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Computerized Cognitive Training in Parkinson's Disease: A Protocol for a Systematic Review and Updated Meta-Analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-040656
Article Type:	Protocol
Date Submitted by the Author:	19-May-2020
Complete List of Authors:	Malmberg Gavelin, Hanna; University of Melbourne Academic Unit for Psychiatry of Old Age; Umea University, Department of Psychology Domellöf, Magdalena; Umea University, Department of Psychology Leung, Isabella; The University of Sydney, Healthy Brain Ageing Program, Brain and Mind Centre; The University of Sydney, Central Clinical School, Faculty of Medicine and Health, Charles Perkins Centre Stigsdotter Neely, Anna; Karlstad University, Department of Social and Psychological Studies Finke, Carsten; Charite Universitätsmedizin Berlin, Department of Neurology; Humboldt-Universität zu Berlin, Berlin School of Mind and Brain Lampit, Amit; University of Melbourne Academic Unit for Psychiatry of Old Age; Charite Universitätsmedizin Berlin, Department of Neurology
Keywords:	Parkinson-s disease < NEUROLOGY, REHABILITATION MEDICINE, GERIATRIC MEDICINE

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Computerized Cognitive Training in Parkinson's Disease: A Protocol for a Systematic Review and Updated Meta-Analysis

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Keywords: Parkinson's disease, cognitive training, systematic review, meta-analysis

Word count: 1988

Abstract

Introduction. Cognitive impairment is recognized as an important non-motor symptom in Parkinson's disease (PD) and there is a need for evidence-based non-pharmacological interventions that may prevent or slow cognitive decline in this patient group. One such intervention is computerized cognitive training (CCT), which has shown efficacious for cognition across older adult populations. This systematic review aims to investigate the efficacy of CCT across cognitive, psychosocial and functional domains for people with PD, and examine study and intervention design factors that could moderate CCT effects on cognition.

Methods and analysis. Randomized controlled trials investigating the effects of CCT in patients with PD without dementia, on cognitive, psychosocial or functional outcomes will be included. The primary outcome is overall cognitive function. Secondary outcomes are domain-specific cognitive function, psychosocial functioning and functional abilities. We will systematically search MEDLINE, Embase and PsycINFO to identify relevant literature. Risk of bias will be assessed using the revised Cochrane Risk of Bias tool. Effect sizes will be calculated as standardized mean difference of baseline to post-intervention change (Hedges' g) with 95% confidence interval for each eligible outcome measure. Pooling of outcomes across studies will be conducted using random-effects models, accounting for dependency structure of effect sizes within studies. Heterogeneity will be assessed using τ^2 and I^2 statistic. Potential moderators, based on key study and intervention design factors, will be investigated using mixed-effects meta-regression models.

Ethics and dissemination. No ethical approval is required. The findings will be disseminated in a peer-reviewed scientific journal.

ARTICLE SUMMARY

Strengths and limitations of this study

- Specification of the eligibility criteria for randomized controlled trials of narrowly-defined computerized cognitive training delineates the effects of this intervention from other cognitive intervention approaches in Parkinson's disease.
- Inclusion of a variety of cognitive, psychosocial and functional outcome measures will improve statistical power to inform efficacy across and within domains.
- Accounting for dependency of effect sizes within studies will reduce overestimation of within-study variance and thus underestimation of between-study heterogeneity, especially since individual studies are expected to be underpowered.
- Multiple methods for investigating heterogeneity can inform intervention and study design, but contingent on the number and size of available studies.
- Analyses are limited to group- rather than individual participant data.

INTRODUCTION

Cognitive decline is one of the most common non-motor symptoms in Parkinson's disease (PD).¹ Approximately 20% of people with PD already have mild cognitive impairment (MCI) at diagnosis, with over 40% conversion to dementia 10 years after PD diagnosis, substantially exceeding age-standardized risk.¹ Considering the negative influence of cognitive impairment on quality of life for patients as well as caregivers and the current lack of effective pharmacological treatments,¹ developing interventions that could maintain cognitive function and delay cognitive and functional decline is a critical area for prevention and treatment research in the field.²

Cognitive training is a non-pharmacological intervention that has shown efficacious for cognition in older adults across the spectrum from cognitively healthy to dementia.³ Specifically, computerized cognitive training (CCT) has received widespread attention in recent years as a safe and scalable intervention that can incorporate important intervention design features such as adaptivity of training difficulty and continuous motivational feedback on training performance.⁴ In addition to efficacy for cognition, individual trials have reported potential benefits on other symptoms such as mood and freezing of gait.⁴

To date, several systematic reviews and meta-analyses have investigated the efficacy of cognitive training on cognitive function in PD. Leung and colleagues⁵ identified seven randomized controlled trials (RCTs) and concluded that cognitive training showed modest efficacy for overall cognition in PD, with larger effect sizes observed within individual cognitive domains.⁵ Similar results were reported by Lawrence and colleagues,⁶ who combined 11 randomized and non-randomized cognitive training trials. More recently, a Cochrane review identified seven RCTs investigating the effects of cognitive training in PD patients with MCI or dementia, reporting imprecise and uncertain evidence for efficacy on

