this outcome

APPENDICES

Appendix 1. MEDLINE search strategy

Medline (OVID)

1 Comorbidity/ (70760)
2 (comorbid$ or co-morbid$).ti,ab. (88707)
3 (multimorbid$ or multi-morbid$).ti,ab. (1544)
4 (multidisease? or multi-disease? or (multiple adj (ill$ or disease? or condition? or syndrom$ or disorder?))).ti,ab. (2649)
5 or/1-4 (139905)
6 Chronic disease/ (223377)
7 (chronic$ adj3 (disease? or ill$ or care or condition? or disorder$ or health$ or medication$ or syndrom$ or symptom$)).ti,ab. (239744)
8 or/6-7 (414800)
9 5 or 8 (539044)
10 exp diabetes mellitus/ or diabet$.ti,ab. (481769)
11 exp hypertension/ or (hypertens$ or "high blood pressure?").ti,ab. (383340)
12 exp heart diseases/ or (((heart or cardiac or cardiovascular or coronary) adj (disease? or disorder? or failure)) or arrythmia?).ti,ab. (1058106)
13 exp cerebrovascular disorders/ or ((cerebrovascular or vascular or carotoid$ or arter$) adj (disorder? or disease?)).ti,ab. (391125)
14 exp asthma/ or asthma$.ti,ab. (142524)
15 exp pulmonary disease chronic obstructive/ or (copd or (pulmonary adj2 (disease? or disorder?))).ti,ab. (75165)
16 exp hyperlipidemia/ or (hyperlipidem$ or Hypercholesterolemia$ or hypertriglyceridemia$).ti,ab. (77201)
17 exp Thyroid diseases/ or ((thyroid adj (disease? or disorder)) or hyperthyroid$ or hypothyroid$).ti,ab. (133490)
18 exp arthritis rheumatoid/ or rheumatoid arthritis.ti,ab. (117852)
19 exp mental disorders/ or (((mental or anxiety or mood or psychological or sleep) adj (disease? or disorder?)) or ((substance or drug or marijuana or cocaine or Amphetamine) adj2 abuse) or depression or schizophren$ or psychos$ or "substance abuse" or addiction?).ti,ab. (1197324)
20 exp epilepsy/ or (epileps$ or seizure?).ti,ab. (172872)
21 exp hiv infections/ or (HIV or acquired immune$ deficiency syndrome? or (aids adj (associated or related or arteritis))).ti,ab. (315376)
22 exp neoplasms/ or (neoplasm? or cancer?).ti,ab. (2892349)
23 exp kidney diseases/ or (kidney adj (disease? or disorder?)).ti,ab. (427328)
24 exp liver diseases/ or (liver adj (disease? or disorder?)).ti,ab. (459512)
25 exp osteoporosis/ or osteoporosis.ti,ab. (63622)
26 or/10-25 (7120398)
27 ((coocur$ or co-ocur$ or coexist$ or co-exist$ or multipl$) adj3 (disease? or ill$ or care or condition? or disorder$ or health$ or medication$ or symptom$ or syndrom$)).ti,ab. (49345)
28 chronic$.ti,ab,hw. (1019698)
29 27 or 28 (1061841)
30 26 and 29 (617619)
31 exp *education, continuing/ (30518)
32 (education$ adj2 (program$ or intervention? or meeting? or session? or strateg$ or workshop? or visit?)).tw. (45769)
33 (behavio?r$ adj2 intervention?).tw. (8293)
34 *pamphlets/ (1414)
35 (leaflet? or booklet? or poster or posters).tw. (22084)
36 ((written or printed or oral) adj information).tw. (1553)
37 (information$ adj2 campaign).tw. (374)
38 (education$ adj1 (method? or material?)).tw. (4879)
39 *advance directives/ (3056)
40 outreach.tw. (8261)
41 ((opinion or education$ or influential) adj1 leader?).tw. (1038)
42 facilitator?.tw. (13634)

43 academic detailing.tw. (367)
44 consensus conference?.tw. (4268)
45 *guideline adherence/ (9909)
46 practice guideline?.tw. (15069)
47 (guideline? adj2 (introduc$ or issu$ or impact or effect? or disseminat$ or distribut$)).tw. (3304)
48 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 training program$).tw. (601)
49 *reminder systems/ (1357)
50 reminder?.tw. (7383)
51 (recall adj2 system$).tw. (400)
52 (prompter? or prompting).tw. (5108)
53 algorithm?.tw. (141491)
54 *feedback/ or feedback.tw. (89372)
55 chart review$.tw. (24320)
56 ((effect? or impact or records or chart?) adj2 audit).tw. (789)
57 compliance.tw. (82344)
58 marketing.tw. (17569)
59 or/31-58 (512958)
60 exp *reimbursement mechanisms/ (17061)
61 fee for service.tw. (3598)
62 *capitation fee/ (2001)
63 *"deductibles and coinsurance"/ (634)
64 cost shar$.tw. (1215)
65 (copayment? or co payment?).tw. (1350)
66 (prepay$ or prepaid or prospective payment?).tw. (4140)
67 *hospital charges/ (957)
68 formular?.tw. (2972)
69 fundhold?.tw. (1)
70 *medicaid/ (10050)
71 *medicare/ (17571)
72 blue cross.tw. (1120)
73 or/60-72 (51790)
74 *nurse clinicians/ (5524)
75 *nurse midwives/ (4677)
76 *nurse practitioners/ (10903)
77 (nurse adj (rehabilitator? or clinician? or practitioner? or midwi$)).tw. (10788)
78 *pharmacists/ (7289)
79 clinical pharmacist?.tw. (1469)
80 paramedic?.tw. (3418)
81 *patient care team/ (21291)
82 exp *patient care planning/ (23599)
83 (team? adj2 (care or treatment or assessment or consultation)).tw. (10376)
84 (integrat$ adj2 (care or service?)).tw. (7706)
85 (care adj2 (coordinat$ or program$ or continuity)).tw. (19568)
86 (case adj1 management).tw. (7865)
87 exp *ambulatory care facilities/ (25328)
88 *ambulatory care/ (15804)
89 or/74-88 (153339)
90 *home care services/ (19987)
91 *hospices/ (3299)
92 *nursing homes/ (19931)
93 *office visits/ (2217)
94 *house calls/ (1457)
95 *day care/ (2918)

