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The Efficiency and Safety of Ginkgo Preparations for Attention Deficit Hyperactivity Disorder: A Systematic Review Protocol

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4 1 The Efficiency and Safety of Ginkgo Preparations for Attention Deficit Hyperactivity Disorder: A
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6 2 Systematic Review Protocol

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24 15 **Abstract**

25 16 **Introduction** Attention Deficit Hyperactivity Disorder (ADHD) is one of the most commonly
26 17 diagnosed and treated childhood psychiatric disorders. Ginkgo preparations have been used in
27 18 treating ADHD. The study aims to assess the efficiency and safety of Ginkgo preparations as
28 19 treatment for ADHD through current published evidence.

29 20 **Materials and methods** We will conduct the comprehensive search for the randomised controlled
30 21 trials to evaluate the effectiveness and tolerance of ginkgo preparations. The following databases
31 22 will be searched from their inception until October 2017: Medline, Embase, the Cochrane Central
32 23 Register of Controlled Trials (CENTRAL), Web of Science (science and social science citation
33 24 index), China Biology Medicine Disc (CBMdisc), China National Knowledge Infrastructure
34 25 Database (CNKI), Wanfang Database and Chinese Scientific Journals Database (VIP). Selection
35 26 of studies, data extraction and assessment of risk of bias will be conducted independently by two
36 27 authors.

37 28 **Ethics and dissemination** This systematic review does not require ethics approval. It will be
38 29 published in a peer-reviewed journal.

39 30 **PROSPERO registration number** CRD42017077190

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44 32 **Strengths and limitations of this study**

45 33 This systematic review will evaluate the efficacy and tolerance of all types of ginkgo preparations
46 34 in treating ADHD and aims to provide appropriate clinical evidence for clinicians, patients and
47 35 parents.

48 36 This review will collect data by unbiased search of various databases without language
49 37 restrictions.

50 38 Clinical heterogeneity maybe exists regarding of changes in different types of ginkgo preparations,
51 39 dosage, duration and the treatment combined.

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55 41 **Introduction**

42 **Description of the condition of ADHD treatment**

43 The prevalence of Attention deficit hyperactivity disorder (ADHD) in children and adolescents is
44 as high as 3.4% in the general population^[1]; and it is considered as one of the most commonly
45 diagnosed and treated childhood psychiatric disorders^[2]. It rises to 6.26% in China^[3]. ADHD is a
46 childhood-onset neurodevelopmental disorder, which can persist into adolescence and adulthood,
47 appearing with a high societal burden. The main symptoms consist of inattention and
48 hyperactivity/impulsivity, often accompanied by other neurodevelopment disorders such as autism
49 spectrum disorder^[4] and intellectual disability^[5]. A large proportion of adolescents and adults with
50 ADHD perform antisocial behavior and criminal activities, including conduct disorder,
51 oppositional defiant disorder^[6], risk of crashing^[7], sexual offenses^[8] and arson^[9], especially among
52 arrested, convicted and imprisoned adolescents and adults, which, has been increasingly
53 considered as a severe social issue.

54 Stimulants such as methylphenidate used for the first-line treatments will lead to substance use
55 disorders (SUDs), one among the most common comorbid psychiatric disorders in adolescent or
56 adult patients^[10-11]. Related adverse side-effects include cardiovascular events, insomnia, appetite
57 loss, hypoevolutism, gastrointestinal symptoms, and tics^[12]. The side effects, nonresponse, abuse
58 and misuse of conventional pharmacological treatments call for complementary or alternative
59 medical treatments for ADHD with mild side-effect, such as plant-based medications,
60 acupuncture^[13] and music therapy^[14].

61 **Description of the intervention**

62 Ginkgo preparations are made of compounds abstracted from ginkgo leaves, including tablets,
63 capsules, granules, oral solution, aerosol and injection. Ginkgo preparations are one of the
64 best-sale botanical dietary supplements all over the world. Evidence indicated that Ginkgo
65 preparations can alleviate cognitive disorders^[15], cerebrovascular insufficiency, peripheral vascular
66 disturbances, degenerative dementia, and various neuropsychiatric symptoms such as autism^[16],
67 depression^[17] and anxiety^[18]. It's reported ginkgo preparations affected ADHD patients on both
68 behaviors and cognitive aspects. The predominant behavioral effects were calming and improved
69 frustration tolerance; while for cognition, ginkgo biloba induced willful cognition, discriminant
70 attention and decreased irritability^[19].

