Quality of life in congenital diaphragmatic hernia survivors treated at a non-ECMO centre from 1998 to 2015: a cross-sectional study

Ulla Lei Larsen, Steven Aagaard Christensen, Anne Maria Herskind, Thomas Strøm, Palle Toft, Susanne Halken

ABSTRACT
Background Survival of infants with congenital diaphragmatic hernia (CDH) has increased and more insight is warranted on the long-term issues of this condition.

Methods We conducted a cross-sectional study on consecutively born infants with CDH treated at a non-extracorporeal membrane oxygenation centre (ECMO) from 1998 to 2015. Quality of life was evaluated using the Pediatric Quality of Life Inventory Generic Core Scale 4.0 (PedsQL(4.0)) Questionnaire and an interview was conducted to assess for CDH-related morbidity.

Results 71 eligible CDH survivors were identified and 51 consented to participate: aged 5–21 years, 28 (54.9%) male, 42 (82.4%) with left-sided hernias, 10 (19.6%) needed patch repair, median length of stay in hospital was 27.96 days (IQR 18.54–61.56). Forty-nine completed the questionnaire with a median PedsQL total score for participants of 82.6 vs 83.7 of the total proxy parent score (p=0.04). Total score was significantly lower for participants aged 5–12 years compared with participants aged 13–21 years (p=0.04); however, when reported by domains, only the physical score remained significantly lower (p=0.048). Two (4.1%) participants’ and 8 (16.7%) proxy parents’ scores were below 70 and considered at risk of impaired quality of life. We identified the presence of CDH-related morbidity in our population, and confirmed an association between respiratory morbidity and lower PedsQL scores (p=0.04).

Conclusion We report an overall good quality of life in our population with CDH. However, a lower physical score was noted when compared with a national Danish cohort and individuals at risk of reduced quality of life were recognised. Structured follow-up programmes to identify and ensure early management of CDH-related issues may prevent a negative impact on quality of life.

OBJECTIVE
Improvements in prenatal and postnatal management of infants with congenital diaphragmatic hernia (CDH) have increased survival, as well as the need for more insight and knowledge on the long-term issues associated with this rare condition.

WHAT IS ALREADY KNOWN ON THIS TOPIC
⇒ Previous studies have reported an overall good quality of life in congenital diaphragmatic hernia (CDH) survivors. Diagnosis, intervention and management of infants with CDH have improved over the past decades and reduced the mortality of this severe condition.

WHAT THIS STUDY ADDS
⇒ As survival of infants with CDH increases, a higher rate of related morbidity might be expected and potentially affect quality of life. Our study provides data on a recent cohort of CDH survivors and contribute to the growing knowledge on the long-term issues of CDH.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY
⇒ Our results confirm the relevance of a structured follow-up programme for early identification and management of CDH-related morbidity. Improved knowledge on the long-term issues will provide better counselling for families expecting an infant with CDH.

Long-term organ dysfunction has been the main concern, but data on overall perception of health and quality of life are emerging. Early studies have reported a good quality of life in populations with less severe CDH. However, subtle tendencies of CDH-related morbidity affecting quality of life have been noted.

A more recent review concluded an overall good quality of life in CDH survivors with four studies reporting quality of life equal to background values and two studies reporting lower scores compared with healthy controls.

The primary aim of this study was to report on quality of life in a Danish population with CDH. The secondary aims were to compare quality of life scores reported by the participants and their parents; and to describe baseline and demographic data of the population.
with CDH, screen for CDH-related morbidity and evaluate on risk factors for low quality of life score.

DESIGN
We conducted a cross-sectional study on consecutively born infants with CDH, treated at a non-extracorporeal membrane oxygenation (ECMO) centre from 1998 to 2015. The study is a substudy to the ongoing project: ‘Mortality and morbidity of infants with symptomatic congenital diaphragmatic hernia treated at Odense University Hospital, a single center without ECMO (1998–2015)’.

PARTICIPANTS
All infants with a history of symptomatic CDH presenting in the first 24 hours of life were included, whereas non-survivors and patients with severe neurological impairment were excluded. Our region covered a population of approximately 3.2 million (Statistics Denmark: 2022Q4) and management was performed according to contemporary international guidelines and local practice. These strategies were implemented in 1997 and have remained largely unchanged, except for a few adjustments, up until 2019. Data on management and survival from our centre were published in 2020. None of the infants received ECMO or transferred out of the region for further treatment. Baseline and demographic data were collected retrospectively from medical journals. Standardised follow-up programmes were not available for any of the participants during the study period.

