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CLINICAL REVIEW

Long-term non-invasive ventilation therapies in children: A scoping review

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SUMMARY

Long-term non-invasive ventilation (NIV) is a common modality of breathing support used for a range of sleep and respiratory disorders. The aim of this scoping review was to provide a summary of the literature relevant to long-term NIV use in children. We used systematic methodology to identify 11,581 studies with final inclusion of 289. We identified 76 terms referring to NIV; the most common term was NIV (22%). Study design characteristics were most often single center (84%), observational (63%), and retrospective (54%). NIV use was reported for 73 medical conditions with obstructive sleep apnea and spinal muscular atrophy as the most common conditions. Descriptive data, including NIV incidence (61%) and patient characteristics (51%), were most commonly reported. Outcomes from sleep studies were reported in 27% of studies followed by outcomes on reduction in respiratory morbidity in 19%. Adverse events and adherence were reported in 20% and 26% of articles respectively. Authors reported positive conclusions for 73% of articles. Long-term use of NIV has been documented in a large variety of pediatric patient groups with studies of lower methodological quality. While there are considerable data for the most common conditions, there are fewer data to support NIV use for many additional conditions.

Introduction

Non-invasive ventilation (NIV), where assistance to breathing or full ventilation is delivered through an interface outside the airway, has become the first line therapy for a wide range of sleep and respiratory disorders in children including upper airway obstruction [1–3], musculoskeletal weakness and chest wall restriction [4–9], chronic lung diseases [10–12], central nervous system disorders [13–15], and other systemic disorders with respiratory insufficiency [16–18]. Technological advances in NIV have provided children requiring long-term respiratory support and their families an acceptable alternative to invasive mechanical ventilation (IMV) via tracheostomy [19]. Additional contributors to the increase in long-term NIV use include increased survival of children with complex medical conditions [20], a shift in health care from hospital to home-based care [20], and increased awareness of the consequences of sleep breathing disorders and their possible treatments [21,22]. NIV use has increased worldwide [23–34], resulting in a reduction in the number of admissions to pediatric

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Glossary of terms

Auto-PAP	auto positive airway pressure
CPAP	continuous positive airway pressure
DMD	Duchenne muscular dystrophy
IMV	invasive mechanical ventilation
NIV	non-invasive ventilation
NMD	neuromuscular disease
NPPV	non-invasive positive pressure ventilation
OSA	obstructive sleep apnea
PAP	positive airway pressure
SMA	spinal muscular atrophy

intensive care units and a greater number of children living at home using NIV [35–37].

There are gaps in our present knowledge on the benefit of long-term NIV in children. For instance, the literature on decreased mortality and morbidity rates and improved longevity with long-term NIV has focused primarily on neuromuscular diseases (NMD) such as Duchenne muscular dystrophy (DMD) and spinal muscular atrophy (SMA), with limited data on the impact on survival in other populations [23,38,39]. Other outcomes, such as improvement in quality of life, neurocognitive and behavioral outcomes have been demonstrated in children using NIV for the treatment of obstructive sleep apnea (OSA); however, these benefits may not generalize to children with other conditions needing NIV [1,40]. Long-term NIV use has been reported for conditions including a range of syndromes [3,17,41–46], congenital heart defects [47], obesity [48], sickle cell disease [16], and cancer [18].

In addition to an expanding range of conditions where NIV may be beneficial, the increase in long-term NIV use at home, as opposed to in hospital, has resulted in a shift in the responsibility of care to parents and caregivers [17,49]. Long-term NIV presents challenges including the use of a mask interface [50,51], adherence [52–54], and funding for equipment as well as access to support services in the community [55]. With increasing use of this technology, it is important to define the evidence-base to support the use of long-term NIV therapy in children, identify evidence gaps, and develop a research strategy to begin to address these gaps in knowledge.

To date, there has been no review of long-term NIV use in children employing systematic methodology. While prior systematic reviews have included information on long-term NIV in children, the focus of these reviews has been on diagnosis or treatment for specific conditions such as OSA, achondroplasia, global developmental delay or chronic cough [1,15,56–62]. The aim of this scoping review is to provide an overview of the literature relevant to long-term NIV use in children. The results of this scoping review will provide a map of all existing literature and will define the volume and characteristics of the primary research pertinent to long-term NIV use in children. We will use this map to identify data appropriate for systematic review and to highlight gaps in knowledge relevant to improving the care of children using long-term NIV.

Materials and methods

The scoping review protocol was designed based on the frameworks developed by Bragge and colleagues and Arksey and O'Malley [63,64] with full details of the protocol published elsewhere [65]. Scoping reviews are used to examine the main sources and types of evidence available with a broad approach to a topic; this is in contrast to a systematic review which usually addresses a narrow research question. As a result, scoping reviews are used to identify the boundaries and context of a topic area as well as summarize the key characteristics and results of included studies rather than appraise the quality of the evidence or provide a synthesis of the data. We created an advisory committee of experts in systematic reviews, pediatric respiratory and sleep medicine, and NIV therapies, to advise on the search strategy as well as in the reporting of the results.

Search strategy

An information specialist developed the search strategy for Ovid Medline with terms related to NIV and a validated child search filter [66], and then translated this into Ovid Embase, PubMed (last year only), CINAHL via EbscoHOST, and 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; see On-line supplement for search strategy). Searches were limited to human studies published after 1990 because the first study of long-term NIV use in children we identified was published in 1992. No language or study design restrictions were applied to the search. Database searches were run between November 17 and November 28, 2014. An update of the literature search was conducted in five databases (Ovid Medline, Cochrane Library, Ovid Embase, CINAHL and PubMed) on April 29, 2016 using the same search strategy to identify recently published studies and abstracts. Gray literature sources were searched between January 7 and January 21, 2015. We searched peer-reviewed abstracts from 10 selected conferences on respiratory, sleep, and neuromuscular medicine conducted between January 2012 and December 2014. We also searched theses and dissertations from 1990 onward via proQuest dissertations & theses global, trial registries from 2012 to 2014 via ClinicalTrials.gov and WHO's International clinical trials registry platform, and regulatory agencies and manufacturer reports from 1990 onward.

