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Effects of adenotonsillectomy on the growth of children with obstructive sleep apnoea-hypopnea syndrome (OSAHS): protocol for a systematic review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030866
Article Type:	Protocol
Date Submitted by the Author:	04-Apr-2019
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Keywords:	Adenoidectomy, Tonsillectomy, Sleep Apnoea Syndromes, Growth, Paediatric otolaryngology < PAEDIATRIC SURGERY, PAEDIATRICS

Effects of adenotonsillectomy on the growth of children with obstructive sleep apnoea-hypopnea syndrome (OSAHS): protocol for a systematic review

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Keywords:

Adenoidectomy, Tonsillectomy, Sleep Apnoea Syndromes, Child, Adolescent, Growth

ABSTRACT

Introduction: Obstructive sleep apnoea-hypopnea syndrome (OSAHS) is characterized by recurring episodes of complete or partial upper airway collapse during sleep. Persistent OSAHS is associated with long-term consequences, such as growth failure, cardiovascular and neurocognitive problems in children. Different from the aetiology of OSAHS in adults, the most common cause of paediatric OSAHS is adenotonsillar hypertrophy. Adenotonsillectomy (AT) has been recommended as the first-line treatment of paediatric OSAHS. Several studies have suggested that retarded growth caused by OSAHS can improve after AT during the prepubertal period. This review will systematically search and summarise the available evidence on the effects of AT on children's growth.

Methods and analysis: We will conduct electronic searches in MEDLINE (via PubMed), Embase, Google Scholar and the Cochrane Central Register of Controlled Trials (CENTRAL) for randomised controlled trials or cohort studies that included a control group. Additional records will be searched by checking the references included in the selected studies and relevant reviews. At least two authors will undertake selection of studies and data extraction independently and in duplicate. The Cochrane Risk of Bias tool and ROBINS-I will be used to assess the risk of bias of RCT and cohort studies, respectively. A random-effects model will be used for meta-analyses. Data synthesis and other analyses will be carried out using the RevMan 5.3 software. GRADE will be used to assess the quality of the supporting evidence behind each main comparison.

Results: The mean difference (MD) and relative risk (RR) with their corresponding 95 % confidence interval (CI) will be chosen as effective measures for continuous and binary outcomes, respectively.

Ethics and dissemination: There is no ethical issue in this systematic review given that we will only include published studies. The results will be disseminated via peer-reviewed publications and social networks.

PROSPERO registration number: CRD42019125882

ARTICLE SUMMARY

Strengths and limitations of this study

- To our knowledge, this will be the first systematic review regarding the effects of AT on children's growth since 2009.
- Both randomised controlled trials and prospective cohort studies will be searched and included (if eligible), which could result in a more comprehensive summary of the available evidence.
- Subgroup and sensitivity analyses will be performed to explore heterogeneity and the robustness of our findings.
- The main limitation might result from a limited number of primary studies that are available.

INTRODUCTION

Background

Obstructive sleep apnoea-hypopnea syndrome (OSAHS) has been defined as "a disorder of breathing during sleep characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction that disrupts normal ventilation during sleep and normal sleep patterns".[1] The reported prevalence of paediatric OSAHS varies from 0.7% to 10.0%, with a peak between 2 and 8 years of age.[2-4] The commonly considered gold standard for diagnosing paediatric OSAHS is overnight polysomnography (PSG).[5] Children with OSAHS may show symptoms such as snoring, mouth breathing, observed episodes of apnoea, as well as attention-deficit or hyperactivity. Also, growth retardation,[6-8] neuropsychological and cognitive deficits,[9] impaired cardiovascular function [10 11] as well as craniofacial development disorders have been reported to be associated with OSAHS.[12 13] However, the pathophysiological mechanism behind poor growth in children with OSAHS is unclear. Possible reasons may include the increased energy expenditure during sleep, abnormal nocturnal growth hormone secretion, nocturnal hypoxemia, nocturnal respiratory acidosis, as well as lower total caloric intake resulting from poor appetite and difficulties in swallowing.[14 15]

Description of the intervention

Adenotonsillar hypertrophy is the most important anatomical factor that has been associated with OSAHS,[16] therefore adenotonsillectomy (AT) has been widely recommended as the first-line treatment.[1 17] For children between 3 and 17 years who are comorbidity free, AT appears to be a safe option with a growing body of evidence.[18] Nowadays, many paediatric ENT surgeons are using the Coblation technique (cold radiofrequency ablation) and a lower complication rate has been reported.[19] For clinicians faced with the decision of whether to perform AT, the severity of obstructive sleep apnoea is an important factor. Removal of the enlarged adenoid and tonsil eliminates the upper airway obstruction, improves the breathing pattern and improves the respiratory parameters as measured by polysomnography in the majority of healthy children.[20]

Why it is important to conduct this review

Recent studies have suggested that retarded growth caused by OSAHS can improve after AT.[14 15 17 21-23] However, there have been few systematic reviews analysing the effects of AT on the growth of children with OSAHS. In 2009, Bonuck et al. [24] carried out a systematic review and meta-analysis regarding the growth and growth biomarker changes after AT, but did not make a comparison between children who received AT and an appropriate control group. To our knowledge, at present there exists no other systematic reviews regarding this question. We therefore have a unique opportunity to systematically review the relevant literature and determine the effects of AT on children's growth.

Objectives

The aim of this systematic review is to comprehensively review the literature and synthesise relevant data to determine the effects of AT on the growth of children with OSAHS.

Review Question

Does AT have any effects on the growth of children with OSAHS, as compared with concurrent controls (either children with OSAHS who did not receive AT or healthy controls)?

METHODS

This protocol was written in accordance with the PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols) reporting guidelines.[25]

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) and prospective cohort studies that:

1) Reported on the growth changes of children before and after AT;

2) Included a concurrent control group; and

3) Had a follow-up length of no less than 6 months.

Types of participants

We will include studies in which the majority of participants were under 18 years of age at the time of recruitment with a diagnosis of OSAHS. For prospective cohort studies, healthy subjects (with age under 18 but without OSAHS) in a concurrent control group will also be considered.