INTERVENTIONS
Interview
Parents and participants were asked to report on: current medication, any medication given within the last year, any noted hearing impairment, symptoms and treatment of gastro-oesophageal reflux, school and social/behavioural performance and respiratory problems such as episodes with airway infection or wheezing/shortness of breath within the last year.

Pediatric Quality of Life Inventory Generic Core Scale 4.0
Assessment of quality of life was conducted using the Pediatric Quality of Life Inventory Generic Core Scale 4.0 (PedsQL(4.0)) developed and validated by Varni et al. The PedsQL(4.0) Questionnaire consists of a child self-report and a proxy parent report. The age-adapted questionnaire evaluates on four domains: physical, emotional, social and school/work function (in total 23 items) and a psychosocial score was generated using the emotional, social and school/work scores (sum/3). The original work by Varni et al reported reliabilities of 0.88 (child self-report) and 0.90 (parent proxy report) on total scale scores and ranged from 0.75 to 0.88 throughout the subdomains. Validity was determined using the known-groups method and the method distinguished between healthy children and children with acute and chronic health conditions. A linguistically validated Danish version was available and answers were ranked on a 0–100 scale, with higher numbers representing a better perception of quality of life.

Information and instructions were given to the child and parents together, thereafter the parents independently completed the questionnaire while the child completed the questionnaire with the interviewer. Questions were read to the youngest children and instructions repeated if necessary.

Statistics
Continuous data were summarised as median and IQR values (25th and 75th percentile) and categorical data were summarised as numbers and percentage. Comparison between groups was performed using the Wilcoxon rank-sum test for continuous data and $\chi^2$ test for categorical data. The Wilcoxon signed-rank test was used to compare participant scores with their proxy parent scores. Association between demographics/baseline parameters, factors included in the interview and lower PedsQL scores were evaluated using linear regression models. All analyses were performed using STATA/IC V.17.0 (Stata Statistical Software: Release 17. College Station, Texas, USA: StataCorp) and $p$ values of <0.05 were considered significant.

RESULTS
We identified a total of 120 CDH cases during the study period, of these 25 were late diagnosed (presenting with symptoms after 24 hours of life) and therefore excluded. Of the 95 infants presenting with symptoms before 24 hours of life, 74 survived (mortality 22.1 %) and 3 children had more severe neurological impairment, leaving 71 eligible children. Fifty-one children and their families (71.8% of the eligible children) consented to participate (figure 1).

All participants were included from November 2018 to September 2021, overlapping the SARS-CoV-2 pandemic. Age at inclusion ranged from 5 to 21 years with a median age of 12 years. Five children in the participating group had associated malformations, which included esophagus atresia, chromosomal abnormalities, and minor cardiac and renal malformations. Baseline and demographic variables showed no significant difference between the participating and the non-participating children (table 1).

Interview
Two participants were interviewed without their parents (age >18 years). One participant reported mild hearing impairment, but no hearing aid was required. Thirteen (25.5%) reported symptoms of gastro-oesophageal reflux at least once a month for the past year or were currently under treatment. Eight received
medical treatment and all were managed without surgical treatment.

Eleven (21.57%) participants were currently on or had received inhaled treatment with salbutamol and/or steroids within the past year. Regarding episodes of ‘airway infection that resulted in treatment with antibiotics or absence from school/work’, 49 participants reported zero to one episode over the past year, and 2 (3.92%) reported two to three episodes. Likewise, on ‘episodes of airway wheezing and/or shortness of breath resulting in initiation of (or increased treatment with) inhaled medication’, 48 reported zero to one episode, and 3 (5.99%) reported two to three episodes within the last year.

At time of follow-up, 48 of the 51 participants were enrolled in age-appropriate school or educational programmes (primary school/high school/vocational training) and had plans for the future as anticipated according to age. Of these, three participants (3 of 48, 6.25%) had required both academic support and support on social/behavioural issues, three (3 of 48, 6.25%) had needed academic support only and six (6 of 48, 12.50%) had needed support on social/behavioural issues only, at some point during childhood. The remaining 3 of the 51 (5.88%) participants attended school in a special needs programme and were expected to have a continued need for further support in the future.

