Airway Clearance Techniques in Primary Ciliary Dyskinesia: A Systematic Review

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Objective: Primary ciliary dyskinesia (PCD) is a respiratory disorder that impairs mucociliary clearance, leading to decreased lung function. Conventional chest physiotherapy (CCP) is the traditional airway clearance technique (ACT) and is considered a standard treatment for PCD patients. This systematic review investigated whether device-supported ACTs are better alternatives for improving lung function and/or quality of life in PCD, compared with CCP.

Methods: The OVID Medline, PubMed, CINAHL, and Cochrane databases were searched. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed, and the Grading of Recommendations, Assessment, Development, and Evaluation approach was used to aggregate the data. This systematic review has been registered on the International Prospective Register of Systematic Reviews website.

Results: Of the 389 citations that resulted from our literature search, 2 randomized crossover trials that included a total of 54 patients were analyzed. The certainty of the aggregated study evidence was very low. No difference was identified between device-supported ACTs and CCP in terms of forced vital capacity and forced expiratory volume in 1 second in PCD patients aged 6 to 20 years.

Conclusion: Device-supported ACTs could be considered alternative treatment options to replace CCP. High-quality research is required to confirm this result.

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Key words: Airway clearance technique, Device-supported ACTs, Lung function, Motility disorder, Primary ciliary dyskinesia

Primary ciliary dyskinesia (PCD) is a rare genetic disorder, affecting 1 in every 10,000 newborns, for which a cure is yet to be discovered (1); PCD affects, primarily, the motility of cilia, organelles that are located mainly in the lungs, sinuses, ears, and nasal passages (2). Normal cilia move in a wave-like motion, whereas abnormal cilia may move in different directions and/or velocities or fail to move at all (1). The clearance of mucus from the respiratory airways depends on cilia motility (3), and a motility disorder leaves healthy tissues susceptible to bacteria and other irritants (2). Patients with PCD struggle with constant lung, sinus, and ear infections, and repeated infections lead to risks of permanent tissue damage (3).

Kartagener syndrome is a variant of PCD in conjunction with situs inversus, in which the internal organs later develop in a mirrored orientation of their normal positions (4, 5). Current treatments can only mitigate symptoms to provide comfort and a better quality of life. As both affect mucociliary clearance, PCD resembles cystic fibrosis (CF) (2). As a result, PCD management is typically based on airway clearance techniques (ACTs) that are used in CF treatment. Conventional chest physiotherapy (CCP) is a traditional ACT that removes mucus and reduces respiratory infection rates; it typically consists of percussion, vibration, postural drainage, and breathing exercises, and it is considered a standard treatment for PCD patients (6, 7, 8, 9, 10, 11). However, CCP requires significant dependence on a caregiver for daily compliance (10). The importance of this factor grows with a given PCD patient's age and advance into adulthood and desire for independence. Thus, device-supported ACTs can be used by patients with chronic respiratory illnesses to move and expel mucus from the respiratory tract to improve breathing and reduce inflammation and infections similar to CCP (10).

However, evidence for the efficacy and safety of device-supported ACTs, such as oscillatory positive expiratory pressure therapy (OPEPT) (Acapella), remains unknown for PCD. It would be beneficial to systematically summarize the available evidence from the medical literature to answer the following research question: Compared with CCP, are device-supported ACTs better at improving lung function (as determined by a spirometry test) and quality of life in patients diagnosed with PCD?

Materials and Methods

The review was registered on PROSPERO (the International Prospective Register of Systematic Reviews) with registration ID CRD42021236838.

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Literature Search

The databases searched were OVID Medline Epub Ahead of Print and In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE, Embase, EBM Reviews - Cochrane Central Register of Controlled Trials, EBM Reviews - Cochrane Database of Systematic Reviews, and CINAHL. The literature search strategies included all expression variations for ACT and PCD, such as Kartagener syndrome, ciliary motility disorders, and Polynesian bronchiectasis shown in Appendix A. The search strategies were modified for use in different databases. The Cochrane Central Register of Controlled Trials was searched for ongoing trials. The reference lists for the eligible studies were reviewed, and study authors were contacted if additional information was required to assess eligibility.