Types of interventions

Treatment group:

AT (Tonsillectomy and/or adenoidectomy)

Control group:

- No intervention or watchful waiting only
- Other pharmacologic or surgical interventions

Types of outcome measures

Primary outcome:

Height or height Z score

Secondary outcomes:

- BMI or BMI Z score
- Weight or weight Z score
- Growth related biomarker concentration or concentration Z score
- AT related *adverse events*

Search strategy

Electronic searches

We will search MEDLINE (via PubMed), Embase, Google Scholar, and the Cochrane Central Register of Controlled Trials (CENTRAL) with no restrictions on language or publication date. The detailed search strategy for MEDLINE is listed in table 1, which will be adapted to the syntax and subject headings of the other databases.

Searching other resources

Additional studies will be sought by manually checking the references of included studies and relevant review articles.

Data collection and analysis

We will follow the relevant guidance provided in the *Cochrane Handbook for Systematic Reviews*. [26]

Study selection

At least two authors will screen the titles and abstracts yielded from the literature searches, independently and in duplicate. Articles, which appear to meet our inclusion criteria, will be downloaded in full. The same group of authors will then examine these full-texts independently for eligibility. Any disagreement will be resolved by discussion and consultation with other authors until consensus is reached. The corresponding author will be contacted if a study has insufficient information. For each excluded study, we will document the reason for exclusion.

Data extraction and management

The bibliographic information and abstracts of all identified items will be imported into the EndNote X8 Software (Clarivate Analytics, Philadelphia). At least two review authors will independently extract the following data from the included studies:

1. General information: title, journal, year, publication status.
2. Study characteristics: sample size, methods used for randomization and allocation concealment, blinding.
3. Participants: age, sex, race, height, weight, BMI, IGF-1, IGFBP-3, time from OSA diagnosis, diagnostic criteria and severity of OSA, related medical history, comorbid conditions, concomitant medication and other sleep treatments.
4. Interventions: type of surgery, pharmacologic treatments, watchful waiting or no intervention.
5. Outcomes: instrument or scale for measurement, follow-up length.
6. Results: point estimates and measures of variability for continuous variables, frequency counts for dichotomous variables, number of patients.

Risk of bias assessment

At least two review authors will assess the risk of bias of each included study independently and in duplicate. RCTs will be assessed using the Cochrane Risk of Bias tool, which include

seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.[26] ROBINS-I (Risk Of Bias In Non-randomised Studies - of Interventions) will be used to assess the risk of bias of cohort studies for seven domains: confounding, selection of participants into the study, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result.[27] According to the guidance for these assessment tools, RCTs will be judged for having a low, high or unclear risk of bias; cohort studies will be judged for having a low, moderate, serious, critical risk of bias or 'no information'.

Measures of treatment effect

Where we identify a sufficient number of studies with homogeneous populations and characteristics, we will carry out meta-analyses of primary and secondary outcomes. For the analysis of dichotomous outcomes, we will use risk ratios with 95% confidence intervals (CIs); for the analysis of continuous outcomes, we will use the mean difference or standardised mean difference and the corresponding 95% CIs.

Missing data

Where necessary, we will contact the authors of studies to obtain missing data / information. For missing standard deviations, we will use the methods detailed in section 7.7.3 of the Cochrane Handbook to impute them.[26] In the discussion section of the review, the potential impact of any missing data will be discussed.

Assessment of reporting biases

Where there are more than 10 studies that can be combined into a meta-analysis, we will use a funnel plot to explore the possibility of small study effects, which may indicate publication bias.

Data synthesis

Analyses will be performed with the Review Manager (RevMan) 5.3 software (Copenhagen: the Nordic Cochrane Centre, Cochrane Collaboration). Meta-analyses will be performed using

a random-effects model. The heterogeneity among studies included in each meta-analysis will be assessed with the Q test statistic and I^2 statistics.

Subgroup analysis and investigation of heterogeneity

We will attempt to perform the following subgroup analyses:

- Study design (e.g. RCTs vs. cohort studies);
- Nutritional status of the patients (e.g. obese vs. non-obese);
- Methods used to diagnose OSAHS (e.g. polysomnographically confirmed OSAHS vs. diagnosed OSAHS based on subjective measurements only);
- Surgical procedures (e.g. temperature controlled radiofrequency tonsillectomy and adenoidectomy, and complete tonsillectomy and adenoidectomy); and
- Age groups.

Sensitivity analyses

If a sufficient number of studies are included in this review, we will perform sensitivity analyses to assess the consistency and robustness of our results. When sufficient data are available, we will perform sensitivity analyses by:

- Including only studies with low risk of bias;
- Excluding studies in which the majority of enrolled subjects were above 18;
- Repeating data syntheses using a fixed-effect model.

Publication bias

Possible publication bias will be investigated with a funnel plot if at least 10 studies are included in a meta-analysis.

Summary of findings tables

We will use the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach [28] to assess the quality of the supporting evidence behind each main comparison. In this process, RCTs will start as high-quality evidence and observational studies

as low-quality evidence. Thereafter, five factors (risk of bias, imprecision, inconsistency, indirectness and publication bias) may lead to rating down the quality of evidence, and three factors (large effect, dose response, and all plausible confounding would reduce a demonstrated effect) may lead to rating up.

Patient and public involvement

The present work is based on a review of relevant studies and does not include original patient data. Therefore, no patients or public were involved in this review protocol.

ETHICS AND DISSEMINATION

Ethical approval is not required. The results of this study will be disseminated via peer-reviewed publications and social networks.

DISCUSSION

Nowadays, OSAHS is a common problem among children. In 2002, the American Academy of Pediatrics identified growth failure as one of the serious complications of untreated OSAHS.[5] Many studies have indicated that growth failure can be reversed after AT.[24] However, a recent RCT with a 7-month follow-up showed that the changes in height and height z score, as well as height velocity measures were similar between the early AT group and watchful waiting control. [29] Therefore, the present systematic review will analyse the association between AT children's height, weight and growth-related biomarkers. To our knowledge, there has been no systematic review regarding this clinical question since 2009.

In this review protocol, we have planned to perform subgroup analyses on different age groups, different nutritional status and different follow-up lengths. First of all, growth failure appears to be more prevalent among younger children with OSAHS. Vontetsianos and colleagues [30] found that height was improved only in children under the age of five, and the "catch-up growth" was not possible if disadvantageous factors were not removed early in life. Therefore, AT performed at an earlier age may lead to a higher degree of growth acceleration, and early diagnosis and timely referral may be helpful for reducing the occurrences of OSAHS-

related growth failures. Second, the previous literature has shown an association between nutritional status and growth, which makes pediatric obesity another potential confounding factor.[31 32] In addition, differences in the findings of relevant studies could be explained by different follow-up lengths.[23]

By summarising the current knowledge in the effects of AT on growth of children with OSAHS, this review can provide a comprehensive summary of the current evidence for clinicians, and help them achieve evidence-based practice when treating children with OSAHS.

