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Does non-invasive ventilation change metabolic markers in children with obstructive sleep apnea? A Systematic Review

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Title

Does non-invasive ventilation change metabolic markers in children with obstructive sleep apnea? A Systematic Review

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Abstract

Introduction

Obstructive Sleep Apnea (OSA) is not only common within pediatrics but is associated with critical childhood metabolic morbidity such as obesity, cardiovascular disease and glucose tolerance impairment. Increasing evidence suggests an association between childhood OSA and metabolic syndrome such as markers of cardiovascular disease, systemic hypertension, glucose intolerance, and increased lipid profile. Recent studies have targeted changes in metabolic markers in children using NIV but no systematic reviews are available to summarize this emerging evidence. The purpose of this systematic review is to provide systematic synthesis of the evidence on the effect of NIV use on metabolic markers in children with OSA.

Methods and Analysis:

A systematic search of electronic databases and grey literature will include will include pediatric interventional studies (RCTs, cohort studies) with and without a comparison group. Two reviewers will independently undertake the two step process of title/abstract and full text screening. Data will be extracted and assessed, with aggregate data being reported. When the data allow, meta-analysis will be performed.

Ethics and Dissemination:

There are no ethical concerns with this systematic review, as data has previously been published. This review will inform clinicians taking care of children with OSA and obesity/metabolic syndrome about the potential effects of NIV therapies on metabolic markers, and has the potential to change the approach to childhood OSA and obesity. Results of this systematic review will be submitted for dissemination in abstract and manuscript form.

Strengths and Limitations of this Study

- We will use comprehensive systematic review and meta-analysis methods to summarize the evidence on the efficacy of a respiratory intervention for an increasing health problem in children worldwide: obesity and metabolic syndrome.
- Methodological experts and pediatric clinical specialists have been consulted to ensure that our search strategy captures all potential metabolic markers that might be impacted by NIV.
- We will attempt a meta-analysis when there is enough homogeneity among populations and measured outcomes.
- Limited appraisal of the grey literature will be performed.

Introduction

Obstructive sleep apnea (OSA) is common in children with an estimated prevalence of 5.7% (1). OSA contributes to childhood morbidity, including impaired cognition, neurodevelopmental delay, cardio-metabolic dysfunction, and reduced quality of life (2). The metabolic consequences of OSA are well known among adult populations, with a clearly demonstrated association between OSA and metabolic syndrome, including systemic hypertension, cardiovascular risk, dyslipidemia, glucose control impairment and systemic inflammation (3, 4). The literature examining the association between metabolic syndrome in children has shown a similar relationship with an emerging body of the literature demonstrating a greater risk of hypertension, dyslipidemia and glucose control in obese children and youths with OSA (5-8).

The first line therapy for the treatment of OSA in children is adenotonsillectomy (2, 9). In both obese and non-obese children, surgical intervention can improve cardio-respiratory parameters in sleep studies including apnea hypopnea Index (AHI) and oxygen saturation values. Surgical management has also been shown to have positive effects on systemic inflammation and dyslipidemia (10-12). However, residual symptoms of OSA after adenotonsillectomy have been shown to be present in up to half of children, which is particularly true in children with obesity (13-15). Given the persistence of OSA after surgery, the metabolic consequences are likely to persist. Non-invasive ventilation, including continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BPAP), is the recommended therapy for children with OSA who are not surgical candidates, or for children with persistent OSA post-surgery. Initiation of NIV has been shown to have significant effects on nocturnal symptoms of OSA and daytime outcomes such as daytime sleepiness, attention, academic performance, and quality of life (16-20), While previous systematic reviews and meta-analysis have summarized the impact of NIV in metabolic markers in the adult population, including hypertension cardiovascular outcomes, glucose control, lipid profile, systemic inflammation and even mortality (19, 21-29), similar systematic reviews are not available in pediatric populations. The purpose of this systematic review is to provide a rigorous overview of the evidence describing the effect of NIV use on metabolic markers in children with OSA.

Methods and Analysis

Study design

The methodology of this systematic review and meta-analysis follows the recommendations made in the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocols (PRISMA-P) 2015 statement " (30). Approval from the NIHR PROSPERO registry is pending.