Eligibility Criteria

The systematic review included randomized studies that incorporated crossover and quasi-randomized trial designs to allocate participants with varying lengths of follow-up. Additionally, conference abstracts from randomized studies with complete data reported were included. The language of the studies was restricted to English.

To participate, a potential participant had to have a confirmed diagnosis of PCD (using any diagnostic criteria); there was no age limitation. Due to disease progression with aging, a subgroup analysis was planned to identify differences between children and adults, if the data were available. The interventions included ACTs such as positive expiratory therapy, airway oscillating devices, active cycle of breathing techniques, high-frequency chest compression devices, and breathing exercises (12). The comparator was CCP, which typically consists of percussion, vibration, and postural drainage for 30 minutes twice daily (or other variations in terms of duration and frequency, adjusted to ensure optimal patient treatment). The types of relevant outcomes included the following: changes in pulmonary function tests (PFTs) for forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1), changes in health-related quality-of-life, changes in oxygen saturation (measured by SpO2), changes in patient comfort, rate of pulmonary exacerbation, time from intervention initiation until first exacerbation, bronchial responsiveness parameters, and relative risk for adverse events.

The most reported spirometry test measurements in PCD research are FEV1 and FVC, and the decision was made to report the 2 values obtained from a PFT. The first of the 2, FEV1, measures the maximum forced volume exhaled in 1 second and indicates disease progression and severity for chronic pulmonary diseases (13). The second, FVC, is the total amount of air expelled during the test, and the ratio of the 2 values can identify the presence of an airflow obstruction (14). Using a ranking system (15), systematic review team members independently ranked the 8 significant outcomes (based on importance) for the study, as shown in the outcome ranking table found in Appendix B. An outcome with an average score of 7 to 9 was considered critical; one with an average score of 4 to 6 was considered important; and one equaling 1 to 3 was considered less important.

Study Selection and Data Extraction

Two independent reviewers screened titles and abstracts for potential studies using Covidence software to record and document decisions (16). Two reviewers independently reviewed the full texts of the articles from the selected studies to determine their eligibility for inclusion. If a disagreement arose, the reviewers discussed it between themselves to arrive at a consensus. If the two reviewers could not agree with each other, a third team member made the final decision about eligibility. When necessary, trial authors were contacted to obtain additional information relevant to the systematic review.

Two independent reviewers extracted the trial characteristics from the eligible studies, including the country, the design, the sample size, the patient's age and sex, intervention details, comparison details, statistical analyses, and any of the above outcomes, if reported. A third independent reviewer resolved disagreements about the extracted data. When data could not be obtained from a publication, its authors were contacted to provide data for the review. All the data were recorded in an Excel spreadsheet for this review.

Risk of Bias in Individual Studies

Using the recommendations of the Cochrane risk of bias tool (RoB 2.0) for randomized trials, the eligible studies were assessed for risk of bias with either the crossover trial or parallel group form (17). Two independent reviewers assessed the risk of bias, independently, and any disagreements were discussed between the reviewers. If a consensus could not be reached, a third independent reviewer finalized the decision. Each outcome was assessed for the following domains: randomization, period and carryover effects for crossover trial, deviations from the intended intervention, missing outcome data, the measurement of outcome, and the selection of the reported results. Each domain was assessed as "low risk," "some concerns," or "high risk," with justifications provided. The overall risk of bias for each outcome was taken as the worst risk from any domain. For conference abstracts that met our preplanned study selection criteria, the risk of bias and certainty of evidence were not assessed, due to limited study information.

Quality of the Evidence

Each outcome was assessed based on the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) method to determine the quality of the evidence (15). There are 5 domains in the GRADE approach: risk of bias across the eligible studies, indirectness, unexplained heterogeneity or inconsistency, imprecision, and publication bias. The quality of evidence was downgraded by 1 or 2 levels for severe offenses, respectively, but could be upgraded if there were significant effects of intervention observed, a dose–response relationship, or no plausible confounding.