96 *aftercare/ (2761)
97 *community health nursing/ (14848)
98 (chang$ adj1 location?).tw. (381)
99 domiciliary.tw. (2254)
100 (home adj1 treat$).tw. (1406)
101 day surgery.tw. (2030)
102 *medical records/ (15972)
103 *medical records systems, computerized/ (12787)
104 (information adj2 (management or system?)).tw. (26991)
105 *peer review/ (3134)
106 *utilization review/ (2535)
107 exp *health services misuse/ (3679)
108 or/90-107 (130606)
109 *physician's practice patterns/ (25519)
110 quality assurance.tw. (18829)
111 *process assessment/ [health care] (1489)
112 *program evaluation/ (7465)
113 *length of stay/ (7564)
114 (early adj1 discharg$).tw. (2209)
115 discharge planning.tw. (2210)
116 offset.tw. (19713)
117 triage.tw. (10142)
118 exp *"Referral and Consultation"/ and "consultation"/ (19518)
119 *drug therapy, computer assisted/ (1138)
120 near patient testing.tw. (188)
121 *medical history taking/ (4446)
122 *telephone/ (4226)
123 (physician patient adj (interaction? or relationship?)).tw. (1987)
124 *health maintenance organizations/ (9387)
125 managed care.tw. (16116)
126 (hospital? adj1 merg$).tw. (370)
127 or/109-126 (146797)
128 ((standard or usual or routine or regular or traditional or conventional or pattern) adj2 care).tw. (40705)
129 (program$ adj2 (reduc$ or increas$ or decreas$ or chang$ or improv$ or modify$ or monitor$ or care)).tw. (41613)
130 (program$ adj1 (health or care or intervention?)).tw. (30335)
131 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 treatment program$).tw. (299)
132 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 care program$).tw. (138)
133 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 screening program$).tw. (531)
134 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 prevent$ program$).tw. (439)
135 (computer$ adj2 (dosage or dosing or diagnosis or therapy or decision?)).tw. (4108)
136 ((introduc$ or impact or effect? or implement$ or computer$) adj2 protocol?).tw. (2897)
137 ((effect or impact or introduc$) adj2 (legislation or regulations or policy)).tw. (1622)
138 or/128-137 (110128)
139 or/59,73,89,108,127,138 (995154)
140 randomized controlled trial.pt. (388780)
141 controlled clinical trial.pt. (89842)
142 random$.ti,ab. (743745)
143 (control$ adj2 (trial? or study or studies)).ti,ab. (296267)
144 double-blind method/ or random allocation/ or single-blind method/ (220817)
145 ((double or single or triple or treble) adj2 blind$).ti,ab. (131548)
146 (quasi-experiment$ or quasiexperiment$).ti,ab. (6593)
147 interrupt$ time series.ti,ab. (1126)
148 or/140-147 (1109791)

149 9 and 139 and 148 (7478)
150 30 and 139 and 148 (5488)
151 149 or 150 [FINAL RESULTS] (9386)
152 (2012$ or 2013$ or 2014$).yr,ed,ep,dp. [Date Limits] (3331408)
153 151 and 152 (2759)

Appendix 2. EMBASE Search Strategy

1 Comorbidity/ (128699)
2 (comorbid$ or co-morbid$).ti,ab. (139103)
3 (multimorbid$ or multi-morbid$).ti,ab. (2207)
4 (multidisease? or multi-disease? or (multiple adj (ill$ or disease? or condition? or syndrom$ or disorder?))).ti,ab. (3322)
5 or/1-4 (203297)
6 Chronic disease/ (153980)
7 (chronic$ adj3 (disease? or ill$ or care or condition? or disorder$ or health$ or medication$ or syndrom$ or symptom$)).ti,ab. (327098)
8 or/6-7 (428343)
9 5 or 8 (611739)
10 exp diabetes mellitus/ or diabet$.ti,ab. (753978)
11 exp hypertension/ or (hypertens$ or "high blood pressure?").ti,ab. (678777)
12 exp heart disease/ or exp myocardial disease/ or (((heart or cardiac or cardiovascular or coronary) adj (disease? or disorder? or failure)) or arrythmia?).ti,ab. (1607262)
13 cerebrovascular disease/ or carotid artery disease/ or ((cerebrovascular or vascular or carotoid$ or arter$) adj (disorder? or disease?)).ti,ab. (215400)
14 exp asthma/ or asthma$.ti,ab. (224969)
15 Chronic Obstructive Lung Disease/ or (copd or ((pulmonary or lung?) adj2 (disease? or disorder?))).ti,ab. (154404)
16 exp hyperlipidemia/ or exp hypercholesterolemia/ or (hyperlipidem$ or Hypercholesterolemia$ or hypertriglyceridemia$).ti,ab. (129249)
17 exp Thyroid disease/ or ((thyroid adj (disease? or disorder)) or hyperthyroid$ or hypothyroid$).ti,ab. (205528)
18 exp rheumatoid arthritis/ or rheumatoid arthritis.ti,ab. (178070)
19 exp mental disease/ or (((mental or anxiety or mood or psychological or sleep) adj (disease? or disorder?)) or ((substance or drug or marijuana or cocaine or Amphetamine) adj2 abuse) or depression or schizophren$ or psychos$ or "substance abuse" or addiction?).ti,ab. (1851216)
20 exp epilepsy/ or (epileps$ or seizure?).ti,ab. (255624)
21 Human Immunodeficiency Virus/ or (HIV or acquired immune$ deficiency syndrome? or (aids adj (associated or related or arteritis)) or human immunodeficiency).ti,ab. (306076)
22 exp neoplasm/ or (neoplasm? or cancer?).ti,ab. (3892558)
23 exp kidney disease/ or ((kidney? or renal) adj (disease? or disorder? or failure)).ti,ab. (763592)
24 exp liver disease/ or (liver adj (disease? or disorder?)).ti,ab. (762255)
25 exp osteoporosis/ or osteoporosis.ti,ab. (110294)
26 or/10-25 (9690063)
27 ((coocur$ or co-ocur$ or coexist$ or co-exist$ or multipl$) adj3 (disease? or ill$ or care or condition? or disorder$ or health$ or medication$ or symptom$ or syndrom$)).ti,ab. (69381)
28 chronic$.ti,ab,hw. (1368721)
29 27 or 28 (1427673)
30 26 and 29 (901927)
31 exp primary health care/ or exp primary medical care/ (110049)
32 (primary adj2 (care? or medical$ or health$ or clinic$ or practitioner? or doctor?)).ti,ab. (120119)
33 General practitioner/ (68322)
34 (((family or general or generalist? or communit$) adj2 (physician? or doctor? or practitioner? or practice)) or GP).ti,ab. (150993)
35 General Practice/ (71860)
36 exp Community Care/ (99509)

