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Protocol for a systematic review on interventions for caregivers to persons with MCI and early dementia: Does early stage intervention improve caregiver wellbeing and ability to provide care?

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TITLE: Protocol for a systematic review on interventions for caregivers to persons with MCI and early dementia: Does early stage intervention improve caregiver wellbeing and ability to provide care?

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Word Count: 3734

ABSTRACT

Introduction:

Caregivers to persons with dementia and mild cognitive impairment (MCI) are at risk for decreased wellbeing. While many interventions for caregivers exist, evidence is sparse regarding intervention timing and effectiveness at an early stage of cognitive decline. Our systematic review aims to answer the following questions: 1) Do interventions for caregivers to persons with early stage dementia or MCI affect their wellbeing and ability to provide care? 2) Are particular types of caregiver interventions most effective during early stage cognitive decline? 3) How does effectiveness differ when early and later intervention are directly compared? 4) Do effects of early stage caregiver intervention vary based on care recipient and caregiver characteristics (e.g., sex, type of dementia)?

Methods and analysis:

The databases MEDLINE, EMBASE, PSYCINFO, and CINAHL, as well as grey literature databases, will be searched for English language studies using search terms related to caregiver interventions and dementia/MCI. Abstracts and full-texts will be screened by two independent reviewers; included studies must assess the effects of an intervention for caregivers to persons with early-stage dementia or MCI on caregiver wellbeing or ability to provide care. Intervention, study, and participant characteristics will be extracted by two independent reviewers, along with outcome data. Risk of bias will be assessed using the Cochrane Risk of Bias tool (for controlled trials with and without randomization). Interventions will be grouped by type (e.g., psychoeducational) and a narrative synthesis is planned due to expected heterogeneity, but meta-analysis will be performed where possible. The GRADE approach will be used to inform conclusions regarding the quality of evidence for each type of intervention.

Ethics and dissemination:

Findings from this review will be disseminated via conferences and peer-reviewed publication, and a summary will be provided to the Alzheimer Society.

Registration: This review protocol has been registered with PROSPERO (#CRD42018114960).

Keywords: caregivers, early intervention, early stage/mild dementia, MCI

ARTICLE SUMMARY

Strengths and Limitations of this study:

-Addresses intervention timing and the effectiveness of early stage caregiver intervention

-Uses a rigorous search and screening process, to maximize comprehensiveness and minimize bias

-Broad and possibly very heterogeneous review

-Will consider findings in relation to assessment of bias and evidence GRADEing

INTRODUCTION

It is well established in the literature that informal caregivers to persons with dementia are at risk for experiencing caregiver burden[1,2]. Caregiver burden may be best understood as a multidimensional construct reflecting caregiver struggles with financial, physical, social, psychological/emotional, and developmental wellbeing, as well as challenges navigating caring demands and restrictions[3,4]. Associated with caregiver burden, psychological issues such as general distress, depression, and anxiety are common among family caregivers to persons with dementia[5-7]. Moreover, a growing body of research suggests that caregiving to a person with dementia negatively affects the caregiver's sleep quality, cognitive functioning, and physiological health (particularly in relation to markers of immune function, cellular aging, and cardiovascular risk factors)[8]. Although there are also gratifying and positive aspects of caregiving for many caregivers to persons with dementia[9], they are often considered a vulnerable population due to the intensity of caring demands and risk of burden and other negative consequences.

Many interventions have been developed to support caregivers to persons with dementia, and enhance both caregiver wellbeing and ability to provide care. A variety of approaches including psychoeducational, cognitive-behavioral therapy, counseling, case management, respite, and general support interventions have been implemented with caregivers to persons with dementia, as well as interventions which combine approaches (i.e., multi-component interventions)[10]. Previous reviews and meta-analyses have demonstrated the effectiveness of many caregiver interventions on a variety of outcomes, although interventions may have only domain-specific effects (e.g., on caregiver depression) and evidence suggests that some types of interventions (e.g., multicomponent and psychoeducational) may be the most beneficial[10-13]. Moreover, effectiveness of these interventions has been found to vary according to caregiver and care recipient characteristics, such as caregiver sex, relationship to the care recipient, and type and severity of dementia[14].

Another factor that may be very important when examining caregiver intervention effectiveness is the timing of intervention: whether it begins early or later in the course of the care recipient's cognitive decline. Few systematic reviews have distinguished between people at different stages of dementia, and Thompson et al.[15] identified intervention timing as a fundamental question for future research in the area. The effects of some caregiver interventions may be greater depending on their timing; Andrén and Elmståhl[16] found that a psychosocial intervention conferred greater benefit to caregivers' wellbeing when provided early in the progression of dementia. Even caregivers to persons with mild cognitive impairment (MCI) are at risk for experiencing burden and depression[17], indicating

the potential utility of interventions at this stage. Moreover, early stage intervention may better position caregivers to cope with dementia progression[18]. While the utility of early stage intervention for caregivers has been suggested[19], the degree to which interventions of various forms are beneficial to early stage dementia caregivers would benefit from systematic review. This is particularly important due to what Boots and colleagues[20] termed the "early needs paradox", wherein later stage caregivers identify early stage support and guidance as being crucial needs yet early stage caregivers may not recognize these needs and find it difficult to accept assistance. Understanding the benefits of early stage intervention for caregivers will allow for evidence-informed decision making around the provision and timing of support. Our aim is therefore to assess potential benefits of intervention for caregivers to persons with early stage dementia or MCI, via a systematic review. This protocol follows the PRISMA-P guidelines developed for systematic review and meta-analysis protocols, in order to document and enhance the rigor and transparency of our planned methods, outcomes, and analyses[21]. A record of the protocol has been registered with PROSPERO (#CRD42018114960).

Research questions

To achieve our goal of examining the potential benefits of early stage intervention for caregivers to persons with dementia, four research questions are being posed: 1) Do interventions aimed at caregivers to persons with early stage dementia or MCI affect their wellbeing and ability to provide care? 2) Are particular types of caregiver interventions more effective than others during early stage cognitive decline? 3) To what extent do benefits to caregivers differ when early and later intervention are directly compared? 4) Is there evidence to suggest that benefits of early stage intervention for caregivers vary based on care recipient and caregiver characteristics (e.g., relationship, sex, type of dementia, rural vs. urban residence)?

METHODS AND ANALYSIS

A systematic review was chosen to answer our research questions. Systematic reviews aim to identify, evaluate, and synthesize the findings of all relevant studies, and can identify what we know about the effects of interventions as well as demonstrate where knowledge is lacking[22]. The guidelines set out by the Centre for Reviews and Dissemination (CRD)[22] are informing our review process, which will consist of the identification of research evidence, study selection, data extraction, quality assessment, data synthesis, and evidence grading and conclusions.

Patient and Public Involvement

Patients and public were not involved in the development of this systematic review protocol.

Step 1: The identification of research evidence

Information sources

Published peer-reviewed research will be included in this systematic review. Based on the topic of interest, the electronic databases MEDLINE, EMBASE, PSYCINFO, and CINAHL will be searched with no limitations placed on year of publication. This search will be supplemented by scanning the reference lists of included studies, to ensure no relevant studies are missed. Due to available resources and feasibility, the search will be limited to English-language studies. If the time from search to data analysis exceeds six months, the literature search will be updated within each database. Details of the search process will be documented throughout, for transparency and replication[22]. As suggested by Paez[23], we will be also be searching the following sources of grey literature to identify key studies which may not be published: grey literature databases (Proquest Dissertations & Theses Global, OpenGrey); conference abstracts (f included databases); and clinical trial databases (WHO International Clinical Trials Registry Platform, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, National Institute on Aging Clinical Trials).

Search strategy

Three main search concepts have been identified as important for this review, namely: dementia/MCI, caregivers, and intervention. Search terms were constructed following a search of previous literature to identify specific terms relevant to these concepts. In order to narrow search outcomes to the topic of interest, terms related to caregiver and intervention will be searched together using the adjacency function, so that articles which use these terms within five words of each other will be identified (the adjacency strategy). Terms incorporating medical subject headings (MeSH), text words, and 'exploded' derivatives related to each concept (the MESH strategy) will be also entered into the included databases using OR. Results from the concepts of dementia/MCI and caregiver interventions (adjacency strategy OR MESH strategy) will then be searched together using AND. The search strategies for each database are being developed by the review team, in consultation with a Health Science Librarian with expertise in systematic reviews. A draft MEDLINE search strategy can be viewed in Table 1. When searching grey literature, we will document the date each database is searched, the search terms used, the number of items retrieved (i.e., search results), and the number of items relevant for screening.

Table 1. Draft Medline search strategy

Caregiver terms	Intervention terms	Dementia terms
Caregiver*	Program*	Dement*
Carer*	Intervention*	Alzheimer*
Care partner	Educat*	Lewy* adj2 bod*

Care partners	Support*	Creutzfeldt or jcd or cjd
Care provider	"Social support"	Pick* adj2 disease
Care providers	Resource?	Semantic adj2 dementia
Caregivers/	Therap*	Parkinson* adj2 dementia)
	Respite*	Frontotemporal* adj2 dementia
	Psychosocial	Vascular* adj2 dementia
	Evaluat*	Huntington*
	Counsel*	Primary progressive aphasia?
	Service*	"Mild cognitive impairment"
	"Case management"	MCI
	Health communication/	exp Dementia/
	exp Community health services/	
	Health services for the aged/	
	Early medical intervention/	
	exp Social support/	
	Respite care/	
	Case management/	
	Psychosocial support systems/	
	exp Psychotherapy/	
	Program development/	
	Program evaluation/	

i.　　"/" indicates MESH terms.

Step 2: Study selection

Data management

Studies identified in the literature search will be uploaded to Distiller Systematic Review software, which allows multiple reviewers to screen studies simultaneously. This software will also be used to screen for duplicates when studies are uploaded. Using Distiller SR, the first author will create screening forms based on our eligibility criteria to determine inclusion/exclusion. Separate forms will be created for title/abstract (level 1) and full text (level 2) review, and each will be pilot-tested by the first author and refined if needed before independent review commences[22].

Eligibility criteria

Studies will be selected according to the inclusion and exclusion criteria outlined below. No restrictions regarding length/timing of follow-up measurement, or intervention setting, will be placed on studies.

Participants

Participants must be caregivers to people with early stage dementia or MCI. The dementia may be any form, including Alzheimer's disease, vascular dementia, dementia related to Parkinson's disease, dementia with Lewy bodies, frontotemporal dementia, Creutzfeldt-Jakob disease, and mixed or unspecified dementia; young-onset dementia will also be included. While not all individuals with MCI will progress to dementia, MCI may still be considered a prodromal or "pre-dementia" stage in the context of early intervention[18]. Caregivers to persons with MCI will therefore be included based on this characterization, the porous clinical boundary between MCI and early stage dementia, and the inclusion of MCI in other reviews on early stage dementia interventions[24,25]. Stage of dementia will be assessed based on author description of the sample (e.g., mild/early stage dementia or MCI were inclusion criteria or they stated all participants had early stage dementia or MCI), and/or care recipients' cognitive testing scores if reported. Studies will be excluded if caregivers are providing care to individuals who are not early in the progression of dementia (they are described as having moderate or severe dementia, CDR scores >1, MMSE <18, or GDS >5), or are a convenience sample of caregivers to individuals across multiple stages of dementia. Studies may compare caregivers to persons with MCI/early stage versus later stage dementia.