Data Synthesis and Analyses

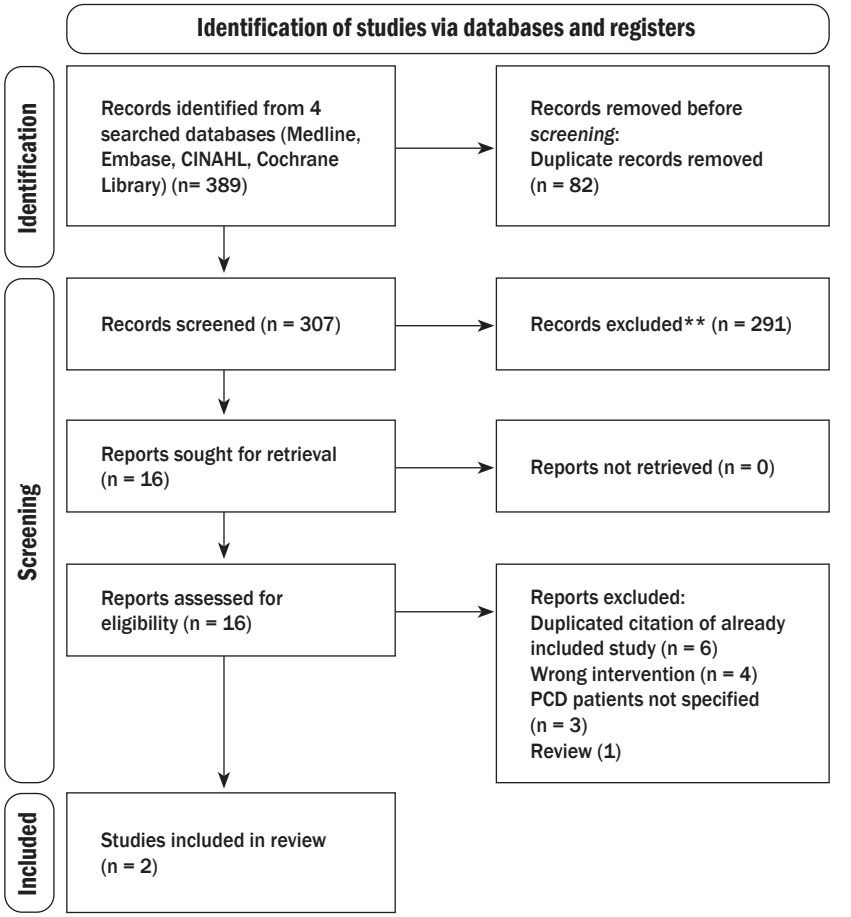
Since the eligible studies were heterogeneous in terms of the sample characteristics and study design, we did not conduct a meta-analysis to synthesize the data. Using the GradePro software (15), a summary of findings table was created to present the results comparing ACTs vs CCP for each study.

Results

Results of the Search

The search was conducted on 26 February 2021 and updated on 21 October 2022, and 389 articles were identified that met the preplanned study selection criteria. A total of 307 studies were screened after removing 82 duplicates, and 291 were excluded after the title and abstract screening. Sixteen articles remained for the full-text review. Of those, 13 were excluded for not meeting the eligibility criteria, with the most common reasons being duplicate or non-randomized control trials. Full details are outlined in the table titled "Table of Characteristics for Excluded Studies" (Appendix C). Multiple citations were found for some studies and were reviewed for additional information. If a study had multiple publications, only the latest with non-duplicated data was included and other citations were excluded. A total of 3 citations were eligible for this review, as shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram (Figure 1). Of them, 1 was a conference abstract of a randomized crossover trial (18) and 2 were randomized crossover trials (9, 19). After confirming with the authors, the eligible conference abstract (18) was fully published as a paper that describes 1 (9) of the 2 randomized crossover trials. Therefore, we removed it to Appendix C. No additional studies were identified after reviewing the reference lists of the eligible publications.

Figure 1. PRISMA Flow Diagram



The 2 included studies were all conducted in Turkey and compared an ACT with CCP (9, 19). One study had an intervention duration of approximately 3 months for each treatment (9), and the other had an intervention duration of 5 days (19).

An adequate washout period to eliminate any carryover effect on PFT measures was determined to be at least 1 day, as identified in similar studies for CF patients evaluating device-supported ACTs compared with CCP (20, 21). Both studies had adequate washout periods, with 2 days (19) and 14 days, respectively (9).