Contributors F.H. and H.H. conceived of this review. F.H. and T.Z. developed the search strategy and drafted the manuscript. T.W., Q.S., X.C., H.W., F.J. and H.H. revised the manuscript. H.H. is the guarantor. All authors participated in the determination of eligibility criteria, the risk of bias assessment strategy and data extraction methods. All authors read and approved the final manuscript.

Funding This work was supported by the National Key Clinical Specialties Construction Program of China (No. [2013]544), China Postdoctoral Science Foundation (No. 2018M630884) and the Fundamental Research Funds for the Central Universities (No. 2042018kf0070, Wuhan University). The funding sources had no involvement in the study design, collection, analysis, and interpretation of data, preparation of the manuscript, or in the decision to publish.

Competing interests None declared.

Patient consent Not required.

Data sharing statement The data may be obtained from the authors for academic purposes.

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Table 1. The search strategy to be used in MEDLINE (via PubMed)

No.	Search terms
#1	"Tonsillectomy"[Mesh]
#2	"Palatine Tonsil/surgery"[Mesh]
#3	adenotonsillecto* OR adenotonsilectom* OR tonsillecto*OR tonsillotom* OR adenoidectom* OR tonsilotom*
#4	adenotonsil* OR tonsil* OR adenoid* OR "Palatine Tonsil"[Mesh] OR "Adenoids"[Mesh]) AND ("Surgery"[Mesh] OR surger* OR surgic* OR excis* OR extract* OR remov*
#5	#1 OR #2 OR #3 OR #4
#6	"Sleep Apnoea Syndromes"[Mesh]
#7	sleep* AND (apnea* OR apnoea*)
#8	hypopnea* OR hypopnoea*
#9	OSA OR OSAHS
#10	#6 OR #7 OR #8 OR #9
#11	child[Mesh] OR adolescent[Mesh]
#12	child* OR adolescent* OR pediatric* OR paediatric*
#13	child*[Title/Abstract] OR adolescent*[Title/Abstract] OR pediatric*[Title/Abstract] OR paediatric*[Title/Abstract]
#14	growth[mesh] OR "body size"[Mesh] OR "body mass index"[Mesh] OR "insulin-like growth factor I"[Mesh] OR "insulin-like growth factor binding proteins"[Mesh]
#15	growth[Title/Abstract] OR development[Title/Abstract] OR height[Title/Abstract] OR weight[Title/Abstract] OR "body size"[Title/Abstract] OR "body mass index"[Title/Abstract] OR BMI[Title/Abstract] OR "insulin-like growth factor I"[Title/Abstract] OR "insulin-like growth factor binding proteins"[Title/Abstract] OR IGF-1[Title/Abstract] OR IGFBP*[Title/Abstract]
#16	#10 AND (#12 OR #13) AND (#14 OR #15)
#17	review[publication type] OR "systematic review"[publication type] OR "meta analysis"[publication type] OR "case reports"[publication type] OR letter[publication type] OR editorial[publication type] OR comment[publication type]
#18	#16 NOT #17

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

Section and topic	Item No	Checklist item	Page No
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	12
Sponsor	5b	Provide name for the review funder and/or sponsor	12
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	12
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5, 6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6, 16
Study records:			

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
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	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

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

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

BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030866.R1
Article Type:	Protocol
Date Submitted by the Author:	18-Jun-2019
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Primary Subject Heading:	Ear, nose and throat/otolaryngology
Secondary Subject Heading:	Dentistry and oral medicine, Evidence based practice, Paediatrics
Keywords:	Adenoidectomy, Tonsillectomy, Sleep Apnoea Syndromes, Growth, Paediatric otolaryngology < PAEDIATRIC SURGERY, PAEDIATRICS

Effects of adenotonsillectomy on the growth of children with obstructive sleep apnoea-hypopnea syndrome (OSAHS): protocol for a systematic review

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Keywords:

Adenoidectomy, Tonsillectomy, Sleep Apnoea Syndromes, Child, Adolescent, Growth

ABSTRACT

Introduction: Obstructive sleep apnoea-hypopnea syndrome (OSAHS) is characterized by recurring episodes of complete or partial upper airway collapse during sleep. Persistent OSAHS is associated with long-term consequences, such as growth failure, cardiovascular and neurocognitive problems in children. Different from the aetiology of OSAHS in adults, the most common cause of paediatric OSAHS is adenotonsillar hypertrophy. Adenotonsillectomy (AT) has been recommended as the first-line treatment of paediatric OSAHS. Several studies have suggested that retarded growth caused by OSAHS can improve after AT during the prepubertal period. This review will systematically search and summarise the available evidence on the effects of AT on children's growth.

Methods and analysis: We will conduct electronic searches in MEDLINE (via PubMed), Embase, Google Scholar and the Cochrane Central Register of Controlled Trials (CENTRAL) for randomised controlled trials or cohort studies that included a control group. Additional records will be searched by checking the references included in the selected studies and relevant reviews. At least two authors will undertake selection of studies and data extraction independently and in duplicate. The Cochrane Risk of Bias tool and ROBINS-I will be used to assess the risk of bias of RCT and cohort studies, respectively. A random-effects model will be used for meta-analyses. Data synthesis and other analyses will be carried out using the RevMan 5.3 software. GRADE will be used to assess the quality of the supporting evidence behind each main comparison.

Ethics and dissemination: There is no ethical issue in this systematic review given that we will only include published studies. The results will be disseminated via peer-reviewed publications and social networks.

PROSPERO registration number: CRD42019125882

ARTICLE SUMMARY

Strengths and limitations of this study

- To our knowledge, this will be the first systematic review regarding the effects of AT on children's growth since 2009.
- Both randomised controlled trials and prospective cohort studies will be searched and included (if eligible), which could result in a more comprehensive summary of the available evidence.
- Subgroup and sensitivity analyses will be performed to explore heterogeneity and the robustness of our findings.
- The main limitation might result from a limited number of primary studies that are available, and a potentially low certainty of evidence from observational studies.
- There is a lack of commonly accepted minimal clinically important difference for the outcome measures of interest and this research question, making it potentially difficult to interpret the clinical significance of synthesized results.

