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## A Multicenter Study on Chronic Cough in Children

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**Original Research**

Signs and Symptoms of Chest Diseases

# A Multicenter Study on Chronic Cough in Children

Burden and Etiologies Based on a Standardized Management Pathway

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## *Background*

*While the burden of chronic cough in children has been documented, etiologic factors across multiple settings and age have not been described. In children with chronic cough, we aimed (1) to evaluate the burden and etiologies using a standard management pathway in various settings, and (2) to determine the influence of age and setting on disease burden and etiologies and etiology on disease burden. We hypothesized that the etiology, but not the burden, of chronic cough in children is dependent on the clinical setting and age.*

## *Methods*

*From five major hospitals and three rural-remote clinics, 346 children (mean age 4.5 years) newly referred with chronic cough (> 4 weeks) were prospectively managed in accordance with an evidence-based cough algorithm. We used a priori definitions, timeframes, and validated outcome measures (parent-proxy cough-specific quality of life [PC-QOL], a generic QOL [pediatric quality of life (PedsQL)], and cough diary).*

## *Results*

*The burden of chronic cough (PC-QOL, cough duration) significantly differed between settings (P = .014, 0.021, respectively), but was not influenced by age or etiology. PC-QOL and PedsQL did not correlate with age. The frequency of etiologies was significantly different in dissimilar settings (P = .0001); 17.6% of children had a serious underlying diagnosis (bronchiectasis, aspiration, cystic fibrosis). Except for protracted bacterial bronchitis, the frequency of other common diagnoses (asthma, bronchiectasis, resolved without specific-diagnosis) was similar across age categories.*

## *Conclusions*

*The high burden of cough is independent of children's age and etiology but dependent on clinical setting. Irrespective of setting and age, children with chronic cough should be carefully evaluated and child-specific evidence-based algorithms used.*

## *Trial registry*

*Australian New Zealand Clinical Trials registry; No.: ACTRN12607000526471; URL: www.anzctr.org.au*

## Abbreviations

GERD

gastroesophageal reflux disease

IQR

interquartile range

PBB

protracted bacterial bronchitis

PC-QOL

parent-proxy cough-specific quality of life

PedsQL

pediatric quality of life

QOL

quality of life

RCT

randomized controlled trial

rs

Spearman correlation

VCD

verbal categorical descriptive

Cough is the most common symptom for which doctors are consulted in affluent countries. [1] , [2] The burden of chronic cough in children has been documented with respect to prevalence, [3] frequent doctor visits, and impact on quality of life (QOL). [4] , [5] In a Brisbane cohort of children newly referred for chronic cough, > 80% had ≥ 5 doctor visits for their cough. [4] In addition, chronic cough negatively impacts on schooling and sleep [3] and substantially reduces the health-related QOL of children and their parents. [4] , [5] Despite the common problem and burden of illness, there is relatively little published high-quality data on the etiology and management of chronic cough. [6] , [7] All published pediatric data on etiology and burden of chronic cough has been restricted to single-center studies and the quality of assessment tools used and analysis varied widely between studies. [7]

The ascribed possible underlying etiologies of chronic cough have a very wide spectrum that ranges from simple nonspecific cough (that is more likely to resolve spontaneously [8] ) to serious causes such as foreign bodies in the airways and bronchiectasis. [9] , [10] Not surprisingly, different centers report highly variable etiologies [11] that are likely (at least in part) related to inherent difficulties in studying chronic cough. [7] , [12] Furthermore, childhood etiologies differ from adults, and child-specific cough management protocols are advocated in Australia, [9] the United States, [13] and the United Kingdom. [10] Single-center data are subject to biases of individual and group practices, particularly when nonvalidated outcomes are used. [7] The influences of the period and placebo effects can only be definitively negated with placebo-controlled studies. Nevertheless, determination of ascribed etiology can be substantially reduced by using validated cough outcome measures along with a priori definitions and timeframes [7] in a multicenter setting.