37 (communit$ adj2 (health or healthcare or service? or clinic$ or setting? or centre? or center?)).ti,ab. (58469)
38 or/31-37 (457608)
39 (education$ adj2 (program$ or intervention? or meeting? or session? or strateg$ or workshop? or visit?)).tw. (58968)
40 (behavio?r$ adj2 intervention?).tw. (10199)
41 (leaflet? or booklet? or poster or posters).tw. (32641)
42 ((written or printed or oral) adj information).tw. (2345)
43 (information$ adj2 campaign).tw. (490)
44 (education$ adj1 (method? or material?)).tw. (7770)
45 outreach.tw. (10348)
46 ((opinion or education$ or influential) adj1 leader?).tw. (1264)
47 facilitator?.tw. (16200)
48 academic detailing.tw. (457)
49 consensus conference?.tw. (5507)
50 practice guideline?.tw. (19137)
51 (guideline? adj2 (introduc$ or issu$ or impact or effect? or disseminat$ or distribut$)).tw. (4969)
52 ((introduc$ or impact or effect? or implement$ or computer$ or compli$) adj2 protocol?).tw. (5088)
53 ((introduc$ or impact or effect? or implement$ or computer$ or compli$) adj2 algorithm?).tw. (6439)
54 clinical pathway?.tw. (2896)
55 critical pathway?.tw. (1515)
56 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 training program$).tw. (766)
57 reminder?.tw. (10142)
58 (recall adj2 system$).tw. (478)
59 (prompter? or prompting).tw. (6829)
60 advance directive?.tw. (3150)
61 *feedback/ or feedback.tw. (107266)
62 chart review$.tw. (39281)
63 ((effect? or impact or records or chart?) adj2 audit).tw. (1119)
64 compliance.tw. (117170)
65 marketing.tw. (23206)
66 ((cost or clinical or medical) adj information).tw. (25105)
67 *medical education/ (100293)
68 *medical audit/ (11760)
69 continuing education/ (27529)
70 postgraduate education/ (12837)
71 or/39-70 (622952)
72 fee for service.tw. (4267)
73 cost shar$.tw. (1439)
74 (copayment? or co payment?).tw. (1808)
75 (prepay$ or prepaid or prospective payment?).tw. (4856)
76 formular?.tw. (4857)
77 fundhold?.tw. (1)
78 blue cross.tw. (1407)
79 voucher?.tw. (1195)
80 (free adj2 care).tw. (1345)
81 exp *health insurance/ (86446)
82 *health care costs/ (29401)
83 *health care financing/ (3133)
84 *medical fee/ (4231)
85 *prospective payment/ (3776)
86 or/72-85 (131153)
87 (nurse adj (rehabilitator? or clinician? or practitioner? or midwi$)).tw. (12811)
88 ((nurse or midwi$ or practitioner) adj managed).tw. (568)
89 clinical pharmacist?.tw. (2991)

90 paramedic?.tw. (4598)
91 exp *paramedical personnel/ (196136)
92 *general practitioner/ (16290)
93 *physician/ (49244)
94 (team? adj2 (care or treatment or assessment or consultation)).tw. (14717)
95 (integrat$ adj2 (care or service?)).tw. (9942)
96 (care adj2 (coordinat$ or program$ or continuity)).tw. (25142)
97 (case adj1 management).tw. (9465)
98 *patient care/ (46965)
99 (chang$ adj1 location?).tw. (459)
100 domiciliary.tw. (3320)
101 (home adj1 (treat$ or visit?)).tw. (8141)
102 day surgery.tw. (2960)
103 exp *primary health care/ (42028)
104 *ambulatory surgery/ (5920)
105 *nursing home/ (22544)
106 *day hospital/ (1428)
107 *outpatient care/ (3552)
108 *terminal care/ (14735)
109 *group practice/ (5739)
110 *general practice/ (38840)
111 *rural health care/ (6703)
112 *community mental health center/ (1910)
113 information system/ (32025)
114 *medical record/ (31657)
115 (information adj2 (management or system?)).tw. (33281)
116 *peer review/ (5654)
117 *professional standards review organization/ (1501)
118 exp *clinical practice/ (26676)
119 quality assurance.tw. (25192)
120 exp *health care delivery/ (497480)
121 *health care quality/ (61935)
122 *professional practice/ (18160)
123 (early adj1 discharg$).tw. (3064)
124 discharge planning.tw. (2722)
125 offset.tw. (22234)
126 triage.tw. (13930)
127 near patient testing.tw. (257)
128 *patient referral/ (12390)
129 (physician patient adj (interaction? or relationship?)).tw. (2250)
130 managed care.tw. (18746)
131 *health care organization/ (46743)
132 *health maintenance organization/ (8566)
133 *health care system/ (13067)
134 *health care access/ (5586)
135 (hospital? adj1 merg$).tw. (418)
136 (computer$ adj2 (dosage or dosing or diagnosis therapy or decision?)).tw. (1690)
137 (computer$ adj2 (diagnosis or therapy)).tw. (3200)
138 gatekeep$.tw. (3814)
139 or/87-138 (1198920)
140 ((standard or usual or routine or regular or traditional or conventional or pattern) adj2 care).tw. (57422)
141 (program$ adj2 (reduc$ or increas$ or decreas$ or chang$ or improv$ or modify$ or monitor$ or care)).tw. (53287)
142 (program$ adj1 (health or care or intervention?)).tw. (37166)

143 ((effect or impact or introduc$) adj2 (legislation or regulations or policy)).tw. (2053)
144 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 treatment program$).tw. (408)
145 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 care program$).tw. (176)
146 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 screening program$).tw. (688)
147 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 prevent$ program$).tw. (486)
148 or/140-147 (136072)
149 71 or 86 or 139 or 148 (1892565)
150 randomized controlled trial/ or controlled clinical trial/ or clinical trial/ or controlled study/ (4910245)
151 random$.ti,ab. (926713)
152 (control$ adj2 (trial? or study or studies)).ti,ab. (363648)
153 ((double or single or triple or treble) adj2 blind$).ti,ab. (168110)
154 (quasi-experiment$ or quasiexperiment$).ti,ab. (7604)
155 interrupt$ time series.ti,ab. (1243)
156 or/150-155 (5433480)
157 9 and 38 and 149 and 156 (4079)
158 9 and 38 and 149 and (intervent$.ti,ab,pt. or evaluat$.ti,hw. or impact$.ti.) (4402)
159 30 and 38 and 149 and 156 (2945)
160 30 and 38 and 149 and (intervent$.ti,ab,pt. or evaluat$.ti,hw. or impact$.ti.) (3015)
161 157 or 159 (4899)
162 (2011$ or 2012$ or 2013$ or 2014$).em,dp,yr. (5117979)
163 161 and 162 (1895)

Appendix 3. CAB Abstracts. Healthstar

Healthstar (OVID)
1 Comorbidity/ (136781)
2 (comorbid$ or co-morbid$).ti,ab. (157159)
3 (multimorbid$ or multi-morbid$).ti,ab. (2688)
4 (multidisease? or multi-disease? or (multiple adj (ill$ or disease? or condition? or syndrom$ or disorder?))).ti,ab. (4246)
5 or/1-4 (255167)
6 Chronic disease/ (354063)
7 (chronic$ adj3 (disease? or ill$ or care or condition? or disorder$ or health$ or medication$ or syndrom$ or symptom$)).ti,ab. (391706)
8 or/6-7 (662434)
9 5 or 8 (888824)
10 exp diabetes mellitus/ or diabet$.ti,ab. (734524)
11 exp hypertension/ or (hypertens$ or "high blood pressure?").ti,ab. (593254)
12 exp heart diseases/ or (((heart or cardiac or cardiovascular or coronary) adj (disease? or disorder? or failure)) or arrythmia?).ti,ab. (1783211)
13 exp cerebrovascular disorders/ or ((cerebrovascular or vascular or carotoid$ or arter$) adj (disorder? or disease?)).ti,ab. (654221)
14 exp asthma/ or asthma$.ti,ab. (221525)
15 exp pulmonary disease chronic obstructive/ or (copd or (pulmonary adj2 (disease? or disorder?))).ti,ab. (121690)
16 exp hyperlipidemia/ or (hyperlipidem$ or Hypercholesterolemia$ or hypertriglyceridemia$).ti,ab. (118845)
17 exp Thyroid diseases/ or ((thyroid adj (disease? or disorder)) or hyperthyroid$ or hypothyroid$).ti,ab. (186611)
18 exp arthritis rheumatoid/ or rheumatoid arthritis.ti,ab. (170399)
19 exp mental disorders/ or (((mental or anxiety or mood or psychological or sleep) adj (disease? or disorder?)) or ((substance or drug or marijuana or cocaine or Amphetamine) adj2 abuse) or depression or schizophren$ or psychos$ or "substance abuse" or addiction?).ti,ab. (1987918)
20 exp epilepsy/ or (epileps$ or seizure?).ti,ab. (250120)
21 exp hiv infections/ or (HIV or acquired immune$ deficiency syndrome? or (aids adj (associated or related or arteritis))).ti,ab. (543535)
22 exp neoplasms/ or (neoplasm? or cancer?).ti,ab. (4417173)

