Comparative effectiveness of different types of exercise in reducing arterial stiffness in children and adolescents: a systematic review and network meta-analysis

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ABSTRACT
Objective Arterial stiffness is an early and detectable marker of vascular changes leading to atherosclerotic cardiovascular disease (ACVD). Our objective was to compare the effectiveness of different types of exercise in reducing arterial stiffness in children and adolescents.

Design A systematic review and network meta-analysis (NMA) was conducted including experimental studies reporting the effects of exercise interventions on pulse wave velocity (PWV) in children and adolescents.

Data sources Cochrane Central Register of Controlled Trials, EMBASE (via Scopus), PubMed (via Medline) and Web of Science from database inception to 25 March 2022.

Eligibility criteria Experimental studies reporting the effects of exercise interventions on PWV in children and adolescents.

Results Fourteen studies were included in the NMA, all of them were randomised controlled trials except one quasi-experimental study, with an overall risk of bias of some concern. Regarding PWV reduction, all exercise modalities were more effective than control, with standardised mean difference ranging from −1.93 (95% CI: −2.84 to −1.02) and −1.11 (95% CI: −2.01 to −0.21) for aerobic exercise and high intensity interval training (HIIT), respectively, to −0.59 (95% CI: −1.39 to 0.22) for combined exercise. Only sensorimotor training was not superior to the control group 0.11 (95% CI: −1.10 to 1.32).

Conclusion Our results support that exercise interventions, especially aerobic exercise or HIIT, can improve arterial stiffness at early ages. The potential to address ACV early and mitigate long-term consequences via exercise interventions in children and adolescents with higher arterial stiffness requires further investigation.

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WHAT IS ALREADY KNOWN ON THIS TOPIC
⇒ Arterial stiffness is one of the earliest and most detectable markers of vascular changes leading to atherosclerotic cardiovascular disease (ACVD).
⇒ Previous evidence supports exercise as an effective approach to reduce arterial stiffness in adults, however, such beneficial effects remain unclear in children and adolescents.

WHAT THIS STUDY ADDS
⇒ Exercise interventions, especially aerobic exercise or high intensity interval training, can improve arterial stiffness in children and adolescents.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY
⇒ Our results support the potential for a new prevention paradigm to mitigate ACV early through the power of an active lifestyle.

INTRODUCTION
Atherosclerotic cardiovascular diseases (ACVDs) are the leading cause of death globally and their prevention is one of the health priorities worldwide.1 The onset of molecular and tissue changes leading to the atherosclerosis process starts in the early years of life.2 3 Thus, because ACV is a reversible process, the recognition and prevention of ACVD risk factors at early ages, when signs of atherosclerosis and endothelial dysfunction are incipient,4 is a pivotal strategy to reduce ACVD morbidity and mortality in the general population.5

One of the earliest and most detectable markers of vascular changes leading to ACVD is arterial stiffness (AS),6 which can be defined as the reduced ability of an artery to expand and contract in response to pressure changes.7 Arterial stiffening is characterised by collagen deposition and cross-linking, elastin fatigue fracture, and other degenerative alterations of the extracellular matrix in the media layer. From a pathological perspective, arterial stiffening differs from atherosclerosis, a condition marked by lipid accumulation, inflammatory cells, vascular smooth muscle cells migration and foam cell production that typically affects the intima layer. However, both pathological processes frequently coexist in the same vascular regions, share some risk factors and are a result of vascular ageing.8 9

AS is an established vascular biomarker of subclinical ACVD and a useful tool for cardiovascular risk stratification, since when measured by pulse wave velocity (PWV), its non-invasive gold-standard measurement,10 it is independently associated...
with the risk of cardiovascular events and mortality.\textsuperscript{11–14} The PWV can be measured using different methods and at different sites depending on the two target arteries.\textsuperscript{14–15} The American Heart Association scientific statement and the European expert consensus\textsuperscript{16–17} consider that carotid–femoral PWV (cfPWV) measured by tonometry is the gold standard method.