Search strategy

An information specialist, systematic review methodologist and clinical experts in pediatric respiratory and sleep medicine and pediatric metabolic syndrome have established a collaborative team to develop a comprehensive search strategy and determined the appropriate information sources. The search strategy includes terms for "NIV" used in a previously published scoping review, a published filter for pediatric populations and addresses the following key concepts: effects on oxidative stress and markers of systemic inflammation, cardiovascular outcomes, changes in weight/body mass index, lipid profile, liver enzymes, glucose control and markers of insulin resistance, renal function and other metabolic markers (See Appendix A) (31). Information sources will include Ovid Medline, Ovid Embase, CINAHL via EbscoHOST, Wiley Cochrane Library (including the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects, the Health Technology Assessment Database, and the NHS Economic Evaluation Database) and PROQUEST Theses and Dissertations. No language restrictions will be applied to the search strategy. Letters, editorials, commentaries and non-intervention studies will be excluded. Reference lists of all studies included in this systematic review will be scanned to identify further relevant studies not detected by the search strategy. Published abstracts from 2018-2019 from the following conferences will be screened: American Thoracic Society Conference, Canadian Thoracic Society Conference, CHEST Congress, European Respiratory Society, Sleep Meeting. The search of the above information sources is planned to occur on April 30, 2020.

Eligibility criteria

Types of participants/population: Studies including children (newborn to age 18 years) will be included. Studies across ages with disaggregated pediatric data will also be included. Eligible studies must pertain to children with OSA or other sleep-related breathing disorders as defined in the International Classification of Sleep Disorders, including obstructive sleep apnea and sleep-related hypoventilation

Types of Interventions: Included studies must contain information on NIV (CPAP or BPAP) use. We will include studies irrespective of the length of NIV usage.

Type of Outcomes: Eligible studies must include data related to metabolic markers, with no outcome restrictions. This includes, but is not limited to: effects on oxidative stress and markers of systemic inflammation, cardiovascular outcomes, changes in weight/body mass index, lipid profile, liver enzymes, glucose control and markers of insulin resistance, renal function and other metabolic markers.

Types of Studies: Interventional studies will be considered for inclusion including randomized and non-randomized clinical trials (RCTs and non-RCTs), controlled before-after studies. No other study designs will be considered for inclusion.

Exclusion: Qualitative and mixed methods research will be excluded, as will case series, case reports, and non-specified grey literature.

Study records

Data management: Records from searches will be imported into an EndNote library (Endnote X9, Clarivate Analytics) and duplicates will be removed. The library will be duplicated for independent screening.

Selection process: Two independent reviewers (MCC, CAG) will screen titles and abstracts of retrieved articles for eligibility based on the inclusion criteria. Full text will be retrieved for all potentially relevant articles, which will be reviewed independently by the two reviewers, and studies that meet the eligibility criteria will be included in the review. Discrepancies between the reviewers will be resolved through discussion. Reasons for exclusion will be recorded at the full-text review level.

Data collection process: Data extraction will be completed by one reviewer using a pre-designed standardized form and entered into RedCap Database (32, 33). Data extraction will be verified by a second reviewer for a sample of 20% of the studies with acceptance if agreement in at least 80% of the data. Duplicate data from the same data set published in different manuscripts will be removed. Data Extraction is expected to be complete by October 1, 2020.

Data synthesis: Once the information has been extracted, we will present findings including the numerical analysis of the number, publication type, publication year and country of publication of the studies included in the review. We will also present a narrative description of the study design, participant characteristics, sample size, NIV type, control group description, outcomes measures, and follow up duration. We will use this information to establish subcategories of studies which may include groupings based on age (i.e., infants, children, and adolescents), intervention type (i.e., CPAP, bi-level,) and outcomes (e.g. oxidative stress, obesity, dyslipidemia, liver disease, glucose intolerance, cardiovascular, renal and other metabolic diseases).

Quality assessment and risk of bias: Risk of bias will be assessed by two independent reviewers (MCC, CAG) specific to the study methodology. Tools will include the Quality Assessment Tool (34) and Cochrane risk of bias tool (35). Discrepancies in decisions will be resolved through discussion.

The reviewers will also use the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) to assess the evidence at the outcome level (36). This will include assessing for risk of bias, imprecision, inconsistency, indirectness and publication bias.