71 **How the intervention might work**

72 Components isolated from ginkgo biloba contain terpene trilactones, flavonol glycosides,
73 isoflavonoids, biflavones, proanthocyanidins, alkylphenols, carboxylic acids,
74 4-O-Methylpyridoxine and polyphenols^[20-22]. Preclinical evidence indicates that ginkgo flavonol
75 glycosides are predominantly responsible for antioxidant activity^[23]. The antioxidant activity of
76 ginkgo flavonol glycosides can reduce the reactive oxygen species (ROS) induced oxidative stress,
77 which contributes to neurodevelopmental disorders by causing membrane damage, changes in
78 proteins' structure and function, lipid denaturation and DNA damage^[24]. The terpene trilactones
79 associated with neuroprotective properties^[25]. Investigations showed that terpene trilactones
80 attenuated the decrease of brain-derived neurotropic factor (BDNF), norepinephrine transporter
81 (NET) and dopamine transporter (DAT)^[26], which were reported to be negatively related to the
82 pathogenesis of ADHD^[27-29].

83 Considering that there hasn't been any updated and comprehensive quantitative review of ginkgo
84 preparations to treat ADHD, it's important to investigate current evidence related to the
85 effectiveness and tolerance of ginkgo preparations therapy for ADHD.

86

87 Materials and methods**88 Registration information**

89 This systematic review protocol adhered to preferred reporting items for systematic review and
90 meta analysis protocols (PRISMA-P) 2015^[30]. The protocol was registered on PROSPERO and
91 the registration number is CRD42017077190.

92 Eligibility criteria**93 Types of study**

94 All prospective randomised controlled trials (RCTs) will be included in this systematic review, but
95 trials without detailed data will be excluded. Abstracts with sufficient outcome data will be
96 included. Cross-over trials will be included with the first phase of the data.

97 Type of participants

98 Children and adolescents between 6-14 years old with ADHD, or hyperkinetic disorder, diagnosed
99 based on American Psychiatric Association's Diagnostic and Statistical Manual of Mental
100 Disorders 4th edition (DSM-IV), the Diagnostic and Statistical Manual of Mental Disorders, Fifth
101 Edition2(DSM-5), and Chinese Classification and Diagnosis of Mental Diseases-3rd edition
102 (CMDD) will be included. There will be no limitations of sex.

103 Type of interventions and controls

104 Randomised studies of the Ginkgo preparations, either as the sole treatment or as an adjunct to
105 other treatments which were applied in both groups (intervention and control groups) in the same
106 manner, will be included. Ginkgo preparations include ginkgo biloba, ginkgolides, bilobalides,
107 ginkgo biloba leaves dispersible tablet, Ginkgo Leaf Capsule, Ginkgo Leaves Soft gel Capsule,
108 Ginkgo damole Injection, Yinxing damo, Ginkgo biloba granule, Yinxing Guttate Dropping Pill,
109 Ginkgo biloba extract injection, Ginkgo distillate, Diterpene Ginkgolides Meglumine Injection,
110 Ginkgolide Injection, Ginkgo Biloba Leaves Extract Oral Solution, Ginkgo Leaf Extract,
111 Armillariella Mellea Powders Oral Solution, Yinxing Guttate Dropping Pills, Egb 761, Ginaton®,
112 Tebonin forte, Rokan®, Tanakan®, Ginkobil®, GBE50, Kaveri® and Shuxuening Zhushuye. The
113 control groups will include psychostimulants drug use, placebo use, psychotherapy and no
114 treatment.

115 Outcomes measures**116 Primary outcomes:**

117 The ADHD rating Scale-IV (ADHD-RS-IV).

118 Conner's Hyperactivity Index.

119 Secondary outcomes:

120 Quality of life.

121 Adverse effects/events.

122 Data sources

123 We will search the following electronic bibliographic databases: Medline, Embase, the Cochrane
124 Central Register of Controlled Trials (CENTRAL), Web of Science (science and social science
125 citation index), China Biology Medicine Disc (CBMdisc), China National Knowledge
126 Infrastructure Database (CNKI), Wanfang Database and Chinese Scientific Journals Database
127 (VIP). The search strategy will include terms relating to or describing the patients and intervention.
128 The terms will be combined with the Cochrane MEDLINE filter for controlled trials of
129 interventions.

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3 130 **Search strategies**

4 131 The search of Medline will be conducted using the following terms: (ginkgo biloba OR
5 132 ginkgolides OR bilobalides OR ginkgo biloba leaves dispersible tablet OR Ginkgo Leaf Capsule
6 133 OR Ginkgo Leaves Soft gel Capsule OR Ginkgo damole Injection OR Yinxing damo OR Ginkgo
7 134 biloba granule OR Yinxing Guttate Dropping Pill OR Ginkgo biloba extract injection OR ginkgo
8 135 distillate OR Diterpene Ginkgolides Meglumine Injection OR Ginkgolide Injection OR Ginkgo
9 136 Biloba Leaves Extract Oral Solution OR Ginkgo Leaf Extract OR Armillariella Mellea Powders
10 137 Oral Solution OR Yinxing Guttate Dropping Pills OR Egb 761 OR Egb761 OR Ginaton® OR
11 138 Tebonin forte OR Tanakan® OR Rökan® OR Ginkobil® OR GBE50 OR Kaveri® OR
12 139 Shuxuening Zhushuye) AND (attention deficit hyperactivity disorder OR ADHD OR hyperkinetic
13 140 disorders). The strategies will be modified for Embase, Cochrane, Web of Science, CBM, CNKI,
14 141 Wanfang and VIP.