Inclusion criteria

Child was defined as newborn to 18 y of age. Studies with both adults and children as subjects were included if data for children were reported separately. Studies which included children and young adults were included if the mean age of the subjects was 18 y or younger. We defined NIV as any mode of ventilatory support that was delivered with a non-invasive interface which avoids tracheal intubation. This included both positive pressure, such as continuous positive airway pressure (CPAP) and bilevel positive airway pressure, and negative pressure ventilation (see On-line supplement for the 48 terms used to define NIV). Long-term use was defined as at least three months of use outside an acute care environment. Study selection was not limited by study design or outcomes assessed. Case reports with three or more subjects were included. Comments, editorials, letters and reviews were excluded.

Study selection

Two reviewers screened English titles and abstracts of retrieved studies for eligibility. The same two reviewers screened full-text studies for the final list of included studies. Discrepancies were resolved by consensus. Studies written in English, Spanish, French, Portuguese, Italian and Catalan were included, with all other languages excluded.

Data extraction

Data extraction was completed using a pre-designed form and entered into a Microsoft Access Database (Microsoft, Redmond, Washington, USA). Extracted data included study design and duration, NIV terms used, medical conditions of studied populations, NIV intervention type and outcomes of interest identified in the methods' section of included articles. Data on NIV terms and medical conditions was exactly extracted as described by authors in the methods sections, with no interpretation of terms (e.g., if authors said OSA, we did not reword it into sleep disordered breathing). More than one term related to NIV or several medical conditions could be extracted from the same paper. Data about sample size, additional outcomes, adverse events, and adherence were extracted from the results sections. Outcomes were not defined a priori and were classified according to the data source (e.g., reported clinical information from medical letters, sleep study results, downloads from NIV machine, etc.). Comparisons where the statistical test had a $p < 0.05$ were considered to show statistically significant differences. Data on author's conclusions and identified gaps in knowledge were gathered from the conclusion sections. Conclusions about NIV were defined as positive, if authors stated a benefit from the NIV therapy, negative, if they concluded a lack of benefit or identified significant adverse events or complications from the NIV therapy, neutral if they did not clearly state positive or negative conclusions, and indeterminate if reviewers were unable to classify authors' conclusions under other headings. Twenty percent of the extracted data were verified by a second reviewer for accuracy and completeness.

Data synthesis

Data were collated in order to present a narrative account of the existing literature [63,64]: The preferred reporting items for systematic reviews and meta-analyses protocols 2015 statement was followed in the reporting of the results [67]. Interpretations or grouping of terms related to NIV therapies were avoided to ensure authors' original terms were preserved. For the data synthesis, MeSH terms (PubMed) were used to define a medical condition when authors used multiple terms to refer to the same medical condition to avoid overlapping. Medical conditions were then classified into disease categories attending to the underlying pathophysiology. Word cloud software (http://www.tagxedo.com) was used to produce qualitative syntheses of NIV terms and medical conditions.

Statistical analysis

SPSS version 24 (1989, 2016) was used for statistical analysis. Descriptive data were reported as absolute numbers and percentages and medians and ranges were calculated for quantitative variables. Age was provided as mean and standard deviation. Pearson chi-square or Fisher's exact test were used to calculate differences by subgroups such as age and disease category.

Results

We identified 11,581 potentially relevant studies; 289 were included in this scoping review (Fig. 1). The majority of the studies were published as journal articles (74%, 215/289). The contributions from gray literature sources represented 26% of included studies (74/289) and these were predominantly conference abstracts (22%, 63/289). The first article on long-term NIV in children identified with our search strategy was published in 1992 with a median year of publication of 2011 (Fig. 2). The majority of studies were conducted in North America (41%, 119/289) and Europe (36%, 104/289) (Fig. 3). A total of 91 studies were excluded due to language: 53 from European countries and 38 from Asian countries.

Non-invasive ventilation terms

Seventy-six terms were used to describe NIV (Fig. 4). The most common terms included non-invasive ventilation (NIV 22%, 65/289), non-invasive positive pressure ventilation (NPPV 12%, 35/289) and positive airway pressure (PAP 9%, 27/289). Different terms were also used to refer to specific NIV modalities including continuous positive pressure ventilation (CPAP 33%, 95/289), bi-level positive airway pressure ventilation (Bi-level 16%, 46/289) and auto-positive airway pressure (Auto-PAP 2%, 7/289).

Study design

Study designs (Table 1) were predominantly quantitative (91%, 263/289) with few qualitative (2%, 5/289), biomedical (6%, 17/289) and manufacturer reports (1%, 4/289). The most common quantitative study design was observational (63%, 182/289) including cohort studies (42%, 122/289), case-control studies (4%, 12/289), and case series (17%, 48/289). Twelve percent of studies (34/289) were cross-sectional surveys with 7% (19/289) randomized and non-randomized controlled trials and 10% (28/289) within subject interventional controlled before–after studies. The majority of studies were single center studies (84%, 244/289) with 16% (45/289) multicenter studies. Only 4% (2/45) of the multicenter studies were also multinational. Fifty-four percent (155/289) of the studies were retrospective. The overall median sample size of included studies was 14 (range 3–658). Multicenter studies had median sample size of 24 (range 6–658). Only 23% (66/289) of studies included a control or comparison group. Median study duration was 40 mo (range 1–552 mo); study duration for interventional studies, however, was shorter, with a median of 25 mo (range 1–102). The duration of the NIV intervention was only reported in 42% (122/289) of the studies. For the studies reporting NIV duration, the median duration of NIV use was 12 mo (0–180 mo).