Meta-analysis

Meta-analysis will be attempted for outcomes with enough homogeneity among the study populations. Homogeneity criteria will include an AHI <5 events/hour to define mild obstructive sleep apnea, 5-10 events/h for moderate and >10 for severe sleep disordered breathing as per the American Academy of Sleep Medicine (AASM) (37, 38). In addition, nocturnal hypoxemia will be defined by sleep time with oxygen saturations below 90% over 5% and nocturnal hypoventilation by over 25% sleep time carbon dioxide levels above 50 mmHg (39). The information will be subcategorized to include grouping based on outcome (changes in the same metabolic marker). For non-randomized studies, we will combine effect estimates from studies adjusted by confounding rather than raw data if available. RCTs will be analyzed separately if available. Risk of bias will be considered and explanations for heterogeneity will be pursued including publication bias. Graphics of pooled data (i.e. forest plots) will be provided. Most outcome data are expected to be continuous.

Ethics and Dissemination

There are no ethical concerns with this systematic review, as data has previously been published. This review will inform clinicians taking care of children with OSA and obesity/metabolic syndrome about the potential effects of NIV therapies on metabolic markers and help plan for necessary assessment of this

group of children in the clinical practice. This information has the potential to change the approach to childhood OSA and obesity and therefore impact future clinical guidelines at national and international level. Results of this systematic review will be submitted for dissemination in abstract and manuscript form at multiple levels to target general pediatricians and pediatric specialists involved in the care of these patients including pediatric respiratory and sleep specialists, endocrinologists, cardiologists and nephrologists. The results of this systematic review will be of interest for general audience, which can be reached through infographics, videos and TED talks to be distributed through social media.

Authors Contributions

MCC, CAG and SRL were involved in idea generation of this study. MCC, CAG, SRL, SP, DKL and MS were involved in study design and protocol development. MS and DKL developed the search strategies and performed literature reviews. MCC and CAG were involved with review of literature for inclusion into the study.

Funding Statement

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Competing Interests Statement

There are no competing interests to declare.

Word Count: (4000 max)

Appendix A (Search Strategies)

NIV

As per (31, 40)

Children

As per (31, 40)

SDB

Sleep Apnea, Obstructive Sleep Apnea, OSA, Central Sleep Apnea, CSA, Primary Central Sleep Apnea, Primary Sleep Apnea of Infancy, Primary Central Sleep Apnea of Prematurity, Treatment-Emergent Central Sleep Apnea, Obesity Hypoventilation Syndrome, Hypoventilation, Central Hypoventilation, Pickwikian Syndrome, Congenital Central Hypoventilation Syndrome, CCHS, Congenital Central Alveolar Hypoventilation Syndrome, Late onset Central Hypoventilation with Hypothalamic Dysfunction, Idiopathic Central Alveolar Hypoventilation, Central Alveolar Hypoventilation, Central Hypoventilation, Sleep related hypoventilation, Sleep related hypoxemia, Snoring, Primary Snoring, Catathrenia

Metabolic Markers

Oxidative stress: Oxidative Stress, inflammation, metabolism, metabolic, CRP, interleukin-6 (IL-6) and 8 (IL), tumor necrosis factor alpha (TNFa), cytokines, adipokines, cortisol, a-amylase, sympathetic dysfunction, endothelial dysfunction, atherosclerosis, arterial stiffness, endothelial nitric oxide synthase (eNOS), nitric oxide (NO), cyclooxygenase (Cox)-1, Cox-2, thromboxane A2, prostacyclin. Circulating progenitor cells (CPCs), 8-isoprostanes, circulating cell-derived MPS: PMPs, LMPs, EMPs, adiponectin, LTB4, TNFR-1, IFN, plasminogen activator inhibitor-1, monocyte chemoattractant protein-1, matrix metalloproteinase-9, apelin C, osteocrin, adropin, TREM-1, pentraxin 3, BNP, MRP 8/14

Obesity: weight, weight gain, weight loss, weight management, obese, obesity, overweight, body mass index, BMI, growth, growth acceleration, anthropometric, leptin, grehlin,

Dyslipidemia: Dislipidemia, lipid, elevated lipid, Triglycerides, cholesterol, Total cholesterol, high-density lipoprotein cholesterol, HDL-C, HDL, apoB, lipoprotein

Liver disease: liver enzymes, Aspartate transaminase, AST, alanine transaminase, ALT, liver disease, nonalcoholic fatty liver disease, NAFLD

Glucose intolerance: glucose, elevated glucose, glucose metabolism, glycemia, hyperglycemia, insulin, elevated insulin, insulin resistance, diabetes, diabetes mellitus, adiponectin, adiposity, HOMA-index (homeostasis model assessment) , HbA1c, fasting plasma glucose (FPG), fasting serum glucose, fasting glucose, fasting plasma insulin (FPI), OGTT, oral glucose tolerance test, glucose tolerance test, acute insulin response to glucose, acute insulin response (FSIGT), C-peptide, glucagon