Interventions

As identified in previous reviews[26,10], a variety of interventions for caregivers to persons with dementia have been developed and evaluated. All approaches to intervention for caregivers to persons with MCI or early stage dementia will be included in this review, including multicomponent interventions. In order to assess the effects of different types of early intervention, interventions will be classified into categories based on their dominant characteristics[10]. For example, programs which focus primarily on formal provision of information and caregiver skills training would be classified as psychoeducational. The study must have a primary focus on supporting caregivers (interventions for the person with dementia or MCI where the caregiver plays a supporting role will not be included).

Comparators

Included studies will include a control or comparison group unless inclusion criteria are relaxed (see Study Design). Comparison groups may include caregivers who did not receive the intervention/received usual care, received it at a different time point (i.e., later in the course of the care recipient's dementia), or received a different type of intervention. Studies may be included if they compare other participant

groups who received the intervention (e.g., caregivers to people with other conditions) with early stage dementia or MCI groups.

Outcomes

Included studies must include evaluation of the effectiveness of an intervention for caregivers that is intended to enhance caregiver wellbeing or ability to provide care to the person with dementia or MCI. Although there are many definitions of wellbeing[27], in the current review the term "enhanced wellbeing" is being used to refer to the positive increases in physical, social, psychological, and spiritual health, and quality of life, that may result from the provision of support and resources to meet caregiver challenges. A variety of relevant outcome variables may be measured in included studies, including (but not limited to) depression, anxiety, stress, quality of life, physical health, emotional wellbeing, socialization, leisure time, time until institutionalization of the person with dementia, caregiver burden, and perceived ability to provide care or cope with caregiving demands. All outcome variables relevant to caregiver wellbeing or ability to provide care will be extracted, along with their definition as reported in individual studies.

Study Design

Randomized controlled trials (RCTs) are considered the gold standard in assessing intervention outcomes and will be included in this review, including randomized cross-over trials and cluster randomized trials. However, implementing randomization, blinding, and control groups may be difficult in psychosocial dementia interventions and it is therefore important to consider evidence from other types of study designs[28]. As such, non-randomized studies with a control or comparison group will be included in this review. If few RCT and controlled studies exist, pre-post case series designs (where a group is given an intervention but no comparisons to a control group are made) will also be included due to their frequency of use given the difficulty of conducting randomized and controlled studies in this area. All other designs including qualitative research will be excluded for the purposes of this review.

Selection process

The first author (MB) and another review author will independently screen titles and abstracts of all studies uploaded into Distiller SR, using the Level 1 form. This form will be used to screen for articles that report on interventions for caregivers aimed at enhancing caregiver wellbeing or ability to provide care to recipients with dementia or MCI, and initial screening for study design. As suggested by CRD guidelines[22], reviewers will err on the side of inclusion during title and abstract review. Studies that appear to meet inclusion criteria, or those where inclusion is uncertain, will progress to Level 2 and full texts will be obtained. The first author and a second reviewer will then screen the full text reports to

determine whether they meet the inclusion criteria. Level two screening will include screening for stage of cognitive impairment, as identified by the authors (e.g., "participants all had early stage dementia") and/or cognitive testing scores. DistillerAI, which is the software's language processing technology, may be used to check for accidental exclusions. Disagreements at both stages of review will be resolved through discussion, and a third author (DM) will be consulted in cases where an agreement is not reached. During full-text review, the reason for exclusion will be documented for each study. The reviewers will not be blind to study titles, authors, or institutions, which is considered acceptable during study selection[22]. A PRISMA flow chart[29] documenting the number of studies at each stage of the selection process and reasons for full text exclusion will be created.

Step 3: Data extraction

Extraction process

An electronic data extraction form will be created based on the items of interest described below (see sample extraction form in Supplementary File 1). Guidelines for data extraction may also be developed to facilitate standardization of the process. The extraction form will be piloted on a small sample of included studies, and refined as necessary. Where reported, data will be extracted into this form for each study by the first author and a second reviewer (JK), in order to reduce errors and missed information[30]. Any disagreements will be discussed and resolved among the review team. As per CRD recommendations[22], multiple reports of the same study (e.g., a preliminary sample followed by the total sample) will be treated as one study for data extraction to reduce biased results. Authors of included studies may be contacted by email to confirm uncertainties or for additional information.

Data items

The following information will be extracted about the study, intervention, and sample:

1) General information: author/s; year; title of the article; source of funding; geographic location of the study (country)

2) Intervention characteristics: criteria distinguishing the intervention as early-stage; intervention name, description, type, and theoretical basis (where relevant); length of intervention, setting in which the intervention is delivered

3) Study characteristics: objectives of the study; study design; recruitment procedures including inclusion and exclusion criteria, comparator group; sample size for each group

4) Participant characteristics (total sample, intervention group, and comparator group/s):
   a. Caregiver characteristics: rural vs. urban; sex; relationship of caregiver to care recipient

    b.   Care recipient characteristics: rural vs. urban; sex; type of dementia; cognitive testing scores

Outcomes

Caregiver wellbeing and ability to provide care may be operationalized in a number of ways; the main outcome variables we are interested in are caregiver burden and depression (given their importance and prevalence in this population and the literature), self-reported quality of life, and perceived ability to provide care. All other variables related to the two broad outcomes being assessed will be considered secondary outcome variables. When extracting data related to these outcomes, time until intervention follow-up and additional follow-up measurements will be charted. The measurement tool or measurement used for each relevant outcome variable will be recorded, as will the statistical techniques used for analysis. Raw means (with standard deviations), change scores, and statistical outcomes will be extracted for each measure pertaining to wellbeing and ability to provide care. As data is extracted, statistical information from studies will be used to calculate standardized mean differences (or odds ratios if relevant, e.g. for risk of institutionalization). This will allow for comparison between variations in measures of effects across individual studies, and helps account for differences in sample sizes that affect statistical significance[31].

Another goal of this review is to assess whether benefits of early and later intervention differ; all statistical summary and outcome information will be extracted if studies compare the effects of early to later intervention. Finally, we are interested in assessing whether benefits of early intervention vary based on care recipient and caregiver characteristics (e.g., sex, type of dementia, rural versus urban residence). All summary data and statistical outcomes pertaining to comparisons of intervention effects between subgroups of caregivers or care recipients will be extracted. These comparisons may be based on the factors noted above which are of particular interest, but may also include other factors (e.g., caregiver personality, socioeconomic status). Additional outcomes (those not pertaining to the foci of this review) reported in the article and other information of interest will be recorded narratively without statistical information.

Step 4: Quality assessment

Quality will be assessed to inform conclusions about the effectiveness of early intervention with caregivers based on how the study was carried out, not to inform inclusion/exclusion in the review. Potential bias (systematic deviations from the "true" effect due to poor study design or implementation) is important to examine, since it can alter findings of effect and explain different findings between studies assessing the same intervention[22]. To assess the possible risk of bias for each included RCT, we

will use the Cochrane Risk of Bias Tool for Randomized Controlled Trials (Table 8.5 in the Cochrane Handbook for Systematic Reviews of Interventions)[32]. This tool assesses five types of potential bias: selection bias, performance bias, detection bias, attrition bias, and reporting bias, as well as additional concerns about bias not addressed by these domains. Based on information in each article, a judgment will be made according to the Cochrane criteria on whether the study is at low risk, high risk, or unclear risk of bias. As suggested in the Cochrane Handbook[32], this tool can also be used for intervention studies that include a control group but are not randomized.

Pre-post case series studies may be included if few RCTs and controlled studies meet inclusion criteria. If these studies are included, the Institute of Health Economics' Quality Appraisal Checklist for Case Series Studies will be used to assess their quality, including risk of bias. This tool has been initially validated and consists of twenty items covering both risk of bias (e.g., pre- and post- outcome measurement, sufficient follow-up, method for recruitment of participants) and quality of reporting (e.g., description of patient characteristics, report of any co-interventions, report of any adverse outcomes)[33]. Based on previous use, a point will be given for every "yes" answer so that studies of higher quality (including lower risk of bias) will have a higher overall score out of 20, while those of lower quality (and higher risk of bias) will have lower scores. Quality assessment will be carried out for each study included in the review.

Step 5: Data synthesis

We anticipate that multiple types of early intervention will be covered in our systematic review, and that studies will report on various outcomes related to wellbeing and ability to provide care. Because of this expected heterogeneity, a narrative synthesis is planned[22,34]. A narrative synthesis relies primarily on textual description to analyze and describe the findings from included studies[34]. Extracted data will be examined for potential relationships between results and key aspects of the studies, and across studies (e.g., sample characteristics, outcomes measured, and intervention characteristics). Of interest also are explanations for why early interventions are effective. Studies will be separated into groups based on type of early stage intervention, in order to better address our second research question (whether effectiveness varies depending on intervention type). Key elements from each study will be presented in summary tables, including results and effect sizes. If studies within intervention subgroups are homogenous enough, statistical pooling of data will be performed through meta-analysis. If relevant evidence exists, differences in effectiveness based on timing of intervention and caregiver or care recipient characteristics will be assessed and presented. Risk of bias assessments will be used to

contextualize findings, evaluate the state of the literature, and potentially explain differences in results across studies.

Step 6: Evidence grading and conclusions

Meta-biases

Unpublished literature is included in this review in an attempt to minimize publication bias. When using the Risk of Bias tool, selective reporting (another area of meta-bias) will be assessed. This will be facilitated by comparing published studies with their protocols when possible, and assessing the degree to which data is reported for relevant outcomes including findings that are not statistically significant.

Confidence in cumulative evidence

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach will be used to rate the evidence regarding the effectiveness of early intervention for caregivers on their wellbeing and ability to provide care to a person living with MCI or dementia. GRADE involves risk of bias assessment but also assessments of imprecision, inconsistency, indirectness, and publication bias. This framework allows informed judgements to be made about the quality of the body of evidence that is being examined[35]: whether we can be confident it accurately represents the true effects of early caregiver interventions. The quality grade (very low, low, moderate, high) helps inform overall conclusions about the state of evidence for each outcome under review.

ETHICS AND DISSEMINATION

While scholars (e.g., Verhey & de Vugt, 2013) have noted the potential importance of intervention for caregivers in the early stages of the care recipient's dementia, including mild cognitive impairment, the efficacy of early interventions for caregivers would benefit from systematic review. This review aims to assess the efficacy of interventions for caregivers to persons with MCI and mild dementia, to determine whether early stage intervention increases caregiver wellbeing and ability to provide care. Additionally, we aim to identify factors which may impact effectiveness (direct evidence of intervention timing and patient and caregiver characteristics on effectiveness). Findings from this review will be shared via conference proceedings and peer-reviewed publication, and a summary to the Alzheimer's Society. A full list of relevant studies that do not have data included in the review (e.g., in-progress protocols) will be created and available upon request. Findings may help inform the use of interventions for caregivers early in the course of the care recipient's cognitive decline.