For the 2 eligible studies, there was a combined total of 54 participants, aged 6 to 20 years, with a mean age of 13.2 years, and 20 (37%) were male (9, 19) (Table 1). Only 1 study stratified its results; where participants aged 6 to 12 years were compared with those older than 12 years (9).

The Gokdemir trial (19) enrolled patients during a stable period, which was classified as not having active symptoms of infection for at least 4 weeks. The Bingol trial (9) required participants to be enrolled without having any pulmonary exacerbations for at least 4 weeks prior to enrollment. The Gokdemir trial (19) excluded individuals with a history of congestive heart failure, pneumothorax, or massive hemoptysis.

The Bingol trial (9) randomized participants to receive either OPEPT with an Acapella medical device intended to provide treatment or CCP at home for 3 months. The Gokdemir trial (19) compared high-frequency chest wall oscillation (HFCWO) chest physiotherapy using a vest (Vest Airway Clearance System, Model 105, HillRom, St. Paul, MN) and performed at home for 5 days with CCP performed by a respiratory physiotherapist in the hospital, also for 5 days. Both studies had CCP comprising postural drainage, percussion, and vibration.

Of the 8 outcomes of interest in this review, 5 were reported in eligible studies: PFT (focusing on FVC and FEV1), oxygen saturation, exacerbation rate, comfort, and adverse events.

Certainty of the Evidence

Outcomes within each study had the same risk of bias for each domain; thus, the risk of bias was reported for each trial. Appendix D summarizes the reviewer's judgment for each risk of bias domain for each outcome by study. The risk of bias was rated as "some concerns" for randomization and the measurement of outcome domains. The domains with the lowest risk of bias were period and carryover effects, deviations from intended interventions for crossover trials, missing

Table 1. Main characteristics of the included studies

Study	Study design	Number of patients	Mean/ median age (range/SD)	Intervention (experimental group)	Control (conventional group)	Treatment duration	Outcomes	Note
Bingol 2020	Randomized crossover trial	30	13.4 (±3.7)	OPEPT of 6 cycles repeated 15 times in the morning and evening at home	CCP for 30 minutes twice daily at home	3 months	Spirometry (FVC, FEV1, PEF, FEF25–75); exacerbation rate; oxygen saturation; comfort; adverse event	15-day washout period
Gokdemir 2014	Randomized crossover trial	24	12.9 (±2.7)	HFCWO from the vest in an upright seated position for 30 mins twice a day at home	CCP for 30 minutes twice daily performed by a physiotherapist in hospital	5 days	Spirometry (FVC, FEV1, PEF, FEF25–75); oxygen saturation; comfort (5-point scale)	2-day washout period

Abbreviations: CCP, conventional chest physiotherapy; FEF25–75, forced expiratory flow between 25% and 75% of the forced vital capacity; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HFCWO, high-frequency chest wall oscillation; OPEPT, oscillatory positive expiratory pressure therapy; PEF, peak expiratory flow

outcome data, and selection of reported results. Considering that the overall sample size across the 2 studies was too small (n = 54), and the 95% CI of the effect for each outcome (Table 2) was too broad, the imprecision domain was severe for all the outcomes. The overall certainty of the evidence for each outcome was very low after considering 5 domains from the GRADE approach (Appendix E) (15).

Effects of Intervention

Due to clinical heterogeneity (such as different intervention types) across the included trials, a meta-analysis could not be performed for this review. The summary results were reported narratively for each study as can be seen in the summary of findings table (Table 2). Subgroup and sensitivity analyses were not performed due to a lack of relevant data from the included studies. After a literature search, we did not find a minimally important difference threshold for the target comparison between intervention and control in this systematic review. We treated the statistically significant difference values as the clinical threshold (i.e., mean difference = 0).

Bingol (9) reported PFT values through spirometry on the effect of OPEPT to have a non-statistically significant different result on the median changes of FVC (25^{th}–75^{th} percentile: 3.0 [95% CI: -4.0, 7.5] versus 1.0 [95% CI: -2.2, 7.0]; $P = .923$) and FEV1 (3.0 [95% CI: -2.0, 8.0] versus 1.0 [95% CI: -2.2, 5.0]; $P = .234$) compared with CCP. The lack of difference in the effect on oxygen saturation between the 2 groups was identified after 3 months of treatment. But OPEPT resulted in greater comfort than did CCP (3.8 ± 0.8 versus 3.4 ± 0.8; $P = .029$). No adverse events were observed in any of the participants during the study.