In addition to the possible differences in practice settings, the etiologies and burden of chronic cough are also potentially influenced by age. While these have been speculated, [13] to date, there are no published studies that have examined these possible influences. Understanding these influences are important for the validation of child-specific cough protocols and improving the management of chronic cough.

In this study, we evaluated the burden (parent-proxy cough-specific QOL [PC-QOL] [5] , [14] and generic health QOL [15] ) and etiology of chronic cough in 346 newly referred children. We used a standard management cough algorithm in Australian cities and rural-remote practices. [16] We also determined the influence of age and clinical setting (urban vs rural-remote, indigenous vs nonindigenous) on disease burden and etiologies of cough as well as etiology on disease burden. We used validated outcomes for cough and a priori determined definitions, based on the protocol for our randomized controlled trial. [16] We hypothesized that the etiology, but not the burden, of chronic cough in children is dependent on the setting of clinical practice and age.

# Materials and Methods

This prospective multicenter cohort study was conducted in five major hospitals (Brisbane, Melbourne, Sydney, Canberra, and Darwin) and three rural-remote clinics (Orange [New South Wales], Anangu Pitjanjatjara Lands in Central Australia [South Australia], and Thursday Island [Queensland]). The study is an extension of our randomized controlled trial (RCT) that examined the early (2 weeks) vs delayed (6 weeks) use of cough pathway algorithm. [16] Of the 346 children included in this study, 253 were from the RCT. In the RCT component, there was no difference in etiologies of chronic cough between the two arms. Also, adherence to the pathway [16] of three sites (random selection of 20 each in Brisbane, Sydney, Melbourne) was assessed and confirmed by chart review.

## Participants and Setting

Children aged < 18 years newly referred with chronic cough (> 4 weeks) to any of the participating sites were eligible. All children were referred either from primary care or from general pediatricians although some parents initiated the referral (Table

1). Children with a known chronic respiratory illness previously diagnosed by a respiratory physician or those who have had diagnoses confirmed on objective tests (eg, cystic fibrosis and bronchiectasis) prior to referral were excluded. Written consent was obtained from parent(s), and the study was approved by the ethics committees of all the participating sites (details in e-Appendix 1).

**Table 1 -- Baseline Data**

| Demographics | Overall Cohort (N = 346) | Brisbane (n = 157) | Melbourne (n = 69) | Sydney (n = 37) | Canberra (n = 41) | Darwin (n = 24) | Rural [a] (n = 18) | *P* Value |
|---|---|---|---|---|---|---|---|---|
| Age, mean (SD), y | 4.5 (3.7) | 4.1 (3.5) | 5.4 (3.9) | 5.1 (3.8) | 4.2 (4.0) | 3.5 (2.7) | 4.3 (4.1) | .07 |
| Sex, M (F), No. | 204 (142) | 90 (67) | 32 (37) | 25 (12) | 27:14 | 16:8 | 14:4 | .08 |
| Household tobacco smoke exposure | 106 (30.6) [b] | 36 (22.9) | 18 (26.1) | 9 (24.3) | 20 (48.8) | 14 (58.3) | 9 (50) | .0001 |
| Children in household, mean (SD) | 2.4 (1.3) | 2.5 (1.3) | 2.0 (0.8) | 2 (0.7) | 2.2 (1.1) | 2.1 (1.5) | 3.1 (1.7) | .11 |
| Wet cough present | 221 (63.9) | 110 (70.1) | 37 (53.6) | 26 (70.2) | 20 (48.8) | 19 (79.1) | 10 (55.5) | .001 |
| Asthma medications used: corticosteroids, $\beta_2$ agonist, or montelukast | 242 (69.9) [c] | 101 (64.3) | 50 (72.5) | 34 (91.9) | 35 (85.4) | 15 (62.5) | 7 (38.9) | .006 |
| Indigenous | 34 (10.1) | 9 (5.7) | 1 (1.4) | 2 (5.4) | 1 (2.4) | 10 (41.7) | 11 (61.1) | .0001 |
| Referral type [d] requested | 136 (40.7) | 54 (34.6) | 31 (48.4) | 25 (71.4) | 15 (37.5) | 4 (18.9) | 7 (41.2) | .0001 |
| GP initiated | 171 (51.2) | 85 (44.5) | 31 (48.4) | 8 (22.9) | 21 (52.5) | 16 (72.7) | 8 (47.5) | … |
| Specialist initiated | 27 (8.1) | 17 (34.6) | 2 (3.1) | 2 (5.7) | 4 (10) | 2 (9.1) | 2 (11.8) | … |

Data given as No. (%) unless otherwise indicated. F = female; GP = general practitioner; M = male.