23 exp kidney diseases/ or (kidney adj (disease? or disorder?)).ti,ab. (660283)
24 exp liver diseases/ or (liver adj (disease? or disorder?)).ti,ab. (674611)
25 exp osteoporosis/ or osteoporosis.ti,ab. (102526)
26 or/10-25 (11129474)
27 ((coocur$ or co-ocur$ or coexist$ or co-exist$ or multipl$) adj3 (disease? or ill$ or care or condition? or disorder$ or health$ or medication$ or symptom$ or syndrom$)).ti,ab. (79174)
28 chronic$.ti,ab,hw. (1549612)
29 27 or 28 (1616705)
30 26 and 29 (984205)
31 exp Primary Health Care/ or (primary adj2 care).ti,ab. or Physicians, Family/ or (((family or general or generalist? or community) adj2 (physician? or doctor? or practitioner? or practice)) or GP).ti,ab. or Family Practice/ or exp Community Health Services/ or (communit$ adj2 (health or healthcare or service?)).ti,ab. (1375407)
32 (or/9,30) and 31 [Multimorb & PC] (89751)
33 exp *education, continuing/ (57497)
34 (education$ adj2 (program$ or intervention? or meeting? or session? or strateg$ or workshop? or visit?)).tw. (83498)
35 (behavio?r$ adj2 intervention?).tw. (14793)
36 *pamphlets/ (2616)
37 (leaflet? or booklet? or poster or posters).tw. (35076)
38 ((written or printed or oral) adj information).tw. (2893)
39 (information$ adj2 campaign).tw. (670)
40 (education$ adj1 (method? or material?)).tw. (8793)
41 *advance directives/ (5936)
42 outreach.tw. (14955)
43 ((opinion or education$ or influential) adj1 leader?).tw. (1889)
44 facilitator?.tw. (20009)
45 academic detailing.tw. (675)
46 consensus conference?.tw. (7903)
47 *guideline adherence/ (19292)
48 practice guideline?.tw. (27928)
49 (guideline? adj2 (introduc$ or issu$ or impact or effect? or disseminat$ or distribut$)).tw. (6072)
50 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 training program$).tw. (1078)
51 *reminder systems/ (2650)
52 reminder?.tw. (12878)
53 (recall adj2 system$).tw. (702)
54 (prompter? or prompting).tw. (8090)
55 algorithm?.tw. (222548)
56 *feedback/ or feedback.tw. (127818)
57 chart review$.tw. (42420)
58 ((effect? or impact or records or chart?) adj2 audit).tw. (1488)
59 compliance.tw. (141617)
60 marketing.tw. (31868)
61 or/33-60 (845682)
62 exp *reimbursement mechanisms/ (33927)
63 fee for service.tw. (6823)
64 *capitation fee/ (3985)
65 *"deductibles and coinsurance"/ (1253)
66 cost shar$.tw. (2265)
67 (copayment? or co payment?).tw. (2521)
68 (prepay$ or prepaid or prospective payment?).tw. (8075)
69 *hospital charges/ (1893)
70 formular?.tw. (5328)
71 fundhold?.tw. (2)
72 *medicaid/ (19969)

73 *medicare/ (34885)
74 blue cross.tw. (2138)
75 or/62-74 (101523)
76 *nurse clinicians/ (10760)
77 *nurse midwives/ (8932)
78 *nurse practitioners/ (21179)
79 (nurse adj (rehabilitator? or clinician? or practitioner? or midwi$)).tw. (20081)
80 *pharmacists/ (13810)
81 clinical pharmacist?.tw. (2662)
82 paramedic?.tw. (6281)
83 *patient care team/ (42259)
84 exp *patient care planning/ (46645)
85 (team? adj2 (care or treatment or assessment or consultation)).tw. (19258)
86 (integrat$ adj2 (care or service?)).tw. (13964)
87 (care adj2 (coordinat$ or program$ or continuity)).tw. (36271)
88 (case adj1 management).tw. (14772)
89 exp *ambulatory care facilities/ (48811)
90 *ambulatory care/ (29666)
91 or/76-90 (292090)
92 *home care services/ (38726)
93 *hospices/ (6323)
94 *nursing homes/ (38729)
95 *office visits/ (4307)
96 *house calls/ (2784)
97 *day care/ (5461)
98 *aftercare/ (5287)
99 *community health nursing/ (29572)
100 (chang$ adj1 location?).tw. (562)
101 domiciliary.tw. (4012)
102 (home adj1 treat$).tw. (2478)
103 day surgery.tw. (3851)
104 *medical records/ (31654)
105 *medical records systems, computerized/ (25331)
106 (information adj2 (management or system?)).tw. (49115)
107 *peer review/ (6217)
108 *utilization review/ (5041)
109 exp *health services misuse/ (7251)
110 or/92-109 (250991)
111 *physician's practice patterns/ (50210)
112 quality assurance.tw. (35457)
113 *process assessment/ [health care] (2910)
114 *program evaluation/ (14556)
115 *length of stay/ (14615)
116 (early adj1 discharg$).tw. (4031)
117 discharge planning.tw. (4209)
118 offset.tw. (29706)
119 triage.tw. (18422)
120 exp *"Referral and Consultation"/ and "consultation"/ (37594)
121 *drug therapy, computer assisted/ (2172)
122 near patient testing.tw. (354)
123 *medical history taking/ (8799)
124 *telephone/ (8039)
125 (physician patient adj (interaction? or relationship?)).tw. (3700)