Previous evidence has shown that exercise is an effective approach to reduce AS in adults, such that moderate-vigorous aerobic, combined, interval training and mind–body exercises are recommended as effective tools to reduce the AS in adults.\textsuperscript{18–21}

However, such beneficial effects remain unclear in children and adolescents, who considering not only the effects of age on AS, but also the tracking of modifiable ACVD risk factors from early ages through adulthood,\textsuperscript{22} postulated as an important target population for these interventions. Moreover, because both cardiovascular risk factors and fitness levels in childhood are predictors of ACVD events in adulthood, and because moderate to vigorous exercise is an effective strategy to modify fitness levels, it is expected that exercise in childhood may decrease the risk of ACVD even at an early age.\textsuperscript{23}

Consequently, the aim of this study was to determine which type of exercise and what dosage in terms of duration, frequency, volume and intensity is the most effective in reducing the subclinical AS process in children and adolescents. For this aims, we used a network meta-analysis (NMA) approach, which allows a comprehensive and consistent analysis of all randomised controlled trials (RCTs) comparing, head-to-head or control the effect of different modalities of exercise while fully respecting randomisation.

**METHODS**

This systematic review and NMA protocol was registered in PROSPERO (registration number: CRD42022322536) and was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement extension for NMA guidelines\textsuperscript{24} and the Cochrane Handbook for Systematic Reviews of Interventions recommendations.\textsuperscript{25}

**Search strategy**

We systematically searched the following electronic databases: Cochrane Central Register of Controlled Trials, EMBASE (via Scopus), PubMed (via Medline) and Web of Science from database inception to 26 December 2022. The search strategy was designed combining the following keywords with Boolean operators: (1) “cardiovascular disease”, “cardiovascular risk”, “arterial stiffness”, “pulse wave velocity”, “PWV” (2) “physical activity”, “physical exercise”, “exercise”, “training”, “HIIT”, “interval training”, “intermittent exercise”, “continuous exercise”, “aerobic exercise”, “endurance training”, “resistance exercise”, “strength”, “stretching”, “mind–body exercises”, “pilates”, “yoga”, “Tai Chi”, “sport” (3) “child*”, “pediatric”, “infan*”, “kids”, “young”, “adolescents”, “teen*” (4) “effectiveness”, “clinical trial”, “trials”, “controlled trial”, “random*”, “clinical trials”. The full search strategy for the MEDLINE database is displayed in online supplemental table S2. We completed the systematic search with a review of the reference lists of articles considered suitable for inclusion and a review of ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform, and the International Standard Randomised Controlled Trial Number Registry (ISRCTN) for all registered clinical trials. Two independent reviewers (IS-D and IC-R) performed the systematic review of the literature and disagreements were resolved by consensus.

**Eligibility**

Both RCTs and non-randomised experimental trials evaluating the effects of exercise on AS measured by PWV in children and adolescents were eligible for inclusion in the systematic review and NMA. No restriction was applied to the type of PWV measurement or the assessing method. Studies were excluded if they reported the acute effect of exercise only (measurement of PWV before and immediately after the exercise intervention), included adult populations where disaggregation of data for children, adolescents and adults was not possible. No language limitations were applied. Screening and trial selection were conducted independently by two reviewers (IS-D and IC-R), and disagreements were resolved by consensus.

**Data extraction and classification of the intervention**

We independently extracted the following information from each study that met the inclusion criteria: (1) study reference, (2) country, (3) study design, (4) population characteristics (sample size, percentage of female participants, mean age and type of population), (5) intervention characteristics (type of exercise, duration, frequency, volume and intensity) and (6) outcome characteristics (type of PWV measurement, measurement method and mean basal PWV measurements).

We classified exercise interventions included in this NMA as aerobic exercise (interventions aimed at increasing heart rate and energy expenditure such as cycling or running), resistance training (aimed at increasing muscle strength and muscle power), high intensity interval training (HIIT) (considered aerobic exercise with alternating periods of low and high intensity), combined exercise (including only aerobic exercise and resistance training) or sensorimotor training (aimed at improving the neuromuscular system through coordination and balance).

**Equity, diversity and inclusion statement**

Our research team is committed to promote diversity, equity and inclusion in our clinical work, research and training programmes. We understand that systemic inequalities and biases can impact the research process, and we are taking steps to address these challenges. Consequently, data extraction, processing and interpretation was performed with minimum restrictions in order to obtain results as reflection of reality that is as accurate and diverse as possible.