INTRODUCTION

Background

Obstructive sleep apnoea-hypopnea syndrome (OSAHS) has been defined as "a disorder of breathing during sleep characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction that disrupts normal ventilation during sleep and normal sleep patterns".[1] The reported prevalence of paediatric OSAHS varies from 0.6% to 44.6% depending on the population studied and the definitions / standards used for diagnosis.[2-4] The commonly considered gold standard for diagnosing paediatric OSAHS is overnight polysomnography (PSG).[1] Children with OSAHS may show symptoms such as snoring, mouth breathing, observed episodes of apnoea, as well as attention-deficit or hyperactivity. Also, growth retardation,[5 6] neuropsychological and cognitive deficits,[7] impaired cardiovascular function [8 9] as well as craniofacial development disorders have been reported to be associated with OSAHS.[10 11] However, the pathophysiological mechanism behind poor growth in children with OSAHS is unclear. Possible reasons may include the increased energy expenditure during sleep, abnormal nocturnal growth hormone secretion, nocturnal hypoxemia, nocturnal respiratory acidosis, as well as lower total caloric intake resulting from poor appetite and difficulties in swallowing.[12 13]

Description of the intervention

There are a variety of therapies available for the treatment of paediatric OSAHS, including surgical and non-surgical treatments.[14-16] Adenotonsillar hypertrophy is the most important anatomical factor that has been associated with OSAHS,[17] therefore adenotonsillectomy (AT) has been widely recommended as the first-line treatment.[1 18] For children between 3 and 17 years who are comorbidity free, AT appears to be a safe option with a growing body of evidence.[19] Nowadays, many paediatric ENT surgeons are using the Coblation technique (cold radiofrequency ablation) and a lower complication rate has been reported.[20] For clinicians faced with the decision of whether to perform AT, the severity of obstructive sleep apnoea is an important factor. Removal of the enlarged adenoid and tonsil eliminates the upper airway obstruction, improves the breathing pattern and improves the respiratory parameters as measured by polysomnography in the majority of healthy children.[21]

Why it is important to conduct this review

Recent studies have suggested that retarded growth caused by OSAHS can improve after AT.[12 13 18 22-24] However, there have been few systematic reviews analysing the effects of AT on the growth of children with OSAHS. In 2009, Bonuck et al. [25] carried out a systematic review and meta-analysis regarding the growth and growth biomarker changes after AT, but did not make a comparison between children who received AT and an appropriate control group. To our knowledge, at present there exists no other systematic reviews regarding this question. We therefore have a unique opportunity to systematically review the relevant literature and determine the effects of AT on children's growth.

Objectives

The main objective of this review is to assess the effects of AT on the growth of children with OSAHS.

Review Question

Does AT have any effects on the growth of children with OSAHS, as compared with concurrent controls (either children with OSAHS who did not receive AT or healthy controls)?

METHODS

This protocol was written in accordance with the PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols) reporting guidelines.[26]

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) and prospective cohort studies that:

1) Reported on the growth changes of children before and after AT;

2) Included a concurrent control group; and

3) Had a follow-up length of no less than 6 months.

According to the Cochrane Handbook, in this review, prospective cohort studies should include two or more groups of participants receiving different intervention. At the same time,

their identification of participants, assessment of baseline and allocation to intervention, assessment of outcomes, as well as the generation of hypotheses should be prospective.[27]

Types of participants

We will include studies in which the majority of participants were under 18 years of age at the time of recruitment with a diagnosis of OSAHS.

Types of interventions

Treatment group:

AT (Tonsillectomy and/or adenoidectomy)

Control group:

- No intervention or watchful waiting only
- Other pharmacologic or surgical interventions

Types of outcome measures

Primary outcome:

- Height Z score (continuous outcome, measured at least 6 months after AT with stadiometer)

Secondary outcomes:

- Raw value of height in cm (continuous outcome, measured at least 6 months after AT with stadiometer)
- Weight Z score (continuous outcome, measured at least 6 months after AT with electronic scale)
- Raw value of weight in kg (continuous outcome, measured at least 6 months after AT with electronic scale)
- BMI Z score (continuous outcome, calculated based on height and weight data meeting the above-mentioned criteria)
- BMI (continuous outcome, calculated based on height and weight data meeting the above-mentioned criteria)

- IGF-1, IGFBP-3, Growth hormone, concentration Z score (continuous outcome, measured at least 6 months after AT using blood samples and chemiluminescence enzyme-linked immunosorbent assay)
- IGF-1, IGFBP-3, Growth hormone, concentration in ng/ml (continuous outcome, measured at least 6 months after AT using blood samples and chemiluminescence enzyme-linked immunosorbent assay)

Search strategy

Electronic searches

We will search MEDLINE (via PubMed), Embase, Google Scholar, and the Cochrane Central Register of Controlled Trials (CENTRAL) with no restrictions on language or publication date. The detailed search strategy for MEDLINE is listed in table 1, which will be adapted to the syntax and subject headings of the other databases.

Searching other resources

Additional studies will be sought by manually checking the references of included studies and relevant review articles.

Data collection and analysis

We will follow the relevant guidance provided in the *Cochrane Handbook for Systematic Reviews*. [27]

Study selection

At least two authors will screen the titles and abstracts yielded from the literature searches, independently and in duplicate. Articles, which appear to meet our inclusion criteria, will be downloaded in full. The same group of authors will then examine these full-texts independently for eligibility. Any disagreement will be resolved by discussion and consultation with other authors until consensus is reached. The corresponding author will be contacted if a study has insufficient information. For each excluded study, we will document the reason for exclusion.

Data extraction and management

The bibliographic information and abstracts of all identified items will be imported into the EndNote X8 Software (Clarivate Analytics, Philadelphia). At least two review authors will independently extract the following data from the included studies:

1. General information: title, journal, year, publication status.
2. Study characteristics: sample size, methods used for randomization and allocation concealment, blinding.
3. Participants: age, sex, race, height, weight, BMI, IGF-1, IGFBP-3, time from OSA diagnosis, diagnostic criteria and severity of OSA, related medical history, comorbid conditions, concomitant medication and other sleep treatments.
4. Interventions: type of surgery, pharmacologic treatments, watchful waiting or no intervention.
5. Outcomes: instrument or scale for measurement, follow-up length.
6. Results: point estimates and measures of variability for continuous variables, frequency counts for dichotomous variables, number of patients.