1
2
3 global cognition.⁷ Approaches for estimating effect sizes across studies varied across reviews,
4
5 and none conducted investigations of heterogeneity.
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8 Taken together, previous reviews have shown mixed and inconclusive results and the
9
10 efficacy of cognitive training in general, and CCT in particular, in people with PD remains
11
12 uncertain. Furthermore, given the limited number of studies in previous reviews as well as
13
14 clinical and methodological heterogeneity, the effects of CCT across different cognitive,
15
16 psychosocial and functional domains as well as design factors that may associated with such
17
18 effects are still unclear.⁴
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23 24 **Objectives**

25
26 The aim of this review is to evaluate the efficacy of CCT on cognitive, psychosocial and
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28 functional outcomes in persons with PD. Specifically, we aim to:
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- 30 1. Investigate the efficacy of CCT on cognitive, psychosocial and daily function in PD,
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32 in comparison to active or passive control.
- 33 2. Examine study and intervention design factors that could moderate CCT effects on
34
35 cognitive function across studies.
- 36 3. Evaluate the strength and quality of the evidence for CCT in PD.
- 37 4. Suggest recommendations for future research and practice in the field.
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47 **METHODS AND ANALYSIS**

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49 This protocol adheres to the Preferred Reporting Items for Systematic Review and Meta-
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51 analysis Protocols (PRISMA-P) guidelines.⁸ The PRISMA-P checklist can be found in the
52
53 online supplementary information. This review updates and further specifies our previous
54
55 systematic review on cognitive training in PD.⁵
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Eligibility criteria

Consistent with our previous systematic reviews of CCT,⁹⁻¹¹ we will include studies that meet the following criteria:

Types of studies

RCTs studying the effects of CCT on one or more cognitive, psychosocial or functional outcome in patients with PD. Eligible studies will provide neuropsychological testing at baseline and post CCT intervention. Randomised crossover trials will be included but only the first treatment phase will be considered and used for analysis. Non-randomised trials will be excluded. Unpublished RCTs or those published as conference abstracts, theses or monographs will be eligible if data needed for analysis and appraisal can be obtained from the authors.

Types of participants

Patients with PD (any age and aetiology), either cognitively healthy, with subjective cognitive decline or MCI. Studies including only or mainly people with dementia will be excluded.

Studies reporting the results from a population with mixed populations (e.g., MCI and dementia) will be eligible if the results for the eligible population are reported or can be obtained separately or if the eligible population (e.g., PD with MCI) constitutes $\geq 50\%$ of the sample.

Types of interventions

Minimum of 4 h of practice on standardized computerized tasks or video games with clear cognitive rationale, administered on personal computers, mobile devices or gaming consoles.

Studies combining CCT with other non-pharmacological interventions (e.g., physical

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3 exercise, brain stimulation) or with pharmacological interventions will be eligible as long as
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5 the CCT condition is the only key difference between the two groups (i.e., study design
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7 allows to delineate the effect of CCT from the composite intervention). Studies will not be
8
9 included if: (1) more than 50% of total intervention time was not CCT; (2) the intervention
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11 does not involve interaction with a computer (e.g., passive viewing or recording of responses
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13 by an experimenter); (3) the CCT intervention is based on lab-specific rather than off-the-
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15 shelf hardware, which makes it less likely to be relevant to clinical practice.
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21 Types of comparators

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23 Eligible control conditions include wait-list, no-contact and active (e.g., sham CCT,
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25 recreational activities) control groups. Combined interventions (e.g., pharmacological,
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27 physical exercise) will be eligible if provided similarly to both groups. All eligible controls in
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29 multi-arm studies will be included.
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34 Types of outcomes

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36 Eligible outcomes are change in performance from baseline to post-intervention in non-
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38 trained measures of cognition (global or domain-specific), assessed through standardised
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40 neuropsychological tests or close equivalents (e.g., a computer-based version of a common
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42 neuropsychological test). Additional outcomes include quality of life (standardised
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44 psychological wellbeing and quality of life questionnaires), mood (e.g., clinical depression
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46 rating scales), subjective cognition and daily function (patient or informant reported activities
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48 of daily living questionnaires or standardised measures, e.g., timed IADL). Outcomes will be
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50 excluded if they were used as (or closely resemble) training tasks or exploratory in nature
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52 (i.e., do not resemble common neuropsychological tests). In studies reporting more than one
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54 outcome measure per category, all eligible outcome measures will be included. The primary
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outcome will be overall cognitive performance.^{5 9-11} Secondary outcomes are domain-specific cognitive performance, classified according to the CHC-M framework,¹² subjective cognition, psychosocial functioning and daily function.

Search strategy

We will search MEDLINE, EMBASE and PsycINFO through the OVID interface for eligible articles. As this is an update of our previous systematic review,⁵ the search will be limited to entries from 1 January 2015. No restrictions on language or type of publication will be applied. The electronic search will be complemented by hand-searching the references of included articles and previous reviews as well as clinical trial registries. The full search strategy is shown in Table 1.