Subject characteristics

NIV was used for a broad range of medical conditions (Fig. 5). Seventy-three medical conditions were identified from the methods section of the included studies. The most common medical conditions reported included OSA (29%, 84/289), SMA (8%, 22/289), sleep disordered breathing (6%, 16/289), and NMD (5%, 14/289). When grouping medical conditions (Table 2), the majority of the studies investigated disorders of upper airway obstruction (33%, 94/289) or neuromuscular and other musculoskeletal disorders (22%, 63/289). Studies investigating NIV as a treatment for sleep disordered breathing in the context of childhood obesity were only published in the last 10 y, with the first study published in 2006. Over time, there has been an increasing proportion of studies focused on cohorts of children using long-term NIV regardless of the medical condition, with 73% (55/75) of the studies with this study design published in the last 10 y.

There was considerable variability in the age when NIV was started. The mean age of NIV initiation was 8.06 ± 3.08 y with the majority of the studies reporting data on children across a wide age span (0–24 y; Fig. 6). Although 39% of the studies (114/289) included infants (under 2 y of age) in their target populations, only 9% of studies (27/289) were exclusively undertaken in this population. The medical conditions studied differed by age group (Fisher's exact test 102.820, $p < 0.05$). In studies focused on infants, the predominant medical condition was upper airway disorders (52%, 14/27) followed by 33% (10/27) of studies focused on NMD (9

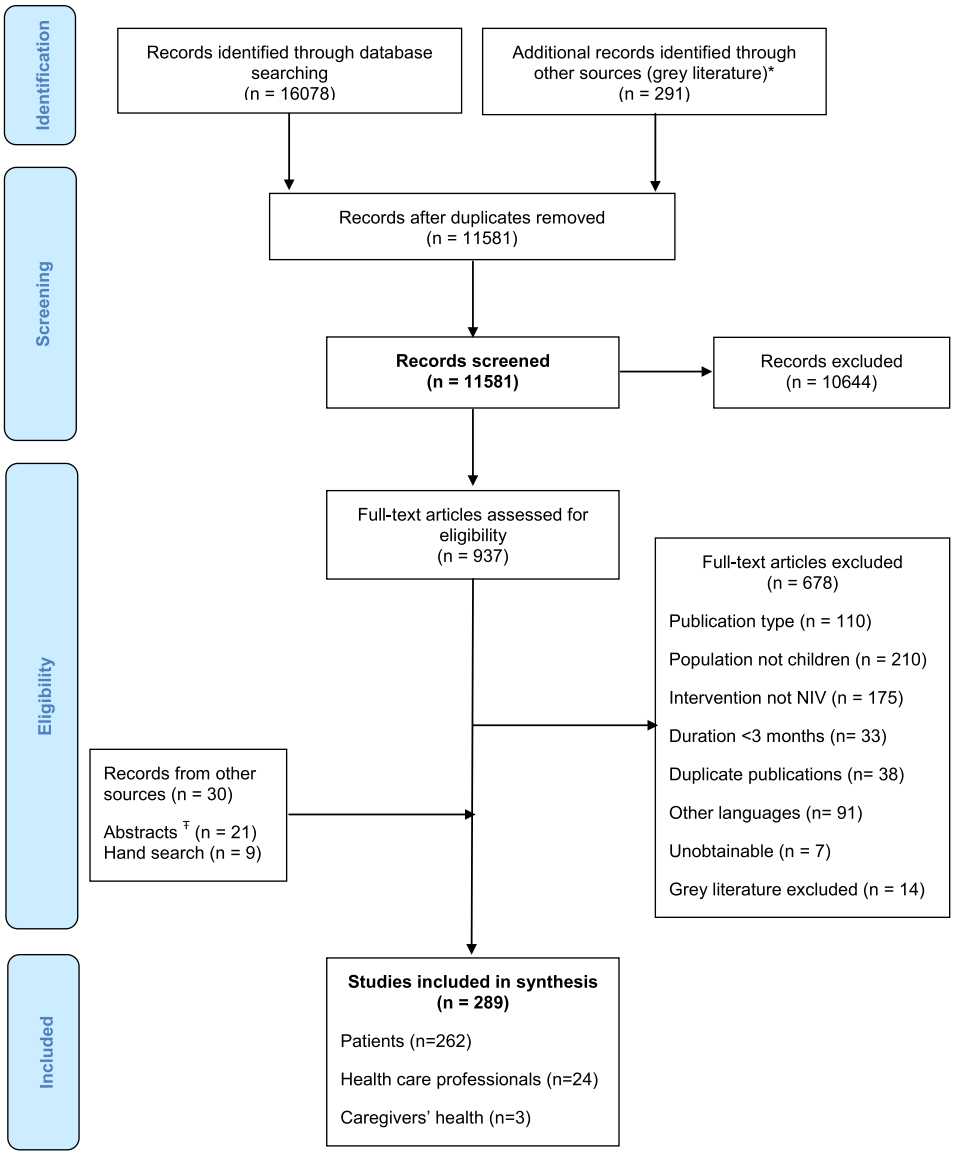

Fig. 1. Flow diagram of screened and included studies (adaption from PRISMA-P 2015). * Each conference proceeding included is counted as a single record. ₸ Individual abstracts from conference proceedings have been added manually and duplicate data removed.

of which were on SMA type 1), 4% (1/27) on congenital central hypoventilation syndrome, and 7% (2/27) on multiple conditions. In studies that included children over 2 y of age (30%, 88/289), 41% (36/88) were focused on upper airway diseases, 20% (18/88) on NMD, 10% (9/88) on sleep disordered breathing related to obesity, 8% (7/88) on pulmonary disease, and 10% (9/88) on multiple diseases. The use of NIV for treatment of obesity related sleep disordered breathing and pulmonary diseases was only reported in older children. Conversely, the studies focused on multiple disease categories where data on age were reported (55/289) were mostly cohorts of children aged 0–18 y (78%, 43/55).