For the Gokdemir trial (19), comparing HFCWO with CCP affected the median changes (25th–75th percentile) of FVC, and FEV1 was 9.0% versus 7.5% ($P = .53$) and 9.7% versus 8.8% ($P = .80$), respectively; the effect of mean difference on oxygen saturation was 0.9 (P >.05); there was a mean difference of 0.7 ($P = .04$) on comfort in favor of HFCWO.

Discussion

Mucus clearance through ACTs is critical to maintaining respiratory function for those suffering from PCD. This systematic review identified 2 randomized trials with consistent effects on FEV1 and FVC. Device-supported ACT and CCP methods increased the PFT values at a similar magnitude without observed adverse events, as OPEPT or HFCWO therapy can be given through vests that patients can wear, without the need to rely on a physical therapist or a dependent for daily airway clearance. Thus, they (OPEPT and HFCWO therapy) can be considered as an option to replace CCP if needed. This result may change PCD patients' lives and reduce a lot of the burden on PCD patients, their families, and hospital facilities.

A meta-analysis could not be conducted due to the clinical heterogeneity of the trials in this systematic review. The quality of the evidence unearthed by these 2 trials was consistently deficient for each outcome, and according to the GRADE approach, this deficiency was caused by uncertainties in the risk of bias, imprecision, and presence of publication bias (15). Therefore, we have very little confidence in the effect estimate, i.e., the actual effect is likely to be substantially different from the impact estimate (15).

There has been only 1 other systematic review to investigate the safety and efficacy of available ACTs in PCD patients (12), including 1 randomized trial, the Gokdemir trial (19). The Schofield review acknowledged the lack of evidence substantiating the efficacy of device-supported ACTs for PCD and the ethical dilemma of withholding such treatments, reiterating the necessity for further evidence. Besides the Gokdemir et al. trial (19), our systematic review included another recent randomized trial (9). Although the overall sample size was small (n = 54), the results from the 2 trials seem to support the theory that device-supported ACTs could have effects similar to those of CCP in terms of increasing PFT values in PCD patients. These 2 trials recruited patients at stable periods in their disease; therefore, there is no evidence to compare device-supported ACTs with CCP in

PCD patients during an exacerbation period. However, 1 study determined that an acceptable and user-friendly method of airway clearance was offered by Acapella's device compared with CCP in adult patients during an acute exacerbation of bronchiectasis requiring oral antibiotic therapy (pulmonary function did not differ between the 2 groups) (22); these findings are consistent with those of our systematic review. Because the effects and durations of different ACTs may vary, ongoing research efforts to build confidence in the available data are needed.

This systematic review has some limitations. First, although our literature search strategies were undertaken with the assistance of a professional librarian and were therefore appropriate, only 4 databases were searched, and these were restricted to English-language publications due to limited resources. Thus, publication bias might exist. Second, we included only English-language publications because of resource limitations; hence, potentially relevant papers in non-English languages may have been missed.

Future Research Directions

Further high-quality research and studies will be required to investigate device-supported ACT effectiveness for PCD patients in mucus clearance during both stable and exacerbation periods. Additionally, studies should focus on long-term treatments, as PCD is a chronic condition requiring increasing treatment as the patient ages and the disease progresses. Participants would probably be most interested in the long-term effects of interventions.

Resumen

Objetivo: La discinesia ciliar primaria (DCP) es un trastorno respiratorio que afecta el aclaramiento mucociliar y conduce a una disminución de la función pulmonar. La fisioterapia torácica convencional es la técnica tradicional de limpieza de las vías respiratorias considerada el tratamiento estándar para los pacientes con DCP. Esta revisión sistemática investigó si las ACTs apoyadas por dispositivos son mejores para mejorar la función pulmonar y/o la calidad de vida en PCD, en comparación con CCP. Métodos: Se realizaron búsquedas en las bases de datos OVID Medline, PubMed, CINAHL y Cochrane. Se siguieron las pautas Artículos de Información Preferidos para Revisiones Sistemáticas y Metaanálisis y se utilizó el enfoque Calificación de Recomendaciones, Evaluación, Desarrollo y Evaluación para agregar los datos. La revisión sistemática ha sido registrada en el sitio web de Registro