Table 1

Search strategy

# 1	((cognit* or attention or neurocognit* or neuropsycholog* or memory or mental or reasoning or executive) adj2 (interven* or training* or rehabilitat* or remediat* or stimulat* or activit* or enhanc* or exercis* or retrain*)).mp.
# 2	((brain) adj2 (training* or rehabilitat* or remediat* or retrain*)).mp.
# 3	(speed adj3 training).mp
# 4	(video gam* or videogam* or wii or computer gam* or virtual reality).mp.
# 5	1 or 2 or 3 or 4
# 6	parkinson\$.mp
# 7	exp Parkinson's disease/
# 8	exp Parkinsonism/
# 9	6 or 7 or 8
# 10	5 and 9
# 11	limit 10 to yr="2015 -Current"

Study selection

Literature search results will be uploaded to a single Covidence library. Duplicates will be removed and articles identified from other sources will be added. Initial screening for eligibility based on titles and abstracts will be conducted by two independent reviewers. Full-

text screening of potentially relevant articles will be conducted by two independent reviewers and disagreements resolved by consensus or by involvement of a third reviewer.

Data extraction

Data will be extracted to a piloted Excel spreadsheet by one reviewer and a senior reviewer will check the data. Any disagreements will be resolved by consensus or by involvement of a third reviewer if necessary. If any additional information is needed, we will contact the corresponding authors of the studies. The following data items will be extracted:

- Study information: first author, year of publication, study location
- Population: mean age, percent male, mean MMSE score (or equivalent), mean Unified Parkinson's Disease Rating score (or equivalent), disease stage (Hoehn & Yahr Scale or equivalent), disease duration, medication use, cognitive status (normal, subjective cognitive complaints or MCI)
- Intervention: type of CCT, program used, training content, delivery format (supervised or unsupervised), total training duration (hours), session frequency (sessions/week), session length (minutes), total number of sessions, intervention duration (weeks), adjacent treatments
- Comparator: type of control, control group activity
- Outcome: name of test, summary data for each group (e.g., mean, standard deviation, sample size) at baseline and post intervention, cognitive domain

Intention-to-treat data will be preferred if reported. Data will be extracted as means and standard deviation for each time point if reported. If such information is not available, data in other formats (e.g., mean change and standard deviation) will be used if the article provides

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3 sufficient information to reliably calculate standardised mean difference. If these data are
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5 unavailable, authors will be contacted to obtain missing data.
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10 **Risk of bias assessment**

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12 Risk of bias in individual RCTs will be assessed using the revised Cochrane Risk of Bias tool
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14 (RoB 2).¹³ Low, high or some concerns risk of bias will be determined for each of the
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16 following domains:
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- 18 1. Bias arising from the randomization process
 - 19 2. Bias due to deviations from intended interventions
 - 20 3. Bias due to missing outcome data
 - 21 4. Bias in measurement of the outcome
 - 22 5. Bias in selection of the reported result
 - 23 6. Overall bias
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33 Studies with “some concerns” or “high” risk of bias in domains 3 or 4 will be considered as
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35 having some concerns or high risk of bias, respectively. Two independent reviewers will
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37 assess the risk of bias and disagreements will be resolved by consensus or consulting a third
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39 reviewer if necessary.
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45 **Data synthesis**

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47 Analyses will be conducted using the packages metafor, metaSEM, robumeta and
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49 clubSandwich for R. Between-group differences in change from baseline to post-intervention
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51 will be converted to standardized mean differences and calculated as Hedges’ *g* with 95%
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53 confidence interval for each eligible outcome measure. Pooling of outcomes across studies
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55 will be conducted using random-effects models, accounting for dependency structure of effect
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57 sizes within studies.^{14 15} Sensitivity analyses for the primary outcome will be conducted by
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3 comparing results from multilevel and robust variance estimation models. Analyses of
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5 secondary outcomes will be contingent on the availability of at least three studies for analysis.
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8 Heterogeneity across studies will be quantified using τ^2 and expressed as a proportion of
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10 overall observed variance using the I^2 statistic.^{16,17} Prediction intervals will be calculated to
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12 assess the dispersion of effects across settings.¹⁸ Provided sufficient statistical power for
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14 investigations of heterogeneity,¹⁹ potential moderators will be investigated using mixed-
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16 effects meta-regression models. The following moderators will be tested, if warranted:
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18 training content and type; control content and type; population (clinical or cognitive status);
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20 delivery format; training dose and frequency. If warranted, potential interactions across
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22 moderators will be tested on an exploratory basis using multivariate meta-regression or
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24 network meta-analysis.
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30 **Meta-bias(es)**

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32 Small-study effect will be assessed by visually inspecting funnel plots of effect size vs
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34 standard error.²⁰ If at least 10 studies are available, small study effect will be formally tested
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36 using a multivariate analogue of the Egger's test,²¹ i.e., a meta-regression using standard error
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38 as covariate. Subgroup analysis of the primary outcome will be conducted based on overall
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40 RoB 2 scores.
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47 **Confidence in cumulative evidence**

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49 The strength of the evidence will be assessed and summarized qualitatively based on risk of
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51 bias for individual studies, precision of the effect estimates, heterogeneity across studies
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53 (including prediction intervals) and evidence for small study effects, with additional
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55 sensitivity analyses conducted if warranted.
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Patient and public involvement

Patients and/or the public will not be involved in this study.