15 142 The search terms will be adapted for use with above bibliographic databases in combination with
16 143 database-specific filters for controlled trials, where these are available. There will be no language
17 144 restrictions. Studies published with no limitations will be sought. The date the searches conducted
18 145 will be recorded.

19 146 **Data collection and analysis**

20 147 **Selection of studies**

21 148 Two authors (SF He and M WANG) will select studies by assessing the titles and abstracts after
22 149 duplication removal. Full-text will be further reviewed for eligibility. Randomized controlled trials
23 150 that investigated the efficacy and safety of meditation therapy in children or adolescents diagnosed
24 151 with ADHD will be selected. Study selection will be documented and summarised in a
25 152 PRISMA-compliant flow chart (Figure 1)(<http://www.prisma-statement.org>).

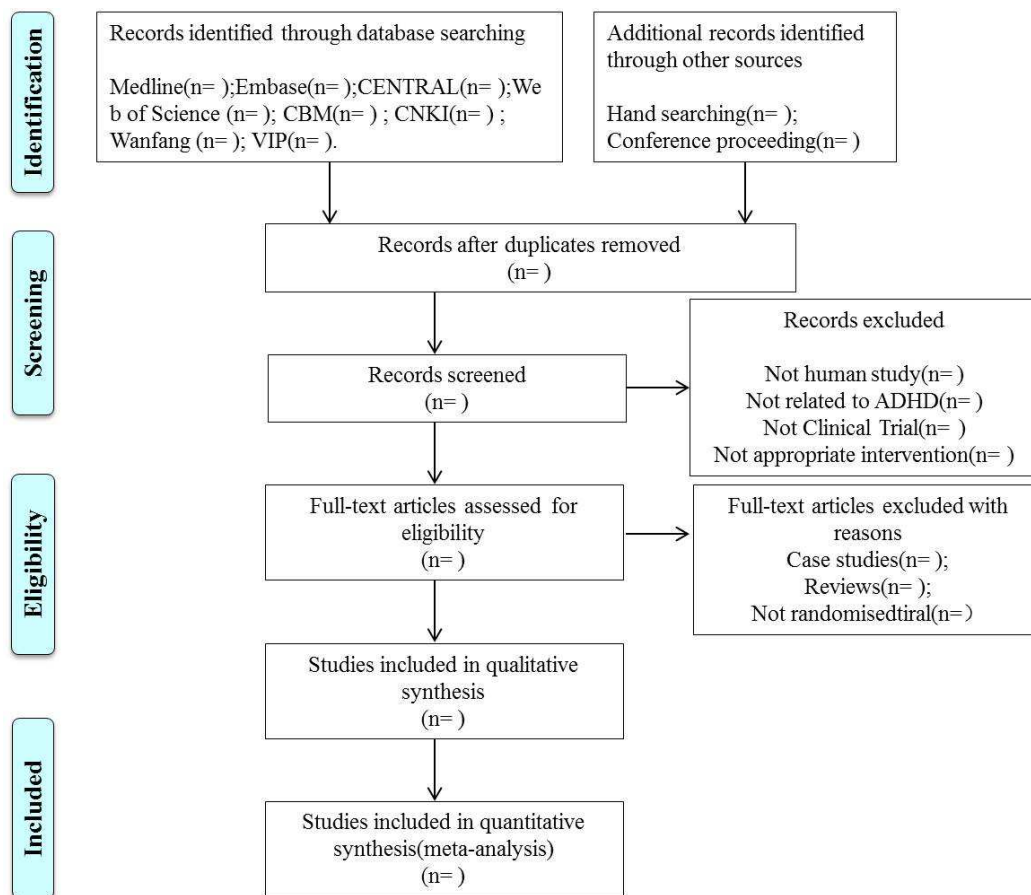


Figure 1 PRISMA flow diagram of searching and screening studies.

Data extraction

Two authors (SF He and M Wang) will independently conduct the data extraction and risk of bias assessment using a predefined data extraction form. Information will be collected with first author, publication year, study design, intervention, dosage, diagnostic criteria, disease duration, number of participants allocation, dropout, duration, outcome, outcome results(e.g., ADHD-RS-IV, Conner's Hyperactivity Index, quality of life and adverse effects/events), follow-up periods, adverse effects/events. We will conduct GRADEpro software to make a summary of findings table.

Any disagreement between two authors will be resolved by discussion, finally judged by XM Gao. When the data are insufficient, TY Zhang will contact the author for additional information by mail.

Assessment of risk of bias in included studies

We will assess risk of bias of included studies by risk of bias assessment tool according to the guidelines of the Cochrane Handbook^[31]. Risk of bias in included studies will be classified as low, unclear and high by SF He and M Wang. The following will be assessed: random sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective outcome reporting.