**a** Children enrolled in Central Australia (n = 5), Orange (n = 6), and Thursday Island (n = 7).

**b** Data not recorded in 8 children.

**c** Data not recorded in 14 children.

**d** Requested indicates parent requested to be referred, GP (data missing in 12).

## Protocol

At enrollment, the child's demographics using a standardized data collection form were collected. Parents were coached on completion of several validated outcome measures: cough-specific QOL (PC-QOL), [5] , [14] a generic QOL (pediatric QOL [PedsQL [15] ]) and a cough diary using the verbal categorical descriptive (VCD) score. [17] All outcomes were collected at baseline and parents maintained the cough diary until cough-free. Enrolled children were managed in accordance to a standardized evidence-based pathway (cough algorithm, [16] e-Figs 1, 2) until the study's end point defined in the next section. The rationale of our cough management approach was largely based on systematic evaluation as previously outlined. [16] The flowchart was adapted from the American College of Chest Physicians (ACCP) pediatric guidelines, [13] combined with updated data and cough definitions from our Australian guideline. [9]

## Definitions and Outcomes

The end point was defined as either primary diagnosis and cough resolution established, the presence of exit criteria, or at 12 months from time of enrollment (whichever occurred earliest). The exit criterion was hospitalization for a condition related to cough before primary diagnosis was established. Cough resolution (considered cough-free) was defined as improvement of ≥ 75% or total resolution according to parental reports and cough diary data [17] for ≥ 3 consecutive days. [18] When the cough only partially resolved (ie, reduction in cough severity that did not meet the definition of "cough resolution"), the management continued in accordance to the pathway. Definitions used for primary diagnosis and other items in the cough algorithm have been published and are available in e-Appendix 1. [16]

Outcome measures used were VCD, PC-QOL, and PedsQL [15] (further described in e-Appendix 1). VCD (score of 0-5, increasing scores reflects worse cough) was validated against an objective cough meter measure. [17] Changes in VCD cough scores reflect changes in objective cough counts. [19] The PC-QOL [5] , [14] is a 27-item questionnaire; higher scores reflect a better QOL, and minimal important difference is 0.62-0.9. [20] We also used the parent-proxy PedsQL, [15] a generic health-related QOL designed for parental reports of their child's QOL. PedsQL data were normalized to allow comparison between groups and diseases. [15]

## Statistics

Data were examined for type of distribution using normality plots. Data that had a normal distribution were described using means and SD; medians and interquartile ranges (IQRs) were used otherwise. $\chi^2$ tests were employed for categorical data. Kruskal-Wallis analyses were used for group comparisons. Spearman correlation (rs) was used to examine between correlations among variables. SPSS software (SPSS, Inc) was used, and a two-tailed *P* value of < .05 was considered significant.

# Results

The demographics of the 346 children (Table 1) were significantly different between the sites for several variables: household smoke exposure (lowest in Brisbane, highest in Darwin), number of children with wet cough (lowest in Canberra, highest in Brisbane), use of asthma medications (lowest in rural sites, highest in Canberra), number of indigenous children (lowest in Melbourne, highest in rural sites), and referral pattern. Age, sex, and number of siblings were not significantly different among sites. Exit criterion (hospitalized for an undiagnosed or misdiagnosed condition related to their cough) was not used for any child.