Ethics and dissemination

No formal ethical assessment or informed consent is required for this study. The findings of the study will be summarised in a manuscript which will be submitted for publication in a peer-reviewed scientific journal.

Author Contributions. Guarantor: AL. Design and conceptualisation: HMG and AL. Data collection: HMG and MD. Risk of bias assessment: HMG and MD. Data analysis and interpretation: HMG, MD, IL, ASN, CF and AL. Drafting and revising the manuscript: HMG, MD, IL, ASN, CF and AL.

Funding. This work was supported by a CR Roper Fellowship from the University of Melbourne provided to AL (2020-1), and by the Swedish Research Council (2017-02371) as well as the Swedish Research Council for Health, Working-Life and Welfare (2014-01654) awarded to ASN.

Competing interests. None declared.

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Reporting checklist for protocol of a systematic review.

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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	1

Registration

#2 If registered, provide the name of the registry Registered with
(such as PROSPERO) and registration PROSPERO on May 14th
number 2020, currently pending
approval by the
PROSPERO editorial
team

Authors

Contact #3a Provide name, institutional affiliation, e-mail 1
address of all protocol authors; provide
physical mailing address of corresponding
author

Contribution #3b Describe contributions of protocol authors 12
and identify the guarantor of the review

Amendments

#4 If the protocol represents an amendment of Amendments will be
a previously completed or published recorded in PROSPERO
protocol, identify as such and list changes; (currently pending
otherwise, state plan for documenting approval)
important protocol amendments

Support

Sources #5a Indicate sources of financial or other support 12
for the review

1	Sponsor	#5b	Provide name for the review funder and / or	12
2			sponsor	
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6	Role of sponsor	#5c	Describe roles of funder(s), sponsor(s), and /	n/a
7	or funder		or institution(s), if any, in developing the	
8			protocol	
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14	Introduction			
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17	Rationale	#6	Describe the rationale for the review in the	4-5
18			context of what is already known	
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22	Objectives	#7	Provide an explicit statement of the	5
23			question(s) the review will address with	
24			reference to participants, interventions,	
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32	Methods			
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35	Eligibility criteria	#8	Specify the study characteristics (such as	6-8
36			PICO, study design, setting, time frame) and	
37			report characteristics (such as years	
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39			be used as criteria for eligibility for the	
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45	Information	#9	Describe all intended information sources	8
46	sources		(such as electronic databases, contact with	
47			study authors, trial registers or other grey	
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1		literature sources) with planned dates of	
2			
3		coverage	
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5			
6	Search strategy	#10 Present draft of search strategy to be used	8
7			
8		for at least one electronic database,	
9			
10		including planned limits, such that it could be	
11			
12		repeated	
13			
14			
15	Study records -	#11a Describe the mechanism(s) that will be used	9
16			
17	data	to manage records and data throughout the	
18			
19	management	review	
20			
21			
22			
23	Study records -	#11b State the process that will be used for	9
24			
25	selection	selecting studies (such as two independent	
26			
27	process	reviewers) through each phase of the review	
28			
29		(that is, screening, eligibility and inclusion in	
30			
31		meta-analysis)	
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35	Study records -	#11c Describe planned method of extracting data	9-10
36			
37	data collection	from reports (such as piloting forms, done	
38			
39	process	independently, in duplicate), any processes	
40			
41		for obtaining and confirming data from	
42			
43		investigators	
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47	Data items	#12 List and define all variables for which data	9-10
48			
49		will be sought (such as PICO items, funding	
50			
51		sources), any pre-planned data assumptions	
52			
53		and simplifications	
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1	Outcomes and	#13	List and define all outcomes for which data	7-8
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3	prioritization		will be sought, including prioritization of main	
4				
5			and additional outcomes, with rationale	
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8	Risk of bias in	#14	Describe anticipated methods for assessing	10
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10	individual		risk of bias of individual studies, including	
11				
12	studies		whether this will be done at the outcome or	
13				
14			study level, or both; state how this	
15				
16			information will be used in data synthesis	
17				
18	Data synthesis	#15a	Describe criteria under which study data will	10-11
19				
20			be quantitatively synthesised	
21				
22	Data synthesis	#15b	If data are appropriate for quantitative	10-11
23				
24			synthesis, describe planned summary	
25				
26			measures, methods of handling data and	
27				
28			methods of combining data from studies,	
29				
30			including any planned exploration of	
31				
32			consistency (such as I ² , Kendall's τ)	
33				
34	Data synthesis	#15c	Describe any proposed additional analyses	10-11
35				
36			(such as sensitivity or subgroup analyses,	
37				
38			meta-regression)	
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40	Data synthesis	#15d	If quantitative synthesis is not appropriate,	n/a
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42			describe the type of summary planned	
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1	Meta-bias(es)	#16	Specify any planned assessment of meta-	11
2			bias(es) (such as publication bias across	
3			studies, selective reporting within studies)	
4				
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8	Confidence in	#17	Describe how the strength of the body of	11
9	cumulative		evidence will be assessed (such as GRADE)	
10	evidence			
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17 CC-BY 4.0. This checklist was completed on 15. May 2020 using <https://www.goodreports.org/>, a tool
18 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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BMJ Open