**Risk of bias assessment**

To assess the potential bias of RCTs, we used the Cochrane Collaboration’s tool for assessing risk of bias.\textsuperscript{26} This tool assesses the risk of bias according to five bias domains that were reviewed: randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. Studies could be rated as ‘low risk of bias’ if all domains are classified as ‘low risk’, ‘some concerns’ if there is at least one domain rated as ‘some concern’ and none rated as ‘high risk’, and ‘high risk of bias’ if there is at least one domain rated as ‘high risk’ or four or more domains rated as ‘some concerns’.

To analyse the risk of bias of quasi-experimental studies, we used the Risk of Bias in Non-randomised Studies of Intervention (ROBINS-I).\textsuperscript{27} This tool assesses the risk of bias according to six domains: bias due to confounding, bias in the selection of participants, bias in the classification of interventions, bias due to deviations from the intended interventions, bias due to missing data and bias in the selection of the reported results. Overall studies bias will be considered a ‘low risk of bias’ if all domains have
been classified as a low, ‘moderate risk of bias’ if all domains have been classified as a low or moderate, ‘serious risk of bias’ if there is at least one domain rated as serious risk, ‘critical risk of bias’ if there is at least one domain rated as critical risk, and ‘no information’ if there is no clear indication that the study is at a serious or critical risk of bias and there is a lack of information about one or more key domains of bias.

Data extraction and quality assessment were independently performed by two reviewers (IS-D and IC-R). Inconsistencies were resolved by consensus or involving a third researcher (AS-L).

**Measures of treatment effect**

Effect estimates were calculated as standardised mean differences (SMD) with their respective 95% compatibility intervals (CIs) using Cohen’s d-index. Negative SMD values indicate an improvement of PWV in favour of the intervention group. Cohen’s d values of approximately 0.2 were considered to indicate weak effects, values of approximately 0.5 were considered to indicate moderate effects, values of approximately 0.8 were considered to indicate strong effects, and values above 1.0 were considered to indicate very strong effects. The SMD was used as the effect size estimate because the included studies provided outcome values using different instruments measuring the same clinical outcome.

**Statistical analysis and data synthesis**

We used a network plot to visualise the geometry of the network in which the nodes represent the different interventions, and the edges display the observed intervention comparisons (direct evidence). The nodes size is proportional to the number of participants randomised to this class. The thickness of the edges indicates the frequency with which each comparison occurs in the network (number of studies). We allow for different colours across edges and nodes to display the distribution of various trial and comparison characteristics.

We checked for whether normality could be assumed for our outcome and consequently, the quantitative synthesis was allowed. For this purpose, we evaluated if authors tested the normality of the outcome through specific tests and we calculated the mean/SD ratio for each intervention group (online supplemental table S5) to evaluate skewness. No studies showed a mean/SD ratio <2, indicating skewness.

A random pairwise meta-analysis was conducted for each direct comparison by using the inverse variance weighting method,

employing the ‘meta’ R package. In addition, we conducted a random effects NMA within a frequentist framework using methods derived from graph theory

to estimate the exercise intervention effects on PWV.

For these analyses, we examined statistical heterogeneity in each comparison by visual inspection of the forest plot. We also calculated the I² statistic, whose values were considered not important (0%–30%), moderate (30%–50%), substantial (50%–75%) or considerable (75%–100%) and corresponding p values were also taken into account.

We displayed NMA results using forest plots and league tables, where all relative effect estimates and their corresponding 95% CI are shown on the lower diagonal, while the upper diagonal includes all direct (pairwise) estimates. We include 95% prediction intervals (PI) to indicate the range within which the results of a future study might lie.

Once comparative estimates of the effectiveness of different types of exercise interventions were calculated, we generated a hierarchy of exercise interventions, using P-scores.

**The main relevant methodological assumptions that should be considered in an NMA are transitivity and consistency.** The transitivity assumption implies the validity of an indirect comparison. We calculated the I² statistic, whose values were considered not important (0%–30%), moderate (30%–50%), substantial (50%–75%) or considerable (75%–100%) and corresponding p values were also taken into account. I² values of approximately 0.2 were considered to indicate weak effects, values of approximately 0.8 were considered to indicate strong effects, and values above 1.0 were considered to indicate very strong effects. The SMD was used as the effect size estimate because the included studies provided outcome values using different instruments measuring the same clinical outcome.