Data synthesis and analysis

A meta-analysis will be conducted with either random-effect model or fixed-effect model when studies are identified. We will use Review Manager 5.3.5 software (RevMan 5.3.5) to combine

175 data from trials. Mean differences (MD) or standardized mean differences (SMD) for continuous
176 outcomes and risk ratio (RR) for dichotomous outcomes with 95% confidence intervals (95% CIs)
177 will be pooled by RevMan 5.3.5. A systematic narrative synthesis will be done to summarise the
178 relationship of the included studies if quantitative synthesis is not appropriate.

179 ***Dealing with missing data***

180 We will attempt to collect data from original study investigators if possible for missing data or
181 incomplete data. If failed to get data, we will consider estimating it.

182 ***Assessment of reporting biases***

183 We will detect reporting biases by funnel plots if more than 10 studies are included. Asymmetry
184 test will be conducted by Egger's method^[32].

185 ***Assessment of heterogeneity***

186 Heterogeneity will be tested with chi-squared (χ^2 , or Chi2) test for P value. I^2 will be calculated.
187 We consider that the I^2 value >50% indicates substantial heterogeneity^[33]. We will either perform
188 subgroup analysis or narrative descriptions according to different situations(e.g., lack of included
189 trials).

190 ***Subgroup analysis and investigation of heterogeneity***

191 Subgroup analysis will be performed to explore the source of heterogeneity by the type of ginkgo
192 preparations, the dose, follow-up period and type of control.

193 ***Sensitivity analysis***

194 Low quality trials will be excluded by conducting sensitivity analysis according to different effect
195 models. Reporting of sensitivity analysis will be done by producing a summary table.

197 **Discussion**

198 The purpose of our systematic review is to give a detailed summary of effectiveness and tolerance
199 assessment of ginkgo preparations treatment for ADHD. Even though ginkgo preparations have
200 been used in ADHD, no systematic reviews on the effects and safety have been published. We will
201 identify subtypes that are particularly useful for specific subgroups according to different types of
202 ginkgo preparations. We hope that our study will provide reference for physicians, patients and
203 parents in ADHD clinical practice.

204
205 **Contributors** The protocol was drafted by SF He, M Wang, XM Gao. The search strategy was
206 developed and will be run by SF He and JH Si. Selection of the studies will be carried out by SF
207 He and M Wang. Extraction of data from studies will conducted by SF He and Hong Cui. Analysis
208 will be performed by SF He and TY Zhang. All authors have read and approved the final protocol.
209 This review will be updated by SF He and M Wang.

210 **Funding** This study is supported by a project of National Natural Science Foundation of China
211 (NO.81630106).

212 **Competing interests** None.

213 **Provenance and peer review** Not commissioned; externally peer reviewed.

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For peer review only

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	28
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	4-12
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	205-209
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	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	210-211
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	210-211
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	210-211
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	14-27

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	16-17
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	90-112
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input checked="" type="checkbox"/>	<input type="checkbox"/>	120-127
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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	128-143
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	151
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	154-155
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>	154-155
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	156-159
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input checked="" type="checkbox"/>	<input type="checkbox"/>	113-119
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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	163-168
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	169-174
	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 (e.g., I^2 , Kendall's tau)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	169-185
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-	<input checked="" type="checkbox"/>	<input type="checkbox"/>	186-191

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		regression)			
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	174-175
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	179-181
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	159

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Efficacy and Safety of Ginkgo Preparations for Attention Deficit Hyperactivity Disorder: A Systematic Review Protocol

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Manuscripts

1 Efficacy and Safety of Ginkgo Preparations for Attention Deficit Hyperactivity Disorder: A
2 Systematic Review Protocol

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15 **Abstract**

16 **Introduction** Attention Deficit Hyperactivity Disorder (ADHD) is one of the most commonly
17 diagnosed and treated childhood psychiatric disorders. The analogous diagnosis adopted in Europe
18 is hyperkinetic disorder, which is defined in the World Health Organization's (WHO's)
19 International Classification of Diseases (10th edition; ICD-10). Hyperkinetic disorder includes
20 more severe conditions. Ginkgo preparations are used in the treatment of ADHD. The present
21 study will assess the efficacy and safety of ginkgo preparations in the treatment of ADHD in the
22 currently published literature.