Competing Interests: The authors have no competing interests to declare.

Data Statement: All data that will be included in this systematic review will be taken from previously published articles or works (e.g., protocols, dissertations) found in databases.

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Data Extraction Form

General Study Information

Author/s:

Year:

Title of the article:

Funding source:

Geographic location (country):

Intervention Characteristics

Classified as "early intervention" based on:

Name of intervention:

Brief description of intervention:

Type of intervention:
*(Psychosocial, cognitive-behavioural, counseling,
case management, respite, support, multi-component)*
      Type of intervention specified in article or during extraction:

Theoretical basis of intervention:

Length of intervention:

Intervention setting for delivery:

Study Characteristics:

Objectives:

Design:
      Design specified in article or during extraction:

Recruitment procedures:

      Inclusion criteria:

      Exclusion criteria:

Comparator group/s:

Sample size of main intervention group:
(actually measured)

Sample size of comparator group/s:
(actually measured)

Participant Characteristics (for total sample; repeat for intervention and comparator groups if able)
Caregivers:

Geographic location:
(rural/urban; frequencies)

Caregiver sex:
(frequencies)

Relationship of caregiver to care recipient:
(frequencies)

Care recipients:

Geographic location:
(rural/urban; frequencies)

Care recipient sex:
(frequencies)

Type of dementia:
(frequencies)

Type of cognitive testing scores and reported mean:

Outcome Information:

For EACH relevant measurement of intervention effect:

Construct measured:

Length of time after intervention before first follow-up:

Additional follow up measurements:
(time)

Measurement tool:

Statistical techniques used for analysis:

Raw mean and standard deviation at each measurement point, intervention group:
(frequencies if applicable)

Raw mean and standard deviation at each measurement point, comparator:
(frequencies if applicable)

Change scores (if applicable), intervention group:

Change scores (if applicable), comparator group:

Statistical outcome/s:
(include p-value)

Confidence intervals:

Effect size:
(reported or calculated standardized mean difference)

Comparison between the effect of early and later intervention:

Timing of intervention, "early" group:

Timing of intervention, "later" group:

Outcome measured:

Measurement tool:

Statistical techniques used for analysis:

Raw mean and standard deviation at each measurement point, early group:
(frequencies if applicable)

Raw mean and standard deviation at each measurement point, later group/s:
(frequencies if applicable)

Change scores, early group (if applicable):

Change scores, later group:

Statistical outcome/s of comparisons:
(include p-value)

Confidence intervals:

Effect size:
(reported or calculated standardized mean difference)

For EACH comparison of intervention effect between subgroups of caregivers

Care recipient or caregiver characteristic examined:

Construct measured:

Measurement tool:

Statistical techniques used for analysis:

Raw mean and standard deviation at each measurement point,
group 1 (repeat for each group being compared):
(frequencies if applicable)

Change scores, group 1 (repeat for each group being compared):

Statistical outcome/s of comparisons:
(include p-value)

Confidence intervals:

Effect size:
(reported or calculated standardized mean difference)

Additional outcomes assessed *(i.e., not measures of wellbeing or ability to provide care. List/describe)*:

Other information of interest to this review:

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Protocol for a systematic review on interventions for caregivers of persons with mild cognitive impairment and early dementia: Does early stage intervention improve caregiver wellbeing and ability to provide care?

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TITLE: Protocol for a systematic review on interventions for caregivers of persons with mild cognitive

impairment and early dementia: Does early stage intervention improve caregiver wellbeing and ability

to provide care?

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Word Count: 3734

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ABSTRACT

Introduction:

Caregivers of persons with dementia and mild cognitive impairment (MCI) are at risk of decreased wellbeing. While many interventions for caregivers exist, evidence is sparse regarding intervention timing and effectiveness at an early stage of cognitive decline. Our systematic review aims to answer the following questions: 1) Do interventions for caregivers of persons with early stage dementia or MCI affect their wellbeing and ability to provide care? 2) Are particular types of caregiver interventions most effective during early stage cognitive decline? 3) How does effectiveness differ when early and later intervention are directly compared? 4) Do effects of early stage caregiver intervention vary based on care recipient and caregiver characteristics (e.g., sex, type of dementia)?

Methods and analysis:

The databases MEDLINE, EMBASE, PSYCINFO, and CINAHL, as well as grey literature databases, will be searched for English language studies using search terms related to caregiver interventions and dementia/MCI. Abstracts and full-texts will be screened by two independent reviewers; included studies must assess the effects of an intervention for caregivers of persons with early-stage dementia or MCI on caregiver wellbeing or ability to provide care. Intervention, study, and participant characteristics will be extracted by two independent reviewers, along with outcome data. Risk of bias will be assessed using the Cochrane Risk of Bias tool (for controlled trials with and without randomization). Interventions will be grouped by type (e.g., psychoeducational) and a narrative synthesis is planned due to expected heterogeneity, but meta-analysis will be performed where possible. The GRADE approach will be used to inform conclusions regarding the quality of evidence for each type of intervention.

Ethics and dissemination:

Findings from this review will be disseminated via conferences and peer-reviewed publication, and a summary will be provided to the Alzheimer Society.

Registration: This review protocol has been registered with PROSPERO (#CRD42018114960).

Keywords: caregivers, early intervention, early stage/mild dementia, MCI

ARTICLE SUMMARY

Strengths and Limitations of this study:

-Addresses intervention timing and the effectiveness of early stage caregiver intervention

-Uses a rigorous search and screening process, to maximize comprehensiveness and minimize bias

-Broad and possibly very heterogeneous review

-Will consider findings in relation to assessment of bias and evidence GRADEing

INTRODUCTION

Informal caregivers are relatives, partners, friends, or neighbours who have a personal relationship with a person with a chronic or disabling condition, and provide various types of assistance to that person[1]. The majority of care recipients with dementia receive assistance (such as with basic and instrumental activities of daily living and general supervision) from multiple informal caregivers, with one person assuming a primary caregiver role[2]. A recent review suggests that informal caregivers of persons with Alzheimer's disease provide an average of 56 hours of assistance per week[3]. Informal caregivers spend significantly more time providing care when they are a spouse/partner of the care recipient, and when the care recipient's functional status is worse or their dementia is more severe[2,3].

Psychological issues such as general distress, depression, and anxiety are common among family caregivers of persons with dementia[4-6]. Moreover, a growing body of research suggests that caregiving to a person with dementia negatively affects the caregiver's sleep quality, cognitive functioning, and physiological health (particularly in relation to markers of immune function, cellular aging, and cardiovascular risk factors)[7]. It is also well established in the literature that informal caregivers of persons with dementia are at risk of experiencing caregiver burden[8,9]. Caregiver burden may be best understood as a multidimensional construct reflecting caregiver struggles with financial, physical, social, psychological/emotional, and developmental wellbeing (perceptions of being "on time" in life circumstances, compared to peers), as well as challenges navigating caring demands and restrictions[10,11]. The burden experienced by dementia caregivers is most frequently measured using the Zarit Burden Interview[12] (ZBI), which assesses possible concerns with health, finances, emotional responses toward the caregiving role, social life, and relationship with the care recipient. A more recent factor analysis of the ZBI suggests that it measures three main dimensions: social consequences for the caregiver, psychological burden, and feelings of guilt[10]. While this does not preclude the existence of other types of burden, the common use of the ZBI means that operationalization of caregiver burden is often capturing emotional and psychological responses to caregiving, and social restrictions associated with this role. Although there are also gratifying and positive aspects of caregiving for many caregivers of persons with dementia[13], they are often considered a vulnerable population due to the intensity of caring demands and risk of burden and other negative consequences. This perspective is reflected in the literature on caregiver wellbeing, which primarily focuses on deficits and how to ameliorate negative caregiver outcomes[14].

Many interventions have been developed to support caregivers of persons with dementia, and enhance both caregiver wellbeing and ability to provide care. A variety of approaches including

psychoeducational, cognitive-behavioral therapy, counseling, case management, respite, and general support interventions have been implemented with caregivers of persons with dementia, as well as interventions which combine approaches (i.e., multi-component interventions)[15]. Previous reviews and meta-analyses have demonstrated the effectiveness of many caregiver interventions on a variety of outcomes, although interventions may have only domain-specific effects (e.g., on caregiver depression) and evidence suggests that some types of interventions (e.g., multicomponent and psychoeducational) may be the most beneficial[15-18]. Moreover, effectiveness of these interventions has been found to vary according to caregiver and care recipient characteristics, such as caregiver sex, relationship to the care recipient, and type and severity of dementia[19].

Another factor that may be very important when examining caregiver intervention effectiveness is the timing of intervention: whether it begins early or later in the course of the care recipient's cognitive decline. Few systematic reviews have distinguished between people at different stages of dementia, and Thompson et al.[20] identified intervention timing as a fundamental question for future research in the area. The effects of some caregiver interventions may be greater depending on their timing; Andrén and Elmståhl[21] found that a psychosocial intervention conferred greater benefit to caregivers' wellbeing when provided early in the progression of dementia. Dementia is a progressive illness and can begin with cognitive impairment, but no functional impairment; this is conceptualized as mild cognitive impairment (MCI)[22,23]. Although less instrumental caregiving support is required for persons with MCI, their caregivers are still at risk of experiencing burden and depression[24] which indicates the potential utility of interventions at this stage. Moreover, early stage intervention may better position caregivers of cope with dementia progression[25]. When the magnitude of cognitive impairment becomes sufficient to impair daily function, dementia can be diagnosed. Although there is no one agreed-upon definition of early stage dementia, the Clinical Dementia Rating scale[26] score of 1 or the Global Deterioration Scale[27] score of 4 are generally seen as staging tools suggesting early stage dementia. At an early stage of dementia, an individual might continue to live independently with minor assistance. Early stage is, perhaps, best defined as what it is not: it is not functional independence such as is seen in MCI, but it is not consistent with later stages of dementia where an individual would not be able to survive without assistance.

While the utility of early stage intervention for caregivers has been suggested[28], the degree to which interventions of various forms are beneficial to early stage dementia caregivers would benefit from systematic review. This is particularly important due to what Boots and colleagues[29] termed the "early needs paradox", wherein caregivers may not fully recognize their needs and find it difficult to

accept assistance at earlier stages of dementia, yet retrospectively identify early stage support and guidance as crucial. Understanding the benefits of early stage intervention for caregivers will allow for evidence-informed decision making around the provision and timing of support. Our aim is therefore to assess the potential benefits of intervention for caregivers of persons with early stage dementia or MCI, via a systematic review. This protocol follows the PRISMA-P guidelines developed for systematic review and meta-analysis protocols, in order to document and enhance the rigor and transparency of our planned methods, outcomes, and analyses[30]. A record of the protocol has been registered with PROSPERO (#CRD42018114960).

Research questions

To achieve our goal of examining the potential benefits of early stage intervention (i.e., intervention aimed at caregivers of persons with MCI or early dementia), four research questions are being posed: 1) Do interventions aimed at caregivers of persons with early stage dementia or MCI affect their wellbeing and ability to provide care? 2) Are particular types of caregiver interventions more effective than others during early stage cognitive decline? 3) To what extent do benefits to caregivers differ when early and later intervention are directly compared? 4) Is there evidence to suggest that benefits of early stage intervention for caregivers vary based on care recipient and caregiver characteristics (e.g., relationship, sex, type of dementia, rural vs. urban residence, co-morbidities, co- vs. separate residence)?