In addition, we explored for small study effects, as a proxy for publication bias, by visual examination of the funnel plots checking only control-exercise comparisons and by Egger's regression asymmetry test, considering p<0.10 as statistically significant.

We performed a sensitivity analysis by removing studies classified as having a high risk of bias. Moreover, we used random-effects (Sidik–Hortonman method) meta-regression models in the pairwise control-exercise studies to evaluate whether summary estimates were influenced by trial-level covariates: mean age of participants, type of population (healthy population vs population with cardiometabolic risk) and type of PWV (central—aortic (a) PWV and cF PWV—or peripheral baPWV). To discriminate the type of population, samples in which an increased cardiometabolic risk was specifically stated (overweight, obesity, pre/hypertension…) were classified as population with cardiometabolic risk. To discriminate the type of PWV measurement, aPWV and cF PWV were considered to reflect central (elastic) AS, while baPWV represented peripheral (muscular) AS.

Because of the small number of included studies, multivariate meta-regression models were not recommended. Hence, univariate meta-regression models were estimated to allow estimation of the proportion of between-trial heterogeneity explained by the model, as well as the change in effect size estimate for each one-unit change in the characteristic included as a predictor in the model.

Due to the scarcity of studies included in the analysis, the meta-regression assumptions were difficult to evaluate. Therefore, a bubble plot with individual studies plotted against a quantitative predictor and the size of the points drawn proportionally to the weight that the studies received in the analysis was used to graphically analyse the lineal assumption.

We also planned a priori subgroup analyses based on the duration, frequency, volume and intensity of the exercise intervention. We generated all analyses in the R Statistical Software, using the ‘netmeta’ package.

To evaluate confidence in the results of the NMA we used Confidence in Network Meta-Analysis web-platform, which considers six domains: within-study bias, reporting bias,
indirectness, impression, heterogeneity and incoherence. The final judgement of the six domains was summarised into a confidence rating (no/some/major concerns).

RESULTS

Systematic review

From the 2414 articles identified in the systematic literature search, 14 studies (1003 participants) were finally included in this NMA (figure 1). We summarised included studies characteristics in online supplemental table S1.

All included studies were RCTs except one that had a quasi-experimental design. There are two three-arm studies. The studies were published between 2015 and 2022 in seven different countries from Asia, Europe and North America. The sample sizes ranged from 30 to 175 subjects (63.7% female, and ages ranged from 4.5 to 16.9 years). Participants met the criteria for obesity in seven of the included studies, over weight in one of them and had a prehypertensive status in two of the included studies.

The most frequently reported type of exercise was combined exercise (five studies), followed by aerobic exercise (four studies), HIIT (four studies), resistance training (two studies) and sensorimotor training (two studies). The intervention duration ranged from 12 to 40 weeks, with a frequency of 1–5 times per week and a volume of 20 to 60 min per session with an intensity matching the type of exercise.

Regarding the PWV measurement procedures, nine studies reported central PWV measurements, six of them of aortic PWV (aPWV) and three of them of cfPWV, while the other five studies reported a peripheral PWV measurement, brachial-ankle PWV (baPWV).

Risk of bias

As evaluated at the study level by the RoB2, one study was assessed as having a low risk of bias, eight as having some concerns and four as having a high risk of bias (online supplemental figure S2). Most studies had a low risk of bias for random sequence generation, deviations from intended intervention and missing outcome data. More than half of the studies had some concerns about selective outcome reporting, mainly due to the lack of a previously published protocol. Thirty per cent of the studies had a high risk of bias for outcome measurement probably owing to blinding shortcomings due to the nature of the intervention. Given the methodological shortcomings emphasised here, one must interpret the findings from these studies with caution.

As evaluated by the ROBINS-I tool, the only quasi-experimental study included was assessed as serious risk of bias.

NMA results

The network geometry graph (figure 2) shows the relative amount of evidence available on the effect of different exercise modalities on AS in children and adolescents. The size of the nodes is proportional to the number of participants randomised to each intervention and nodes are coloured according to the proportion of studies with low (green), moderate (yellow) and high (red) indirectness. The edges width corresponds to the number of studies directly comparing the two interventions while edges are coloured according to average RoB2 status on each comparison, where green colour refers to low risk, yellow to some concerns and red to high risk of bias. Dashed lines represent indirect comparisons. PWV, pulse wave velocity; ROB2, Risk of Bias 2.