**PedsQL Questionnaire**

Data were missing from two participants due to a lack of sufficient cooperation and from two parents. Median
self-reported total score for the population was 82.61 (80.43–91.30) and the median proxy parent score was 83.70 (76.10–88.59) with a statistically significant difference (p<0.039). The self-reported and the proxy parents’ scores were highest on the physical domain and lowest on the emotional domain. The highest self-reported total score was 99.23, and two (4.1%) participants reported a total score below 70 (61.96 and 66.30). The highest proxy parent score was 100, and eight (16.67%) reported a total score below 70, ranging from 47.83 to 65.30. The parents reported a significantly higher median total score (p<0.039), but with lower 25th and 75th percentile values, when compared with the self-reported total scores (as shown in figure 2).

In the physical domain, no significant difference was found between the self-reported and the proxy parent scores, but parents scored their children’s psychosocial well-being significantly lower (p=0.004) than the children themselves (carried by a lower score in the emotional and school/work domains). Total self-reported and proxy parent scores were not significantly different when grouped according to age at follow-up: 5–12 years (n=26) and 13–25 years (n=23) (using Wilcoxon signed-rank test, p=0.060 and p=0.056). Higher total and physical scores were noted in the older age group with p<0.05, but no difference was found in the psychosocial scores (table 2).

Factors associated with quality of life
Baseline parameters: APGAR score at 5 min, time on mechanical ventilation, treatment with inhaled nitric oxide in the intensive care unit, requirement of patch for surgical repair and length of stay in hospital, were evaluated as potential risk factors. However, none of the mentioned factors were associated with a lower total PedsQL score (linear regression model, p>0.05) (table 3).

We also evaluated on the association between factors indicating CDH morbidity and lower total PedsQL scores using a linear regression model. A lower total PedsQL score was significantly associated with reporting two to three episodes of wheezing/shortness of breath within the last year and the need for support on behavioural/social issues (table 4).

**DISCUSSION**
We demonstrated an overall good quality of life in our population of CDH survivors with a median total PedsQL score of 82.61, and the vast majority (94.12%) of the participating children were managed in age-appropriate school and educational programmes. Despite the collective good results, our data do suggest the presence of CDH-related morbidity, warranting a structured follow-up programme. Gastro-oesophageal reflux and respiratory morbidity were the most common reported potential CDH-related conditions.

Our results are the first data presented on quality of life in a Danish population of CDH survivors, and included all cases of symptomatic CDH from our region, which represent approximately half of the cases in Denmark.

The total proxy parent score was significantly higher than the self-reported total scores. However, the subscores in the physical and psychosocial domains revealed a different trend. A higher proxy parent score was noted on physical health but did not remain statistically significant. Adversely, a lower proxy parent score was noted on...
psychosocial health with a clear statistically significant difference compared with the self-reported scores.

Varni et al validated the PedsQL(4.0) Questionnaire using diverse samples of children from a background population and reported a total PedsQL score of 83.00 in healthy children (n=401) and 77.19 in children with chronic conditions (n=367). From a larger sample of children (n=5480), they reported a total score of 83.84 in healthy children. Furthermore, this study demonstrated a reduced total score across a range of disease clusters, where diabetes was associated with the highest score of 80.35 and cerebral palsy with the lowest score of 66.85. The results from our population were similar to those reported by Varni et al in the healthy background populations and higher than the scores reported by children with chronic diseases.

Varni et al proposed a cut-off value for ‘at risk of impaired quality of life’ of 69.7. Although the collective reported quality of life was good in our population, we identified children who fulfilled the criteria to be at risk.

![Boxplot of total PedsQL scores: self-reported and proxy parent report. PedsQL, Pediatric Quality of Life Inventory Generic Core Scale.](image)

**Figure 2** Boxplot of total PedsQL scores: self-reported and proxy parent report. PedsQL, Pediatric Quality of Life Inventory Generic Core Scale.