Computerized Cognitive Training in Parkinson's Disease: A Protocol for a Systematic Review and Updated Meta-Analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-040656.R1
Article Type:	Protocol
Date Submitted by the Author:	11-Aug-2020
Complete List of Authors:	Malmberg Gavelin, Hanna; University of Melbourne Academic Unit for Psychiatry of Old Age; Umea University, Department of Psychology Domellöf, Magdalena; Umea University, Department of Psychology Leung, Isabella; The University of Sydney, Healthy Brain Ageing Program, Brain and Mind Centre; The University of Sydney, Central Clinical School, Faculty of Medicine and Health, Charles Perkins Centre Stigsdotter Neely, Anna; Karlstad University, Department of Social and Psychological Studies Finke, Carsten; Charite Universitätsmedizin Berlin, Department of Neurology; Humboldt-Universität zu Berlin, Berlin School of Mind and Brain Lampit, Amit; University of Melbourne Academic Unit for Psychiatry of Old Age; Charite Universitätsmedizin Berlin, Department of Neurology
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Parkinson-s disease < NEUROLOGY, REHABILITATION MEDICINE, GERIATRIC MEDICINE

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Computerized Cognitive Training in Parkinson's Disease: A Protocol for a Systematic Review and Updated Meta-Analysis

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Keywords: Parkinson's disease, cognitive training, systematic review, meta-analysis

Word count: 2011

Abstract

Introduction. Cognitive impairment is recognized as an important non-motor symptom in Parkinson's disease (PD) and there is a need for evidence-based non-pharmacological interventions that may prevent or slow cognitive decline in this patient group. One such intervention is computerized cognitive training (CCT), which has shown efficacious for cognition across older adult populations. This systematic review aims to investigate the efficacy of CCT across cognitive, psychosocial and functional domains for people with PD, and examine study and intervention design factors that could moderate CCT effects on cognition.

Methods and analysis. Randomized controlled trials investigating the effects of CCT in patients with PD without dementia, on cognitive, psychosocial or functional outcomes will be included. The primary outcome is overall cognitive function. Secondary outcomes are domain-specific cognitive function, psychosocial functioning and functional abilities. We systematically searched MEDLINE, Embase and PsycINFO through May 14 2020 to identify relevant literature. Risk of bias will be assessed using the revised Cochrane Risk of Bias tool. Effect sizes will be calculated as standardized mean difference of baseline to post-intervention change (Hedges' g) with 95% confidence interval for each eligible outcome measure. Pooling of outcomes across studies will be conducted using random-effects models, accounting for dependency structure of effect sizes within studies. Heterogeneity will be assessed using τ^2 and I^2 statistic. Potential moderators, based on key study and intervention design factors, will be investigated using mixed-effects meta-regression models.

Ethics and dissemination. No ethical approval is required. The findings will be disseminated in a peer-reviewed scientific journal.

PROSPERO registration number: CRD42020185386.

1 **ARTICLE SUMMARY**

2 **Strengths and limitations of this study**

- 3 • Specification of the eligibility criteria for randomized controlled trials of narrowly-
4 defined computerized cognitive training delineates the effects of this intervention from
5 other cognitive intervention approaches in Parkinson's disease.
- 6 • Inclusion of a variety of cognitive, psychosocial and functional outcome measures will
7 improve statistical power to inform efficacy across and within domains.
- 8 • Accounting for dependency of effect sizes within studies will reduce overestimation of
9 within-study variance and thus underestimation of between-study heterogeneity,
10 especially since individual studies are expected to be underpowered.
- 11 • Multiple methods for investigating heterogeneity can inform intervention and study
12 design, but contingent on the number and size of available studies.
- 13 • Analyses are limited to group- rather than individual participant data.

1 INTRODUCTION

2 Cognitive decline is one of the most common non-motor symptoms in Parkinson's disease
3 (PD).¹ Approximately 20% of people with PD already have mild cognitive impairment (MCI)
4 at diagnosis, with over 40% conversion to dementia 10 years after PD diagnosis, substantially
5 exceeding age-standardized risk.¹ Considering the negative influence of cognitive impairment
6 on quality of life for patients as well as caregivers and the current lack of effective
7 pharmacological treatments,¹ developing interventions that could maintain cognitive function
8 and delay cognitive and functional decline is a critical area for prevention and treatment
9 research in the field.²