METHODS AND ANALYSIS

A systematic review was chosen to answer our research questions. Systematic reviews aim to identify, evaluate, and synthesize the findings of all relevant studies, and can identify what we know about the effects of interventions as well as demonstrate where knowledge is lacking[31]. The guidelines set out by the Centre for Reviews and Dissemination (CRD)[31] are informing our review process, which will consist of the identification of research evidence, study selection, data extraction, quality assessment, data synthesis, and evidence grading and conclusions. The planned start date for this review was November 2018, and the estimated date of completion is November 2019.

Patient and Public Involvement

Patients and public were not involved in the development of this systematic review protocol.

Step 1: The identification of research evidence

Information sources

Published peer-reviewed research will be included in this systematic review. Based on the topic of interest, the electronic databases MEDLINE, EMBASE, PSYCINFO, and CINAHL will be searched with no limitations placed on year of publication. This search will be supplemented by scanning the reference

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lists of included studies, to ensure no relevant studies are missed. If the time from search to data analysis exceeds six months, the literature search will be updated within each database. Details of the search process will be documented throughout, for transparency and replication[31]. As suggested by Paez[32], we will be also be searching the following sources of grey literature to identify key studies which may not be published: grey literature databases (Proquest Dissertations & Theses Global, OpenGrey); conference abstracts (of included databases); and clinical trial databases (WHO International Clinical Trials Registry Platform, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, National Institute on Aging Clinical Trials). Due to available resources and feasibility, only English-language studies will be included.

Search strategy

Three main search concepts have been identified as important for this review, namely: dementia/MCI, caregivers, and intervention. Search terms were constructed following a search of previous literature to identify specific terms relevant to these concepts. In order to narrow search outcomes to the topic of interest, terms related to caregiver and intervention will be searched together using the adjacency function, so that articles which use these terms within five words of each other will be identified (the adjacency strategy). Terms incorporating medical subject headings (MeSH), text words, and 'exploded' derivatives related to each concept (the MESH strategy) will be also entered into the included databases using OR. Results from the concepts of dementia/MCI and caregiver interventions (adjacency strategy OR MESH strategy) will then be searched together using AND. The search strategies for each database are being developed by the review team, in consultation with a Health Science Librarian with expertise in systematic reviews. Draft MEDLINE search terms can be viewed in Table 1, and the full strategy in Supplementary file 1. When searching grey literature, we will document the date each database is searched, the search terms used, the number of items retrieved (i.e., search results), and the number of items relevant for screening.

Table 1. Draft Medline search terms

Caregiver terms	Intervention terms	Dementia terms
Caregiver*	Program*	Dement*
Carer*	Intervention*	Alzheimer*
Care partner	Educat*	Lewy* adj2 bod*
Care partners	Support*	Creutzfeldt or jcd or cjd
Care provider	"Social support"	Pick* adj2 disease
Care providers	Resource?	Semantic adj2 dementia

Caregivers/	Therap*	Parkinson* adj2 dementia)
	Respite*	Frontotemporal* adj2 dementia
	Psychosocial	Vascular* adj2 dementia
	Evaluat*	Huntington*
	Counsel*	Primary progressive aphasia?
	Service*	"Mild cognitive impairment"
	"Case management"	MCI
	Health communication/	exp Dementia/
	exp Community health services/	
	Health services for the aged/	
	Early medical intervention/	
	exp Social support/	
	Respite care/	
	Case management/	
	Psychosocial support systems/	
	exp Psychotherapy/	
	Program development/	
	Program evaluation/	

i.   "/" indicates MESH terms.

Step 2: Study selection

Data management

Studies identified in the literature search will be uploaded to Distiller Systematic Review software, which allows multiple reviewers to screen studies simultaneously. This software will also be used to screen for duplicates when studies are uploaded. Using Distiller SR, the first author will create screening forms based on our eligibility criteria to determine inclusion/exclusion. Separate forms will be created for title/abstract (level 1) and full text (level 2) review, and each will be pilot-tested by the first author and refined if needed before independent review commences[31].

Eligibility criteria

Studies will be selected according to the inclusion and exclusion criteria outlined below. No restrictions regarding length/timing of follow-up measurement, or intervention setting, will be placed on studies.

Participants

Participants must be caregivers of people with early stage dementia or MCI, who are living in the community. The dementia may be any form, including Alzheimer's disease, vascular dementia, dementia related to Parkinson's disease, dementia with Lewy bodies, frontotemporal dementia, Creutzfeldt-Jakob disease, and mixed or unspecified dementia; young-onset dementia will also be included. While not all individuals with MCI will progress to dementia, MCI may still be considered a prodromal or "pre-dementia" stage in the context of early stage intervention[25]. Caregivers of persons with MCI will therefore be included based on the characterization of cognitive impairment on a spectrum and the inclusion of MCI in other reviews on early stage dementia interventions[33,34]. Stage of dementia will be assessed based on author description of the sample (e.g., mild/early stage dementia or MCI are inclusion criteria or it is stated that all participants had early stage dementia or MCI), and/or care recipients' cognitive testing scores if reported. Studies will be excluded if caregivers are providing care to individuals who do not have MCI or are not early in the progression of dementia (they are described as having moderate or severe dementia, Clinical Dementia Rating Scale scores >1, Mini-Mental State Examination scores <18, or Global Deterioration scale scores >5), or are a convenience sample of caregivers of individuals across multiple stages of dementia. Studies may compare caregivers of persons with MCI/early stage versus later stage dementia.

Interventions

As identified in previous reviews[35,15], a variety of interventions for caregivers of persons with dementia have been developed and evaluated. All approaches to intervention for caregivers of persons with MCI or early stage dementia will be included in this review, including multicomponent interventions. In order to assess the effects of different types of early stage intervention, interventions will be classified into categories based on their dominant characteristics[15]. For example, programs which focus primarily on formal provision of information and caregiver skills training would be classified as psychoeducational. The study must have a primary focus on supporting caregivers (interventions primarily for the person with dementia or MCI where the caregiver plays a supporting role will not be included).

Comparators

Included studies will include a control or comparison group unless inclusion criteria are relaxed (see Study Design). Comparison groups may include caregivers who did not receive the intervention/received usual care, received it at a different time point (i.e., later in the course of the care recipient's dementia), or received a different type of intervention. Studies may be included if they compare other participant groups who received the intervention (e.g., caregivers of people with other conditions) with early stage dementia or MCI groups.

Outcomes

Included studies must include evaluation of the effectiveness of an intervention for caregivers that is intended to enhance caregiver wellbeing or ability to provide care to the person with dementia or MCI. Although there are many definitions of wellbeing[36], in the current review the term "enhanced wellbeing" is being used to refer to the positive increases in physical, social, psychological, and spiritual domains, and quality of life, that may result from the provision of support and resources to meet caregiver challenges. This inclusive conceptualization of wellbeing is in line with the large variety of definitions (both conceptual and operational) in the literature, and with authors who have theorized that decreased wellbeing occurs when individuals are facing challenges that require additional adaptation and resources to meet[36]. A recent systematic review of reviews illustrated that within the literature on caregivers of persons with dementia, wellbeing is most frequently operationalized as burden, depression, stress, quality of life, physical and mental health, and the caregiver-recipient relationship[14]. Based on their review, the authors suggested that quality of life can be considered one part of wellbeing, along with intrinsic feelings and emotions (positive mental attributes such as self-efficacy, negative mental attributes such as depression, subjective perceptions of one's own health or wellbeing) and what they called "extrinsic factors" (interactions with others, mental or physical health). A variety of relevant outcome variables may be measured in the studies included in our review, including (but not limited to) measures of depression, anxiety, stress, quality of life, physical health, emotional wellbeing, socialization, leisure time, caregiver burden, time until institutionalization of the person with dementia, knowledge regarding caregiving/dementia, and perceived ability to provide care or cope with caregiving demands. All outcome variables relevant to caregiver wellbeing or ability to provide care will be extracted, along with their definition as reported in individual studies.

Study Design

Randomized controlled trials (RCTs) are considered the gold standard in assessing intervention outcomes and will be included in this review, including randomized cross-over trials and cluster randomized trials. However, implementing randomization, blinding, and control groups may be difficult in psychosocial dementia interventions and it is therefore important to consider evidence from other types of study designs[37]. As such, non-randomized studies with a control or comparison group will be included in this review. If few RCT and controlled studies exist, pre-post case series designs (where a group is given an intervention but no comparisons to a control group are made) will also be included due to their frequency of use given the difficulty of conducting randomized and controlled studies in this area. All other designs including qualitative research will be excluded for the purposes of this review.

Selection process

The first author (MB) and another review author will independently screen titles and abstracts of all studies uploaded into Distiller SR, using the Level 1 form. This form will be used to screen for articles that report on interventions for caregivers aimed at enhancing caregiver wellbeing or ability to provide care to recipients with dementia or MCI, and initial screening for study design. As suggested by CRD guidelines[31], reviewers will err on the side of inclusion during title and abstract review. Studies that appear to meet inclusion criteria, or those where inclusion is uncertain, will progress to Level 2 and full texts will be obtained. The first author and a second reviewer will then screen the full text reports to determine whether they meet the inclusion criteria. Level two screening will include screening for stage of cognitive impairment, as identified by the authors (e.g., "participants all had early stage dementia") and/or cognitive testing scores. DistillerAI, which is the software's language processing technology, may be used to check for accidental exclusions. Disagreements at both stages of review will be resolved through discussion, and a third author (DM) will be consulted in cases where an agreement is not reached. During full-text review, the reason for exclusion will be documented for each study. The reviewers will not be blind to study titles, authors, or institutions, which is considered acceptable during study selection[31]. A PRISMA flow chart[38] documenting the number of studies at each stage of the selection process and reasons for full text exclusion will be created.

Step 3: Data extraction

Extraction process

An electronic data extraction form will be created based on the items of interest described below (see sample extraction form in Supplementary File 2). Guidelines for data extraction may also be developed to facilitate standardization of the process. The extraction form will be piloted on a small sample of included studies, and refined as necessary. Where reported, data will be extracted into this form for each study by the first author and a second reviewer (JK), in order to reduce errors and missed information[39]. Any disagreements will be discussed and resolved among the review team. As per CRD recommendations[31], multiple reports of the same study (e.g., a preliminary sample followed by the total sample) will be treated as one study for data extraction to reduce biased results. Authors of included studies may be contacted by email to confirm uncertainties or for additional information.