Risk of bias assessment

At least two review authors will assess the risk of bias of each included study independently and in duplicate. RCTs will be assessed using the Cochrane Risk of Bias tool, which include seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.[27] ROBINS-I (Risk Of Bias In Non-randomised Studies - of Interventions) will be used to assess the risk of bias of cohort studies for seven domains: confounding, selection of participants into the study, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result.[28] According to the guidance for these assessment tools, RCTs will be judged for having a low, high or unclear risk of bias; cohort studies will be judged for having a low, moderate, serious, critical risk of bias or 'no information'.

Measures of treatment effect

Where we identify a sufficient number of studies with homogeneous populations and characteristics, we will carry out meta-analyses of primary and secondary outcomes. For the analysis of dichotomous outcomes, we will use risk ratios with 95% confidence intervals (CIs);

for the analysis of continuous outcomes, we will use the mean difference or standardised mean difference and the corresponding 95% CIs.

Missing data

Where necessary, we will contact the authors of studies to obtain missing data / information. For missing standard deviations, we will use the methods detailed in section 7.7.3 of the Cochrane Handbook to impute them.[27] In the discussion section of the review, the potential impact of any missing data will be discussed.

Assessment of reporting biases

Where there are more than 10 studies that can be combined into a meta-analysis, we will use a funnel plot to explore the possibility of small study effects, which may indicate publication bias.

Data synthesis

Analyses will be performed with the Review Manager (RevMan) 5.3 software (Copenhagen: the Nordic Cochrane Centre, Cochrane Collaboration). Meta-analyses will be performed using a random-effects model. The heterogeneity among studies included in each meta-analysis will be assessed with the Q test statistic and I^2 statistics. Data from RCTs and those from cohort studies will not be combined in any meta-analyses.

Subgroup analysis and investigation of heterogeneity

We will attempt to perform the following subgroup analyses:

- Study design (e.g. RCTs vs. cohort studies);
- Nutritional status of the patients (e.g. obese vs. non-obese);
- Methods used to diagnose OSAHS (e.g. polysomnographically confirmed OSAHS vs. diagnosed OSAHS based on subjective measurements only);
- Surgical procedures (e.g. temperature controlled radiofrequency tonsillectomy and adenoidectomy, and complete tonsillectomy and adenoidectomy);
- Time point of outcome measurement (e.g. long-term vs. short-term);
- Scales used to measure outcome;

- Definition of outcomes; and
- Age groups.

Sensitivity analyses

If a sufficient number of studies are included in this review, we will perform sensitivity analyses to assess the consistency and robustness of our results. When sufficient data are available, we will perform sensitivity analyses by:

- Including only studies with low risk of bias;
- Excluding studies in which the majority of enrolled subjects were above 18;
- Repeating data syntheses using a fixed-effect model.

Publication bias

Possible publication bias will be investigated with a funnel plot if at least 10 studies are included in a meta-analysis.

Summary of findings tables

We will use the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach [29 30] to assess the certainty of the supporting evidence behind each main comparison. In this process, RCTs will start as high certainty evidence and observational studies as low certainty evidence. Thereafter, five factors (risk of bias, imprecision, inconsistency, indirectness and publication bias) may lead to rating down the certainty of evidence, and three factors (large effect, dose response, and all plausible confounding would reduce a demonstrated effect) may lead to rating up.

Patient and public involvement

The present work is based on a review of relevant studies and does not include original patient data. Therefore, no patients or public were involved in this review protocol.

ETHICS AND DISSEMINATION

Ethical approval is not required. The results of this study will be disseminated via peer-reviewed publications and social networks.

DISCUSSION

Nowadays, OSAHS is a common problem among children. In 2002, the American Academy of Pediatrics identified growth failure as one of the serious complications of untreated OSAHS.[31] Many studies have indicated that growth failure can be reversed after AT.[25] However, a recent RCT with a 7-month follow-up showed that the changes in height and height z score, as well as height velocity measures were similar between the early AT group and watchful waiting control. [32] Therefore, the present systematic review will analyse the association between AT children's height, weight and growth-related biomarkers. To our knowledge, there has been no systematic review regarding this clinical question since 2009.

In this review protocol, we have planned to perform subgroup analyses on different age groups, different nutritional status and different follow-up lengths. First of all, growth failure appears to be more prevalent among younger children with OSAHS. Vontetsianos and colleagues [33] found that height was improved only in children under the age of five, and the "catch-up growth" was not possible if disadvantageous factors were not removed early in life. Therefore, AT performed at an earlier age may lead to a higher degree of growth acceleration, and early diagnosis and timely referral may be helpful for reducing the occurrences of OSAHS-related growth failures. Second, the previous literature has shown an association between nutritional status and growth, which makes pediatric obesity another potential confounding factor.[34 35] In addition, differences in the findings of relevant studies could be explained by different follow-up lengths.[24]

By summarising the current knowledge in the effects of AT on growth of children with OSAHS, this review can provide a comprehensive summary of the current evidence for clinicians, and help them achieve evidence-based practice when treating children with OSAHS.

Contributors F.H. and H.H. conceived of this review. F.H. and T.Z. developed the search strategy and drafted the manuscript. T.W., Q.S., X.C., H.W., F.J. and H.H. revised the manuscript. H.H. is the guarantor. All authors participated in the determination of eligibility criteria, the risk of bias assessment strategy and data extraction methods. All authors read and approved the final manuscript.

Funding This work was supported by the National Key Clinical Specialties Construction Program of China (No. [2013]544), China Postdoctoral Science Foundation (No. 2018M630884) and the Fundamental Research Funds for the Central Universities (No. 2042018kf0070, Wuhan University). The funding sources had no involvement in the study design, collection, analysis, and interpretation of data, preparation of the manuscript, or in the decision to publish.

Competing interests None declared.

Patient consent Not required.

Data sharing statement The data may be obtained from the authors for academic purposes.