23 **Materials and methods** All prospective randomized controlled trials (RCTs) will be included in
24 this systematic review. Patients diagnosed with ADHD according to American Psychiatric
25 Association's Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV),
26 Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), ICD-10, or
27 Chinese Classification and Diagnosis of Mental Diseases-3rd edition (CMDD) will be included. A
28 comprehensive search for randomized controlled trials to evaluate the effectiveness and tolerance
29 of ginkgo preparations will be performed. The primary outcomes are the ADHD rating Scale-IV
30 (ADHD-RS-IV) and Revised Conners' Parent Rating Scale (CPRS-R). The secondary outcomes
31 are quality of life evaluated by the KINDL scale, adverse effects/events, Conners' Teacher Rating
32 Scale (CTRS), Strengths and Weaknesses of ADHD Symptoms and Normal Behaviour (SWAN)
33 Scale, and Fremdbeurteilungsbogen für Hyperkinetische Störungen (FBB-HKS). Exclusion
34 criteria are the following: 1) Case reports; not randomized trial; non-comparative studies, 2)
35 Patients who were not diagnosed based on DSM-IV, DSM-5, ICD-10 or CMDD. The following
36 databases will be searched from their inception until Jan 2018: Medline, Embase, the Cochrane
37 Central Register of Controlled Trials, Web of Science, China Biology Medicine Disc, China
38 National Knowledge Infrastructure Database, Wanfang Database and Chinese Scientific Journals
39 Database. Two authors will independently perform the study selection, extract the data, and assess
40 the study quality and risk of bias.

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3 41 **Ethics and dissemination** This systematic review does not require ethics approval. It will be
4 42 published in a peer-reviewed journal.

5 43 **PROSPERO registration number** CRD42017077190
6
7 44

8 45 **Strengths and limitations of this study**

9 46 This study will evaluate the safety of ginkgo preparations as a sole or adjunct agent for ADHD
10 47 treatment.

11 48 Our review will be useful to clinicians, patients and parents who use ginkgo preparations for
12 49 ADHD treatment.

13 50 Clinical heterogeneity may exist for different dosage forms of ginkgo preparations, doses,
14 51 durations and combined treatments.

15 52 There may be a language bias with the limitation of English and Chinese studies.
16 53

17 54 **Introduction**

18 55 **Description of the condition of ADHD treatment**

19 56 The prevalence of attention deficit hyperactivity disorder (ADHD) in children and adolescents is
20 57 as high as 3.4% in the general population^[1], and it is one of the most commonly diagnosed and
21 58 treated childhood psychiatric disorders^[2]. The diagnosis rate rises to 6.26% in China^[3]. The
22 59 analogous diagnosis adopted in Europe is hyperkinetic disorder, which is defined in the ICD-10.
23 60 Hyperkinetic disorder includes more severe conditions.^[4] ADHD is a childhood-onset
24 61 neurodevelopmental disorder that may persist into adolescence and adulthood, and it has a high
25 62 societal burden. The primary symptoms consist of inattention and hyperactivity/impulsivity that
26 63 are often accompanied by other neurodevelopment disorders, such as autism spectrum disorder^[5]
27 64 and intellectual disability^[6]. A large proportion of adolescents and adults with ADHD exhibit
28 65 antisocial behaviour and criminal activities, including conduct disorder, oppositional defiant
29 66 disorder^[7], risk of crashing^[8], sexual offenses^[9] and arson^[10], especially among arrested, convicted
30 67 and imprisoned adolescents and adults. Therefore, ADHD has been increasingly considered a
31 68 severe social issue.

32 69 Stimulants are the first-line medications for ADHD treatment. Patients with ADHD manage their
33 70 symptoms by using stimulants. However, the risk of substance abuse may increase in this patient
34 71 population, and substance use disorder (SUD) is one of the most common comorbid psychiatric
35 72 disorders in adolescent and adult patients^[11-12]. The related adverse side-effects of stimulants
36 73 include cardiovascular events, insomnia, appetite loss, hypoevolutism, gastrointestinal symptoms,
37 74 and tics^[13]. Complementary or alternative medical treatments for ADHD, such as plant-based
38 75 medications, acupuncture^[14] and music therapy^[15], are considered because of the side effects,
39 76 abuse and misuse of conventional pharmacological treatments. It is also important to evaluate the
40 77 efficacy and safety of plant-based medications and acupuncture.

41 78 **Description of the intervention**

42 79 Ginkgo biloba preparations, including tablets, granules, pills, injection distillates, oral solutions,
43 80 extracts, and dropping pills, are approved for commercial marketing. Egb 761®, Ginaton®,
44 81 Tebonin®, Rokan®, Tanakan®, Ginkobil®, GBE50®, and Kaveri® are approved in the USA and
45 82 Europe. Ginkgo Biloba Leaves Dispersible Tablet, Ginkgo Leaf Capsule, Ginkgo Leaves Soft Gel
46 83 Capsule, Ginkgo Damole Injection, YinxingDamo, Ginkgo Biloba Granule, YinxingGuttate
47 84 Dropping Pill, Ginkgo Biloba Extract Injection, Ginkgo Distillate, Diterpene Ginkgolides

85 Meglumine Injection, Ginkgolide Injection, Ginkgo Biloba Leaves Extract Oral Solution, Ginkgo
86 Leaf Extract, Armillariella Mellea Powders Oral Solution, YinXingGuttate Dropping Pills, and
87 Shuxuening Zhusheye are approved by the China Food and Drug Administration (CFDA). Ginkgo
88 preparations are among the best-selling botanical dietary supplements worldwide. Clinical
89 evidence indicates that Ginkgo biloba is safe and exhibits no excess side effects compared with
90 placebo for cognitive impairment and dementia^[16]. However, the evidence of efficacy is
91 equivocal.^[17]

92 Ginkgo preparations alleviate the conditions such as autism^[18], depression^[19], and
93 neuropsychiatric symptoms such as anxiety^[20]. Ginkgo preparations may affect the behavioral and
94 cognitive aspects of ADHD. The predominant behavioral effects are calming and improved
95 frustration tolerance. Ginkgo biloba induces willful cognition, discriminant attention and
96 decreases irritability^[21].