Data items

The following information will be extracted about the study, intervention, and sample:

1) General information: author/s; year; title of the article; source of funding; geographic location of the study (country)

2) Intervention characteristics: criteria distinguishing the intervention as early-stage; intervention name, description, type, and theoretical basis (where relevant); length of intervention, setting in which the intervention is delivered

3) Study characteristics: objectives of the study; study design; recruitment procedures including inclusion and exclusion criteria, comparator group; sample size for each group

4) Participant characteristics (total sample, intervention group, and comparator group/s):

   a. Caregiver characteristics: rural vs. urban; sex; relationship of caregiver to care recipient; definition of caregiver; time spent caregiving; primary caregiver status; lives with care recipient

   b. Care recipient characteristics: rural vs. urban; sex; type of dementia; cognitive testing scores; co-morbidities

Outcomes

Caregiver wellbeing and ability to provide care may be operationalized in a number of ways; the main outcome variables we are interested in are caregiver burden and depression (given their importance and prevalence in this population and the literature), self-reported quality of life, and perceived ability to provide care. All other variables related to wellbeing and ability to provide care will be considered secondary outcome variables. When extracting data related to these outcomes, time until intervention follow-up and additional follow-up measurements will be charted. The measurement tool or measurement used for each relevant outcome variable will be recorded, as will the statistical techniques used for analysis. Raw means (with standard deviations), change scores, and statistical outcomes will be extracted for each measure pertaining to wellbeing and ability to provide care. As data is extracted, statistical information from studies will be used to calculate standardized mean differences (or odds ratios if relevant, e.g. for risk of institutionalization). This will allow for comparison between variations in measures of effects across individual studies, and helps account for differences in sample sizes that affect statistical significance[40].

Another goal of this review is to assess whether benefits differ between early and later-stage intervention; all statistical summary and outcome information will be extracted if studies compare the effects of early to later intervention. Finally, we are interested in assessing whether benefits of early stage intervention vary based on care recipient and caregiver characteristics (e.g., sex, type of dementia, rural versus urban residence). All summary data and statistical outcomes pertaining to comparisons of intervention effects between subgroups of caregivers or care recipients will be extracted. These comparisons may be based on the factors noted above which are of particular interest, but may also

include other factors (e.g., caregiver personality, socioeconomic status). Additional outcomes (those not pertaining to the foci of this review) reported in the article and other information of interest will be recorded narratively without statistical information. We would like to note that while care recipient outcomes of early stage caregiver intervention are also important, they are not included in the current review given our already broad focus and feasibility constraints. The potential impacts of early caregiver interventions on care recipients is a topic that should be addressed in a future review.

Step 4: Quality assessment

Quality will be assessed to inform conclusions about the effectiveness of early stage intervention with caregivers based on how the study was carried out, not to inform inclusion/exclusion in the review. This means that studies will not be excluded based on poor quality. Potential bias (systematic deviations from the "true" effect due to poor study design or implementation) is important to examine, since it can alter findings of effect and explain different findings between studies assessing the same intervention[31]. To assess the possible risk of bias for each included RCT, we will use the Cochrane Risk of Bias Tool for Randomized Controlled Trials (Table 8.5 in the Cochrane Handbook for Systematic Reviews of Interventions)[41]. This tool assesses five types of potential bias: selection bias, performance bias, detection bias, attrition bias, and reporting bias, as well as additional concerns about bias not addressed by these domains. Based on information in each article, a judgment will be made according to the Cochrane criteria on whether the study is at low risk, high risk, or unclear risk of bias. As suggested in the Cochrane Handbook[41], this tool can also be used for intervention studies that include a control group but are not randomized.

Pre-post case series studies may be included if few RCTs and controlled studies meet inclusion criteria. If these studies are included, the Institute of Health Economics' Quality Appraisal Checklist for Case Series Studies will be used to assess their quality, including risk of bias. This tool has been initially validated and consists of twenty items covering both risk of bias (e.g., pre- and post- outcome measurement, sufficient follow-up, method for recruitment of participants) and quality of reporting (e.g., description of patient characteristics, report of any co-interventions, report of any adverse outcomes)[42]. Based on previous use, a point will be given for every "yes" answer so that studies of higher quality (including lower risk of bias) will have a higher overall score out of 20, while those of lower quality (and higher risk of bias) will have lower scores. Quality assessment will be carried out for each study included in the review.

Step 5: Data synthesis

We anticipate that multiple types of early stage intervention will be covered in our systematic review, and that studies will report on various outcomes related to wellbeing and ability to provide care. Because of this expected heterogeneity, a narrative synthesis is planned[31,43]. A narrative synthesis relies primarily on textual description to analyze and describe the findings from included studies[43]. Extracted data will be examined for potential relationships between results and key aspects of the studies, and across studies (e.g., sample characteristics, outcomes measured, and intervention characteristics). Explanations for why early stage interventions are effective are also of interest. Studies will be separated into groups based on type of early stage intervention, in order to better address our second research question (whether effectiveness varies depending on intervention type). Key elements from each study will be presented in summary tables, including results and effect sizes. If studies within intervention subgroups are homogenous enough, statistical pooling of data will be performed through meta-analysis. If relevant evidence exists, differences in effectiveness based on timing of intervention and caregiver or care recipient characteristics will be assessed and presented. Risk of bias assessments will be used to contextualize findings, evaluate the state of the literature, and explain potential differences in results across studies.

Step 6: Evidence grading and conclusions

Meta-biases

Unpublished literature is included in this review in an attempt to minimize publication bias. When using the Risk of Bias tool, selective reporting (another area of meta-bias) will be assessed. This will be facilitated by comparing published studies with their protocols when possible, and assessing the degree to which data is reported for relevant outcomes including findings that are not statistically significant.

Confidence in cumulative evidence

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach will be used to rate the evidence regarding the effectiveness of early stage intervention for caregivers on their wellbeing and ability to provide care to a person living with MCI or dementia. GRADE involves risk of bias assessment but also assessments of imprecision, inconsistency, indirectness, and publication bias. This framework allows informed judgements to be made about the quality of the body of evidence that is being examined[44]: whether we can be confident it accurately represents the true effects of early caregiver interventions. The quality grade (very low, low, moderate, high) helps inform overall conclusions about the state of evidence for each outcome under review.

<div align="center">

ETHICS AND DISSEMINATION

</div>

Findings from this review will be shared via conference proceedings and peer-reviewed publication, and a summary to the Alzheimer's Society. A full list of relevant studies that do not have data included in the review (e.g., in-progress protocols) will be created and available upon request. Findings may help inform the use of interventions for caregivers early in the course of the care recipient's cognitive decline.

Data Statement: All data that will be included in this systematic review will be taken from previously published articles or works (e.g., dissertations) found in databases.

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Medline search strategy

1. ((caregiver* or carer* or "care partner" or "care partners" or "care provider" or "care providers") adj5 (program* or intervention or educat* or support* or therap* or respite* or psychosocial or evaluat* or "case management" or counsel* or service*)).tw.

2. caregivers/

3. (program* or intervention*or education* or resource? or "social support" or respite).mp. or "case management".tw.

4. health communication/ or exp community health services/ or health services for the aged/ or early medical intervention/

5. exp social support/

6. RESPITE CARE/

7. Case Management/

8. PSYCHOSOCIAL SUPPORT SYSTEMS/

9. exp psychotherapy/

10. Program Development/ or Program Evaluation/

11. 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

12. 2 and 11

13. dement*.mp.

14. alzheimer*.mp.

15. (lewy* adj2 bod*).mp.

16. (creutzfeldt or jcd or cjd).mp.

17. (pick* adj2 disease).mp.

18. ((semantic or vascular or fronto-temporal* or Parkinson*) adj2 dementia).mp.

19. huntington*.mp.

20. primary progressive aphasia?.mp.

21. exp dementia/

22. "mild cognitive impairment".mp.

23. MCI.mp.

24. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23

25. 1 or 12

26. 24 and 25

No restrictions were placed on this search.

1

<u>Data Extraction Form</u>

General Study Information

Author/s:

Year:

Title of the article:

Funding source:

Geographic location (country):

Intervention Characteristics

Classified as "early intervention" based on:

Name of intervention:

Brief description of intervention:

Type of intervention:
(Psychosocial, cognitive-behavioural, counseling,
case management, respite, support, multi-component)
    Type of intervention specified in article or during extraction:

Theoretical basis of intervention:

Length of intervention:

Intervention setting for delivery:

Study Characteristics:

Objectives:

Design:
    Design specified in article or during extraction:

Recruitment procedures:

    Inclusion criteria:

    Exclusion criteria:

2

Comparator group/s:

Sample size of main intervention group:
(actually measured)

Sample size of comparator group/s:
(actually measured)

Participant Characteristics (for total sample; repeat for intervention and comparator groups if possible)

Caregivers:

Definition of "caregiver":

Geographic location:
(rural/urban; frequencies)

Caregiver sex:
(frequencies)

Relationship of caregiver to care recipient:
(frequencies)

Time spent caregiving (record both time in months/years and time per week/day)
(mean)

Primary caregiver status reported? (Yes/no)
(frequencies if available)

Lives in same dwelling as care recipient
(frequencies)

Care recipients:

Geographic location:
(rural/urban; frequencies)

Care recipient sex:
(frequencies)

Type of dementia:
(frequencies)

3

Co-morbidities:
(frequencies or mean)

Type of cognitive testing scores and reported mean or category:

Outcome Information:

For EACH relevant measurement of intervention effect:

Construct measured:

Length of time after intervention before first follow-up:

Additional follow up measurements:
(time)

Measurement tool:

Statistical techniques used for analysis:

Raw mean and standard deviation at each measurement point, intervention group:
(frequencies if applicable)

Raw mean and standard deviation at each measurement point, comparator:
(frequencies if applicable)

Change scores (if applicable), intervention group:

Change scores (if applicable), comparator group:

Statistical outcome/s:
(include p-value)

Confidence intervals:

Effect size:
(reported or calculated standardized mean difference)

Comparison between the effect of early and later intervention:

Timing of intervention, "early" group:

Timing of intervention, "later" group:

4

Outcome measured:

Measurement tool:

Statistical techniques used for analysis:

Raw mean and standard deviation at each measurement point, early group:
(frequencies if applicable)

Raw mean and standard deviation at each measurement point, later group/s:
(frequencies if applicable)

Change scores, early group (if applicable):

Change scores, later group:

Statistical outcome/s of comparisons:
(include p-value)

Confidence intervals:

Effect size:
(reported or calculated standardized mean difference)

For EACH comparison of intervention effect between subgroups of caregivers

Care recipient or caregiver characteristic examined:

Construct measured:

Measurement tool:

Statistical techniques used for analysis:

Raw mean and standard deviation at each measurement point,
group 1 (repeat for each group being compared):
(frequencies if applicable)

Change scores, group 1 (repeat for each group being compared):

Statistical outcome/s of comparisons:
(include p-value)

Confidence intervals:

Effect size:
(reported or calculated standardized mean difference)

Additional outcomes assessed *(i.e., not measures of wellbeing or ability to provide care. List/describe)*:

Other information of interest to this review:

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review (Title (p 1), Abstract (p 2), Page 5)
Update	1b	If the protocol is for an update of a previous systematic review, identify as such NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number (Page 5)
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author (Page 1)
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review (Page 14)
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments NA
Support:		
Sources	5a	Indicate sources of financial or other support for the review (Page 14)
Sponsor	5b	Provide name for the review funder and/or sponsor (Page 14)
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol (Page 14)
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known (Page 3-5)
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) (Page 5)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review (Page 5-10)
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage (Page 5-6)
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated (Supplementary File 1)
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review (Page 7)

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) (Page 7, Page 10)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators (Page 10-11)
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications (Supplementary File 2, Page 10-11)
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale (Page 9, 11-12)
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis (Page 12-13)
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised (Page 13)
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) (Page 13)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) (Page 13)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned (Page 13)
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)(Page 13)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) (Page 13)

* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Protocol for a systematic review on interventions for caregivers of persons with mild cognitive impairment and early dementia: Does early stage intervention improve caregiver wellbeing and ability to provide care?