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Table 1. The search strategy to be used in MEDLINE (via PubMed)

No.	Search terms
#1	"Tonsillectomy"[Mesh]
#2	"Palatine Tonsil/surgery"[Mesh]
#3	adenotonsillecto* OR adenotonsilectom* OR tonsillecto*OR tonsillotom* OR adenoidectom* OR tonsilotom*
#4	adenotonsil* OR tonsil* OR adenoid* OR "Palatine Tonsil"[Mesh] OR "Adenoids"[Mesh]) AND ("Surgery"[Mesh] OR surger* OR surgic* OR excis* OR extract* OR remov*
#5	#1 OR #2 OR #3 OR #4
#6	"Sleep Apnoea Syndromes"[Mesh]
#7	sleep* AND (apnea* OR apnoea*)
#8	hypopnea* OR hypopnoea*
#9	OSA OR OSAHS
#10	#6 OR #7 OR #8 OR #9
#11	child[Mesh] OR adolescent[Mesh]
#12	child* OR adolescent* OR pediatric* OR paediatric*
#13	child*[Title/Abstract] OR adolescent*[Title/Abstract] OR pediatric*[Title/Abstract] OR paediatric*[Title/Abstract]
#14	growth[mesh] OR "body size"[Mesh] OR "body mass index"[Mesh] OR "insulin-like growth factor I"[Mesh] OR "insulin-like growth factor binding proteins"[Mesh]
#15	growth[Title/Abstract] OR development[Title/Abstract] OR height[Title/Abstract] OR weight[Title/Abstract] OR "body size"[Title/Abstract] OR "body mass index"[Title/Abstract] OR BMI[Title/Abstract] OR "insulin-like growth factor I"[Title/Abstract] OR "insulin-like growth factor binding proteins"[Title/Abstract] OR IGF-1[Title/Abstract] OR IGFBP*[Title/Abstract]
#16	#10 AND (#12 OR #13) AND (#14 OR #15)
#17	review[publication type] OR "systematic review"[publication type] OR "meta analysis"[publication type] OR "case reports"[publication type] OR letter[publication type] OR editorial[publication type] OR comment[publication type]
#18	#16 NOT #17

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

Section and topic	Item No	Checklist item	Page No
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	12
Sponsor	5b	Provide name for the review funder and/or sponsor	12
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	12
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5, 6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6, 16
Study records:			

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
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	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

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

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

BMJ Open

Effects of adenotonsillectomy on the growth of children with obstructive sleep apnoea-hypopnea syndrome (OSAHS): protocol for a systematic review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030866.R2
Article Type:	Protocol
Date Submitted by the Author:	16-Jul-2019
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Primary Subject Heading:	Ear, nose and throat/otolaryngology
Secondary Subject Heading:	Dentistry and oral medicine, Evidence based practice, Paediatrics
Keywords:	Adenoidectomy, Tonsillectomy, Sleep Apnoea Syndromes, Growth, Paediatric otolaryngology < PAEDIATRIC SURGERY, PAEDIATRICS

Effects of adenotonsillectomy on the growth of children with obstructive sleep apnoea-hypopnea syndrome (OSAHS): protocol for a systematic review

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Keywords:

Adenoidectomy, Tonsillectomy, Sleep Apnoea Syndromes, Child, Adolescent, Growth

ABSTRACT

Introduction: Obstructive sleep apnoea-hypopnea syndrome (OSAHS) is characterized by recurring episodes of complete or partial upper airway collapse during sleep. Persistent OSAHS is associated with long-term consequences, such as growth failure, cardiovascular and neurocognitive problems in children. Different from the aetiology of OSAHS in adults, the most common cause of paediatric OSAHS is adenotonsillar hypertrophy. Adenotonsillectomy (AT) has been recommended as the first-line treatment of paediatric OSAHS. Several studies have suggested that retarded growth caused by OSAHS can improve after AT during the prepubertal period. This review will systematically search and summarise the available evidence on the effects of AT on children's growth.

Methods and analysis: We will conduct electronic searches in MEDLINE (via PubMed), Embase, Google Scholar and the Cochrane Central Register of Controlled Trials (CENTRAL) for randomised controlled trials or cohort studies that included a control group. Additional records will be searched by checking the references included in the selected studies and relevant reviews. At least two authors will undertake selection of studies and data extraction independently and in duplicate. The Cochrane Risk of Bias tool and ROBINS-I will be used to assess the risk of bias of RCT and cohort studies, respectively. A random-effects model will be used for meta-analyses. Data synthesis and other analyses will be carried out using the RevMan 5.3 software. GRADE will be used to assess the quality of the supporting evidence behind each main comparison.

Ethics and dissemination: There is no ethical issue in this systematic review given that we will only include published studies. The results will be disseminated via peer-reviewed publications and social networks.

PROSPERO registration number: CRD42019125882

ARTICLE SUMMARY

Strengths and limitations of this study

- To our knowledge, this will be the first systematic review regarding the effects of AT on children's growth since 2009.
- Both randomised controlled trials and prospective cohort studies will be searched and included (if eligible), which could result in a more comprehensive summary of the available evidence.
- Subgroup and sensitivity analyses will be performed to explore heterogeneity and the robustness of our findings.
- The main limitation might result from a limited number of primary studies that are available, and a potentially low certainty of evidence from observational studies.
- There is a lack of commonly accepted minimal clinically important difference for the outcome measures of interest and this research question, making it potentially difficult to interpret the clinical significance of synthesized results.

INTRODUCTION

Background

Obstructive sleep apnoea-hypopnea syndrome (OSAHS) has been defined as "a disorder of breathing during sleep characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction that disrupts normal ventilation during sleep and normal sleep patterns".[1] The reported prevalence of paediatric OSAHS varies from 0.6% to 44.6% depending on the population studied and the definitions / standards used for diagnosis.[2-4] The commonly considered gold standard for diagnosing paediatric OSAHS is overnight polysomnography (PSG).[1] Children with OSAHS may show symptoms such as snoring, mouth breathing, observed episodes of apnoea, as well as attention-deficit or hyperactivity. Also, growth retardation,[5 6] neuropsychological and cognitive deficits,[7] impaired cardiovascular function [8 9] as well as craniofacial development disorders have been reported to be associated with OSAHS.[10 11] However, the pathophysiological mechanism behind poor growth in children with OSAHS is unclear. Possible reasons may include the increased energy expenditure during sleep, abnormal nocturnal growth hormone secretion, nocturnal hypoxemia, nocturnal respiratory acidosis, as well as lower total caloric intake resulting from poor appetite and difficulties in swallowing.[12 13]