97 **How the intervention might work**

98 Components isolated from ginkgo biloba contain terpene trilactones, flavonol glycosides,
99 isoflavonoids, biflavones, proanthocyanidins, alkylphenols, carboxylic acids,
100 4-O-Methylpyridoxine and polyphenols^[22-24]. Preclinical evidence indicates that ginkgo flavonol
101 glycosides are predominantly responsible for the antioxidant activity^[25]. The antioxidant activity
102 of ginkgo flavonol glycosides reduce reactive oxygen species (ROS)-induced oxidative stress,
103 which contributes to neurodevelopmental disorders by causing membrane damage, changes in
104 protein structure and function, lipid denaturation and DNA damage^[26]. Terpene trilactones are
105 associated with neuroprotective properties^[27]. Investigations have demonstrated that terpene
106 trilactones attenuate the decrease in brain-derived neurotropic factor (BDNF), norepinephrine
107 transporter (NET) and dopamine transporter (DAT)^[28], which are negatively related to ADHD
108 pathogenesis^[29-31].

109 No comprehensive quantitative reviews of treatments of ADHD with ginkgo preparations have
110 been performed. Therefore, it is important to investigate the current evidence of the efficacy and
111 tolerance of ginkgo preparations therapy for ADHD.

112 **Materials and methods**

113 **Registration information**

114 This systematic review protocol adheres to the preferred reporting items for systematic review and
115 meta-analysis protocols (PRISMA-P) 2015^[32]. The protocol was registered on PROSPERO, and
116 the registration number is CRD42017077190.

117 **Inclusion criteria**

118 ***Types of study***

119 All prospective randomized controlled trials (RCTs) will be included in this systematic review, but
120 trials without detailed data will be excluded. Abstracts with sufficient outcome data will be
121 included. Cross-over trials will be included with the two phases of data if there is sufficient
122 washout and return to baseline.

123 ***Type of participants***

124 Patients with ADHD or hyperkinetic disorder who were diagnosed based on American Psychiatric
125 Association's Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV);
126 Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5); WHO's
127 International Classification of Diseases (10th edition; ICD-10); or Chinese Classification and
128

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2
3 129 Diagnosis of Mental Diseases-3rd edition (CMDD) will be included. There will be no limitations
4 130 on age or sex.

5 131 ***Types of interventions and controls***

6 132 Randomized studies of the ginkgo preparations, as the sole treatment or as an adjunct to other
7 133 treatments, that were used in the intervention and control groups in the same manner will be
8 134 included. Ginkgo preparations include Egb 761®, Ginaton®, Tebonin®, Rokan®, Tanakan®,
9 135 Ginkobil®, GBE50®, and Kaveri®, Ginkgo Biloba Leaves Dispersible Tablet, Ginkgo Leaf
10 136 Capsule, Ginkgo Leaves Soft Gel Capsule, Ginkgo Damole Injection, YinxingDamo, Ginkgo
11 137 Biloba Granule, YinxingGuttate Dropping Pill, Ginkgo Biloba Extract Injection, Ginkgo Distillate,
12 138 Diterpene Ginkgolides Meglumine Injection, Ginkgolide Injection, Ginkgo Biloba Leaves Extract
13 139 Oral Solution, Ginkgo Leaf Extract, Armillariella Mellea Powders Oral Solution, YinxingGuttate
14 140 Dropping Pills, and Shuxuening Zhushuye. The control groups will include psychostimulant drug
15 141 use, placebo use, psychotherapy and no treatment.

16 142 **Outcomes measures**

17 143 ***Primary outcomes:***

18 144 The ADHD rating Scale-IV (ADHD-RS-IV).

19 145 The Revised Conners' Parent Rating Scale (CPRS-R).^[33]

20 146 ***Secondary outcomes:***

21 147 Quality of life on the KINDL scale.^[34]

22 148 Adverse effects/events.

23 149 Conners' Teacher Rating Scale (CTRS).^[35]

24 150 Strengths and Weaknesses of ADHD Symptoms and Normal Behaviour (SWAN) Scale.^[36]

25 151 Fremdbeurteilungsbogen für Hyperkinetische Störungen (FBB-HKS).^[37]

26 152 **Exclusion criteria**

27 153 1) Case reports; not randomized trial; non-comparative studies.