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028441.R2
Article Type:	Protocol
Date Submitted by the Author:	12-Apr-2019
Complete List of Authors:	Bayly, Melanie; University of Saskatchewan, Canadian Centre for Health and Safety in Agriculture Morgan, Debra; University of Saskatchewan, Centre for Health and Safety in Agriculture Kosteniuk, Julie; University of Saskatchewan, Canadian Centre for Health and Safety in Agriculture Elliot, Valerie; University of Saskatchewan, Canadian Centre for Health and Safety in Agriculture Froehlich Chow, Amanda; University of Saskatchewan, Canadian Centre for Health and Safety in Agriculture Peacock, Shelley; University of Saskatchewan, Nursing McLean, Allen; University of Saskatchewan, College of Medicine O'Connell, Megan; University of Saskatchewan, Psychology
Primary Subject Heading:	Health services research
Secondary Subject Heading:	Health services research
Keywords:	caregivers, early intervention, Dementia < NEUROLOGY, MCI

SCHOLARONE™
Manuscripts

TITLE: Protocol for a systematic review on interventions for caregivers of persons with mild cognitive impairment and early dementia: Does early stage intervention improve caregiver wellbeing and ability to provide care?

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Word Count: 3734

ABSTRACT

Introduction:

Caregivers of persons with dementia and mild cognitive impairment (MCI) are at risk of decreased wellbeing. While many interventions for caregivers exist, evidence is sparse regarding intervention timing and effectiveness at an early stage of cognitive decline. Our systematic review aims to answer the following questions: 1) Do interventions for caregivers of persons with early stage dementia or MCI affect their wellbeing and ability to provide care? 2) Are particular types of caregiver interventions most effective during early stage cognitive decline? 3) How does effectiveness differ when early and later intervention are directly compared? 4) Do effects of early stage caregiver intervention vary based on care recipient and caregiver characteristics (e.g., sex, type of dementia)?

Methods and analysis:

The databases MEDLINE, EMBASE, PSYCINFO, and CINAHL, as well as grey literature databases, will be searched for English language studies using search terms related to caregiver interventions and dementia/MCI. Abstracts and full-texts will be screened by two independent reviewers; included studies must assess the effects of an intervention for caregivers of persons with early-stage dementia or MCI on caregiver wellbeing or ability to provide care. Intervention, study, and participant characteristics will be extracted by two independent reviewers, along with outcome data. Risk of bias will be assessed using the Cochrane Risk of Bias tool (for controlled trials with and without randomization). Interventions will be grouped by type (e.g., psychoeducational) and a narrative synthesis is planned due to expected heterogeneity, but meta-analysis will be performed where possible. The GRADE approach will be used to inform conclusions regarding the quality of evidence for each type of intervention.

Ethics and dissemination:

Findings from this review will be disseminated via conferences and peer-reviewed publication, and a summary will be provided to the Alzheimer Society.

Registration: This review protocol has been registered with PROSPERO (#CRD42018114960).

Keywords: caregivers, early intervention, early stage/mild dementia, MCI

ARTICLE SUMMARY

Strengths and Limitations of this study:

-This work addresses intervention timing and the effectiveness of early stage intervention for caregivers of persons with dementia, which is a meaningful gap in this body of literature.

-This review will involve a rigorous search and screening process, to maximize comprehensiveness and minimize bias.

3

-Many different types of caregiver interventions will be included for review, and significant heterogeneity may limit our ability to conduct statistical meta-analyses of effects.

-A strength of this review will be the consideration of findings in relation to assessment of bias and evidence GRADEing; this will help inform conclusions about the state of evidence for the effectiveness of early stage intervention on included outcomes.

4

INTRODUCTION

Informal caregivers are relatives, partners, friends, or neighbours who have a personal relationship with a person with a chronic or disabling condition, and provide various types of assistance to that person[1]. The majority of care recipients with dementia receive assistance (such as with basic and instrumental activities of daily living and general supervision) from multiple informal caregivers, with one person assuming a primary caregiver role[2]. A recent review suggests that informal caregivers of persons with Alzheimer's disease provide an average of 56 hours of assistance per week[3]. Informal caregivers spend significantly more time providing care when they are a spouse/partner of the care recipient, and when the care recipient's functional status is worse or their dementia is more severe[2,3].

Psychological issues such as general distress, depression, and anxiety are common among family caregivers of persons with dementia[4-6]. Moreover, a growing body of research suggests that caregiving to a person with dementia negatively affects the caregiver's sleep quality, cognitive functioning, and physiological health (particularly in relation to markers of immune function, cellular aging, and cardiovascular risk factors)[7]. It is also well established in the literature that informal caregivers of persons with dementia are at risk of experiencing caregiver burden[8,9]. Caregiver burden may be best understood as a multidimensional construct reflecting caregiver struggles with financial, physical, social, psychological/emotional, and developmental wellbeing (perceptions of being "on time" in life circumstances, compared to peers), as well as challenges navigating caring demands and restrictions[10,11]. However, it is important to note that there is heterogeneity among definitions of caregiver burden in the literature, along with inconsistencies in which elements of the concept are included across different measurement tools[12,13]. The burden experienced by dementia caregivers is most frequently measured using the Zarit Burden Interview[14] (ZBI), which a recent factor analysis suggests measures three main dimensions: social consequences for the caregiver, psychological burden, and feelings of guilt[10]. The common use of the ZBI means that operationalization of caregiver burden is often capturing emotional and psychological responses to caregiving, and social restrictions associated with this role, although this does not preclude the existence of other types of burden. In fact, it has been argued that assessing burden quantitatively fails to capture all elements of caregivers' experiences of the phenomenon, and that cultural context is crucial to how caregivers experience and communicate burden[12,13]. Despite critiques of the concept of caregiver burden[12], it is a significant concern and thus remains a main focus within many caregiver studies. Although there are also gratifying and positive aspects of caregiving for many caregivers of persons with dementia[15], they are often considered a vulnerable population due to the intensity of caring demands, and risk of burden and other negative consequences. This perspective is

reflected in the literature on caregiver wellbeing, which primarily focuses on deficits and how to ameliorate negative caregiver outcomes[16].

Many interventions have been developed to support caregivers of persons with dementia, and enhance both caregiver wellbeing and ability to provide care. A variety of approaches including psychoeducational, cognitive-behavioral therapy, counseling, case management, respite, and general support interventions have been implemented with caregivers of persons with dementia, as well as interventions which combine approaches (i.e., multi-component interventions)[17]. Previous reviews and meta-analyses have demonstrated the effectiveness of many caregiver interventions on a variety of outcomes, although interventions may have only domain-specific effects (e.g., on caregiver depression) and evidence suggests that some types of interventions (e.g., multicomponent and psychoeducational) may be the most beneficial[17-20]. Moreover, effectiveness of these interventions has been found to vary according to caregiver and care recipient characteristics, such as caregiver sex, relationship to the care recipient, and type and severity of dementia[21].

Another factor that may be very important when examining caregiver intervention effectiveness is the timing of intervention: whether it begins early or later in the course of the care recipient's cognitive decline. Few systematic reviews have distinguished between people at different stages of dementia, and Thompson et al.[22] identified intervention timing as a fundamental question for future research in the area. The effects of some caregiver interventions may be greater depending on their timing; Andrén and Elmståhl[23] found that a psychosocial intervention conferred greater benefit to caregivers' wellbeing when provided early in the progression of dementia. Dementia is a progressive illness and can begin with cognitive impairment, but no functional impairment; this is conceptualized as mild cognitive impairment (MCI)[24,25]. Although less instrumental caregiving support is required for persons with MCI, their caregivers are still at risk of experiencing burden and depression[26] which indicates the potential utility of interventions at this stage. Moreover, early stage intervention may better position caregivers of cope with dementia progression[27]. When the magnitude of cognitive impairment becomes sufficient to impair daily function, dementia can be diagnosed. Although there is no one agreed-upon definition of early stage dementia, the Clinical Dementia Rating scale[28] score of 1 or the Global Deterioration Scale[29] score of 4 are generally seen as staging tools suggesting early stage dementia. At an early stage of dementia, an individual might continue to live independently with minor assistance. Early stage is, perhaps, best defined as what it is not: it is not functional independence such as is seen in MCI, but it is not consistent with later stages of dementia where an individual would not be able to survive without assistance.

While the utility of early stage intervention for caregivers has been suggested[30], the degree to which interventions of various forms are beneficial to early stage dementia caregivers would benefit from systematic review. This is particularly important due to what Boots and colleagues[31] termed the "early needs paradox", wherein caregivers may not fully recognize their needs and find it difficult to accept assistance at earlier stages of dementia, yet retrospectively identify early stage support and guidance as crucial. Understanding the benefits of early stage intervention for caregivers will allow for evidence-informed decision making around the provision and timing of support. Our aim is therefore to assess the potential benefits of intervention for caregivers of persons with early stage dementia or MCI, via a systematic review. This protocol follows the PRISMA-P guidelines developed for systematic review and meta-analysis protocols, in order to document and enhance the rigor and transparency of our planned methods, outcomes, and analyses[32]. A record of the protocol has been registered with PROSPERO (#CRD42018114960).

Research questions

To achieve our goal of examining the potential benefits of early stage intervention (i.e., intervention aimed at caregivers of persons with MCI or early dementia), four research questions are being posed: 1) Do interventions aimed at caregivers of persons with early stage dementia or MCI affect their wellbeing and ability to provide care? 2) Are particular types of caregiver interventions more effective than others during early stage cognitive decline? 3) To what extent do benefits to caregivers differ when early and later intervention are directly compared? 4) Is there evidence to suggest that benefits of early stage intervention for caregivers vary based on care recipient and caregiver characteristics (e.g., relationship, sex, type of dementia, rural vs. urban residence, co-morbidities, co- vs. separate residence)?

METHODS AND ANALYSIS

A systematic review was chosen to answer our research questions. Systematic reviews aim to identify, evaluate, and synthesize the findings of all relevant studies, and can identify what we know about the effects of interventions as well as demonstrate where knowledge is lacking[33]. The guidelines set out by the Centre for Reviews and Dissemination (CRD)[33] are informing our review process, which will consist of the identification of research evidence, study selection, data extraction, quality assessment, data synthesis, and evidence grading and conclusions. The planned start date for this review was November 2018, and the estimated date of completion is November 2019.

Patient and Public Involvement

Patients and public were not involved in the development of this systematic review protocol.