126 *health maintenance organizations/ (18678)
127 managed care.tw. (31562)
128 (hospital? adj1 merg$).tw. (722)
129 or/111-128 (274522)
130 ((standard or usual or routine or regular or traditional or conventional or pattern) adj2 care).tw. (72645)
131 (program$ adj2 (reduc$ or increas$ or decreas$ or chang$ or improv$ or modify$ or monitor$ or care)).tw. (73494)
132 (program$ adj1 (health or care or intervention?)).tw. (55222)
133 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 treatment program$).tw. (540)
134 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 care program$).tw. (255)
135 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 screening program$).tw. (990)
136 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 prevent$ program$).tw. (810)
137 (computer$ adj2 (dosage or dosing or diagnosis or therapy or decision?)).tw. (7595)
138 ((introduc$ or impact or effect? or implement$ or computer$) adj2 protocol?).tw. (4756)
139 ((effect or impact or introduc$) adj2 (legislation or regulations or policy)).tw. (2959)
140 or/130-139 (196108)
141 or/61,75,91,110,129,140 (1750807)
142 randomized controlled trial.pt. (751676)
143 controlled clinical trial.pt. (175463)
144 random$.ti,ab. (1251769)
145 (control$ adj2 (trial? or study or studies)).ti,ab. (524250)
146 double-blind method/ or random allocation/ or single-blind method/ (386514)
147 ((double or single or triple or treble) adj2 blind$).ti,ab. (246759)
148 (quasi-experiment$ or quasiexperiment$).ti,ab. (11844)
149 interrupt$ time series.ti,ab. (2028)
150 or/142-149 (1900410)
151 32 and 150 (12342)
152 9 and 141 and 150 (13829)
153 30 and 141 and 150 (10150)
154 152 or 153 [FINAL RESULTS] (17364)
155 limit 154 to yr="2011 -Current" (5406)
156 (2011$ or 2012$ or 2013$ or 2014$).ed,ep,dp. [Date Limits] (6025081)
157 (or/152-153) and 156 (5893)
158 155 or 157 (5893)
159 exp Primary Health Care/ or (primary adj2 care).ti,ab. or Physicians, Family/ or (((family or general or generalist? or community) adj2 (physician? or doctor? or practitioner? or practice)) or GP).ti,ab. or Family Practice/ or exp Community Health Services/ or (communit$ adj2 (health or healthcare or service?)).ti,ab. (1375407)
160 (randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti. (1679885)
161 exp animals/ not humans.sh. (4076816)
162 160 not 161 [Cochrane RCT Filter] (1607573)
163 5 and 159 and 162 [Multimorbidity & PC & Cochrane RCT Filter] (2678)
164 163 not 158 [RCT Multimorbidity all years ML] (2222)
165 remove duplicates from 164 (1103)
166 remove duplicates from 158 (3111)
167 from 165 keep 1-966 (966)
168 from 166 keep 1-2435 (2435)

Appendix 4. Cochrane Central Register of Controlled Trials Strategy

#1 MeSH descriptor: [Comorbidity] this term only 2634
#2 (comorbid* or co-morbid* or multimorbid* or multi-morbid* or multidisease or multidiseases or multi-disease or multi-diseases):ti 992
#3 MeSH descriptor: [Chronic Disease] this term only 11236
#4 #1 or #2 or (#2 and #3) 3340
#5 MeSH descriptor: [Diabetes Mellitus] 1 tree(s) exploded 16930
#6 diabet*:ti,ab 33844
#7 MeSH descriptor: [Hypertension] explode all trees 14236
#8 (hypertens* or "high blood pressure"):ti,ab 30517
#9 MeSH descriptor: [Heart Diseases] explode all trees 38087
#10 MeSH descriptor: [Cerebrovascular Disorders] 1 tree(s) exploded 10092
#11 (cerebrovascular disorder* or cerebrovascular disease* or vascular disorder* or vascular disease* or carotoid* disorder* or carotoid disease* or arter* disorder* or arter* disease*):ti 5257
#12 MeSH descriptor: [Asthma] 1 tree(s) exploded 9189
#13 asthma*:ti 17198
#14 MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees 2683
#15 (copd or pulmonary disease* or pulmonary disorder*):ti 7855
#16 MeSH descriptor: [Hyperlipidemias] explode all trees 4608
#17 (hyperlipidem* or Hypercholesterolemia* or hypertriglyceridemia*):ti 2357
#18 MeSH descriptor: [Thyroid Diseases] explode all trees 1689
#19 (thyroid disease* or thyroid disorder*):ti 129
#20 MeSH descriptor: [Mental Disorders] explode all trees 44778
#21 ((mental or anxiety or mood or psychological or sleep) near/2 (disease* or disorder*)):ti 2376
#22 ((substance or drug or marijuana or cocaine or Amphetamine) near/2 abuse):ti 740
#23 (depression or schizophren* or psychos* or "substance abuse" or addiction or addictions):ti 22617
#24 MeSH descriptor: [Epilepsy] explode all trees 2330
#25 (epileps* or seizure or seizures):ti 3195
#26 MeSH descriptor: [HIV Infections] 1 tree(s) exploded 8289
#27 (HIV or acquired immune* deficiency syndrome*):ti 7826
#28 MeSH descriptor: [Neoplasms] explode all trees 54236
#29 (neoplasm or cancer):ti 48221
#30 MeSH descriptor: [Kidney Diseases] 1 tree(s) exploded 10187
#31 (kidney disease* or kidney disorder*):ti 1400
#32 MeSH descriptor: [Liver Diseases] explode all trees 10502
#33 (liver disease* or liver disorder*):ti 1024
#34 MeSH descriptor: [Osteoporosis] explode all trees 3230
#35 osteoporosis:ti 2125
#36 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 302338
#37 ((coocur* or co-ocur* or coexist* or co-exist* or multipl*) near/2 (disease or diseases or ill* or care or condition or conditions or disorder* or health* or medication* or symptom* or syndrom*)):ti,ab 1292
#38 #36 and #37 510
#39 #4 or #38 3797
#40 #39 Publication Year from 2011 to 2014 957

Appendix 5. CINHAL search

Search ID#	Search Terms	Search Options	Actions
S70	S26 or S66 or S67 or S68 or S69	**Limiters** - Published Date: 20110101-20141031; Exclude MEDLINE records **Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (477)
S69	S3 AND S51 AND S64	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (9,758)
S68	(S24 or S25) AND S51	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (628)
S67	(S24 or S25) AND S58	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (167)
S66	S3 and S58	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (3,313)
S65	S59 or S60 or S61 or S62 or S63	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (1,253,245)
S64	S59 or S60 or S61 or S62 or S63	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (1,253,245)
S63	MW care or patient or community	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (1,171,117)
S62	(MH "Community Health Services+")	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (240,736)
S61	(MH "Primary Health Care")	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (30,993)
S60	(MH "Physicians, Family") or TI (family physician? or family doctor?) or AB (family doctor? or family physician?)	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (10,844)
S59	(MH "Family Practice") or (family practice) or (general practice) or (family practitioner*) or (general practitioner*) or (family doctor*)	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (23,973)
S58	S52 or S53 or S54 or S55 or S56 or S57	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (139,879)

(*Continued*)

S57	TI controlled	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (22,469)
S56	TI ("control* N1 clinical" or "control* N1 group*" or "control* N1 trial*" or "control* N1 study" or "control* N1 studies" or "control* N1 design*" or "control* N1 method*") or AB ("control* N1 clinical" or "control* N1 group*" or "control* N1 trial*" or "control* N1 study" or "control* N1 studies" or "control* N1 design*" or "control* N1 method*")	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (1)
S55	TI random* or AB random*	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (118,220)
S54	TI ("clinical study" or "clinical studies") or AB ("clinical study" or "clinical studies")	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (7,503)
S53	(MM "Clinical Trials+")	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (8,746)
S52	TI ((multicent* n2 design*) or (multicent* n2 study) or (multicent* n2 studies) or (multicent* n2 trial*)) or AB ((multicent* n2 design*) or (multicent* n2 study) or (multicent* n2 studies) or (multicent* n2 trial*))	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (9,047)
S51	S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (463,591)
S50	TI ((time points n3 over) or (time points n3 multiple) or (time points n3 three) or (time points n3 four) or (time points n3 five) or (time points n3 six) or (time points n3 seven) or (time points n3 eight) or (time points n3 nine) or (time points n3 ten) or (time points n3 eleven) or (time points n3 twelve) or (time points n3 month*) or (time points n3 hour*) or (time points n3 day*) or (time points n3 "more than")) or AB ((time points n3 over)	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (1,824)