Description of the intervention

There are a variety of therapies available for the treatment of paediatric OSAHS, including surgical and non-surgical treatments.[14-16] Adenotonsillar hypertrophy is the most important anatomical factor that has been associated with OSAHS,[17] therefore adenotonsillectomy (AT) has been widely recommended as the first-line treatment.[1 18] For children between 3 and 17 years who are comorbidity free, AT appears to be a safe option with a growing body of evidence.[19] Nowadays, many paediatric ENT surgeons are using the Coblation technique (cold radiofrequency ablation) and a lower complication rate has been reported.[20] For clinicians faced with the decision of whether to perform AT, the severity of obstructive sleep apnoea is an important factor. Removal of the enlarged adenoid and tonsil eliminates the upper airway obstruction, improves the breathing pattern and improves the respiratory parameters as measured by polysomnography in the majority of healthy children.[21]

Why it is important to conduct this review

Recent studies have suggested that retarded growth caused by OSAHS can improve after AT.[12 13 18 22-24] However, there have been few systematic reviews analysing the effects of AT on the growth of children with OSAHS. In 2009, Bonuck et al. [25] carried out a systematic review and meta-analysis regarding the growth and growth biomarker changes after AT, but did not make a comparison between children who received AT and an appropriate control group. To our knowledge, at present there exists no other systematic reviews regarding this question. We therefore have a unique opportunity to systematically review the relevant literature and determine the effects of AT on children's growth.

Objectives

The main objective of this review is to assess the effects of AT on the growth of children with OSAHS.

Review Question

Does AT have any effects on the growth of children with OSAHS, as compared with concurrent controls (either children with OSAHS who did not receive AT or healthy controls)?

METHODS

This protocol was written in accordance with the PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols) reporting guidelines.[26]

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) and prospective cohort studies that:

1) Reported on the growth changes of children before and after AT;

2) Included a concurrent control group; and

3) Had a follow-up length of no less than 6 months.

For a prospective cohort study to be eligible in the review it should meet the following criteria: 1) it should include two or more groups of participants; 2) the identification of participants, the assessment of baseline, the allocation to intervention, and the assessment of

outcomes should be done prospectively. We will not require that the study hypothesis was generated prospectively as this aspect is generally poorly reported.[27]

Types of participants

We will include studies in which the majority of participants were under 18 years of age at the time of recruitment with a diagnosis of OSAHS.

Types of interventions

Treatment group:

AT (Tonsillectomy and/or adenoidectomy)

Control group:

- No intervention or watchful waiting only
- Other pharmacologic or surgical interventions

Types of outcome measures

Primary outcome:

- Height Z score (continuous outcome, measured at least 6 months after AT with stadiometer)

Secondary outcomes:

- Raw value of height in cm (continuous outcome, measured at least 6 months after AT with stadiometer)
- Weight Z score (continuous outcome, measured at least 6 months after AT with electronic scale)
- Raw value of weight in kg (continuous outcome, measured at least 6 months after AT with electronic scale)
- BMI Z score (continuous outcome, calculated based on height and weight data meeting the above-mentioned criteria)
- BMI (continuous outcome, calculated based on height and weight data meeting the above-mentioned criteria)

- IGF-1, IGFBP-3, Growth hormone, concentration Z score (continuous outcome, measured at least 6 months after AT using blood samples and chemiluminescence enzyme-linked immunosorbent assay)
- IGF-1, IGFBP-3, Growth hormone, concentration in ng/ml (continuous outcome, measured at least 6 months after AT using blood samples and chemiluminescence enzyme-linked immunosorbent assay)

Search strategy

Electronic searches

We will search MEDLINE (via PubMed), Embase, Google Scholar, and the Cochrane Central Register of Controlled Trials (CENTRAL) with no restrictions on language or publication date. The detailed search strategy for MEDLINE is listed in table 1, which will be adapted to the syntax and subject headings of the other databases.

Searching other resources

Additional studies will be sought by manually checking the references of included studies and relevant review articles.

Data collection and analysis

We will follow the relevant guidance provided in the *Cochrane Handbook for Systematic Reviews*. [28]

Study selection

At least two authors will screen the titles and abstracts yielded from the literature searches, independently and in duplicate. Articles, which appear to meet our inclusion criteria, will be downloaded in full. The same group of authors will then examine these full-texts independently for eligibility. Any disagreement will be resolved by discussion and consultation with other authors until consensus is reached. The corresponding author will be contacted if a study has insufficient information. For each excluded study, we will document the reason for exclusion.

Data extraction and management

The bibliographic information and abstracts of all identified items will be imported into the EndNote X8 Software (Clarivate Analytics, Philadelphia). At least two review authors will independently extract the following data from the included studies:

1. General information: title, journal, year, publication status.
2. Study characteristics: sample size, methods used for randomization and allocation concealment, blinding.
3. Participants: age, sex, race, height, weight, BMI, IGF-1, IGFBP-3, time from OSA diagnosis, diagnostic criteria and severity of OSA, related medical history, comorbid conditions, concomitant medication and other sleep treatments.
4. Interventions: type of surgery, pharmacologic treatments, watchful waiting or no intervention.
5. Outcomes: instrument or scale for measurement, follow-up length.
6. Results: point estimates and measures of variability for continuous variables, frequency counts for dichotomous variables, number of patients.

Risk of bias assessment

At least two review authors will assess the risk of bias of each included study independently and in duplicate. RCTs will be assessed using the Cochrane Risk of Bias tool, which include seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.[28] ROBINS-I (Risk Of Bias In Non-randomised Studies - of Interventions) will be used to assess the risk of bias of cohort studies for seven domains: confounding, selection of participants into the study, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result.[29] According to the guidance for these assessment tools, RCTs will be judged for having a low, high or unclear risk of bias; cohort studies will be judged for having a low, moderate, serious, critical risk of bias or 'no information'.

Measures of treatment effect

Where we identify a sufficient number of studies with homogeneous populations and characteristics, we will carry out meta-analyses of primary and secondary outcomes. For the analysis of dichotomous outcomes, we will use risk ratios with 95% confidence intervals (CIs);

for the analysis of continuous outcomes, we will use the mean difference or standardised mean difference and the corresponding 95% CIs.

Missing data

Where necessary, we will contact the authors of studies to obtain missing data / information. For missing standard deviations, we will use the methods detailed in section 7.7.3 of the Cochrane Handbook to impute them.[28] In the discussion section of the review, the potential impact of any missing data will be discussed.