## Burden of Cough

The burden of cough quantified by the various outcome measures and the number of doctor consultations for their cough preenrollment are summarized in Table 2. There were significant differences among sites for number of doctor visits (highest proportion of > 20 visits in Darwin), duration of cough (lowest in Darwin, highest in Brisbane), and PC-QOL (best in Darwin, worst in Sydney). However, there was no significant difference among sites for PedsQL and cough score.

**Table 2 -- Burden of Cough at Enrollment**

| Burden Variable | Overall Cohort (N = 346) | Brisbane (n = 157) | Melbourne (n = 69) | Sydney (n = 37) | Canberra (n = 41) | Darwin (n = 24) | Rural [a] (n = 18) | *P* Value |
|---|---|---|---|---|---|---|---|---|
| Doctor visits | | | | | | | | .0001 |
| < 5 | 86 (24.9) | 32 (20.4) | 27 (39.1) | 2 (5.4) | 7 (17.5) | 8 (36.4) | 10 (62.5) | |
| 5–10 | 106 (30.6) | 45 (28.7) | 21 (30.4) | 16 (43.2) | 17 (42.5) | 4 (16.7) | 3 (18.8) | |
| 10–15 | 70 (20.2) | 36 (22.9) | 12 (17.4) | 7 (18.9) | 9 (22.5) | 5 (20.8) | 1 (6.3) | |
| 15–20 | 36 (10.4) | 17 (10.8) | 3 (4.3) | 9 (24.3) | 4 (9.8) | 1 (4.2) | 2 (12.5) | |
| > 20 | 27 (7.8) | 16 (10.2) | 3 (4.3) | 1 (2.7) | 3 (7.3) | 4 (16.7) | 0 (0) | |
| Data not filled | 21 (6.1) | 11 | 3 | 2 | 1 | 2 | 2 | … |
| Cough score, [17] mean (SD) | 2.7 (1.2) | 2.5 (1.3) | 2.9 (1.2) | 2.9 (1.1) | 2.6 (1.3) | 2.8 (1.4) | 2.9 (1.2) | .49 |
| Duration of cough, median (IQR), wk | 16 (8,32) | 26 (9.2, 52) | 17 (8.2, 29) | 16 (8, 26) | 16 (6.5, 30.5) | 9 (4.5, 26) | 12 (4.5, 30) | .021 |

| Burden Variable | Overall Cohort (N = 346) | Brisbane (n = 157) | Melbourne (n = 69) | Sydney (n = 37) | Canberra (n = 41) | Darwin (n = 24) | Rural [a] (n = 18) | *P* Value |
|---|---|---|---|---|---|---|---|---|
| PC-QOL, median (IQR) | 3.8 (2.7, 5.0) | 3.9 (2.9, 5.0) | 3.7 (2.6, 4.8) | 3.2 (2.3, 3.9) | 3.5 (2.5, 5.3) | 4.9 (3.4, 5.6) | 4.6 (3.3, 5.3) | .014 |
| PedsQL, median (IQR) | 77.3 (64.3, 87) | 75 (65.3, 82.9) | 81.5 (64.8, 87.8) | 81.9 (63.3, 89.9) | 69.4 (59.2, 86.9) | 77.9 (69.6, 92.2) | 76.6 (62, 91.3) | .61 |
| Mean PedsQL, [b] mean (SD) | 74.7 (15.5) | 72.9 (15.3) | 76.9 (14.0) | 76.1 (16.8) | 72.7 (18.4) | 79.8 (11.6) | 76.6 (20.7) | … |

Data given as No. (%) unless otherwise indicated. IQR = interquartile range; PC-QOL = parent-proxy-cough quality of life [5]; PedsQL = pediatric quality of life 4.0. [15]

**a** Children enrolled in Central Australia (n = 5), Orange (n = 6), and Thursday Island (n = 7).

**b** Mean of PedsQL is provided to allow comparison of our data to internationally published data. [21]

Both PC-QOL and PedsQL did not correlate with age (rs = 0.05, *P* = .39 and rs = 0.02, *P* = .8, respectively). Also, neither PC-QOL nor PedsQL correlated with duration of cough (rs = -0.01, *P* = .92 and rs = 0.03, *P* = .70, respectively). However, there was a weak but significant correlation between cough score and age (rs = 0.13, *P* = .02).