Table 2. Summary of findings

Studies	Study design	Impact	Certainty	Importance
		FVC (follow-up: range, 12 days to 6 months; assessed with spirometry)		
Bingol 2020	randomized crossover trials	median changes (25th–75th percentile): OPEPT = 3.0 (95% CI: -4.0, 7.5); CCP = 1.0 (95% CI: -2.2, 7.0); P = .923	⊕◯◯◯ very low	critical
Gokdemir 2014	randomized crossover trials	median changes: HFCWO = 9.0; CCP = 7.5; P = .53	⊕◯◯◯ very low	critical
		FEV1 (follow-up: range, 12 days to 6 months; assessed with spirometry)		
Bingol 2020	randomized crossover trials	median changes (25th–75th percentile): OPEPT = 3.0 (95% CI: -2.0, 8.0); CCP = 1.0 (95% CI: -2.2, 5.0); P = .234	⊕◯◯◯ very low	critical
Gokdemir 2014	randomized crossover trials	median changes: HFCWO = 9.7; CCP = 8.8; P = .80	⊕◯◯◯ very low	critical
		Exacerbation rate (follow-up: mean 6 months; assessed by principal investigator using tracking)		
Bingol 2020	randomized crossover trials	OPEPT: median = 0.5 (25–75th percentile: 0.2, 2.2), CCP: median = 1.0 (25–75th percentile: 0.5, 1.7); P = .823	⊕◯◯◯ very low	critical
		Oxygen Saturation (follow-up: range, 12 days to 6 months; assessed transcutaneously with fingertip pulse oximeter)		
Bingol 2020	randomized crossover trials	P > .05	⊕◯◯◯ very low	important
Gokdemir 2014	randomized crossover trials	HFCWO: median = 96.7; CCP: median = 95.8; P = .89	⊕◯◯◯ very low	important
		Comfort (follow-up: range, 12 days to 6 months; assessed with 5-point Likert-type scale)		
Bingol 2020	randomized crossover trials	OPEPT: mean = 3.8 (SD = 0.8); CCP: mean = 3.4 (SD = 0.8); mean difference = 0.40 (95% CI: 0.00, 0.80); P = .029	⊕◯◯◯ very low	important
Gokdemir 2014	randomized crossover trials	HFCWO: mean = 4.3; CCP: mean = 3.6; P = .04	⊕◯◯◯ very low	important
		Adverse event (assessed with "noted during study period")		
Bingol 2020	randomized crossover trial	No adverse events reported for either therapy.	⊕◯◯◯ very low	critical

Prospectivo Internacional de Revisiones Sistemáticas. Resultados: De las 389 citas que resultaron de nuestra búsqueda de literatura, se analizaron 2 ensayos cruzados aleatorios que incluyeron un total de 54 pacientes. La certeza de la evidencia del estudio agregado fue muy baja. No se identificó ninguna diferencia entre las ACTs apoyadas por dispositivos y CCP en términos de capacidad vital forzada y volumen espiratorio forzado en 1 segundo en pacientes con PCD de 6 a 20 años. Conclusión: La fisioterapia torácica asistida por dispositivo podría considerarse como tratamiento alternativo de la fisioterapia torácica convencional. Se requiere investigación de alta calidad para confirmar este resultado.

Abbreviations

ACT: airway clearance technique
CCP: conventional chest physiotherapy
CF: cystic fibrosis
FEV1: forced expiratory volume in 1 second
FVC: forced vital capacity
GRADE: Grading of Recommendations, Assessment, Development, and Evaluation
HFCWO: high-frequency chest wall oscillation
OPEPT: oscillatory positive expiratory pressure therapy
PCD: primary ciliary dyskinesia
PEF: peak expiratory flow
PFT: pulmonary function test
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Authors' contributions

Liling Qian, Bonnie Lam: conceptualization, methodology, data curation, formal analysis, validation, writing (original draft), reviewing, & editing. Tun Zheng, Daniela Russo: data curation, formal analysis, writing, reviewing, & editing. Jinhui Ma, Xiaomei Yao: conceptualization, methodology, supervision, writing, reviewing, & editing.

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