(*Continued*)

	or (time points n3 multiple) or (time points n3 ..		
S49	TI ((control w3 area) or (control w3 cohort*) or (control w3 compar*) or (control w3 condition) or (control w3 group*) or (control w3 intervention*) or (control w3 participant*) or (control w3 study)) or AB ((control w3 area) or (control w3 cohort*) or (control w3 compar*) or (control w3 condition) or (control w3 group*) or (control w3 intervention*) or (control w3 participant*) or (control w3 study))	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (50,695)
S48	TI (multicentre or multicenter or multi-centre or multi-center) or AB random*	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (107,535)
S47	TI random* OR controlled	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (37,554)
S46	TI (trial or (study n3 aim) or "our study") or AB ((study n3 aim) or "our study")	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (94,494)
S45	TI (pre-workshop or preworkshop or post-workshop or postworkshop or (before n3 workshop) or (after n3 workshop)) or AB (pre-workshop or preworkshop or post-workshop or postworkshop or (before n3 workshop) or (after n3 workshop))	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (354)
S44	TI (demonstration project OR demonstration projects OR preimplement* or pre-implement* or post-implement* or postimplement*) or AB (demonstration project OR demonstration projects OR preimplement* or pre-implement* or post-implement* or postimplement*)	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (1,447)
S43	(intervention n6 clinician*) or (intervention n6 community) or (intervention n6 complex) or (intervention n6 design*) or (intervention n6 doctor*) or (intervention n6 educational) or (intervention n6 family doctor*) or	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (46,411)

(*Continued*)

	(intervention n6 family physician*) or (intervention n6 family practitioner*) or (intervention n6 financial) or (intervention n6 GP) or (intervention n6 general practice*) Or (intervention n6 hospital*) or (intervention n6 impact*) Or (intervention n6 improv*) or (interven ..		
S42	TI (collaborativ* or collaboration* or tailored or personalised or personalized) or AB (collaborativ* or collaboration* or tailored or personalised or personalized)	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (40,174)
S41	TI pilot	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (13,068)
S40	(MH "Pilot Studies")	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (32,990)
S39	AB "before-and-after"	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (18,791)
S38	AB time series	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (1,950)
S37	TI time series	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (282)
S36	AB (before* n10 during or before n10 after) or AU (before* n10 during or before n10 after)	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (35,192)
S35	TI ((time point*) or (period* n4 interrupted) or (period* n4 multiple) or (period* n4 time) or (period* n4 various) or (period* n4 varying) or (period* n4 week*) or (period* n4 month*) or (period* n4 year*)) or AB ((time point*) or (period* n4 interrupted) or (period* n4 multiple) or (period* n4 time) or (period* n4 various) or (period* n4 varying) or (period* n4 week*) or (period* n4 month*) or (period* n4 year*))	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (52,920)
S34	TI ((quasi-experiment* or quasi-experiment* or quasi-random* or quasirandom* or quasi control* or	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (13,277)

(*Continued*)

	quasicontrol* or quasi* W3 method* or quasi* W3 study or quasi* W3 studies or quasi* W3 trial or quasi* W3 design* or experimental W3 method* or experimental W3 study or experimental W3 studies or experimental W3 trial or experimental W3 design*)) or AB ((quasi-experiment* or quasiexperiment* or quasi-random* or quasirandom* or quasi control* or quasicontrol* or quasi* W3 method* or quasi* W3 s ..		
S33	TI pre w7 post or AB pre w7 post	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (10,391)
S32	MH "Multiple Time Series" or MH "Time Series"	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (1,476)
S31	TI ((comparative N2 study) or (comparative N2 studies) or evaluation study or evaluation studies) or AB ((comparative N2 study) or (comparative N2 studies) or evaluation study or evaluation studies)	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (11,498)
S30	MH Experimental Studies or Community Trials or Community Trials or Pretest-Posttest Design + or Quasi-Experimental Studies + Pilot Studies or Policy Studies + Multicenter Studies	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (38,238)
S29	TI (pre-test* or pretest* or posttest* or post-test*) or AB (pre-test* or pretest* or posttest* or "post test*) OR TI (preimplement*" or pre-implement*) or AB (pre-implement* or preimplement*)	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (7,482)
S28	TI (intervention* or multiintervention* or multi-intervention* or postintervention* or post-intervention* or preintervention* or pre-intervention*) or AB (intervention* or multiintervention* or multi-intervention* or postintervention* or post-intervention* or preintervention* or pre-intervention*)	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (161,816)

(*Continued*)

S27	(MH "Quasi-Experimental Studies")	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (6,593)
S26	TI (multimorbid* or multi-morbid*) or AB (multimorbid* or multi-morbid*)	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (314)
S25	s22 and s23	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (2,157)
S24	S6 and S23	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (223)
S23	TI (coocurr* or coexist* or co-ocurr* or coexist* or co-exist*) or AB (coocurr* or coexist* or co-ocurr* or coexist* or co-exist*)	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (3,577)
S22	S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or 21	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (911,807)
S21	TI diabet* or asthma* or chronic or disease	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (170,650)
S20	MW (disease OR diseases) or MW syndrome? or MW chronic	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (355,215)
S19	(MM "Kidney Diseases+")	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (22,918)
S18	(MM "Osteoporosis+")	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (6,954)
S17	(MM "Neoplasms+")	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (157,781)
S16	(MM "Liver Diseases+")	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (16,641)
S15	(MM "Human Immunodeficiency Virus+")	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (2,596)
S14	(MH "Mental Disorders, Chronic") OR (MM "Mental Disorders+")	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (188,092)
S13	(MM "Epilepsy+")	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (5,260)

(*Continued*)

S12	(MM "Arthritis+")	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (22,648)
S11	(MM "Thyroid Diseases+")	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (4,262)
S10	(MM "Lung Diseases, Obstructive+") OR (MM "Pulmonary Disease, Chronic Obstructive+") OR (MM "Asthma+")	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (24,299)
S9	(MM "Cardiovascular Diseases+")	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (205,579)
S8	(MM "Hypertension+") OR (MM "Cerebrovascular Disorders+")	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (59,999)
S7	(MH "Diabetes Mellitus+")	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (72,183)
S6	S4 or S5	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (46,597)
S5	TI (chronic* W3 disease? or chronic* W3 ill* or chronic* W3 care or chronic* W3 condition? or chronic* W3 disorder* or chronic* W3 health* or chronic* W3 medication* or chronic* W3 syndrom* or chronic* W3 symptom*) or AB (chronic* W3 disease? or chronic* W3 ill* or chronic* W3 care or chronic* W3 condition? or chronic* W3 disorder* or chronic* W3 health* or chronic* W3 medication* or chronic* W3 syndrom* or chronic* W3 symptom*)	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (23,896)
S4	(MH "Chronic Disease")	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (30,061)
S3	S1 or S2	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (39,568)
S2	TI (multimorbid* or multi-morbid* or comorbid* or co-morbid* or multidisease? or multi-disease?) or AB (multimorbid* or multi-morbid* or comorbid* or co-morbid* or multidisease? or multi-disease?) or TI (mul-	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	**View Results** (22,735)