10 Cognitive training is a non-pharmacological intervention that has shown efficacious for
11 cognition in older adults across the spectrum from cognitively healthy to dementia.³
12 Specifically, computerized cognitive training (CCT) has received widespread attention in
13 recent years as a safe and scalable intervention that can incorporate important intervention
14 design features such as adaptivity of training difficulty and continuous motivational feedback
15 on training performance.⁴ In addition to efficacy for cognition, individual trials have reported
16 potential benefits on other symptoms such as mood and freezing of gait.⁴

17 To date, several systematic reviews and meta-analyses have investigated the efficacy of
18 cognitive training on cognitive function in PD⁵⁻⁸. Leung and colleagues⁵ identified seven
19 randomized controlled trials (RCTs) and concluded that cognitive training showed modest
20 efficacy for overall cognition in PD, with larger effect sizes observed within individual
21 cognitive domains.⁵ Similar results were reported by Lawrence and colleagues,⁶ who
22 combined 11 randomized and non-randomized cognitive training trials. More recently, a
23 Cochrane review identified seven RCTs investigating the effects of cognitive training in PD
24 patients with MCI or dementia, reporting imprecise and uncertain evidence for efficacy on
25 global cognition.⁷ Approaches for estimating effect sizes across studies varied across reviews,

1 and none conducted investigations of heterogeneity. Finally, a recent systematic review
2 focusing specifically on CCT reported evidence for cognitive benefits based on seven RCTs;
3 however, no meta-analysis was performed nor were potential effect modifiers explored.⁸

4 Taken together, previous reviews have shown mixed and inconclusive results and the
5 efficacy of cognitive training in general, and CCT in particular, in people with PD remains
6 uncertain. Furthermore, given the limited number of studies in previous reviews as well as
7 clinical and methodological heterogeneity, the effects of CCT across different cognitive,
8 psychosocial and functional domains as well as design factors that may associated with such
9 effects are still unclear.⁴

11 Objectives

12 The aim of this review is to evaluate the efficacy of CCT on cognitive, psychosocial and
13 functional outcomes in persons with PD. Specifically, we aim to:

- 14 1. Investigate the efficacy of CCT on cognitive, psychosocial and daily function in PD,
15 in comparison to active or passive control.
- 16 2. Examine study and intervention design factors that could moderate CCT effects on
17 cognitive function across studies.
- 18 3. Evaluate the strength and quality of the evidence for CCT in PD.
- 19 4. Suggest recommendations for future research and practice in the field.

21 METHODS AND ANALYSIS

22 This protocol adheres to the Preferred Reporting Items for Systematic Review and Meta-
23 analysis Protocols (PRISMA-P) guidelines⁹ and the protocol was prospectively registered
24 with PROSPERO (CRD42020185386). The PRISMA-P checklist can be found in the online

1
2
3 1 supplementary information. This review updates and further specifies our previous systematic
4
5 2 review on cognitive training in PD.⁵
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11 5 **Eligibility criteria**

12
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14 6 Consistent with our previous systematic reviews of CCT,¹⁰⁻¹² we will include studies that
15
16
17 7 meet the following criteria:
18
19 8

20 21 9 Types of studies

22
23
24 10 RCTs studying the effects of CCT on one or more cognitive, psychosocial or functional
25
26 11 outcome in patients with PD. Eligible studies will provide neuropsychological testing at
27
28 12 baseline and post CCT intervention. Randomised crossover trials will be included but only the
29
30 13 first treatment phase will be considered and used for analysis. Non-randomised trials will be
31
32 14 excluded. Unpublished RCTs or those published as conference abstracts, theses or
33
34 15 monographs will be eligible if data needed for analysis and appraisal can be obtained from the
35
36 16 authors.
37
38
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40 17

41 42 18 Types of participants

43
44 19 Patients with PD (any age and aetiology), either cognitively healthy, with subjective cognitive
45
46 20 decline or MCI. Studies including only or mainly people with dementia will be excluded.
47
48 21 Studies reporting the results from a population with mixed populations (e.g., MCI and
49
50 22 dementia) will be eligible if the results for the eligible population are reported or can be
51
52 23 obtained separately or if the eligible population (e.g., PD with MCI) constitutes $\geq 50\%$ of the
53
54 24 sample.
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1 Types of interventions

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1 Minimum of 4 h of practice on standardized computerized tasks or video games with clear
2 cognitive rationale, administered on personal computers, mobile devices or gaming consoles.
3 Interventions can be delivered individually or in group settings, with or without therapist
4 supervision. Studies combining CCT with other non-pharmacological interventions (e.g.,
5 physical exercise, brain stimulation) or with pharmacological interventions will be eligible as
6 long as the CCT condition is the only key difference between the two groups (i.e., study
7 design allows to delineate the effect of CCT from the composite intervention). Studies will
8 not be included if: (1) more than 50% of total intervention time was not CCT; (2) the
9 intervention does not involve interaction with a computer (e.g., passive viewing or recording
10 of responses by an experimenter); (3) the CCT intervention is based on lab-specific rather
11 than off-the-shelf hardware, which makes it less likely to be relevant to clinical practice.
12
13