28 154 2) Patients who were not diagnosed based on DSM-IV, DSM-5, ICD-10 or CMDD.

29 155 **Data sources**

30 156 We will search the following electronic bibliographic databases: Medline, Embase, the Cochrane
31 157 Central Register of Controlled Trials (CENTRAL), Web of Science (science and social science
32 158 citation index), China Biology Medicine Disc (CBMdisc), China National Knowledge
33 159 Infrastructure Database (CNKI), Wanfang Database and the Chinese Scientific Journals Database
34 160 (VIP). The search strategy will include terms relating to or describing the patients and intervention.
35 161 The terms will be combined with the Cochrane MEDLINE filter for controlled trials of
36 162 interventions.

37 163 **Search strategies**

38 164 A search of Medline will be performed using the following terms: (ginkgo biloba OR ginkgolides
39 165 OR bilobalides OR ginkgo biloba leaves dispersible tablet OR Ginkgo Leaf Capsule OR Ginkgo
40 166 Leaves Soft gel Capsule OR Ginkgo damole Injection OR Yinxing damo OR Ginkgo biloba
41 167 granule OR Yinxing Guttate Dropping Pill OR Ginkgo biloba extract injection OR ginkgo
42 168 distillate OR Diterpene Ginkgolides Meglumine Injection OR Ginkgolide Injection OR Ginkgo
43 169 Biloba Leaves Extract Oral Solution OR Ginkgo Leaf Extract OR Armillariella Mellea Powders
44 170 Oral Solution OR Yinxing Guttate Dropping Pills OR Egb 761 OR Egb761 OR Ginaton® OR
45 171 Tebonin forte OR Tanakan® OR Rökan® OR Ginkobil® OR GBE50 OR Kaveri® OR
46 172 Shuxuening Zhushuye) AND (attention deficit hyperactivity disorder OR ADHD OR hyperkinetic

173 disorders). The strategies will be modified for Embase, Cochrane, Web of Science, CBM, CNKI,
174 Wanfang and VIP.

175 The search terms will be adapted for use with the above bibliographic databases in combination
176 with database-specific filters for controlled trials, when available. Language is limited with
177 English and Chinese. The databases will be searched from their inception until Jan 2018.

178 **Data collection and analysis**

179 ***Selection of studies***

180 Two authors (SF He and M WANG) will select studies by assessing the titles and abstracts after
181 duplication removal. The full text will be further reviewed for inclusion. Randomized controlled
182 trials that investigated the efficacy and safety of meditation therapy in patients diagnosed with
183 ADHD will be selected. Study selection will be documented and summarized in a
184 PRISMA-compliant flow chart (Figure 1)(<http://www.prisma-statement.org>).

185 ***Data extraction***

186 Two authors (SF He and H Cui) will independently perform data extraction and risk of bias
187 assessments using a predefined data extraction form. The first author, publication year, study
188 design, intervention, dosage, diagnostic criteria, disease duration, number of participants
189 allocation, dropout, duration, outcome, outcome results (e.g., ADHD-RS-IV, CPRS-R, quality of
190 life on the KINDL scale and adverse effects/events, et al) and follow-up periods will be collected.
191 We will use GRADEpro software to create a summary of findings table.

192 Any disagreement between the two authors will be resolved by discussion, and XM Gao will make
193 the final decision. TY Zhang will contact the authors for additional information by mail when the
194 data are insufficient.

195 ***Assessment of study quality and risk of bias***

196 The quality of the studies for each outcome will be assessed using the Grading of
197 Recommendations Assessment, Development and Evaluation classification system (GRADE),
198 which will be judged by limitations in the design and implementation, imprecision, inconsistency,
199 indirectness and reporting bias. Evidence quality will be classified into four levels: high, moderate,
200 low or very low.

201 We will assess the risk of bias of the included studies using a risk of bias assessment tool
202 according to the guidelines of the Cochrane Handbook^[38]. SF He and M Wang will classify the
203 risk of bias in the included studies as low risk, unclear risk and high risk. The following factors
204 will be assessed: random sequence generation, allocation sequence concealment, blinding of
205 participants and personnel, blinding of outcome assessment, incomplete outcome data and
206 selective outcome reporting.

207 ***Data synthesis and analysis***

208 A meta-analysis will be performed using a random-effect model or fixed-effect model for the
209 identified studies. We will use Review Manager 5.3.5 software (RevMan 5.3.5) to combine the
210 data from the trials. The mean differences (MD) or standardized mean differences (SMD) for
211 continuous outcomes and risk ratio (RR) for dichotomous outcomes with 95% confidence
212 intervals (95% CIs) will be pooled in RevMan 5.3.5. A systematic narrative synthesis will be
213 performed to summarize the relationship of the included studies when quantitative synthesis is not
214 appropriate.