(*Continued*)

	tiple N2 ill* or multiple N2 disease? or multiple N2 condition? or multiple N2 syndrom* or multiple N2 disorder?) or AB (multiple N2 ill* or multiple N2 disease? or multiple N2 condition? or multiple N2 syndrom* or multiple N2 disorder?) or TI (coocur* N3 disease? or coocur* N3 ill* or ..		
S1	(MH "Comorbidity")	**Expanders** - Apply related words **Search modes** - Boolean/Phrase	

Appendix 6. EPOC search

EPOC Specialised Register, Reference Manager 12

Connector	Field	Parameter	Results
	All Indexed Fields		
OR	All Non-Indexed Fields		

Appendix 7. AMED (Allied and Complimentary Medicine) (OVID)

1 Comorbidity/ (71202)
2 (comorbid$ or co-morbid$).ti,ab. (90329)
3 (multimorbid$ or multi-morbid$).ti,ab. (1577)
4 (multidisease? or multi-disease? or (multiple adj (ill$ or disease? or condition? or syndrom$ or disorder?))).ti,ab. (2688)
5 or/1-4 (141817)
6 Chronic disease/ (228383)
7 (chronic$ adj3 (disease? or ill$ or care or condition? or disorder$ or health$ or medication$ or syndrom$ or symptom$)).ti,ab. (246673)
8 or/6-7 (425175)
9 5 or 8 (550980)
10 exp diabetes mellitus/ or diabet$.ti,ab. (486603)
11 exp hypertension/ or (hypertens$ or "high blood pressure?").ti,ab. (385060)
12 exp heart disease/ or (((heart or cardiac or cardiovascular or coronary) adj (disease? or disorder? or failure)) or arrythmia?).ti,ab. (1063644)
13 exp cerebrovascular disorders/ or ((cerebrovascular or vascular or carotoid$ or arter$) adj (disorder? or disease?)).ti,ab. (399702)
14 exp asthma/ or asthma$.ti,ab. (144387)
15 exp pulmonary disease chronic obstructive/ or (copd or (pulmonary adj2 (disease? or disorder?))).ti,ab. (78374)
16 exp hyperlipidemia/ or (hyperlipidem$ or Hypercholesterolemia$ or hypertriglyceridemia$).ti,ab. (77660)
17 exp Thyroid disease/ or ((thyroid adj (disease? or disorder)) or hyperthyroid$ or hypothyroid$).ti,ab. (133854)
18 exp arthritis rheumatoid/ or rheumatoid arthritis.ti,ab. (120182)
19 exp mental disorders/ or (((mental or anxiety or mood or psychological or sleep) adj (disease? or disorder?)) or ((substance or drug or marijuana or cocaine or Amphetamine) adj2 abuse) or depression or schizophren$ or psychos$ or "substance abuse" or addiction?).ti,ab. (1228206)

20 exp epilepsy/ or (epileps$ or seizure?).ti,ab. (173788)
21 exp hiv infections/ or (HIV or acquired immune$ deficiency syndrome? or (aids adj (associated or related or arteritis))).ti,ab. (317967)
22 exp neoplasms/ or (neoplasm? or cancer?).ti,ab. (2911249)
23 exp kidney disease/ or (kidney adj (disease? or disorder?)).ti,ab. (428395)
24 exp liver disease/ or (liver adj (disease? or disorder?)).ti,ab. (461371)
25 exp osteoporosis/ or osteoporosis.ti,ab. (65004)
26 or/10-25 (7197068)
27 ((coocur$ or co-ocur$ or coexist$ or co-exist$ or multipl$) adj3 (disease? or ill$ or care or condition? or disorder$ or health$ or medication$ or symptom$ or syndrom$)).ti,ab. (50430)
28 chronic$.ti,ab,hw. (1036888)
29 27 or 28 (1079867)
30 26 and 29 (624934)
31 exp Primary Health Care/ or (primary adj2 care).ti,ab. or Physicians, Family/ or (((family or general or generalist? or community) adj2 (physician? or doctor? or practitioner? or practice)) or GP).ti,ab. or Family Practice/ or exp Community Health Services/ or (communit$ adj2 (health or healthcare or service?)).ti,ab. (744825)
32 (or/9,30) and 31 [Multimorb & PC] (48396)
33 exp *education, continuing/ (30556)
34 (education$ adj2 (program$ or intervention? or meeting? or session? or strateg$ or workshop? or visit?)).tw. (47997)
35 (behavio?r$ adj2 intervention?).tw. (8798)
36 *pamphlets/ (1418)
37 (leaflet? or booklet? or poster or posters).tw. (22316)
38 ((written or printed or oral) adj information).tw. (1616)
39 (information$ adj2 campaign).tw. (375)
40 (education$ adj1 (method? or material?)).tw. (5063)
41 *advance directives/ (3060)
42 outreach.tw. (8506)
43 ((opinion or education$ or influential) adj1 leader?).tw. (1064)
44 facilitator?.tw. (14027)
45 academic detailing.tw. (371)
46 consensus conference?.tw. (4351)
47 *guideline adherence/ (9932)
48 practice guideline?.tw. (15621)
49 (guideline? adj2 (introduc$ or issu$ or impact or effect? or disseminat$ or distribut$)).tw. (3402)
50 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 training program$).tw. (797)
51 *reminder systems/ (1364)
52 reminder?.tw. (7519)
53 (recall adj2 system$).tw. (400)
54 (prompter? or prompting).tw. (5216)
55 algorithm?.tw. (142589)
56 *feedback/ or feedback.tw. (91349)
57 chart review$.tw. (24793)
58 ((effect? or impact or records or chart?) adj2 audit).tw. (842)
59 compliance.tw. (84218)
60 marketing.tw. (18043)
61 or/33-60 (523395)
62 exp *reimbursement mechanisms/ (17092)
63 fee for service.tw. (3651)
64 *capitation fee/ (2001)
65 *"deductibles and coinsurance"/ (635)
66 cost shar$.tw. (1221)
67 (copayment? or co payment?).tw. (1351)
68 (prepay$ or prepaid or prospective payment?).tw. (4227)