<table>
<thead>
<tr>
<th>PedsQL(4.0)</th>
<th>Participants, all (n=49)</th>
<th>Parents, all (n=49)</th>
<th>P value</th>
<th>Participants 5–12 years (n=26)</th>
<th>Participants 13–25 years (n=23)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total score</td>
<td>82.61 (80.43–91.30)</td>
<td>83.70 (76.10–88.59)</td>
<td>0.039</td>
<td>82.61 (80.43–91.30)</td>
<td>83.70 (76.10–88.59)</td>
<td>0.040</td>
</tr>
<tr>
<td>Physical score</td>
<td>87.5 (81.25–93.75)</td>
<td>90.63 (81.25–98.44)</td>
<td>0.600</td>
<td>87.5 (81.25–93.75)</td>
<td>90.63 (81.25–98.44)</td>
<td>0.048</td>
</tr>
<tr>
<td>Psychosocial score</td>
<td>83.33 (78.33–91.67)</td>
<td>80.0 (70.83–86.67)</td>
<td>0.004</td>
<td>83.33 (78.33–91.67)</td>
<td>80.0 (70.83–86.67)</td>
<td>0.062</td>
</tr>
<tr>
<td>Emotional score</td>
<td>80.0 (65.0–90.0)</td>
<td>72.5 (62.50–85.00)</td>
<td>0.024</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social score</td>
<td>90.0 (80.00–100)</td>
<td>90.0 (75.0–100)</td>
<td>0.170</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>School/work</td>
<td>80.0 (80.00–90.00)</td>
<td>75.00 (65.00–90.00)</td>
<td>0.004</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The Wilcoxon signed-rank test was used to compare self-reported scores with their proxy parent scores. P values of <0.05 were considered statistically significant. (psychosocial score = emotional + social + school/work score/3).

Self-reported PedsQL scores were according to age at follow-up. Data were presented as median and IQR values (25th and 75th percentile) and compared using Wilcoxon rank-sum test and p values of <0.05 were considered statistically significant.

PedsQL(4.0), Pediatric Quality of Life Inventory Generic Core Scale 4.0.
risk of impaired quality of life and more children were perceived by their parents to be at risk. Total scores below this cut-off value were noted in two participant (4.1%) and eight proxy parent (16.32%) scores. Of note, the majority of children with a total proxy parent score below 70 were in the older age group, had postnatally diagnosed CDH and endured some degree of asphyxia at birth, but our data do not allow any further conclusions on this issue.

We found a trend across the domains with higher scores in the physical and social domains and lower scores in the emotional domain; this was consistent with recent published data on populations with CDH from other centres. Compared with these centres, our population with CDH reported higher or similar total scores.17–19 Background data on paediatric quality of life in Denmark are limited, and normative values based on the PedsQL Questionnaire were not available. However, data on more specific Danish populations have been reported (table 5). A 10-year old study by Idorn et al reported on Fontan-operated children (staged surgical procedure in children with single-ventricle heart defects) and found reduced PedsQL scores in all case groups.20 Studies on obese paediatric populations also reported reduced quality of life compared with controls.21–23 The largest dataset on PedsQL scores in Denmark was reported in a recent nationwide study by Kikkenborg et al and revealed no difference between controls and children with post-COVID-19 symptoms.24 Kikkenborg et al included 38,709 children (aged 4–14 years) during the pandemic. Across age and case–control groups, the physical scores ranged from 91.2 to 94.7 and the psychosocial scores from 82.4 to 85.8. Conclusions on a more general quality of life in the paediatric population of Denmark should be drawn cautiously due to the apparent connection to the pandemic.

In general, we found the quality of life of our population with CDH better or comparable with data reported from other populations with CDH and with the work done by Varni et al on healthy and chronically ill children. However, unmeasured confounders such as differences in socioeconomically related factors between regions/countries or populations would challenge such a comparison. We believe a comparison with our own background population to be much more relevant. Kikkenborg et al provided the most recent data on a Danish background population and in this context, our population with CDH scored lower on the physical score but similar on the psychosocial score. Of note, the Kikkenborg et al study was directly related to the SARS-CoV-2 pandemic and our study was partly conducted during the same period. Therefore, difficulties during the lockdown periods may reflect in the results.