NIV equipment

CPAP use was reported in 25% (73/289) of studies compared to 21% (61/289) for bi-level therapies and 2% (7/289) for auto-PAP; 22% (63/289) of the studies reported data on combined CPAP and bi-level therapies and 20% (57/289) on disaggregated data for NIV and IMV therapies (Table 2). In 9% (27/289) of the studies, there is no specific description in the methodology of the non-invasive intervention used; that is, CPAP and/or bilevel were not specified. There was only one study reporting on negative pressure ventilation exclusively and 11 articles included negative pressure ventilation among other ventilator therapies.

There were differences in NIV type use according to the disease category (Fisher's exact test 166.164, $p < 0.05$). Seventy-eight percent (62/79) of studies reporting on CPAP and auto-PAP included children with upper airway disorders, obesity or other medical conditions. Studies on bilevel therapies were focused on children with musculoskeletal diseases (48%, 29/61), cohorts of children including multiple medical conditions (18%, 11/61), and children with pulmonary conditions (16%, 10/61), with few reports in children with upper airway disorders (7%, 4/61). Studies reporting CPAP and bilevel interventions together were mostly done in children with upper airway disorders (46%, 29/63) and cohorts of children including multiple medical conditions (33%, 21/63), with few reports in children with musculoskeletal diseases (11%, 7/63). Studies including NIV and IMV therapies together reported data mostly on cohorts of children with multiple medical conditions (54%, 31/57) and children with musculoskeletal diseases (21%, 12/57).

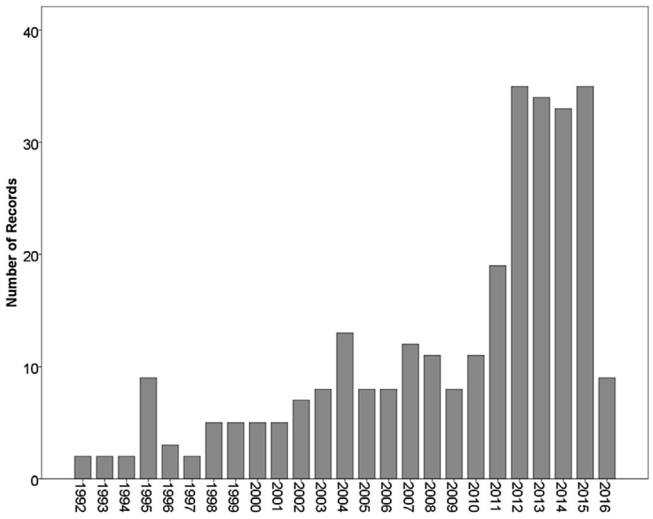

Fig. 2. Number of publications by year of publication. The most noticeable increase in publications began in 2011. Publications for 2016 include only those published before 2 May 2016.

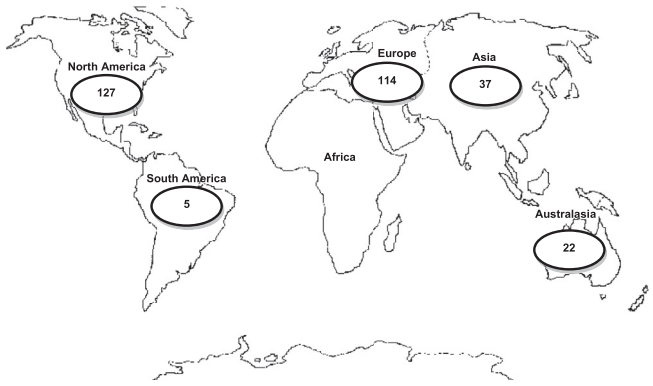

Fig. 3. Geographical distribution of contributing authors. Publications with authors from multiple continents were counted in each contributing nation resulting in a higher total number than publications included.

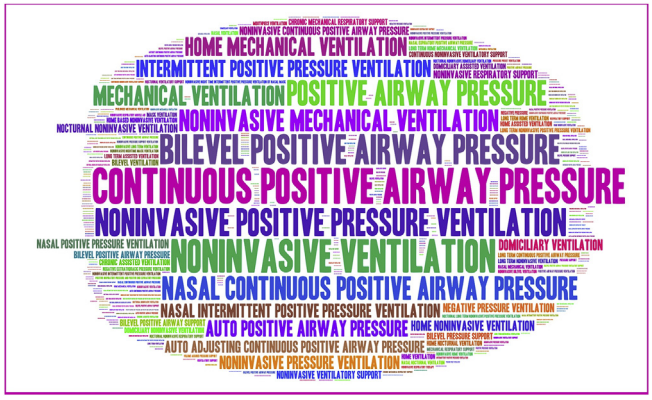

Fig. 4. Word cloud created with tagxedo software (www.tagxedo.com) summarizing 76 terms used to describe long-term non-invasive ventilation in children. The size of the words represents the frequency of the use of each term; larger words correspond to the terms that are used more frequently. Share under creative copyright under a Creative Commons Attribution-Noncommercial-ShareAlike License 3.0 (https://creativecommons.org/licenses/by-nc-sa/3.0/us/).

Table 1
Summary of publication type and study design for 289 included studies. Numbers represent the number of studies with percentage in parentheses unless otherwise indicated.

Description	n (%)
Type of publication:	
Journal	215 (74)
Abstract	63 (22)
Dissertation	1 (1)
Manufacturer report	4 (1)
Unpublished trial	6 (2)
Type of study:	
Quantitative:	
Observational (cohort, case series, case-control)	182 (63)
Cross sectional/survey	34 (12)
Controlled before–after	28 (10)
Randomized/non-randomized controlled trial	19 (7)
Qualitative	5 (2)
Bench study	17 (6)
Manufacturer reports	4 (1)
Single vs multi-center:	
Single-center	244 (84)
Multi-center	45 (16)
Prospective vs retrospective:	
Prospective	134 (46)
Retrospective	155 (54)
Control group:	
Yes	66 (23)
No treatment	29 (43)
Invasive ventilation	13 (20)
Tonsillectomy and/or adenoidectomy	5 (7)
Other	19 (31)
No	223 (77)
Number of study subjects using NIV (median, range)	14 (3–658)
Study duration (months; median range)	40 (1–552)
Duration of NIV intervention (months; median, range)	12 (0–180)

NIV, non-invasive ventilation.