14 Types of comparators

15 Eligible control conditions include wait-list, no-contact and active (e.g., sham CCT,
16 recreational activities) control groups. Combined interventions (e.g., pharmacological,
17 physical exercise) will be eligible if provided similarly to both groups. All eligible controls in
18 multi-arm studies will be included.
19

20 Types of outcomes

21 Eligible outcomes are change in performance from baseline to post-intervention in non-
22 trained measures of cognition (global or domain-specific), assessed through standardised
23 neuropsychological tests or close equivalents (e.g., a computer-based version of a common
24 neuropsychological test). Additional outcomes include quality of life (standardised
25 psychological wellbeing and quality of life questionnaires), mood (e.g., clinical depression

1 rating scales), subjective cognition and daily function (patient or informant reported activities
 2 of daily living questionnaires or standardised measures, e.g., timed IADL). Outcomes will be
 3 excluded if they were used as (or closely resemble) training tasks or exploratory in nature
 4 (i.e., do not resemble common neuropsychological tests). In studies reporting more than one
 5 outcome measure per category, all eligible outcome measures will be included. The primary
 6 outcome will be overall cognitive performance.^{5 10-12} Secondary outcomes are domain-
 7 specific cognitive performance, classified according to the CHC-M framework,¹³ subjective
 8 cognition, psychosocial functioning and daily function. Outcomes from longitudinal follow-
 9 ups will be included when available and meta-analytically investigated if appropriate.

10

11 **Search strategy**

12 We will search MEDLINE, EMBASE and PsycINFO through the OVID interface for eligible
 13 articles. As this is an update of our previous systematic review,⁵ the search will be limited to
 14 entries from 1 January 2015 and records from the updated search will be combined with
 15 eligible trials identified through the systematic literature search in the original version of the
 16 review. No restrictions on language or type of publication will be applied. The electronic
 17 search will be complemented by hand-searching the references of included articles and
 18 previous reviews as well as clinical trial registries. The full search strategy is shown in Table
 19 1. A systematic literature search was conducted on May 14 2020.

20

21 Table 1

22 *Search strategy*

# 1	((cognit* or attention or neurocognit* or neuropsycholog* or memory or mental or reasoning or executive) adj2 (interven* or training* or rehabilitat* or remediat* or stimulat* or activit* or enhanc* or exercis* or retrain*)).mp.
# 2	((brain) adj2 (training* or rehabilitat* or remediat* or retrain*)).mp.
# 3	(speed adj3 training).mp
# 4	(video gam* or videogam* or wii or computer gam* or virtual reality).mp.

# 5	1 or 2 or 3 or 4
# 6	parkinson\$.mp
# 7	exp Parkinson's disease/
# 8	exp Parkinsonism/
# 9	6 or 7 or 8
# 10	5 and 9
# 11	limit 10 to yr="2015 -Current"

2 Study selection

3 Literature search results will be uploaded to a single Covidence library. Duplicates will be
 4 removed and articles identified from other sources will be added. Initial screening for
 5 eligibility based on titles and abstracts will be conducted by two independent reviewers. Full-
 6 text screening of potentially relevant articles will be conducted by two independent reviewers
 7 and disagreements resolved by consensus or by involvement of a third reviewer.

9 Data extraction

10 Data will be extracted to a piloted Excel spreadsheet by one reviewer and a senior reviewer
 11 will check the data. Any disagreements will be resolved by consensus or by involvement of a
 12 third reviewer if necessary. If any additional information is needed, we will contact the
 13 corresponding authors of the studies. The following data items will be extracted:

- 14 - Study information: first author, year of publication, study location
- 15 - Population: mean age, percent male, mean MMSE score (or equivalent), mean Unified
 16 Parkinson's Disease Rating score (or equivalent), disease stage (Hoehn & Yahr Scale
 17 or equivalent), disease duration, medication use, cognitive status (normal, subjective
 18 cognitive complaints or MCI)
- 19 - Intervention: type of CCT, program used, training content, delivery format (supervised
 20 or unsupervised), total training duration (hours), session frequency (sessions/week),
 21 session length (minutes), total number of sessions, intervention duration (weeks),
 22 adjacent treatments

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- 2
- 3 1 - Comparator: type of control, control group activity
- 4
- 5 2 - Outcome: name of test, summary data for each group (e.g., mean, standard deviation,
- 6
- 7 sample size) at baseline and post intervention, cognitive domain
- 8
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10 4

11

12 5 Intention-to-treat data will be preferred if reported. Data will be extracted as means and

13

14 6 standard deviation for each time point if reported. If such information is not available, data in

15

16 7 other formats (e.g., mean change and standard deviation) will be used if the article provides

17

18 8 sufficient information to reliably calculate standardised mean difference. If these data are

19

20 9 unavailable, authors will be contacted to obtain missing data.