Step 1: The identification of research evidence

Information sources

Published peer-reviewed research will be included in this systematic review. Based on the topic of interest, the electronic databases MEDLINE, EMBASE, PSYCINFO, and CINAHL will be searched with no limitations placed on year of publication. This search will be supplemented by scanning the reference lists of included studies, to ensure no relevant studies are missed. If the time from search to data analysis exceeds six months, the literature search will be updated within each database. Details of the search process will be documented throughout, for transparency and replication[33]. As suggested by Paez[34], we will be also be searching the following sources of grey literature to identify key studies which may not be published: grey literature databases (Proquest Dissertations & Theses Global, OpenGrey); conference abstracts (of included databases); and clinical trial databases (WHO International Clinical Trials Registry Platform, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, National Institute on Aging Clinical Trials). Due to available resources and feasibility, only English-language studies will be included.

Search strategy

Three main search concepts have been identified as important for this review, namely: dementia/MCI, caregivers, and intervention. Search terms were constructed following a search of previous literature to identify specific terms relevant to these concepts. In order to narrow search outcomes to the topic of interest, terms related to caregiver and intervention will be searched together using the adjacency function, so that articles which use these terms within five words of each other will be identified (the adjacency strategy). Terms incorporating medical subject headings (MeSH), text words, and 'exploded' derivatives related to each concept (the MESH strategy) will be also entered into the included databases using OR. Results from the concepts of dementia/MCI and caregiver interventions (adjacency strategy OR MESH strategy) will then be searched together using AND. The search strategies for each database are being developed by the review team, in consultation with a Health Science Librarian with expertise in systematic reviews. Draft MEDLINE search terms can be viewed in Table 1, and the full strategy in Supplementary file 1. When searching grey literature, we will document the date each database is searched, the search terms used, the number of items retrieved (i.e., search results), and the number of items relevant for screening.

Table 1. Draft Medline search terms

Caregiver terms	Intervention terms	Dementia terms
Caregiver*	Program*	Dement*
Carer*	Intervention*	Alzheimer*

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Care partner	Educat*	Lewy* adj2 bod*
Care partners	Support*	Creutzfeldt or jcd or cjd
Care provider	"Social support"	Pick* adj2 disease
Care providers	Resource?	Semantic adj2 dementia
Caregivers/	Therap*	Parkinson* adj2 dementia)
	Respite*	Frontotemporal* adj2 dementia
	Psychosocial	Vascular* adj2 dementia
	Evaluat*	Huntington*
	Counsel*	Primary progressive aphasia?
	Service*	"Mild cognitive impairment"
	"Case management"	MCI
	Health communication/	exp Dementia/
	exp Community health services/	
	Health services for the aged/	
	Early medical intervention/	
	exp Social support/	
	Respite care/	
	Case management/	
	Psychosocial support systems/	
	exp Psychotherapy/	
	Program development/	
	Program evaluation/	

i.   "/" indicates MESH terms.

Step 2: Study selection

Data management

Studies identified in the literature search will be uploaded to Distiller Systematic Review software, which allows multiple reviewers to screen studies simultaneously. This software will also be used to screen for duplicates when studies are uploaded. Using Distiller SR, the first author will create screening forms based on our eligibility criteria to determine inclusion/exclusion. Separate forms will be created for title/abstract (level 1) and full text (level 2) review, and each will be pilot-tested by the first author and refined if needed before independent review commences[33].

Eligibility criteria

Studies will be selected according to the inclusion and exclusion criteria outlined below. No restrictions regarding length/timing of follow-up measurement, or intervention setting, will be placed on studies.

Participants

Participants must be caregivers of people with early stage dementia or MCI, who are living in the community. The dementia may be any form, including Alzheimer's disease, vascular dementia, dementia related to Parkinson's disease, dementia with Lewy bodies, frontotemporal dementia, Creutzfeldt-Jakob disease, and mixed or unspecified dementia; young-onset dementia will also be included. While not all individuals with MCI will progress to dementia, MCI may still be considered a prodromal or "pre-dementia" stage in the context of early stage intervention[27]. Caregivers of persons with MCI will therefore be included based on the characterization of cognitive impairment on a spectrum and the inclusion of MCI in other reviews on early stage dementia interventions[35,36]. Stage of dementia will be assessed based on author description of the sample (e.g., mild/early stage dementia or MCI are inclusion criteria or it is stated that all participants had early stage dementia or MCI), and/or care recipients' cognitive testing scores if reported. Studies will be excluded if caregivers are providing care to individuals who do not have MCI or are not early in the progression of dementia (they are described as having moderate or severe dementia, Clinical Dementia Rating Scale scores >1, Mini-Mental State Examination scores <18, or Global Deterioration scale scores >5), or are a convenience sample of caregivers of individuals across multiple stages of dementia. Studies may compare caregivers of persons with MCI/early stage versus later stage dementia.

Interventions

As identified in previous reviews[37,17], a variety of interventions for caregivers of persons with dementia have been developed and evaluated. All approaches to intervention for caregivers of persons with MCI or early stage dementia will be included in this review, including multicomponent interventions. In order to assess the effects of different types of early stage intervention, interventions will be classified into categories based on their dominant characteristics[17]. For example, programs which focus primarily on formal provision of information and caregiver skills training would be classified as psychoeducational. The study must have a primary focus on supporting caregivers (interventions primarily for the person with dementia or MCI where the caregiver plays a supporting role will not be included).

Comparators

Included studies will include a control or comparison group unless inclusion criteria are relaxed (see Study Design). Comparison groups may include caregivers who did not receive the intervention/received usual care, received it at a different time point (i.e., later in the course of the care recipient's dementia),

or received a different type of intervention. Studies may be included if they compare other participant groups who received the intervention (e.g., caregivers of people with other conditions) with early stage dementia or MCI groups.

Outcomes

Included studies must include evaluation of the effectiveness of an intervention for caregivers that is intended to enhance caregiver wellbeing or ability to provide care to the person with dementia or MCI. Although there are many definitions of wellbeing[38], in the current review the term "enhanced wellbeing" is being used to refer to the positive increases in physical, social, psychological, and spiritual domains, and quality of life, that may result from the provision of support and resources to meet caregiver challenges. This inclusive conceptualization of wellbeing is in line with the large variety of definitions (both conceptual and operational) in the literature, and with authors who have theorized that decreased wellbeing occurs when individuals are facing challenges that require additional adaptation and resources to meet[38]. A recent systematic review of reviews illustrated that within the literature on caregivers of persons with dementia, wellbeing is most frequently operationalized as burden, depression, stress, quality of life, physical and mental health, and the caregiver-recipient relationship[16]. Based on their review, the authors suggested that quality of life can be considered one part of wellbeing, along with intrinsic feelings and emotions (positive mental attributes such as self-efficacy, negative mental attributes such as depression, subjective perceptions of one's own health or wellbeing) and what they called "extrinsic factors" (interactions with others, mental or physical health). A variety of relevant outcome variables may be measured in the studies included in our review, including (but not limited to) measures of depression, anxiety, stress, quality of life, physical health, emotional wellbeing, socialization, leisure time, caregiver burden, time until institutionalization of the person with dementia, knowledge regarding caregiving/dementia, and perceived ability to provide care or cope with caregiving demands. All outcome variables relevant to caregiver wellbeing or ability to provide care will be extracted, along with their definition as reported in individual studies.

Study Design

Randomized controlled trials (RCTs) are considered the gold standard in assessing intervention outcomes and will be included in this review, including randomized cross-over trials and cluster randomized trials. However, implementing randomization, blinding, and control groups may be difficult in psychosocial dementia interventions and it is therefore important to consider evidence from other types of study designs[39]. As such, non-randomized studies with a control or comparison group will be included in this review. If few RCT and controlled studies exist, pre-post case series designs (where a

group is given an intervention but no comparisons to a control group are made) will also be included due to their frequency of use given the difficulty of conducting randomized and controlled studies in this area. All other designs including qualitative research will be excluded for the purposes of this review.

Selection process

The first author (MB) and another review author will independently screen titles and abstracts of all studies uploaded into Distiller SR, using the Level 1 form. This form will be used to screen for articles that report on interventions for caregivers aimed at enhancing caregiver wellbeing or ability to provide care to recipients with dementia or MCI, and initial screening for study design. As suggested by CRD guidelines[33], reviewers will err on the side of inclusion during title and abstract review. Studies that appear to meet inclusion criteria, or those where inclusion is uncertain, will progress to Level 2 and full texts will be obtained. The first author and a second reviewer will then screen the full text reports to determine whether they meet the inclusion criteria. Level two screening will include screening for stage of cognitive impairment, as identified by the authors (e.g., "participants all had early stage dementia") and/or cognitive testing scores. DistillerAI, which is the software's language processing technology, may be used to check for accidental exclusions. Disagreements at both stages of review will be resolved through discussion, and a third author (DM) will be consulted in cases where an agreement is not reached. During full-text review, the reason for exclusion will be documented for each study. The reviewers will not be blind to study titles, authors, or institutions, which is considered acceptable during study selection[33]. A PRISMA flow chart[40] documenting the number of studies at each stage of the selection process and reasons for full text exclusion will be created.

Step 3: Data extraction

Extraction process

An electronic data extraction form will be created based on the items of interest described below (see sample extraction form in Supplementary File 2). Guidelines for data extraction may also be developed to facilitate standardization of the process. The extraction form will be piloted on a small sample of included studies, and refined as necessary. Where reported, data will be extracted into this form for each study by the first author and a second reviewer (JK), in order to reduce errors and missed information[41]. Any disagreements will be discussed and resolved among the review team. As per CRD recommendations[33], multiple reports of the same study (e.g., a preliminary sample followed by the total sample) will be treated as one study for data extraction to reduce biased results. Authors of included studies may be contacted by email to confirm uncertainties or for additional information.

Data items

The following information will be extracted about the study, intervention, and sample:

1) General information: author/s; year; title of the article; source of funding; geographic location of the study (country)

2) Intervention characteristics: criteria distinguishing the intervention as early-stage; intervention name, description, type, and theoretical basis (where relevant); length of intervention, setting in which the intervention is delivered

3) Study characteristics: objectives of the study; study design; recruitment procedures including inclusion and exclusion criteria, comparator group; sample size for each group

4) Participant characteristics (total sample, intervention group, and comparator group/s):
   a. Caregiver characteristics: rural vs. urban; sex; relationship of caregiver to care recipient; definition of caregiver; time spent caregiving; primary caregiver status; lives with care recipient
   b. Care recipient characteristics: rural vs. urban; sex; type of dementia; cognitive testing scores; co-morbidities

Outcomes

Caregiver wellbeing and ability to provide care may be operationalized in a number of ways; the main outcome variables we are interested in are caregiver burden and depression (given their importance and prevalence in this population and the literature), self-reported quality of life, and perceived ability to provide care. All other variables related to wellbeing and ability to provide care will be considered secondary outcome variables. When extracting data related to these outcomes, time until intervention follow-up and additional follow-up measurements will be charted. The measurement tool or measurement used for each relevant outcome variable will be recorded, as will the statistical techniques used for analysis. Raw means (with standard deviations), change scores, and statistical outcomes will be extracted for each measure pertaining to wellbeing and ability to provide care. As data is extracted, statistical information from studies will be used to calculate standardized mean differences (or odds ratios if relevant, e.g. for risk of institutionalization). This will allow for comparison between variations in measures of effects across individual studies, and helps account for differences in sample sizes that affect statistical significance[42].