The interface type was only specified in 46% (132/289) of studies. In those where details of the interface were reported, nasal masks were most commonly used alone (52%, 69/132) or in combination with full face masks (20%, 27/132).

Outcomes of interest

A wide range of outcomes of interest was described. This included objective measurements (e.g., apnea–hypopnea index, blood gas measurements, oxygen saturation, validated questionnaire scores,

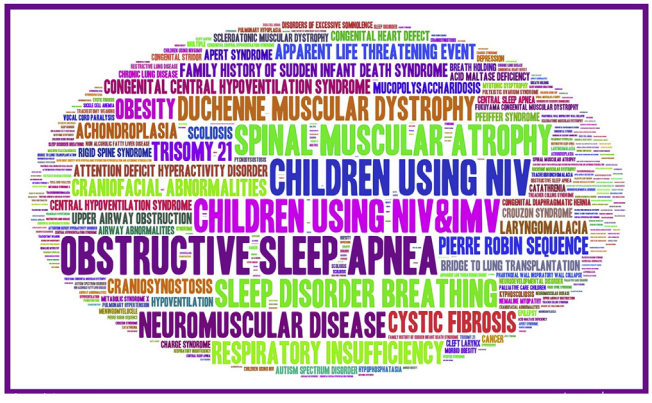

Fig. 5. Word cloud with tagxedo software (www.tagxedo.com) summarizing 73 medical conditions for which the use long-term non-invasive ventilation (NIV) in children has been reported. The size of the words represents the frequency of the use of each medical condition; larger words correspond to the medical conditions with more reports of long-term NIV use in children. Share under creative copyright under a Creative Commons Attribution-Noncommercial-ShareAlike License 3.0 (https://creativecommons.org/licenses/by-nc-sa/3.0/us/).

Table 2
Subject characteristics and NIV interventions reported in 289 included studies. Numbers represent the number of studies with percentage in parentheses unless otherwise indicated.

Characteristics	
Age at NIV start (y) (mean ± SD)	8.06 ± 3.09
Disease category:	**n (%)**
Upper airway obstruction	94 (33)
Neuromuscular/musculoskeletal	63 (22)
Pulmonary	16 (6)
Obesity	9 (3)
CNS	8 (3)
Multiple medical conditions	75 (26)
Other medical conditions (including cardiac, syndrome)	10 (3)
Not reported	14 (5)
Type of NIV:	**n (%)**
CPAP	73 (25)
Bi-level	61 (21)
CPAP + bi-level	63 (22)
NIV not specified	27 (9)
NIV + IMV	57 (20)
Negative pressure ventilation	1 (1)
Auto-PAP	7 (2)
Time of NIV use:	**n (%)**
Day and night	45 (16)
Night only	112 (39)
Day only	2 (1)
Not reported	130 (45)
Interface type:	**n (%)**
Nasal	69 (24)
Nasal + full face	27 (9)
Multiple	20 (7)
Other: full face, mouth piece, negative pressure	6 (2)
Not reported	167 (58)
Author's conclusion:	**n (%)**
Positive	203 (70)
Negative	10 (4)
Neutral/indeterminate	65 (23)
Not reported	11 (4)

Auto-PAP, auto positive airway pressure; CNS, central nervous system; CPAP, continuous positive pressure; IMV, invasive mechanical ventilation; NIV: non-invasive ventilation; SD, standard deviation.

adherence rate from NIV machine downloads) in 63% (182/289) of the studies, subjective information from medical letters (e.g., improvement on clinical symptoms reported by physician, adverse events) in 50% (145/289) of the studies, subjective data collected directly from patients and families in 10% (30/289), and surveys of health care providers asking for descriptive data of their patient populations, practice patterns or assessing their knowledge in 9% (27/289).

Descriptive data such as the number of patients initiated on NIV, patient characteristics and NIV discontinuation rates were reported on 61% (177/289), 51% (147/289) and 7% (20/289) respectively (Table 3). A variety of diagnostic tests to measure efficacy of NIV were used, which was most commonly data from sleep studies, including polysomnography (24%, 69/289) and polygraphy (2%, 6/289). Examples of measured outcomes from sleep studies were apnea–hypopnea index, end tidal or transcutaneous carbon dioxide, oxygen saturation, sleep architecture, arousal index. A combination of home overnight pulse oximetry and transcutaneous carbon dioxide levels was reported in 1% (2/289) of the studies. In a smaller proportion, blood gas measurements (e.g., partial pressure of oxygen and carbon dioxide) were used (5%, 14/289) to measure efficacy of NIV. Fifteen percent (43/289) of the studies reported reduction of respiratory morbidity such as improvement of respiratory symptoms, tracheostomy avoidance or decannulation, or reduction in post-operative complications. Reduction of healthcare encounters related to respiratory exacerbations was reported in 5% (13/289) of the studies. Improvements of symptoms in other areas affected by sleep breathing disorders were not well described. For instance, improvements in sleep symptoms, neurocognitive outcomes, mood and behavior, and quality of life were reported in 5% or less (14/289, 13/289, 5/289 and 14/289, respectively) of studies. Mortality rates were an outcome of interest in 6% (18/289) of the studies. Ten percent of the studies (28/289) tested the efficiency of NIV technology either assessing NIV machine settings or interfaces.