Cardiovascular: heart function, cardiovascular disease, cardiovascular diseases, Blood pressure, systolic blood pressure (SBP), diastolic blood pressure (DBP), hypertension, hypertensive, high blood pressure, High blood pressures, elevated blood pressure, elevated blood pressures, prehypertension, 24-hour ambulatory blood pressure monitoring (ABPM), nocturnal blood pressure dipping, nocturnal dipping, blood pressure variability, nocturnal blood pressure variability, Left ventricular hypertrophy, LVH, right ventricular hypertrophy, RVH, ventricular hypertrophy, echocardiogram, systolic function impairment, diastolic function impairment, cardiac events, cardiac event, cardiac events, cardiac, heart, hearts,

coronary disease, coronary diseases, sudden cardiac death, sudden cardiac deaths, cardiac sudden death, sudden cardiac deaths, sudden cardiac arrest, sudden cardiac arrests, cardiac arrest, cardiac arrests, heart failure, right heart failure, acute right heart failure, chronic right heart failure,

Renal involvement: Proteinuria, Microalbuminuria, Focal segmental glomerulosclerosis (FSGS), kidney, renal

Other: Metabolic disease,

Appendix B: Published Abstracts from Prominent Conferences and Thesis Dissertations

American Thoracic Society

Canadian Respiratory Conference

CHEST

European Respiratory Society International Congress

Sleep Meeting

World Sleep Congress

Thesisdissertations.org

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3,4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Does non-invasive ventilation change metabolic markers in children with obstructive sleep apnea? A Systematic Review and Meta-Analysis Study Protocol

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Title

Does non-invasive ventilation change metabolic markers in children with obstructive sleep apnea? A Systematic Review and Meta-Analysis Study Protocol

Authors:

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Abstract

Introduction

Obstructive Sleep Apnea (OSA) is not only common within pediatrics but is associated with critical childhood metabolic morbidity such as obesity, cardiovascular disease and glucose tolerance impairment. Increasing evidence suggests an association between childhood OSA and metabolic syndrome such as markers of cardiovascular disease, systemic hypertension, glucose intolerance, and increased lipid profile. Recent studies have targeted changes in metabolic markers in children using NIV but no systematic reviews are available to summarize this emerging evidence. The purpose of this systematic review is to provide systematic synthesis of the evidence on the effect of NIV use on metabolic markers in children with OSA.

Methods and Analysis:

A systematic search of electronic databases and grey literature will include pediatric interventional studies (RCTs, cohort studies) with and without a comparison group. Two reviewers will independently undertake the two step process of title/abstract and full text screening. Data will be extracted and assessed, with aggregate data being reported. When the data allow, meta-analysis will be performed.

Ethics and Dissemination:

There are no ethical concerns with this systematic review, as data has previously been published. This review will inform clinicians taking care of children with OSA and obesity/metabolic syndrome about the potential effects of NIV therapies on metabolic markers, and has the potential to change the approach to childhood OSA and obesity. Results of this systematic review will be submitted for dissemination in abstract and manuscript form.

Strengths and Limitations of this Study

- We will use comprehensive systematic review and meta-analysis methods to summarize the evidence on the efficacy of a respiratory intervention for an increasing health problem in children worldwide: obesity and metabolic syndrome.
- Methodological experts and pediatric clinical specialists have been consulted to ensure that our search strategy captures all potential metabolic markers that might be impacted by NIV.
- We will attempt a meta-analysis when there is enough homogeneity among populations and measured outcomes.
- Limited appraisal of the grey literature will be performed.

Introduction

Obstructive sleep apnea (OSA) is common in children with an estimated prevalence of 5.7% (1). OSA contributes to childhood morbidity, including impaired cognition, neurodevelopmental delay, cardio-metabolic dysfunction, and reduced quality of life (2). The metabolic consequences of OSA are well known among adult populations, with a clearly demonstrated association between OSA and metabolic syndrome, including systemic hypertension, cardiovascular risk, dyslipidemia, glucose control impairment and systemic inflammation (3, 4). The literature examining the association between metabolic syndrome in children has shown a similar relationship with an emerging body of the literature demonstrating a greater risk of hypertension, dyslipidemia and glucose control in obese children and youths with OSA (5-8).