None of the postnatal parameters often used as surrogate markers of severity showed any association with quality of life. This correlates with data from the study by Sheikh et al, who failed to demonstrate a difference in quality of life when comparing populations with less severe and severe CDH, but contrasts other studies reporting lower quality of life in more severe cases indicated by prenatal diagnosis and hospital length of stay.6 7 17
Other authors have reported an association between quality of life and CDH-related morbidity and clinical issues. We demonstrated the presence of potential CDH-related morbidity in our population with the most common sequela being gastro-oesophageal reflux. Respiratory morbidity was noted as episodes of shortness of breath/need of inhalation medication, and in line with the findings of Darmaun et al, we found an association with lower quality of life. Current treatment for respiratory symptoms and gastro-oesophageal reflux showed no association with lower PedsQL scores, but as successful treatment might mitigate the symptoms, these factors may not affect quality of life scores in a well-medicated cohort.

Need for social/behavioural support throughout childhood was also associated with reduced PedsQL scores. This may represent a possible confounder and we cannot elaborate further on the social/behavioural challenges of our CDH survivors, nor the duration and characteristics of the provided support.

The impact of sex and age on our results poses a potential bias. Previous work on normative values, from different background populations, has described a general decline in quality of life from childhood evolving into adolescence, affecting females more than males. A recent study reporting longitudinal data on CDH survivors showed a decline in PedsQL scores from 8 to 12 years, with a statistically significant difference in the male population, but not in the female population. The authors discuss the risk of ‘growing into deficit’ as an explanation for the decline in PedsQL scores, which may be more apparent for boys due to gender roles and expectations of more physically oriented behaviour. Our study did not indicate a risk of ‘growing into deficit’, as the older age group (13–25 years) reported higher physical scores than the younger age group, but as we did not include longitudinal data or present our data according to sex, we cannot contribute any further on this issue. It is essential to address this concern with more longitudinal studies on quality of life in both the population with CDH and in the background population to enable adjustment for national differences.

Our finding of lower physical scores and comparable psychosocial scores with the results of Kikkenborg et al's study on Danish pediatric populations.

**Table 5** PedsQL scores published on Danish pediatric populations

<table>
<thead>
<tr>
<th>Publication</th>
<th>Population</th>
<th>Total score</th>
<th>Physical score/psychosocial scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idorn et al&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Fontan operation 5–9 years, n=37</td>
<td>NA</td>
<td>75 (63–82) 65 (57–72)</td>
</tr>
<tr>
<td></td>
<td>Control 5–9 years, n=24</td>
<td>NA</td>
<td>98 (94–100) 92 (87–98)</td>
</tr>
<tr>
<td></td>
<td>Fontan operation 10–15 years, n=34</td>
<td>NA</td>
<td>83 (69–92) 80 (66–88)</td>
</tr>
<tr>
<td></td>
<td>Control 10–15 years, n=56</td>
<td>NA</td>
<td>97 (94–100) 92 (87–97)</td>
</tr>
<tr>
<td>Brodsgaard et al&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Overweight, n=95</td>
<td>76.5 (74.2–78.8)</td>
<td>78.0 (75.6–80.3) 75.8 (73.78.5)</td>
</tr>
<tr>
<td></td>
<td>Obese, n=16</td>
<td>71.9 (64.3–79.4)</td>
<td>73.1 (66.8–79.3) 71.3 (62.4–80.1)</td>
</tr>
<tr>
<td></td>
<td>Control n=149</td>
<td>78.6 (77.1–80.2)</td>
<td>79.7 (78.2–81.3) 78.0 (76.2–79.8)</td>
</tr>
<tr>
<td>Mollerup et al&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Overweight, n=317</td>
<td>78.3 (39.1–100)</td>
<td>84.4 (21.9–100) 75.0 (33.3–100)</td>
</tr>
<tr>
<td>Fenger et al&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Overweight with OSA, n=56</td>
<td>67.3 (16.9)</td>
<td>75.0 (62.5–84.4) 65.4 (18.0)</td>
</tr>
<tr>
<td></td>
<td>Overweight, n=74</td>
<td>70.9 (13.7)</td>
<td>79.7 (68.8–87.5) 67.7 (15.3)</td>
</tr>
<tr>
<td></td>
<td>Control, n=28</td>
<td>85.3 (79.1–90.2)</td>
<td>87.5 (84.4–93.8) 85.8 (79.1–90.4)</td>
</tr>
<tr>
<td>Kikkenborg et al&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Symptoms after COVID-19 4–11 years, n=6032</td>
<td>NA</td>
<td>94.7 (11.4) 85.8</td>
</tr>
<tr>
<td></td>
<td>Control 4–11 years, n=18 372</td>
<td>NA</td>
<td>92.9 (11.8) 82.4</td>
</tr>
<tr>
<td></td>
<td>Symptoms after COVID-19 12–14 years, n=3516</td>
<td>NA</td>
<td>93.0 (13.0) 82.7</td>
</tr>
<tr>
<td></td>
<td>Control 12–14 years, n=10 789</td>
<td>NA</td>
<td>91.2 (13.3) 82.7</td>
</tr>
</tbody>
</table>