Assessment of reporting biases

Where there are more than 10 studies that can be combined into a meta-analysis, we will use a funnel plot to explore the possibility of small study effects, which may indicate publication bias.

Data synthesis

Analyses will be performed with the Review Manager (RevMan) 5.3 software (Copenhagen: the Nordic Cochrane Centre, Cochrane Collaboration). Meta-analyses will be performed using a random-effects model. The heterogeneity among studies included in each meta-analysis will be assessed with the Q test statistic and I^2 statistics. Data from RCTs and those from cohort studies will not be combined in any meta-analyses.

Subgroup analysis and investigation of heterogeneity

We will attempt to perform the following subgroup analyses:

- Study design (e.g. RCTs vs. cohort studies);
- Nutritional status of the patients (e.g. obese vs. non-obese);
- Methods used to diagnose OSAHS (e.g. polysomnographically confirmed OSAHS vs. diagnosed OSAHS based on subjective measurements only);
- Surgical procedures (e.g. temperature controlled radiofrequency tonsillectomy and adenoidectomy, and complete tonsillectomy and adenoidectomy);
- Time point of outcome measurement (e.g. long-term vs. short-term);
- Scales used to measure outcome;

- Definition of outcomes; and
- Age groups.

Sensitivity analyses

If a sufficient number of studies are included in this review, we will perform sensitivity analyses to assess the consistency and robustness of our results. When sufficient data are available, we will perform sensitivity analyses by:

- Including only studies with low risk of bias;
- Excluding studies in which the majority of enrolled subjects were above 18;
- Repeating data syntheses using a fixed-effect model.

Publication bias

Possible publication bias will be investigated with a funnel plot if at least 10 studies are included in a meta-analysis.

Summary of findings tables

We will use the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach [30 31] to assess the certainty of the supporting evidence behind each main comparison. In this process, RCTs will start as high certainty evidence and observational studies as low certainty evidence. Thereafter, five factors (risk of bias, imprecision, inconsistency, indirectness and publication bias) may lead to rating down the certainty of evidence, and three factors (large effect, dose response, and all plausible confounding would reduce a demonstrated effect) may lead to rating up.

Patient and public involvement

The present work is based on a review of relevant studies and does not include original patient data. Therefore, no patients or public were involved in this review protocol.

ETHICS AND DISSEMINATION

Ethical approval is not required. The results of this study will be disseminated via peer-reviewed publications and social networks.

DISCUSSION

Nowadays, OSAHS is a common problem among children. In 2002, the American Academy of Pediatrics identified growth failure as one of the serious complications of untreated OSAHS.[32] Many studies have indicated that growth failure can be reversed after AT.[25] However, a recent RCT with a 7-month follow-up showed that the changes in height and height z score, as well as height velocity measures were similar between the early AT group and watchful waiting control. [33] Therefore, the present systematic review will analyse the association between AT children's height, weight and growth-related biomarkers. To our knowledge, there has been no systematic review regarding this clinical question since 2009.

In this review protocol, we have planned to perform subgroup analyses on different age groups, different nutritional status and different follow-up lengths. First of all, growth failure appears to be more prevalent among younger children with OSAHS. Vontetsianos and colleagues [34] found that height was improved only in children under the age of five, and the "catch-up growth" was not possible if disadvantageous factors were not removed early in life. Therefore, AT performed at an earlier age may lead to a higher degree of growth acceleration, and early diagnosis and timely referral may be helpful for reducing the occurrences of OSAHS-related growth failures. Second, the previous literature has shown an association between nutritional status and growth, which makes pediatric obesity another potential confounding factor.[35] [36] In addition, differences in the findings of relevant studies could be explained by different follow-up lengths.[24]

By summarising the current knowledge in the effects of AT on growth of children with OSAHS, this review can provide a comprehensive summary of the current evidence for clinicians, and help them achieve evidence-based practice when treating children with OSAHS.

Contributors F.H. and H.H. conceived of this review. F.H. and T.Z. developed the search strategy and drafted the manuscript. T.W., Q.S., X.C., H.W., F.J. and H.H. revised the manuscript. H.H. is the guarantor. All authors participated in the determination of eligibility criteria, the risk of bias assessment strategy and data extraction methods. All authors read and approved the final manuscript.

Funding This work was supported by the National Key Clinical Specialties Construction Program of China (No. [2013]544), China Postdoctoral Science Foundation (No. 2018M630884) and the Fundamental Research Funds for the Central Universities (No. 2042018kf0070, Wuhan University). The funding sources had no involvement in the study design, collection, analysis, and interpretation of data, preparation of the manuscript, or in the decision to publish.

Competing interests None declared.

Patient consent Not required.

Data sharing statement The data may be obtained from the authors for academic purposes.

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Table 1. The search strategy to be used in MEDLINE (via PubMed)

No.	Search terms
#1	"Tonsillectomy"[Mesh]
#2	"Palatine Tonsil/surgery"[Mesh]
#3	adenotonsillecto* OR adenotonsilectom* OR tonsillecto*OR tonsillotom* OR adenoidectom* OR tonsilotom*
#4	adenotonsil* OR tonsil* OR adenoid* OR "Palatine Tonsil"[Mesh] OR "Adenoids"[Mesh]) AND ("Surgery"[Mesh] OR surger* OR surgic* OR excis* OR extract* OR remov*
#5	#1 OR #2 OR #3 OR #4
#6	"Sleep Apnoea Syndromes"[Mesh]
#7	sleep* AND (apnea* OR apnoea*)
#8	hypopnea* OR hypopnoea*
#9	OSA OR OSAHS
#10	#6 OR #7 OR #8 OR #9
#11	child[Mesh] OR adolescent[Mesh]
#12	child* OR adolescent* OR pediatric* OR paediatric*
#13	child*[Title/Abstract] OR adolescent*[Title/Abstract] OR pediatric*[Title/Abstract] OR paediatric*[Title/Abstract]
#14	#5 AND #10 AND (#11 OR #12 OR #13)
#15	review[publication type] OR "systematic review"[publication type] OR "meta analysis"[publication type] OR "case reports"[publication type] OR letter[publication type] OR editorial[publication type] OR comment[publication type]
#16	#14 NOT #15

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

Section and topic	Item No	Checklist item	Page No
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	12
Sponsor	5b	Provide name for the review funder and/or sponsor	12
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	12
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5, 6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6, 16
Study records:			

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
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	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

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

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