The first line therapy for the treatment of OSA in children is adenotonsillectomy (2, 9). In both obese and non-obese children, surgical intervention can improve cardio-respiratory parameters in sleep studies including apnea hypopnea Index (AHI) and oxygen saturation values. Surgical management has also been shown to have positive effects on systemic inflammation and dyslipidemia (10-12). However, residual symptoms of OSA after adenotonsillectomy have been shown to be present in up to half of children, which is particularly true in children with obesity (13-15). Given the persistence of OSA after surgery, the metabolic consequences are likely to persist. Non-invasive ventilation, including continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BPAP), is the recommended therapy for children with OSA who are not surgical candidates, or for children with persistent OSA post-surgery. Initiation of NIV has been shown to have significant effects on nocturnal symptoms of OSA and daytime outcomes such as daytime sleepiness, attention, academic performance, and quality of life (16-20), While previous systematic reviews and meta-analysis have summarized the impact of NIV in metabolic markers in the adult population, including hypertension cardiovascular outcomes, glucose control, lipid profile, systemic inflammation and even mortality (19, 21-29), similar systematic reviews

are not available in pediatric populations. The purpose of this systematic review is to provide a rigorous overview of the evidence describing the effect of NIV use on metabolic markers in children with OSA.

Methods and Analysis

Study design

The methodology of this systematic review and meta-analysis follows the recommendations made in the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocols (PRISMA-P) 2015 statement " (30). Approval from the NIHR PROSPERO registry is pending.

Search strategy

An information specialist, systematic review methodologist and clinical experts in pediatric respiratory and sleep medicine and pediatric metabolic syndrome have established a collaborative team to develop a comprehensive search strategy and determined the appropriate information sources. The search strategy includes terms for "NIV" used in a previously published scoping review (31, 32), a published filter for pediatric populations (31, 32) and addresses the following key concepts: effects on oxidative stress and markers of systemic inflammation, cardiovascular outcomes, changes in weight/body mass index, lipid profile, liver enzymes, glucose control and markers of insulin resistance, renal function and other metabolic markers (See Appendix A) (31). Information sources will include Ovid Medline, Ovid Embase, CINAHL via EbscoHOST, Wiley Cochrane Library (including the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects, the Health Technology Assessment Database, and the NHS Economic Evaluation Database) and PROQUEST Theses and Dissertations. No language restrictions will be applied to the search strategy. Letters, editorials, commentaries and non-intervention studies will be excluded. Reference lists of all studies included in this systematic review will be scanned to identify further relevant studies not detected by the search strategy. Published abstracts from 2018-2019 from the following conferences will be screened: American Thoracic Society Conference, Canadian Thoracic Society Conference, CHEST Congress, European Respiratory Society, Sleep Meeting (Appendix B). The search of the above information sources is planned to occur on April 30, 2020.

Eligibility criteria

Types of participants/population: Studies including children (newborn to age 18 years) will be included. Studies across ages with disaggregated pediatric data will also be included. Eligible studies must pertain to children with OSA or other sleep-related breathing disorders as defined in the International Classification of Sleep Disorders, including obstructive sleep apnea and sleep-related hypoventilation

Types of Interventions: Included studies must contain information on NIV (CPAP or BPAP) use. We will include studies irrespective of the length of NIV usage.

Type of Outcomes: Eligible studies must include data related to metabolic markers, with no outcome restrictions. This includes but is not limited to: effects on oxidative stress and markers of systemic inflammation, cardiovascular outcomes, changes in weight/body mass index, lipid profile, liver enzymes, glucose control and markers of insulin resistance, renal function and other metabolic markers. Inflammatory markers, cardiovascular outcomes and other outcomes of metabolic syndrome are described in Appendix A.

Types of Studies: Interventional studies will be considered for inclusion including randomized and non-randomized clinical trials (RCTs and non-RCTs), controlled before-after studies. No other study designs will be considered for inclusion.

Exclusion: Qualitative and mixed methods research will be excluded, as will case series, case reports, and non-specified grey literature.

Study records

Data management: Records from searches will be imported into an EndNote library (Endnote X9, Clarivate Analytics) and duplicates will be removed. The library will be duplicated for independent screening.