There were 34 indigenous children in the cohort, and no significant differences between indigenous and nonindigenous children in any burden of cough data were found. When diagnoses were categorized to serious underlying disease (aspiration, bronchiectasis, cystic fibrosis, pneumonia; Table 3) and nonserious underlying conditions (other diagnoses), there was no significant difference between groups for PC-QOL (*P* = .42), PedsQL (*P* = .07), duration of cough (*P* = .69), or cough score (*P* = .50).

**Table 3 -- Primary Etiology**

| Diagnosis, Defined in e-Appendix 1 | Overall Cohort (N = 346) | Brisbane (n = 157) | Melbourne (n = 69) | Sydney (n = 37) | Canberra (n = 41) | Darwin (n = 24) | Rural [a] (n = 18) |
|---|---|---|---|---|---|---|---|
| Protracted bacterial bronchitis | 142 (41.0) | 84 (53.5) | 11 (15.9) | 18 (48.6) | 9 (22.0) | 13 (54.2) | 7 (38.9) |
| Asthma/RAD | 55 (15.9) | 10 (6.4) | 11 (15.9) | 9 (24.3) | 20 (48.8) | 1 (4.2) | 4 (22.2) |
| Bronchiectasis | 31 (9.0) | 24 (15.3) | 0 | 0 | 0 | 4 (16.7) | 3 (16.7) |
| Resolved without specific diagnosis | 48 (13.9) | 7 (4.5) | 31 (44.9) | 1 (2.7) | 6 (14.6) | 1 (4.2) | 2 (11.1) |
| Tracheomalacia | 21 (6.1) | 14 (8.9) | 5 (7.2) | 0 | 0 | 2 (8.3) | 0 |
| Habitual-psychogenic | 15 (4.3) | 7 (4.5) | 3 (4.3) | 3 (8.1) | 1 (2.4) | 1 (4.2) | 0 |
| Pertussis | 12 (3.5) | 1 (0.6) | 6 (8.7) | 3 (8.1) | 0 | 1 (4.2) | 1 (5.6) |
| Aspiration lung disease | 8 (2.3) | 7 (4.5) | 0 | 0 | 0 | 0 | 1 (5.6) |
| Pneumonia | 3 (0.9) | 1 (0.6) | 1 (1.4) | 0 | 1 (2.4) | 0 | 0 |
| Upper airways | 5 (1.4) | 2 (1.3) | 1 (1.4) | 1 (2.7) | 0 | 1 (4.2) | 0 |
| *Mycoplasma* | 5 (1.4) | 0 | 0 | 2 (5.4) | 3 (7.3) | 0 | 0 |
| Cystic fibrosis | 1 (0.3) | 0 | 0 | 0 | 1 (2.4) | 0 | 0 |

Data given as No. (%). RAD = reactive airway disease.

**a** Children enrolled in Central Australia (n = 5), Orange (n = 6), and Thursday Island (n = 7).

## Etiologies of Cough

The primary diagnoses (see e-Appendix 1 for criteria) varied widely from "resolved without specific diagnosis" to cystic fibrosis (Table 3). When considered as a single entity, the difference among study sites was significant ($P = .0001$). However, within the top five diagnoses, there were significant differences among sites for the diagnoses of protracted bacterial bronchitis (PBB), asthma, bronchiectasis and "resolved without specific diagnosis" ($P = .0001$ for all) but not for tracheomalacia ($P = .12$). Brisbane (53.3%) had significantly more children with PBB than Melbourne (15.9%) ($P = .0001$). Also, indigenous children (10 of 34 [29.4%]) were significantly more likely to have bronchiectasis than nonindigenous children (21 of 312 [6.7%]) ($P = .001$).