Reported as median/IQR or mean/SD according to the original paper.
study population raises the question on exercise and physical activities of CDH survivors. An explanation could be that CDH survivors underestimate their physical capacity, which may be supported by protective behaviour of the parents and result in less encouragement to participate in sports and physical activities. Reduced exercise capacity in CDH survivors has been reported by several authors, but also a positive impact of physical activity. Improvements in both exercise capacity and total PedsQL scores were noted after targeted respiratory muscle training in CDH survivors. We recognise that physical training, to obtain a better exercise capacity and improve physical well-being and quality of life, is speculative. However, physical development and benefits of physical activities remain important areas of focus for CDH survivors.

We recognise several limitations of our study. CDH is a rare condition and despite the high rate of participation (68.9% of the study population and 71.8% of the eligible children were included), the cohort is small with a large range in age. Structured follow-up programmes were not available during the study period and we relied on parental recall to identify the presence of CDH-related morbidity using a non-standardised interview. Also, the prenatal screening programme with ultrasound performed in gestational week of 20 was not fully implemented until 2004, which may introduce a selection bias in the older versus younger age group in our study. Observed / expected Lung-to-head ratio (O/E LHR) was not recorded in a structured manner before 2010 and therefore omitted from the stratification of our cohort.

CONCLUSION

Overall, we documented a good quality of life in our cohort of CDH survivors. However, scores in the physical domain were lower than reported in a national Danish cohort. Our data confirmed the presence of CDH-related morbidity in our population, and scores below the cut-off value for ‘at risk of impaired quality of life’ were recognised. We emphasise the importance of early and continuous screening for CDH-related morbidity and assessment of physical development to identify individuals at risk of impaired quality of life. Furthermore, longitudinal studies are needed to characterise the development of quality of life across age and sex in this population.

Acknowledgements We are thankful to Dr Søren Jepsen and Professor Niels Ovist for inspiration and supervision.

Contributors ULL— guarantor author; collection and management of data; work design, analysis and interpretation of data; critical revision and approval of the final manuscript. SAC—management of data, analysis and interpretation of data; critical revision and approval of the final manuscript. TS—work design; analysis and interpretation of data; critical revision and approval of the final manuscript. PT—work design, analysis and interpretation of data; critical revision and approval of the final manuscript. SH—work design, analysis and interpretation of data; critical revision and approval of the final manuscript.

Funding This work was supported by the Child Lung Foundation in Denmark (Børnemelungefonden), Læge Else Poulsens Mindelegat (grant number 53-A2591) and DASAiMs Research initiative fund (Danske Selskab for Anaestesiologi og Intensiv Medicin), as well as through scholarships from the University of Southern Denmark (Sydansk Universitet) and the Research Council of the region of Southern Denmark (grant number 18/17564).

Competing interests None declared.

Patient and public involvement Patients and the public were not directly involved in the planning or design of this study; however, the participants and families were encouraged to express their opinions and needs in regard to follow-up and aftercare of their child’s condition.

Patient consent for publication Parental/guardian consent obtained.

Ethics approval This study involves human participants. Permission to collect historical data from medical journals was granted by the Danish Health and Medicines Authority (jr no: 3-2013-1121/1) and the study was approved by the Southern Region Committees on Health Research Ethics (sags no: S-20170177), the National Ethic Committee (sags no: 221257) and the Danish data protection agency (jr no: 18/2814). All eligible participants were contacted by mail and written informed consent was obtained from participants 18 years or older and from parents of participants younger than 18 years.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplemental information.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD

Ulla Lei Larsen http://orcid.org/0000-0002-6986-2907

REFERENCES