Selection process: Two independent reviewers (MCC, CAG) will screen titles and abstracts of retrieved articles for eligibility based on the inclusion criteria. Full text will be retrieved for all potentially relevant articles, which will be reviewed independently by the two reviewers, and studies that meet the eligibility criteria will be included in the review. Discrepancies between the reviewers will be resolved through discussion. Reasons for exclusion will be recorded at the full-text review level.

Data collection process: Data extraction will be completed by one reviewer using a pre-designed standardized form and entered into RedCap Database (33, 34). Data extraction will be verified by a second reviewer for a sample of 20% of the studies with acceptance if agreement in at least 80% of the data. Duplicate data from the same data set published in different manuscripts will be removed. Data Extraction is expected to be complete by October 1, 2020.

Data synthesis: Once the information has been extracted, we will present findings including the numerical analysis of the number, publication type, publication year and country of publication of the studies included in the review. We will also present a narrative description of the study design, participant characteristics, sample size, NIV type, control group description, outcomes measures, and follow up duration. We will use this information to establish subcategories of studies which may include groupings based on age (i.e., infants, children, and adolescents), intervention type (i.e., CPAP, bi-level,) and outcomes (e.g. oxidative stress, obesity, dyslipidemia, liver disease, glucose intolerance, cardiovascular, renal and other metabolic diseases).

Quality assessment and risk of bias: Risk of bias will be assessed by two independent reviewers (MCC, CAG) specific to the study methodology. Tools will include the Quality Assessment Tool (35) and Cochrane risk of bias tool (36). Discrepancies in decisions will be resolved through discussion.

The reviewers will also use the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) to assess the evidence at the outcome level (37). This will include assessing for risk of bias, imprecision, inconsistency, indirectness and publication bias.

Meta-analysis

Meta-analysis will be attempted for outcomes with enough homogeneity among the study populations. Homogeneity criteria will include an AHI <5 events/hour to define mild obstructive sleep apnea, 5-10 events/h for moderate and >10 for severe sleep disordered breathing as per the American Academy of Sleep Medicine (AASM) (38, 39). In addition, nocturnal hypoxemia will be defined by sleep time with oxygen saturations below 90% over 5% and nocturnal hypoventilation by over 25% sleep time carbon

dioxide levels above 50 mmHg (40). The information will be subcategorized to include grouping based on outcome (changes in the same metabolic marker). For non-randomized studies, we will combine effect estimates from studies adjusted by confounding rather than raw data if available. RCTs will be analyzed separately if available. Risk of bias will be considered and explanations for heterogeneity will be pursued including publication bias. Graphics of pooled data (i.e. forest plots) will be provided. Most outcome data are expected to be continuous. Heterogeneity in the pooled data will be minimized, by pooling data based on outcome, as well as the indication for NIV. In the event that pooled data remains heterogeneous within these pooled groups, a narrative description will be included. If the data allows, we will analyze the data with respect to NIV adherence and the length of time wearing NIV.

Patient and Public Involvement

Patients and public were not involved in the design of this study. Dissemination of the information may include targeting patients and their care providers, as the results of the study may inform us of the effect of NIV on metabolic outcomes in children with sleep related breathing disorders.

Ethics and Dissemination

There are no ethical concerns with this systematic review, as data has previously been published. This review will inform clinicians taking care of children with OSA and obesity/metabolic syndrome about the potential effects of NIV therapies on metabolic markers and help plan for necessary assessment of this group of children in the clinical practice. This information has the potential to change the approach to childhood OSA and obesity and therefore impact future clinical guidelines at national and international level. Results of this systematic review will be submitted for dissemination in abstract and manuscript form at multiple levels to target general pediatricians and pediatric specialists involved in the care of these patients including pediatric respiratory and sleep specialists, endocrinologists, cardiologists and nephrologists. The results of this systematic review will be of interest for general audience, which can be reached through infographics, videos and TED talks to be distributed through social media.

Authors Contributions

MCC, CAG and SRL were involved in idea generation of this study. MCC, CAG, SRL, SP, DKL and MS were involved in study design and protocol development. MS and DKL developed the search strategies and performed literature reviews. MCC and CAG were involved with review of literature for inclusion into the study.

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Competing Interests Statement

There are no competing interests to declare.