There was also an overall significant difference for primary diagnosis when children were grouped into four age categories ($P = .0001$) (e-Table 1); ≤ 2 years (n = 124), 2-6 years (n = 126), 6-12 years (n = 82), and > 12 years (n = 14). We then analyzed the top five etiologies (Figure 1). For PBB, there was a significant difference among age categories groups ($P = .001$) with a significant trend; the younger the age group, the more likely PBB was found ($\chi^2$ linear-by-linear association; $P = .0001$). However for asthma, there was no significant difference among age groups ($P = .203$) with an absence of a linear trend ($P = .225$). There was also no significant difference for diagnosis of bronchiectasis ($P = .07$), "resolved without a specific diagnosis" ($P = .13$) or tracheomalacia ($P = .89$).

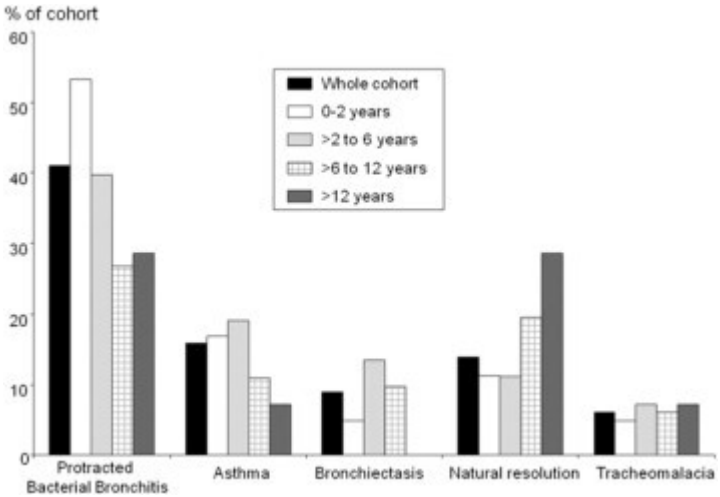


**Figure 1** Distribution of the five most frequent diagnoses, grouped according to age categories.

Sixty-one of the 346 children (17.6%) had more than one diagnosis. These were coexistent tracheomalacia with PBB (n = 27), coexistent asthma with PBB (n = 13), and mycoplasma (n = 2), coexistent PBB with asthma (n = 8) and aspiration lung disease (n = 4), coexistent upper airways syndrome with asthma (n = 2) and PBB (n = 2), coexistent aspiration lung disease with bronchiectasis (n = 1), and coexistent gastroesophageal reflux disease (GERD) with PBB (n = 2).

# Discussion

In this first prospective multicenter cohort study, we used an evidence-based cough algorithm to manage the chronic cough of 346 newly referred children. Using validated cough outcome measures and a priori definitions and timeframes to define cough resolution, we found that the burden of chronic cough (PC-QOL) differed significantly between clinical settings, but was not influenced by age, nor etiology of cough. There was a wide spectrum of etiology of chronic cough that was significantly different in dissimilar clinical settings. Diagnoses were not significantly different in the various age categories other than for the most common diagnosis (PBB) which was significantly higher in the youngest age group.

There are no published studies that have evaluated cough etiologies across different clinical settings using a standard management pathway. Thus, we evaluated the collective chronic cough etiologies using a standard pathway and determined whether these were dependent on settings, as it is important that protocols used are able to detect differences across various settings. Also, pediatric cohort studies that used a standardized management [18] , [22] were limited to a single center and, thus, potential biases. These studies (albeit different definitions used) have shown that causes of chronic cough in children are significantly different to adults, [18] , [22] as in adults who seek medical attention, GERD, asthma and upper airway syndrome are the three most commonly reported etiologies. [23] In our evaluation of the etiologies across settings, we found that the top four diagnoses in our cohort were PBB, asthma, bronchiectasis, and "resolved without specific diagnosis," and that the frequency of these etiologies significantly varied across settings. This was expected, given the known differences in health-care setting and access to respiratory expertise (which influences referral patterns, Table 1). Other possible differences between centers can only be

speculated about and include variations in primary care practice, as reflected in prior use of asthma medications in Table 1. Marked differences in etiologies were present for bronchiectasis in indigenous children, which was expected as previously described. [24] Melbourne had significantly fewer children with PBB than others. Melbourne had more children who had the diagnosis of "resolved without a specific diagnosis" while Canberra had more with asthma. Brisbane, Darwin, and rural centers had more children with bronchiectasis. Thus, our cough algorithm can be applied across various settings but setting-specific adjustments may be required.