Table 1 provides detailed results of the pairwise comparison meta-analyses (online supplemental figure S3) and NMA estimates (online supplemental figure S2) with their respective 95% CIs. In terms of PWV reduction, all exercise modalities showed a higher compatibility with effectiveness than control, with SMD ranging from −1.93 (95% CI: −2.84 to −1.02) and −1.11 (95% CI: −2.01 to −0.21) for aerobic exercise and HIIT, respectively, to −0.59 (95% CI: −1.39 to 0.22) for combined exercise. Only sensorimotor showed low compatibility with effectiveness in the reduction of PWV when compared with the control group 0.11 (95% CI: −1.10 to 1.32). All PIs were much wider than their corresponding CIs and none were statistically significant, suggesting that the amount of heterogeneity was substantial and affects the inference. Online supplemental table S4 shows the ES.
estimates of all the head-to-head studies separately (upper diagonal) and the indirect ES estimates (lower diagonal).

Considering that the standard random-effects model performs poor when the number of included studies in the meta-analysis is low and the scarcity of studies meeting the inclusion criteria for the NMA, we furtherly performed a pairwise analysis using the Hartung-Knapp-Sidik-Jonkman random effects method as an alternative appropriate for meta-analysis of few studies online supplemental figure S4.

The overall test of inconsistency showed global inconsistency (p<0.001) in the NMA. However, no concerns were raised regarding local inconsistency as evaluated by the node-splitting method (online supplemental figure S5), and net-heat plot (online supplemental figure S6). Considering the detection of incoherence in the NMA, the transitivity assumption is compromised, and hence, our results must be interpreted cautiously.

### Treatment ranking

Table 1 displays a ranking based on P-scores values for each intervention, the highest being for aerobic exercise (0.96), followed by HIIT (0.67). In addition, we present the rankograms in online supplemental figure S7.

### Meta-regression and subgroup analyses

Random effects meta-regression models, assuming only control-exercise studies, showed that the type of PWV measurement could have influenced the pooled SMD estimates while neither the mean age of participants nor the type of population or the type of PWV assessment method used showed high compatibility with statistically significant modifications of the effect of exercise on AS as displayed on the bubble plots (online supplemental figures S11–S14).

A priori subgroup analyses based on the duration, frequency, volume and intensity of the exercise intervention could not be conducted due to the scarcity of studies in each subgroup.

### Sensitivity analysis

We performed a sensitivity NMA excluding studies at high risk of bias, which showed results largely similar to the main NMA including all studies, except for sensorimotor training interventions whose effect changed to SMD: 0.00 (95% CI: −1.83 to 1.83) (online supplemental figure S8 and S9).

### Publication bias/small study effects

We found evidence of small studies effect after visual examination of the funnel plot (online supplemental figure S10) and Egger’s test calculation (p=0.03), however, such evidence must be interpreted cautiously due to large heterogeneity, as displayed in the funnel plot.

### Confusion in Network Meta-Analysis confidence rating

Online supplemental table S3 presents detailed results from the Confusion in Network Meta-Analysis approach for the NMA. Most comparisons showed some concerns for the domains ‘within-study bias’ and ‘reporting bias’. Concerns for the domain ‘within-study bias’ were mainly due to the lack of blinding of personnel and participants due to the blinding difficulties of exercise interventions. We assessed each comparison ‘some concerns’ for reporting bias as there is no established statistical method to evaluate this domain. The domains ‘incoherence’, ‘imprecision’ and ‘heterogeneity’ were also evaluated as some concerns for the majority of comparisons, which affects the confidence of the results. Considering relative SMD estimates below −1.000 and above 1.000 clinically important none of the comparisons showed concerns for the ‘incoherence’ domain. Based on the assessment, for 5 of the 15 comparisons the confidence in the treatment effect was considered high.