Some of the outcomes of interest differed by disease category (Fisher's exact test 19.035, $p < 0.05$). Of 69 studies reporting outcomes from sleep studies (including polysomnography, polygraphy and limited channel studies), 54% (37/69) of studies were conducted in children with upper airway obstruction disorders, 22% (15/69) in children with musculoskeletal and neuromuscular diseases, and 14% (10/69) in cohorts combining children with multiple underlying conditions. Studies reporting data on mortality (6%, 18/289) were exclusively conducted in children with musculoskeletal and neuromuscular diseases (44%, 8/18) or cohorts of children with multiple underlying conditions (50%, 9/18) (Fisher's exact test 16.462, $p < 0.05$). Looking at studies reporting respiratory morbidity or reduction of health care encounters due to respiratory exacerbations (17%, 50/289), 24% (12/50) were in children with upper airway obstruction disorders, 38% (19/50) in musculoskeletal and neuromuscular diseases, and 26% (13/50) on children with multiple diseases, (Fisher's exact test 11.412, $p < 0.05$). The proportion of studies reporting outcomes on sleep symptoms, mood and behavior, neurocognition and quality of life did not differ by disease category.

Adverse events were reported in 20% (59/289) of the studies. The most common complications found were skin lesions (e.g., irritation, redness, breakdown; 6%, 18/289), mask intolerance, leak or NIV therapy intolerance (5%, 15/289), nasal symptoms (e.g., congestion, rhinorrhea, epistaxis, sinusitis; 2%, 7/289), device failure (2%, 7/289), midface hypoplasia (2%, 6/289), abdominal distension (2%, 6/289), and death (2%, 5/289).

Adherence to NIV was reported in 26% (74/289) of the studies. Of note, while the first report on adherence was in 1992, the majority of studies reporting on adherence (77%, 57/74) were published in the last 10 y. Only 3% of the studies (10/289) analyzed data on treatment burden of long-term NIV for children and their caregivers.

Statistical analysis

Purely descriptive data were reported in 28% of the studies (81/289), while 63% of studies (182/289) were designed to measure differences in outcomes between groups or time points. Seven percent (21/289) of the studies reported only narrative data on NIV, including case series (4%, 12/289), qualitative studies (2%, 5/289), and manufacturer reports (1%, 4/289). There were ongoing interventional studies (2%, 5/289) for which data are not yet available.

Authors' conclusions

In the majority of studies, the authors stated a conclusion about NIV (96%, 278/289). Overall, 73% (203/278) of the studies included a conclusion that the long-term use of NIV in children may provide benefits while 4% (10/278) had a negative conclusion (i.e., no benefit of NIV or adverse events), 16% (45/278) were indeterminate, and 7% (20/278) neutral. In the studies where authors stated positive conclusions of NIV, 59% (119/203) authors performed statistical analysis to test for significant differences for at least one of their outcomes, with 30% of the studies (60/203) supporting their positive conclusions with descriptive data only and the remaining 7% (14/203) reporting narrative outcome data (Pearson chi-square 17.089, $p < 0.04$).

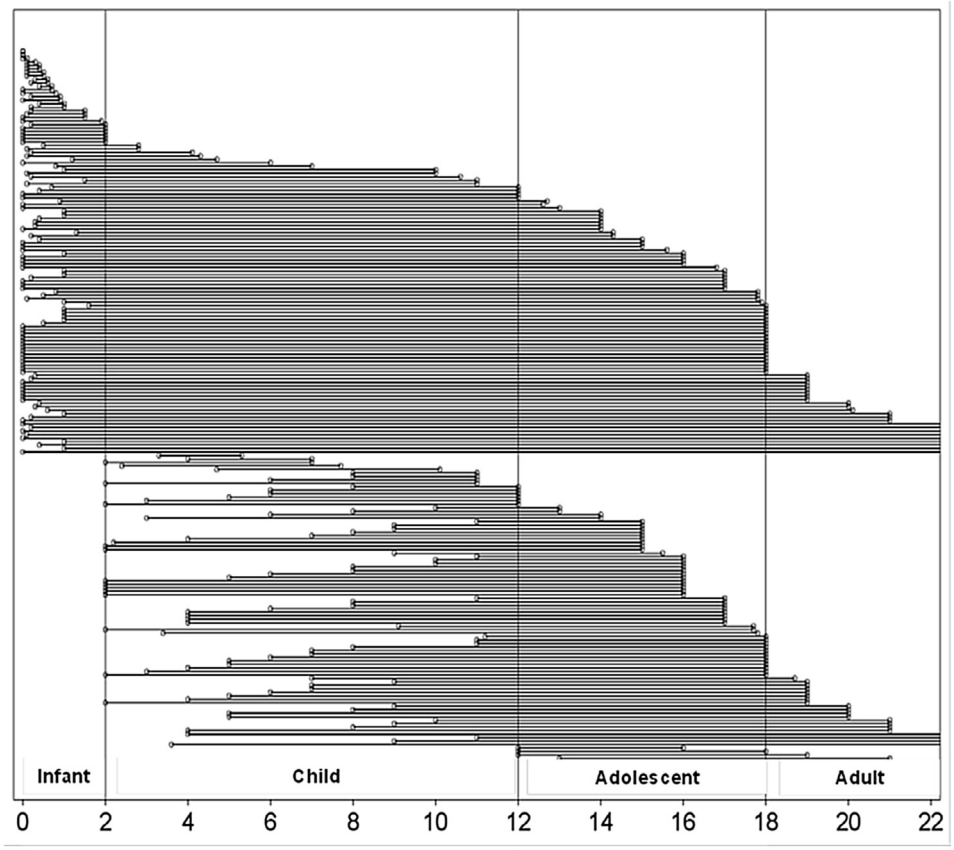

Fig. 6. Age range (years) included in studies. Vertical axis markers at 2 y of age to indicate infancy, 12 y of age to indicate childhood, and 18 y to indicate adolescence. Each line represents one article.