The etiologies we have found in this study have to be interpreted in the context of the sampling frame. Almost 70% of the children had received asthma medications, reflecting the overuse of asthma medications for cough in children. [25] , [26] Nevertheless, it is also possible that our cohort may be depleted of asthma because asthma medications were widely used. In addition, controversies about etiology and management of chronic cough are abundant with substantial differences in opinions about conditions such as GERD, [27] , [28] cough-variant asthma in children, [29] and upper airway cough syndrome, [30] particularly when data for causation are systematically examined. While there are some biologic reasons for these differences, other substantial contributors include the differences in definitions used (including duration of chronic cough), quality of the studies, [7] for example, failure of some studies to use validated outcomes and lack of a priori definitions. Given the controversies and strict methodology applied in our study, it is not surprising that our multicenter data differ from some cohorts.

It is well accepted among child-centered doctors that child-centered protocols should be used when treating children. Indeed, there are child-specific guidelines based in the United States for asthma, [31] GERD, [32] and interstitial lung disease [33] ; all conditions associated with cough. In the field of cough, the reasons that underpin this rationale include the known physiologic differences that influence etiologic factors, outcome measures, and investigation tests of children compared with adults. [34] However, what has remained elusive is the age threshold at which adult-based protocols should be used instead of child-specific ones. In asthma, not only does the threshold vary among guidelines, but there is little published evidence-based data on the age when an adult-based approach should be applied in pediatrics for physiologic reasons as opposed to psychologic-cognitive rationales. The British [35] and US [31] asthma guidelines recommend three different age-specific stepwise protocols for children; those aged ≥ 12 years are assigned to the adult protocol. In the Australian guideline, child-specific protocols are applied to adolescents (no cutoff given), whereas in the Global Initiative for Asthma (GINA) guidelines, the steps recommended for adults are the same for children aged as young as 5 years. [36] To date, no published studies are large enough to examine the influence of age on etiologies of chronic cough in children. Our study has shown that, other than PBB, the etiologies of cough are similar in the different age groups up to 12 years. Thus, the age threshold for child-specific cough protocols should be at least 12 years. As there were only 14 children aged > 12 years, we cannot validly conclude whether children aged > 12 years should be managed with adult protocols. However, notably absent from all sites was GERD as the primary diagnosis, and few children had upper airway syndrome, two diagnoses that are common in adult cohorts. [37] Furthermore, 28.6% of children aged > 12 years had PBB. This is important as PBB, first described in children by our group [18] as a diagnostic entity, is increasingly recognized as a clinically significant pediatric condition across the continents. [38] , [39] , [40] In adults, Schaefer and Irwin [41] had described 15 with chronic cough who had unsuspected bacterial suppurative disease. We had previously shown the validity of wet cough as a symptom [42] and, we and others have documented the response of wet cough to appropriate antibiotics. [38] , [39] , [40] , [43] PBB is easily treatable (thus improving health-related QOL), and wet cough and/or PBB, if left untreated, may possibly progress to chronic suppurative lung disease, [38] , [44] in the context of persistent lower airway infection and intense neutrophilia demonstrated in the BAL of children with PBB [45] and wet cough. [38] , [40] , [46] Airway infection and neutrophilia are the main components of the Cole postulate. [47]

Our study's limitations include the lack of an objective measurement of cough. However, we used cough outcome measures (PC-QOL [5] , [14] and VCD [17] scores) that were previously validated against objective cough counts. Furthermore, most of the children in our study were managed by pediatric pulmonologists and application of the pathway in primary care may have different findings. However, the majority of children had diagnoses that can be easily managed by primary care practitioners. Only 17.6% of children in the cohort had an etiology (bronchiectasis, cystic fibrosis, tracheomalacia, aspiration lung disease) that is generally diagnosed and managed by pediatric pulmonologists.