Another goal of this review is to assess whether benefits differ between early and later-stage intervention; all statistical summary and outcome information will be extracted if studies compare the effects of early to later intervention. Finally, we are interested in assessing whether benefits of early

stage intervention vary based on care recipient and caregiver characteristics (e.g., sex, type of dementia, rural versus urban residence). All summary data and statistical outcomes pertaining to comparisons of intervention effects between subgroups of caregivers or care recipients will be extracted. These comparisons may be based on the factors noted above which are of particular interest, but may also include other factors (e.g., caregiver personality, socioeconomic status). Additional outcomes (those not pertaining to the foci of this review) reported in the article and other information of interest will be recorded narratively without statistical information. We would like to note that while care recipient outcomes of early stage caregiver intervention are also important, they are not included in the current review given our already broad focus and feasibility constraints. The potential impacts of early caregiver interventions on care recipients is a topic that should be addressed in a future review.

Step 4: Quality assessment

Quality will be assessed to inform conclusions about the effectiveness of early stage intervention with caregivers based on how the study was carried out, not to inform inclusion/exclusion in the review. This means that studies will not be excluded based on poor quality. Potential bias (systematic deviations from the "true" effect due to poor study design or implementation) is important to examine, since it can alter findings of effect and explain different findings between studies assessing the same intervention[33]. To assess the possible risk of bias for each included RCT, we will use the Cochrane Risk of Bias Tool for Randomized Controlled Trials (Table 8.5 in the Cochrane Handbook for Systematic Reviews of Interventions)[43]. This tool assesses five types of potential bias: selection bias, performance bias, detection bias, attrition bias, and reporting bias, as well as additional concerns about bias not addressed by these domains. Based on information in each article, a judgment will be made according to the Cochrane criteria on whether the study is at low risk, high risk, or unclear risk of bias. As suggested in the Cochrane Handbook[43], this tool can also be used for intervention studies that include a control group but are not randomized.

Pre-post case series studies may be included if few RCTs and controlled studies meet inclusion criteria. If these studies are included, the Institute of Health Economics' Quality Appraisal Checklist for Case Series Studies will be used to assess their quality, including risk of bias. This tool has been initially validated and consists of twenty items covering both risk of bias (e.g., pre- and post- outcome measurement, sufficient follow-up, method for recruitment of participants) and quality of reporting (e.g., description of patient characteristics, report of any co-interventions, report of any adverse outcomes)[44]. Based on previous use, a point will be given for every "yes" answer so that studies of higher quality (including lower risk of bias) will have a higher overall score out of 20, while those of

lower quality (and higher risk of bias) will have lower scores. Quality assessment will be carried out for each study included in the review.

Step 5: Data synthesis

We anticipate that multiple types of early stage intervention will be covered in our systematic review, and that studies will report on various outcomes related to wellbeing and ability to provide care. Because of this expected heterogeneity, a narrative synthesis is planned[33,45]. A narrative synthesis relies primarily on textual description to analyze and describe the findings from included studies[45]. Extracted data will be examined for potential relationships between results and key aspects of the studies, and across studies (e.g., sample characteristics, outcomes measured, and intervention characteristics). Explanations for why early stage interventions are effective are also of interest. Studies will be separated into groups based on type of early stage intervention, in order to better address our second research question (whether effectiveness varies depending on intervention type). Key elements from each study will be presented in summary tables, including results and effect sizes. If studies within intervention subgroups are homogenous enough, statistical pooling of data will be performed through meta-analysis. If relevant evidence exists, differences in effectiveness based on timing of intervention and caregiver or care recipient characteristics will be assessed and presented. Risk of bias assessments will be used to contextualize findings, evaluate the state of the literature, and explain potential differences in results across studies.

Step 6: Evidence grading and conclusions

Meta-biases

Unpublished literature is included in this review in an attempt to minimize publication bias. When using the Risk of Bias tool, selective reporting (another area of meta-bias) will be assessed. This will be facilitated by comparing published studies with their protocols when possible, and assessing the degree to which data is reported for relevant outcomes including findings that are not statistically significant.

Confidence in cumulative evidence

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach will be used to rate the evidence regarding the effectiveness of early stage intervention for caregivers on their wellbeing and ability to provide care to a person living with MCI or dementia. GRADE involves risk of bias assessment but also assessments of imprecision, inconsistency, indirectness, and publication bias. This framework allows informed judgements to be made about the quality of the body of evidence that is being examined[46]: whether we can be confident it accurately represents the true effects of early

caregiver interventions. The quality grade (very low, low, moderate, high) helps inform overall conclusions about the state of evidence for each outcome under review.

ETHICS AND DISSEMINATION

Findings from this review will be shared via conference proceedings and peer-reviewed publication, and a summary to the Alzheimer's Society. A full list of relevant studies that do not have data included in the review (e.g., in-progress protocols) will be created and available upon request. Findings may help inform the use of interventions for caregivers early in the course of the care recipient's cognitive decline.

Data Statement: All data that will be included in this systematic review will be taken from previously published articles or works (e.g., dissertations) found in databases.

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Medline search strategy

1. ((caregiver* or carer* or "care partner" or "care partners" or "care provider" or "care providers") adj5 (program* or intervention or educat* or support* or therap* or respite* or psychosocial or evaluat* or "case management" or counsel* or service*)).tw.

2. caregivers/

3. (program* or intervention*or education* or resource? or "social support" or respite).mp. or "case management".tw.

4. health communication/ or exp community health services/ or health services for the aged/ or early medical intervention/

5. exp social support/

6. RESPITE CARE/

7. Case Management/

8. PSYCHOSOCIAL SUPPORT SYSTEMS/

9. exp psychotherapy/

10. Program Development/ or Program Evaluation/

11. 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

12. 2 and 11

13. dement*.mp.

14. alzheimer*.mp.

15. (lewy* adj2 bod*).mp.

16. (creutzfeldt or jcd or cjd).mp.

17. (pick* adj2 disease).mp.

18. ((semantic or vascular or fronto-temporal* or Parkinson*) adj2 dementia).mp.

19. huntington*.mp.

20. primary progressive aphasia?.mp.

21. exp dementia/

22. "mild cognitive impairment".mp.

23. MCI.mp.

24. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23

25. 1 or 12

26. 24 and 25

No restrictions were placed on this search.

1

Data Extraction Form

General Study Information

Author/s:

Year:

Title of the article:

Funding source:

Geographic location (country):

Intervention Characteristics

Classified as "early intervention" based on:

Name of intervention:

Brief description of intervention:

Type of intervention:
(Psychosocial, cognitive-behavioural, counseling,
case management, respite, support, multi-component)
    Type of intervention specified in article or during extraction:

Theoretical basis of intervention:

Length of intervention:

Intervention setting for delivery:

Study Characteristics:
Objectives:

Design:
    Design specified in article or during extraction:

Recruitment procedures:

    Inclusion criteria:

    Exclusion criteria:

2

Comparator group/s:

Sample size of main intervention group:
(actually measured)

Sample size of comparator group/s:
(actually measured)

Participant Characteristics (for total sample; repeat for intervention and comparator groups if possible)

Caregivers:

Definition of "caregiver":

Geographic location:
(rural/urban; frequencies)

Caregiver sex:
(frequencies)

Relationship of caregiver to care recipient:
(frequencies)

Time spent caregiving (record both time in months/years and time per week/day)
(mean)

Primary caregiver status reported? (Yes/no)
(frequencies if available)

Lives in same dwelling as care recipient
(frequencies)

Care recipients:

Geographic location:
(rural/urban; frequencies)

Care recipient sex:
(frequencies)

Type of dementia:
(frequencies)

3

Co-morbidities:
(frequencies or mean)

Type of cognitive testing scores and reported mean or category:

Outcome Information:

For EACH relevant measurement of intervention effect:

Construct measured:

Length of time after intervention before first follow-up:

Additional follow up measurements:
(time)

Measurement tool:

Statistical techniques used for analysis:

Raw mean and standard deviation at each measurement point, intervention group:
(frequencies if applicable)

Raw mean and standard deviation at each measurement point, comparator:
(frequencies if applicable)

Change scores (if applicable), intervention group:

Change scores (if applicable), comparator group:

Statistical outcome/s:
(include p-value)

Confidence intervals:

Effect size:
(reported or calculated standardized mean difference)

Comparison between the effect of early and later intervention:

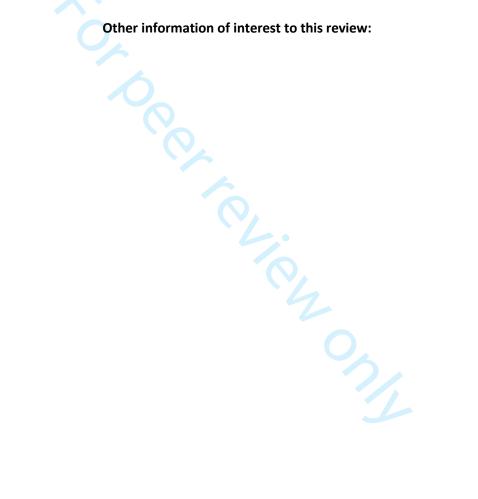Timing of intervention, "early" group:

Timing of intervention, "later" group:

4

Outcome measured:

Measurement tool:

Statistical techniques used for analysis:

Raw mean and standard deviation at each measurement point, early group:
(frequencies if applicable)

Raw mean and standard deviation at each measurement point, later group/s:
(frequencies if applicable)

Change scores, early group (if applicable):

Change scores, later group:

Statistical outcome/s of comparisons:
(include p-value)

Confidence intervals:

Effect size:
(reported or calculated standardized mean difference)

For EACH comparison of intervention effect between subgroups of caregivers

Care recipient or caregiver characteristic examined:

Construct measured:

Measurement tool:

Statistical techniques used for analysis:

Raw mean and standard deviation at each measurement point,
group 1 (repeat for each group being compared):
(frequencies if applicable)

Change scores, group 1 (repeat for each group being compared):

Statistical outcome/s of comparisons:
(include p-value)

5

Confidence intervals:

Effect size:
(reported or calculated standardized mean difference)

Additional outcomes assessed *(i.e., not measures of wellbeing or ability to provide care. List/describe)*:

Other information of interest to this review:

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review (Title (p 1), Abstract (p 2); Page 5)
Update	1b	If the protocol is for an update of a previous systematic review, identify as such NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number (Page 5)
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author (Page 1)
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review (Page 14)
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments NA
Support:		
Sources	5a	Indicate sources of financial or other support for the review (Page 14)
Sponsor	5b	Provide name for the review funder and/or sponsor (Page 14)
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol (Page 14)
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known (Page 3-5)
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) (Page 5)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review (Page 5-10)
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage (Page 5-6)
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated (Supplementary File 1)
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review (Page 7)

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) (Page 7, Page 10)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators (Page 10-11)
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications (Supplementary File 2, Page 10-11)
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale (Page 9, 11-12)
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis (Page 12-13)
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised (Page 13)
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) (Page 13)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) (Page 13)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned (Page 13)
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)(Page 13)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) (Page 13)

* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.