Discussion

This is the first systematic overview of the literature on long-term NIV in children. The topic of this scoping review was intentionally broad with the goal of identifying the nature and extent of the literature relevant to long-term use of NIV in children. The results highlight the diversity of medical conditions for which long-term NIV has been reported and the variability of the information available to support its use across medical conditions. We also identified that the evidence for long-term NIV use differs by age group, with some medical conditions studied predominantly or exclusively in certain age groups. There is a paucity of multicenter, randomized, and interventional studies with predominantly descriptive results. While there are a range of outcome measurements studied to determine the benefits of NIV in children populations, there is less emphasis on other aspects of the NIV therapies such as treatment burden and most research available does not seem to be patient-prioritized. The results of this scoping review provide a detailed analysis of the existing evidence supporting the use of long-term NIV in children.

We identified a variety of terms referring to the description of NIV therapies. Differences in terms appear to relate to the definition of the technology (e.g., positive airway pressure), the specific NIV modality (e.g., CPAP, bi-level, auto-PAP), the time of the day for NIV use (e.g., nocturnal ventilation), the type of interface used (e.g., nasal ventilation), or simply the author's preference. The meaning of certain terms was not always clear, presenting a challenge for identification of the relevant literature. For example, terms referring to the use of ventilatory support technology at home (e.g., home mechanical ventilation, long-term ventilation, domiciliary ventilation) often included both children on NIV and IMV or did not clearly define the type of interface. Based on our results, we would recommend the use of the term 'non-invasive ventilation' (abbreviated as NIV) to denote the use of methods of ventilatory support delivered with an interface outside the airway. Using this definition, CPAP, bi-level, auto-PAP and other modalities of delivering ventilatory support with an interface outside the airway are included as sub-types of NIV. This definition is consistent with the medical subject heading for NIV, used for indexing articles in PubMed which defines NIV as '*techniques for administering artificial respiration without the need of intratracheal intubation*' (http://www.ncbi.nlm.nih.gov/mesh/D063087). We recognize that CPAP is not considered by many to provide ventilation support; CPAP is, however, included under the MeSH term 'positive pressure ventilation' defined as 'a method of mechanical ventilation in which pressure is maintained to increase the volume of gas remaining in the lungs at the end of expiration, thus reducing the shunting of blood through the lungs and improving gas exchange', supporting our recommendation that CPAP is a method of ventilatory support. In addition, CPAP can be used both with an invasive and non-invasive interface so it is important to distinguish these treatment modalities. Our results show that other authors have reported trends and outcomes combining children using both CPAP and bilevel [23,25,31,32]. This makes sense given children using CPAP and bilevel therapies share common challenges related to adherence and complications with the non-invasive interface, similar methods of monitoring therapy and overlap in the outcome measures. Lastly, there is overlap in the medical conditions of children using CPAP and bilevel. While certain medical conditions are exclusively treated with bilevel therapy (e.g., congenital central

Table 3
Summary of outcomes described in the 289 included studies. Numbers represent the number of studies with percentage in parentheses unless otherwise indicated.

Outcomes	n (%)
Descriptive data	
Number of patients initiated NIV	177 (61)
Patient characteristics	147 (51)
Discontinuation of NIV	20 (7)
Efficacy of NIV	
Sleep studies (including PSG, PG, limited channel studies)	77 (27)
Respiratory gases	14 (5)
Other respiratory tests (pulmonary function test, airway pressures, chest X-ray)	7 (2)
Metabolic outcomes	4 (1)
Other (echocardiogram, EEG)	4 (1)
Benefit from NIV	
Respiratory symptoms (airway obstruction, hypoventilation, postoperative complications, tracheostomy avoidance or decannulation)	43 (15)
Reduction of health care encounters due to respiratory exacerbation	13 (5)
Sleep	14 (5)
Neurocognition	13 (5)
Quality of life	14 (5)
Mood/behavior	5 (2)
Growth and development	5 (2)
Increased survival	8 (3)
Other symptoms	2 (<1)
Mortality rate	18 (6)
Adverse events	59 (20)
Compliance/adherence	74 (26)
NIV machine settings and interfaces	28 (10)
Healthcare providers knowledge/practice	7 (3)
Other (optimal pressure requirements, predictors of NIV need …)	19 (6)

NIV, non-invasive ventilation. PG, polygraphy. PSG, polysomnography. EEG, electroencephalogram.

hypoventilation syndrome), many others have pathophysiology that can be treated with CPAP or bilevel (e.g., upper airway obstruction, obesity). Other methods of NIV such as auto-PAP and negative pressure ventilation have been less well described in the literature. The use of the term NIV to refer to any ventilatory support administered through a non-invasive interface will simplify the literature search and allow clear differentiation from invasive methods of ventilation.

Starting in the 1980's, when the first case reports on long-term NIV use in children were published [68–70], there is substantial literature documenting the long-term use of NIV in children with a large variety of underlying conditions. Over the subsequent two decades, there has been a steady increase in the number of publications investigating the use of long-term NIV in children, with the greatest increase in the last 5 y. This pattern confirms the reported trends of increased use of long-term NIV worldwide [23–34]. The drivers of this increase in use are likely multi-factorial and include improvements in the technology for children using NIV, greater awareness of the potential use of NIV, as well as changes in funding for NIV. While there is an extensive literature on long-term NIV use in children, there are clearly gaps in our understanding of the use of this technology, and a pressing need to fill these gaps in this growing field.

Our results highlight the low methodological quality of the literature in long-term NIV use in children. The majority of the available data come from descriptive studies, with small sample sizes and a paucity of randomized controlled clinical trials. We identified many single-center descriptive studies with similar methodology where the combination of data would enable larger sample size to allow subgroup analysis. This could facilitate the identification of common characteristics of those children that benefit most from long-term NIV and improve the power to detect between group differences. Randomized trials may be challenging given that NIV is an accepted therapy for many medical conditions, hence calling into question the ethics of randomizing subjects to alternative therapies or placebo. However, before–after comparisons within the same subjects provide an assessment of risks and benefits despite lower rigor than randomization.