There are currently limited data on the burden of cough in children and, indeed, no studies that have compared cough with other pediatric chronic conditions. Thus, in this study, we used a widely accepted generic QOL to allow this comparison between cough and other disease. We found that our cohort's mean normalized PedsQL score of 74.7 was in the realm of children with other chronic illness (cardiac = 79.4, diabetes = 76.6, obesity = 75, gastrointestinal conditions = 72.4) but better than children with cancer (68.5) and end-stage renal disease (69.6). [21]

As there are also no studies outside Brisbane that have reported PC-QOL scores, we determined PC-QOL scores in our multicenter study. In agreement with our previous unicenter studies, [4] , [14] we found that etiology did not influence PC-QOL. Furthermore, we evaluated other markers of burden and found that PedsQL, PC-QOL, duration of cough, and cough score were no different in children with a serious underlying disease compared with those with less-serious conditions. This suggests that it is the cough itself, rather than the underlying etiology that drives the disease burden at the point of referral. Given the burden of illness significantly reduces with evaluation, [4] it is arguably more appropriate to use a 4-week cutoff than any longer period in defining chronic cough in children. This reason is in addition to the safety aspects relevant to chronic cough in children, that is, early diagnosis of serious underlying illness. For example, early diagnosis and management of missed foreign body [48] and bronchiectasis [49] prevents future respiratory morbidity. Karakoç et al [48] found that "long-term complications increased with

increasing elapsed time from aspiration to diagnosis; complications were as high as 60% in children who were diagnosed 30 day after inhalation." [48] Thus, while it may not be necessary to treat all children with cough at the 4-week mark (as depicted in a "watch-and-wait approach" for those with non-specific cough [13]) children should be evaluated carefully at this point, as advocated in the ACCP cough guidelines. Further reasons for the 4-week definition for chronic cough (as opposed to 8 weeks in adults), include the known natural history of cough in children. [9] , [50] This is in contrast to the duration of 5-7 days in children aged < 10 years for acute episodes reported in prospective community studies. [51]

In summary, our large multicenter study that used a child-specific evidence-based protocol with validated outcomes and a priori defined timeframes has several new findings. These include the finding that, irrespective of etiology and age, the burden of chronic cough is high. The frequency of etiologies of chronic cough is dependent on the clinical setting and age has less influence. Thus, irrespective of setting and age, children with chronic cough should be carefully evaluated and child-specific protocols used, as the underlying etiologies we described here, were different to that reported in adult studies. While the age threshold when adult protocols are appropriate is above 12 years, the exact age cutoff remains unknown until larger studies in adolescents are performed.

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**Author contributions:** Dr Chang had full access to the data and takes responsibility for the integrity of all of the data and the accuracy of the data analysis.

*Dr Chang:* contributed to drafting, preparing, and critically reviewing the manuscript, was responsible for the study concept and design, and coordinated the study.

*Dr Robertson:* contributed to the study design; data collection, analyses, and interpretation; and revising the manuscript.

*Dr Van Asperen:* contributed to the study design; data collection, analyses, and interpretation; and revising the manuscript.

*Dr Glasgow:* contributed to the study design, data interpretation, and revising the manuscript.

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*Dr Masters:* contributed to the study design; data collection, analyses, and interpretation; and revising the manuscript.

*Dr Teoh:* contributed to data collection and interpretation and revising the manuscript.

*Dr Tjhung:* contributed to data collection and interpretation and revising the manuscript.

*Dr Morris:* contributed to the study design; data collection, analyses, and interpretation; and revising the manuscript.

*Ms Petsky:* contributed to data collection and interpretation and revising the manuscript.

*Ms Willis:* contributed by creating and maintaining the database, participated in data collection, and revising the manuscript.

*Dr Landau:* contributed to the study design, data interpretation, and revising the manuscript.

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**Additional information:** The e-Appendix, e-Figures, and e-Tables can be found in the "Supplemental Materials" area of the online article.

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