21

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10

11 **Risk of bias assessment**

12 Risk of bias in individual RCTs will be assessed using the revised Cochrane Risk of Bias tool

13 (RoB 2).¹⁴ Low, high or some concerns risk of bias will be determined for each of the

14 following domains:

- 15 1. Bias arising from the randomization process
- 16 2. Bias due to deviations from intended interventions
- 17 3. Bias due to missing outcome data
- 18 4. Bias in measurement of the outcome
- 19 5. Bias in selection of the reported result
- 20 6. Overall bias

21 Studies with “some concerns” or “high” risk of bias in domains 3 or 4 will be considered as

22 having some concerns or high risk of bias, respectively. Two independent reviewers will

23 assess the risk of bias and disagreements will be resolved by consensus or consulting a third

24 reviewer if necessary.

25

1 **Data synthesis**

2 Analyses will be conducted using the packages metafor, metaSEM, robumeta and
3 clubSandwich for R. Between-group differences in change from baseline to post-intervention
4 will be converted to standardized mean differences and calculated as Hedges' g with 95%
5 confidence interval for each eligible outcome measure. Pooling of outcomes across studies
6 will be conducted using random-effects models, accounting for dependency structure of effect
7 sizes within studies.^{15 16} Sensitivity analyses for the primary outcome will be conducted by
8 comparing results from multilevel and robust variance estimation models. Analyses of
9 secondary outcomes will be contingent on the availability of at least three studies for analysis.

10 Heterogeneity across studies will be quantified using τ^2 and expressed as a proportion of
11 overall observed variance using the I^2 statistic.^{17 18} Prediction intervals will be calculated to
12 assess the dispersion of effects across settings.¹⁹ Provided sufficient statistical power for
13 investigations of heterogeneity,²⁰ potential moderators will be investigated using mixed-
14 effects meta-regression models. The following moderators will be tested, if warranted:
15 training content and type; control content and type; population (clinical or cognitive status);
16 delivery format; training dose and frequency. Meta-regressions will not be conducted if
17 heterogeneity in the overall model is negligible (i.e., $\tau^2 < 0.01$) or when there are less than
18 three studies within a planned subgroup. If warranted, potential interactions across moderators
19 will be tested on an exploratory basis using multivariate meta-regression or network meta-
20 analysis.

21 **Meta-bias(es)**

22 Small-study effect will be assessed by visually inspecting funnel plots of effect size vs
23 standard error.²¹ If at least 10 studies are available, small study effect will be formally tested
24 using a multivariate analogue of the Egger's test,²² i.e., a meta-regression using standard error
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3 1 as covariate. Subgroup analysis of the primary outcome will be conducted based on overall
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5 2 RoB 2 scores.
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10 4 **Confidence in cumulative evidence**

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12 5 The strength of the evidence will be assessed and summarized qualitatively based on risk of
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14 6 bias for individual studies, precision of the effect estimates, heterogeneity across studies
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17 7 (including prediction intervals) and evidence for small study effects, with additional
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19 8 sensitivity analyses conducted if warranted.
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24 10 **Patient and public involvement**

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26 11 Patients and/or the public will not be involved in this study.
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31 13 **Ethics and dissemination**

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33 14 No formal ethical assessment or informed consent is required for this study. The findings of
34
35 15 the study will be summarised in a manuscript which will be submitted for publication in a
36
37 16 peer-reviewed scientific journal.
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42 18 **Author Contributions.** Guarantor: AL. Design and conceptualisation: HMG and AL. Data
43
44 19 collection: HMG, MD and IL. Risk of bias assessment: HMG, MD and IL. Data analysis and
45
46 20 interpretation: HMG, MD, IL, ASN, CF and AL. Drafting and revising the manuscript: HMG,
47
48 21 MD, IL, ASN, CF and AL.

49
50
51 22 **Funding.** This work was supported by a CR Roper Fellowship from the University of
52
53 23 Melbourne provided to AL (2020-1), and by the Swedish Research Council (2017-02371) as
54
55 24 well as the Swedish Research Council for Health, Working-Life and Welfare (2014-01654)
56
57 25 awarded to ASN.
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3 1 **Competing interests.** None declared.
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For peer review only

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For peer review only

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preorting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015;4(1):1.

	Reporting Item	Page Number
Title		
Identification	#1a Identify the report as a protocol of a systematic review	1
Update	#1b If the protocol is for an update of a previous systematic review, identify as such	1
Registration		
	#2 If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors		
Contact	#3a Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1

1	Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	12
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4	Amendments			
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7		#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	Amendments will be recorded in PROSPERO
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13	Support			
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16	Sources	#5a	Indicate sources of financial or other support for the review	12
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20	Sponsor	#5b	Provide name for the review funder and / or sponsor	12
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24	Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	n/a
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27	Introduction			
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30	Rationale	#6	Describe the rationale for the review in the context of what is already known	4-5
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34	Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
35				
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39	Methods			
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42	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	6-8
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50	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	8
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1	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	8-9
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6	Study records -	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9
7	data management			
8				
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10	Study records -	#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)	9
11	selection process			
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17	Study records -	#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	9-10
18	data collection			
19	process			
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24	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	9-10
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29	Outcomes and	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7-8
30	prioritization			
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34	Risk of bias in	#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	10
35	individual studies			
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43	Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	11
44				
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46	Data synthesis	#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)	11
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55	Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
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1	Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	n/a
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4	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	11-12
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10	Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	12
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