Despite evidence of long-term NIV use in a large number of medical conditions, the majority of the current literature is focused on a small number of diseases including OSA and NMD. While these conditions are likely the most common ones leading to NIV use, this focus limits the extrapolation of this information to children with other medical conditions. Efforts to apply further systematic review methods to summarize data examining studies addressing specific outcomes for these more common conditions or broader outcomes for less prevalent conditions would be of value. For example, prior systematic reviews on OSA have included aspects of diagnosis, comorbidities, and surgical treatment options [1,56,59,61]; a similar systematic review focused on adherence to NIV in OSA would be informative. Systematic review or meta-analysis of long-term NIV outcomes for children with NMD such as SMA, or DMD would also provide stronger evidence than individual study results. While there has been a previous systematic review on nocturnal mechanical ventilation in patients with neuromuscular and chest wall disorders of all ages, data were not separated into IMV and NIV [62]. Other medical conditions where long-term NIV use has been described, such as congenital central hypoventilation syndrome, cystic fibrosis, obesity, trisomy 21, or craniofacial abnormalities, present different challenges for NIV where a systematic review could help clarify what is known and not known about specific outcomes related to NIV use in these conditions. Future research efforts focused on multi-centre studies or the development of national or multi-national patient registries may be the best means of developing robust data to support NIV use for less common medical conditions.

Few studies focus exclusively on infant populations. Infancy represents a time when both breathing and sleep control mechanisms are evolving and, therefore, is a unique physiological period distinct from older children [71]. Studies on long-term NIV use for medical conditions with significant respiratory morbidity during the neonatal period, such as craniofacial disorders, laryngomalacia, SMA type 1, or congenital central hypoventilation syndrome, are almost exclusively descriptive [72–75]. Long-term NIV use may be an alternative to IMV as many of these infants improve with time, allowing discontinuation of ventilatory support and preventing complications related to tracheostomy and IMV [72,76]. Future studies exclusive to infants or including infants as a distinct group should assess outcomes that emphasize the unique sleep and respiratory physiology of infancy and take into account normal developmental changes across infancy when considering the impact of long-term NIV use.

Specific gaps in the literature include some negative aspects of long-term NIV therapies. While approximately 20% of the studies identified report on adverse events and adherence rates, other relevant outcomes such as treatment burden or barriers to adherence for children and caregivers were included in only 3% of included studies. This means there are limited data on the impact of long-term NIV on children and their families. No studies examining funding or community supports for long-term NIV were identified. The paucity of studies exploring the experience of NIV from the child, family and community viewpoints is an important gap. As the use of long-term NIV requires a significant investment, both with respect to the work involved in using NIV and in some cases the financial cost, the lack of information on the child, family and community experience with long-term NIV may limit our ability to provide the best possible care.

This scoping review provides a comprehensive and exhaustive examination of the literature on long-term NIV use in children. However, there are several limitations that must be acknowledged.

As with any systematic review methodologies, a publication bias towards studies conducted in English-speaking countries is likely. In our case, research done in certain geographical areas of Europe and Asia may be underrepresented. However, no articles from Africa or South America were excluded for that reason. Limited resources for translation might have resulted in some selection bias during the full-text screening. We did not contact authors for clarification of information. While contacting authors would have filled gaps in our data extraction, this scoping review is intended to represent the information that is most easily accessible and, therefore, available to parents, clinicians, and policy makers to support decision making relevant to long-term NIV use in children. Our inclusive approach was deliberate and allows us to define the scope of the literature relevant to our topic. However, it also limits our ability to summarize details of diverse methods and outcomes. As such, our results represent the first step in describing the literature relevant to long-term NIV use in children with work underway for further analysis of these important data in more detail.

Conclusions

This scoping review has mapped the existing literature on the long-term use of NIV in children. Long-term NIV use has been documented in a great diversity of pediatric patient groups and NIV modalities. However, most of the studies to date have been observational and descriptive in nature. While more robust information exists for some conditions, there is a paucity of data relevant to many pediatric populations currently using NIV. In addition, outcomes studied may not be those of highest priority for children using NIV and their families. The results of this scoping review provide a rigorous overview of the existing literature and a context on which to build a research agenda aimed at improving the lives of children using long-term NIV.

Practice points

1) The term non-invasive ventilation better describes the techniques for administering ventilatory support through an interface outside the airway.
2) Long-term use of non-invasive ventilation is a therapeutic option in a variety of pediatric groups although the available data are not evenly distributed across medical conditions or age groups.
3) The majority of studies of long-term NIV use in children are observational and predominantly descriptive in nature.

Research agenda

1) Identify populations for whom sufficient data are available for systematic review or meta-analysis to provide comprehensive summary of the data currently available for specific childhood populations.
2) Establish multicenter or multinational studies or patient registries to enable larger sample size and studies of more robust study design including clinical trials of long-term NIV use in children.
3) Design patient-oriented studies with a focus on the experience and impact of long-term NIV use on the children that use this therapy, their families and their communities.

Conflicts of interest

Vicki Woolf has a financial interest in a private company that sells non-invasive ventilation products. No other conflicts of interest have been disclosed.

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MCC, RF, LH, and JM conceived the idea of this study and designed the methodology. KW, CM, SK, EC, GB, CS, FA, RY, DO, and VW reviewed and provided suggestions on the methods. RF conducted the literature searches. MCC, JM screened all articles. MCC, KD and PB performed the data extraction with contributions from SK, GB, EC, RY, DO, JM. MCC and JM analyzed and interpreted the data. MCC wrote the initial draft of the manuscript. All authors reviewed the manuscript and approved the final version.

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Appendix A. Supplementary data

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