215 ***Dealing with missing data***

216 We will attempt to collect data from original study investigators if possible for missing or

1
2
3 217 incomplete data. We will consider estimating data if we cannot obtain the original source.

4 218 **Assessment of reporting biases**

5 219 We will detect reporting biases using funnel plots if more than 10 studies are included. An
6 220 asymmetry test will be performed using Egger's method^[39].

7 221 **Assessment of heterogeneity**

8 222 Heterogeneity will be tested using the chi-squared (χ^2 , or Chi2) test for the P value. I^2 will be
9 223 calculated. An I^2 value >50% will indicate substantial heterogeneity^[40]. We will perform subgroup
10 224 analyses or narrative descriptions based on the situation (e.g., lack of included trials).

11 225 **Subgroup analysis and investigation of heterogeneity**

12 226 Subgroup analysis will be performed to explore the source of heterogeneity by the different dosage
13 227 forms of ginkgo preparations, dose, follow-up period and type of control.

14 228 **Sensitivity analysis**

15 229 Low-quality trials will be excluded from sensitivity analyses according to the different effect
16 230 models. A summary table will report the results of the sensitivity analyses.

17 231

18 232 **Discussion**

19 233 Our systematic review will provide a detailed summary of the efficacy and tolerance of ginkgo
20 234 preparations for the treatment of ADHD. Ginkgo preparations are used in ADHD treatment, but no
21 235 systematic reviews on the efficacy or safety have been published. We will identify ginkgo
22 236 preparation subtypes that are particularly useful in specific subgroups. We hope that our study will
23 237 provide a reference for physicians, patients and parents in ADHD clinical practice.

24 238

25 239 **Contributors** SF He, M Wang, and XM Gao drafted the protocol. SF He and JH Si developed and
26 240 will perform the search strategy. SF He and M Wang will select the studies. SF He and Hong Cui
27 241 will extract data from selected studies. SF He and TY Zhang will perform the analyses. All of the
28 242 authors read and approved the final protocol. SF He and M Wang will update this review.

29 243 **Funding** This study is supported by the National Natural Science Foundation of China (No.
30 244 81630106).

31 245 **Competing interests** None.

32 246 **Provenance and peer review** Not commissioned; externally peer reviewed.

33 247 **Ethics and dissemination** This systematic review does not require ethics approval. It will be
34 248 published in a peer-reviewed journal.

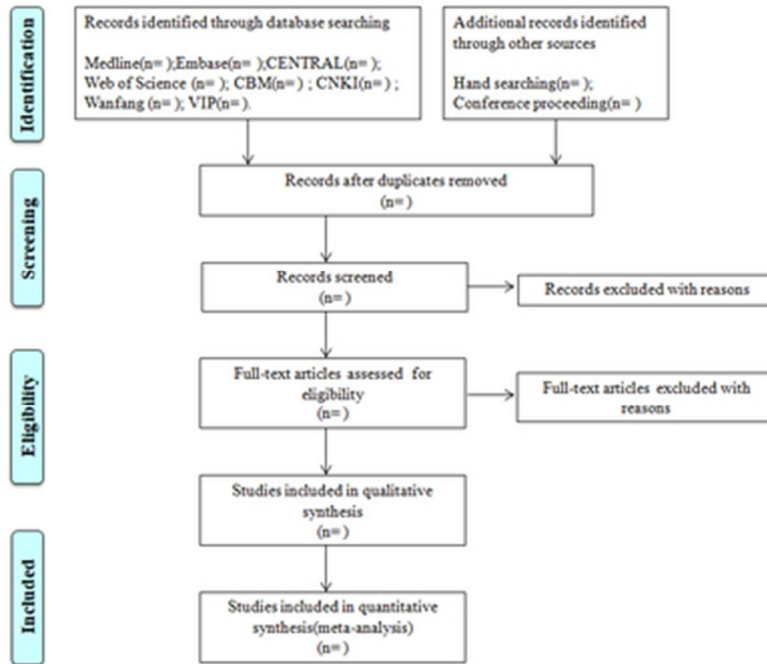
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17 363 Cochrane Collaboration. <http://www.cochrane-handbook.org>, 2011.
- 18 364 Figure 1 PRISMA flow diagram of the study searching and screening.
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PRISMA flow diagram of the study searching and screening studies

16x14mm (600 x 600 DPI)

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	43
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	3-14
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	239-242
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	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	243-244
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	243-244
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	243-244
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	55-108
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	23-33

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	118-151
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input checked="" type="checkbox"/>	<input type="checkbox"/>	155-162
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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	163-177
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	185-230
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	179-184
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>	185-194
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	187-190
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input checked="" type="checkbox"/>	<input type="checkbox"/>	142-151
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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	195-206
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	207-210
	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 (e.g., I^2 , Kendall's tau)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	210-214 221-224
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	225-230
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	212-214
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective	<input checked="" type="checkbox"/>	<input type="checkbox"/>	218-220

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Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		reporting within studies)			
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	195-200

For peer review only