**DISCUSSION**

This NMA aimed to determine which type of exercise was the most effective in reducing the subclinical AS process in children and adolescents. Data from our NMA showed that aerobic exercise appeared to be the most effective exercise intervention for reducing AS in this population. Additionally, HIIT, resistance training and combined exercise training were also effective in reducing AS in children and adolescents. For children and adolescents at increased cardiometabolic risk, HIIT interventions stood out as the most effective exercise intervention, above aerobic exercise interventions. However, the paucity of data prevents us from suggesting the most appropriate dose (duration, frequency, volume and intensity) of each exercise modality, so more studies are needed that not only compare different exercise types, but also different doses for each type of exercise.

These findings are consistent with previous studies performed in the adult population indicating that aerobic exercise at a moderate–vigorous intensity is an effective type of exercise to reduce AS, additionally proposing HIIT or mind–body exercises as effective types of exercise for reducing AS. Such findings could be explained by the physiological changes induced by aerobic exercise, including vascular remodelling and regeneration by mobilisation of endothelial progenitor cells, improvement of endothelial function by improving endothelium-mediated flow-induced vasodilatation in conduit arteries and larger resistance arteries, decreased oxidative stress and protective effects against low-grade inflammation.

As in previous studies in adult populations that reported a neutral effect of low-intensity to moderate-intensity resistance training on arterial stiffening, our data did not support a statistically significant effect of combined or resistance training, probably owing to the acute intermittent increase in blood pressure.
pressure during high-intensity resistance training which might induce AS that may partially fade the benefits of the intervention. Moreover, our results show that sensorimotor training has no effect on AS, however, this specific exercise intervention was only performed in healthy preschool children, which leads us to hypothesise that the lack of a beneficial effect on AS may be due to the expected growth-related increase in PWV, rather than a detrimental effect caused by the intervention.

Subclinical atherosclerosis has become the most common cause of ACVD among children and adolescents in Western societies, affecting approximately between 5% and 15% of them, but up to 53% in obese children, and the tracking of ACVD risk factors from childhood and adolescence through adulthood has been documented. Thus, this systematic review and the NMA findings are clinically significant, as an exercise-mediated reduction in PWV not only implies a punctual improvement in cardiovascular risk, but also the possibility of generating exercise habits in this population, which, if maintained, could become an essential tool for the prevention of ACVD.

Some limitations may have compromised the results of the study and should be acknowledged. First, due to the nature of exercise interventions, it is difficult to elude some methodological biases that could have affected the estimates, such as blinding or daily physical activity of control groups, but also not measuring sedentary compensatory behaviours in the intervention group, which may have led to a large proportion of studies being assessed as having some concerns (64%) and high risk of bias (29%). Second, considering the different instruments the studies used for PWV, we had to use SMD estimations since it allows us to combine trials that use different instruments to measure the same clinical outcome. Third, because of the scarcity of studies and to maintain sufficient statistical power for the NMA, we were unable to distinguish between different intensities, frequencies, volumes and durations of interventions, and this scarcity may have affected the magnitude of our findings. Third, there was evidence of high heterogeneity which might be due to the different samples, exercise intervention characteristics and devices used to evaluate PWV across studies, which may have affected the results. Finally, the small sample sizes of some of the included studies undermine the reliability of their estimates.

CONCLUSION
This systematic review and the NMA results support that exercise programmes, especially aerobic exercise or HIIT programmes, can improve AS even at early ages. Despite the for caution in the interpretation of our results, due to large heterogeneity and lack of further high-quality RCTs, our results unfold a new paradigm of prevention possibilities. Considering AS as a subclinical process common in most cardiovascular diseases, the potential to address it early to mitigate the consequences of ACVDs might help us realise the power of an active lifestyle in children with higher AS. However, further research is required in order to enable comparison between different intensities, frequencies, volumes and durations of physical exercise interventions since the scarcity of studies limits our ability to make specific recommendations on the dose of activity required to benefit arterial health.

Contributors IS-D and IC-R conceptualised and designed the study, drafted the initial manuscript, coordinated and supervised data collection, and reviewed and revised the manuscript. ADSL and SNdAA collected data and reviewed and provided relevant intellectual content. VM-V and DM designed the study and critically reviewed the manuscript for important intellectual content. IS-D was responsible for the overall content as guarantor. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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REFERENCES
In the context of publication and other biases in meta-analysis, Mavridis D, Salanti G, Demystifying fixed and random effects meta-analysis: Evid Based Ment Health 2019;2:e199735.