69 *hospital charges/ (960)
70 formular?.tw. (2997)
71 fundhold?.tw. (1)
72 *medicaid/ (10071)
73 *medicare/ (17594)
74 blue cross.tw. (1125)
75 or/62-74 (52023)
76 *nurse clinicians/ (5524)
77 *nurse midwives/ (4679)
78 *nurse practitioners/ (10912)
79 (nurse adj (rehabilitator? or clinician? or practitioner? or midwi$)).tw. (10929)
80 *pharmacists/ (7303)
81 clinical pharmacist?.tw. (1484)
82 paramedic?.tw. (3441)
83 *patient care team/ (21355)
84 exp *patient care planning/ (23648)
85 (team? adj2 (care or treatment or assessment or consultation)).tw. (12673)
86 (integrat$ adj2 (care or service?)).tw. (8332)
87 (care adj2 (coordinat$ or program$ or continuity)).tw. (20929)
88 (case adj1 management).tw. (8243)
89 exp *ambulatory care facilities/ (25365)
90 *ambulatory care/ (15818)
91 or/76-90 (158006)
92 *home care services/ (20009)
93 *hospices/ (3300)
94 *nursing homes/ (19956)
95 *office visits/ (2222)
96 *house calls/ (1459)
97 *day care/ (2919)
98 *aftercare/ (2761)
99 *community health nursing/ (14860)
100 (chang$ adj1 location?).tw. (398)
101 domiciliary.tw. (2351)
102 (home adj1 treat$).tw. (1496)
103 day surgery.tw. (2080)
104 *medical records/ (15985)
105 *medical records systems, computerized/ (12790)
106 (information adj2 (management or system?)).tw. (27432)
107 *peer review/ (3136)
108 *utilization review/ (2535)
109 health services misuse.hw. (3823)
110 or/92-109 (131421)
111 *physician's practice patterns/ (25602)
112 quality assurance.tw. (19322)
113 *process assessment/ [health care] (1490)
114 *program evaluation/ (7476)
115 *length of stay/ (7593)
116 (early adj1 discharg$).tw. (2271)
117 discharge planning.tw. (2337)
118 offset.tw. (19965)
119 triage.tw. (10232)
120 exp *"Referral and Consultation"/ and "consultation"/ (19551)
121 *drug therapy, computer assisted/ (1140)

122 near patient testing.tw. (187)
123 *medical history taking/ (4454)
124 *telephone/ (4231)
125 (physician patient adj (interaction? or relationship?)).tw. (2036)
126 *health maintenance organizations/ (9388)
127 managed care.tw. (16605)
128 (hospital? adj1 merg$).tw. (370)
129 or/111-128 (148510)
130 ((standard or usual or routine or regular or traditional or conventional or pattern) adj2 care).tw. (42136)
131 (program$ adj2 (reduc$ or increas$ or decreas$ or chang$ or improv$ or modify$ or monitor$ or care)).tw. (44374)
132 (program$ adj1 (health or care or intervention?)).tw. (31916)
133 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 treatment program$).tw. (347)
134 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 care program$).tw. (169)
135 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 screening program$).tw. (540)
136 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 prevent$ program$).tw. (458)
137 (computer$ adj2 (dosage or dosing or diagnosis or therapy or decision?)).tw. (4570)
138 ((introduc$ or impact or effect? or implement$ or computer$) adj2 protocol?).tw. (3051)
139 ((effect or impact or introduc$) adj2 (legislation or regulations or policy)).tw. (1689)
140 or/130-139 (115558)
141 or/61,75,91,110,129,140 (1015057)
142 randomized controlled trial.pt. (392659)
143 controlled clinical trial.pt. (89968)
144 random$.ti,ab. (758832)
145 double-blind method/ or random allocation/ or single-blind method/ (222022)
146 ((double or single or triple or treble) adj2 blind$).ti,ab. (133866)
147 (quasi-experiment$ or quasiexperiment$).ti,ab. (6980)
148 interrupt$ time series.ti,ab. (1141)
149 (control$ adj2 (trial? or study or studies)).ti,ab. (304877)
150 or/142-149 (1128989)
151 32 and 150 (6732)
152 9 and 141 and 150 (7802)
153 30 and 141 and 150 (5700)
154 152 or 153 [FINAL RESULTS] (9769)
155 limit 154 to yr="2011 -Current" (3258)
156 from 155 keep 1-81 (81)

WHAT'S NEW

Last assessed as up-to-date: 28 September 2015.

Date	Event	Description
15 January 2016	New citation required but conclusions have not changed	Conclusions of the review are similar to those previously reported, but the addition of new studies in this update allows us to be more confident that certain interventions seem more effective than others This review includes 18 studies

(*Continued*)

28 September 2015	New search has been performed	New searches performed to 28 September 2015. Eight new studies identified

HISTORY

Protocol first published: Issue 2, 2007

Review first published: Issue 4, 2012

Date	Event	Description
18 March 2015	Amended	New author added (E Wallace) and two original authors withdrew (H Soubhi and C Hudon)
1 May 2013	Amended	Minor edits, fixed ref for Katon 2010
24 May 2011	Amended	Search updated Feb 2011
12 June 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Susan Smith (SS) conceived, co-ordinated, and designed the review. Emma Wallace (EW) helped co-ordinate the update of the review, assessed studies for inclusion, and extracted data from included studies. Susan Smith, Martin Fortin (MF) , Emma Wallace, and Tom O'Dowd (TOD) contributed to all stages of the review, and were involved in writing all review drafts and responding to peer review comments.

DECLARATIONS OF INTEREST

SS has no conflict of interest. EW has no conflict of interest. TOD has no conflict of interest. MF has no conflict of interest.

SOURCES OF SUPPORT

Internal sources

- Health Research Board Primary Care Research Centre, Ireland.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

During the initial review process, the authors decided, following a suggestion from a peer reviewer, that interventions should be excluded if they only targeted one condition as this was contrary to the emphasis on multimorbidity. This led to the exclusion of some studies examining comorbid depression and other conditions where the intervention was only targeted at depression treatment.

Changes were also made to the original search strategy in the protocol, based on initial results from the original searches. The searches used in the review are presented as appendices.

We had planned to contact authors of other reviews in the field of multimorbidity that were retrieved during the search process regarding relevant studies that they may be aware of, but no other reviews of interventions were identified.

We had planned to prepare tables and funnel plots comparing effect sizes of studies grouped according to potential effect modifiers (for example, simple versus multifaceted interventions) if sufficient studies had been identified but this was not possible.

If there had been enough studies, we had planned to use meta-regression to see whether the effect sizes could be predicted by study characteristics. These could, for example, include duration of the intervention, age groups, and simple versus multifaceted interventions (Cooper 1994). We also considered formal tests of homogeneity (Petitti 1994). None of these quantitative methods were possible for this version of the review but will be considered for future review updates

We had planned, if possible, to consider subgroup analyses based on the degree of multimorbidity of participants. This would have been based on the number of conditions per person. This was not possible.

We initially used the term psychosocial measures to group measures of well-being, quality of life, function and psychological measures such as illness perceptions. We have replaced this with the more commonly used term 'patient-reported outcome measures'. We have re-named 'physical health outcomes' as 'clinical outcomes' for this update of the review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Primary Health Care; Age Factors; Chronic Disease [*therapy]; Community Health Services; Comorbidity; Disease Management; Patient-Centered Care [methods]; Randomized Controlled Trials as Topic; Risk Factors; Treatment Outcome

MeSH check words

Humans