Word Count: (4000 max)

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Supplemental Material

Appendix A (Search Strategies)

NIV

As per (31, 41)

Children

As per (31, 41)

SDB

Sleep Apnea, Obstructive Sleep Apnea, OSA, Central Sleep Apnea, CSA, Primary Central Sleep Apnea, Primary Sleep Apnea of Infancy, Primary Central Sleep Apnea of Prematurity, Treatment-Emergent Central Sleep Apnea, Obesity Hypoventilation Syndrome, Hypoventilation, Central Hypoventilation, Pickwikian Syndrome, Congenital Central Hypoventilation Syndrome, CCHS, Congenital Central Alveolar Hypoventilation Syndrome, Late onset Central Hypoventilation with Hypothalamic Dysfunction, Idiopathic Central Alveolar Hypoventilation, Central Alveolar Hypoventilation, Central Hypoventilation, Sleep related hypoventilation, Sleep related hypoxemia, Snoring, Primary Snoring, Catathrenia

Metabolic Markers

Oxidative stress: Oxidative Stress, inflammation, metabolism, metabolic, CRP, interleukin-6 (IL-6) and 8 (IL), tumor necrosis factor alpha (TNFa), cytokines, adipokines, cortisol, a-amylase, sympathetic dysfunction, endothelial dysfunction, atherosclerosis, arterial stiffness, endothelial nitric oxide synthase (eNOS), nitric oxide (NO), cyclooxygenase (Cox)-1, Cox-2, thromboxane A2, prostacyclin. Circulating progenitor cells (CPCs), 8-isoprostanes, circulating cell-derived MPS: PMPs, LMPs, EMPs, adiponectin, LTB4, TNFR-1, IFN, plasminogen activator inhibitor-1, monocyte chemoattractant protein-1, matrix metalloproteinase-9, apelin C, osteocrin, adropin, TREM-1, pentraxin 3, BNP, MRP 8/14

Obesity: weight, weight gain, weight loss, weight management, obese, obesity, overweight, body mass index, BMI, growth, growth acceleration, anthropometric, leptin, grehlin, Dyslipidemia: Dislipidemia, lipid, elevated lipid, Triglycerides, cholesterol, Total cholesterol, high-density lipoprotein cholesterol, HDL-C, HDL, apoB, lipoprotein

Liver disease: liver enzymes, Aspartate transaminase, AST, alanine transaminase, ALT, liver disease, nonalcoholic fatty liver disease, NAFLD

Glucose intolerance: glucose, elevated glucose, glucose metabolism, glycemia, hyperglycemia, insulin, elevated insulin, insulin resistance, diabetes, diabetes mellitus, adiponectin, adiposity, HOMA-index (homeostasis model assessment) , HbA1c, fasting plasma glucose (FPG), fasting serum glucose, fasting glucose, fasting plasma insulin (FPI), OGTT, oral glucose tolerance test, glucose tolerance test, acute insulin response to glucose, acute insulin response (FSIGT), C-peptide, glucagon

Cardiovascular: heart function, cardiovascular disease, cardiovascular diseases, Blood pressure, systolic blood pressure (SBP), diastolic blood pressure (DBP), hypertension, hypertensive, high blood pressure, High blood pressures, elevated blood pressure, elevated blood pressures, prehypertension, 24-hour ambulatory blood pressure monitoring (ABPM), nocturnal blood pressure dipping, nocturnal dipping, blood pressure variability, nocturnal blood pressure variability, Left ventricular hypertrophy, LVH, right ventricular hypertrophy, RVH, ventricular

hypertrophy, echocardiogram, systolic function impairment, diastolic function impairment, cardiac events, cardiac event, cardiac events, cardiac, heart, hearts, coronary disease, coronary diseases, sudden cardiac death, sudden cardiac deaths, cardiac sudden death, sudden cardiac deaths, sudden cardiac arrest, sudden cardiac arrests, cardiac arrest, cardiac arrests, heart failure, right heart failure, acute right heart failure, chronic right heart failure,
Renal involvement: Proteinuria, Microalbuminuria, Focal segmental glomerulosclerosis (FSGS), kidney, renal
Other: Metabolic disease

Appendix B: Published Abstracts from Prominent Conferences and Thesis Dissertations

American Thoracic Society
Canadian Respiratory Conference
CHEST
European Respiratory Society International Congress
Sleep Meeting
World Sleep Congress
Thesisdissertations.org

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
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 5
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	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	
Sponsor	5b	Provide name for the review funder and/or sponsor	Page 5
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 2
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	Page 3
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	Page 3
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	Page 3
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 4

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)	Page 4
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	Page 4
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	Page 4
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 4
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	Page 4
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page 4
	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)	Page 4
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 4
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 4
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 4

*** 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.**

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