





RESEARCH ARTICLE

Children with Hirschsprung's disease have high morbidity in the first 5 years of life

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Funding information

Horizon 2020 Framework Programme, Grant/Award Number: 733001

Abstract

Background: Hirschsprung's disease is a rare congenital anomaly of the colon with absence of the ganglionic nerve cells. The treatment of the anomaly is surgical.

Methods: This population-based data-linkage cohort study was part of the EUROLINKCAT project and investigated mortality and morbidity for the first 5 years of life for European children diagnosed with Hirschsprung's disease. Nine population-based registries in five countries from the European surveillance of congenital anomalies network (EUROCAT) participated. Data on children born 1995–2014 and diagnosed with Hirschsprung's disease were linked to hospital databases. All analyses were adjusted for region and length of follow-up, which differed by registry.

Results: The study included 680 children with Hirschsprung's disease. One-year survival was 97.7% (95% CI: 96.4–98.7). Overall, 85% (82–87) had a code for a specified intestinal surgery within the first year increasing to 92% (90–94) before age 5 years. The median age at the first intestinal surgery up to 5 years

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was 28 days (11–46) and the median number of intestinal surgical procedures was 3.5 (3.1–3.9). Thirty days mortality after neonatal surgery (within 28 days after birth) was 0.9% (0.2–2.5) for children with a code for intestinal surgery within the first 28 days after birth and there were no deaths for children with a code for stoma surgery in the neonatal period.

Conclusion: Children with Hirschsprung's disease have a high morbidity in the first 5 years of life requiring more surgical procedures in addition to the initial surgery. Mortality after neonatal surgery is low.

KEYWORDS

EUROlinkCAT, Hirschsprung's disease, morbidity, surgery

1 | INTRODUCTION

Hirschsprung's disease, also known as congenital aganglionic megacolon, is a congenital anomaly in the colon where ganglionic neuroblasts originating from the neural crest fail to migrate into the distal colon (Fu et al., 2004). Hirschsprung's disease affects ~0.01% of livebirths in Europe (Best et al., 2014). The anomaly may affect all of the colon (long-segment disease), but the majority of cases are limited to the rectosigmoid part of the colon (short-segment disease) (Kyrklund et al., 2020). Failure of the enteric nervous system to develop in Hirschsprung's disease leads to a lack of peristalsis and functional bowel obstruction. The symptoms are severe constipation and dilatation of the intestine. Half of children are diagnosed within the first week after birth, with the remaining half being diagnosed between 1 week and 5 years of age (Best et al., 2012). The traditional treatment is staged surgery, with an initial diverting colostomy to allow the dilated proximal bowel to decompress, and then later definitive repair. The newer approach is definitive primary repair in one pull-through procedure. There is no consensus on the surgical management and optimal age at surgery (Allin et al., 2017; Best et al., 2012; Roorda et al., 2022).

The EUROlinkCAT study analyzed morbidity for live-born children with congenital anomalies by linking data from population-based EUROCAT registries of congenital anomalies to hospital databases to obtain information on length of hospital stays and surgical procedures (Morris et al., 2021). We have previously published that the children diagnosed with Hirschsprung's disease had very long hospital stays with a median length of stay in the first year of 31.2 days (95% CI: 25.4–36.9) and 1.7 days per year at age 1–4 years (95% CI: 1.2–2.2). The children had a median number of 3.5 (95% CI: 3.1–3.9) surgical procedures (any type of surgery) within the first 5 years (Garne et al., 2023).

The aims of this study are to report morbidity for children born with Hirschsprung's disease with a focus on stoma and intestinal surgery, mortality after neonatal surgery and to compare the burden of hospitalizations to children without congenital anomalies and to all children with congenital anomalies.

2 | METHODS

This is a European, population-based data-linkage cohort study using routinely collected data from hospital discharge databases. The study includes data from nine registries (national and regional) in five countries (Finland, Denmark, United Kingdom, Italy, and Spain, see Table 1) from the European surveillance of congenital anomalies (EUROCAT) network.

The inclusion criteria were all children born alive between 1995 and 2014 in the geographic areas covered by the EUROCAT registries and diagnosed with Hirschsprung's disease. All children in the study were followed from birth to their 5th birthday or to the end of 2015 whichever came first, thus all children had at least 1 year of follow-up. For comparison of morbidity, we also included data on all children born with major congenital anomalies defined by EUROCAT as “All anomalies” (EUROCAT children). All children without a congenital anomaly from the same birth years and from the same geographical area covered by the registry were included as a reference population (reference children; Morris et al., 2021). The registry in Tuscany used a 10% random sample of their population as reference children.

Data on hospitalizations and surgical procedures were obtained by electronic linkage to the hospital databases used in the regions and countries. Further details of the linkage methods used in the EUROlinkCAT study have been published previously (Loane et al., 2023; Urhoj

TABLE 1 Registries and children included in the study.

EUROCAT registry	Birth years included	Number of children		
		Reference children ^a	EUROCAT children ^b	Number of children with Hirschsprung's disease
Denmark, Funen	1995–2014	100,748	2423	25
Finland	1997–2014	911,679	38,324	251
Italy, Emilia-Romagna	2008–2014	223,995	5381	41
Italy, Tuscany	2005–2014	23,503 ^c	4225	12
Spain, Valencian Region	2010–2014	168,563	4260	40
UK, Wales	1998–2014	531,784	17,448	121
UK, East Midlands & South Yorkshire	2003–2012	Data for reference children not available	11,278	87
UK, Thames Valley	2005–2013		3845	44
UK, Wessex	2004–2014		4320	59
Total		1,960,272	91,504	680

^aAll Children from the registry areas without congenital anomalies.

^bAll children with major congenital anomalies in the EUROCAT registries.

^cRandom sample of 10% of the reference children.

et al., 2022). For six of the nine registries the hospital databases covered hospital stays in the whole country. For Wales, hospital stays in Wales and England were included. For the Valencian Region in Spain and Emilia Romagna in Italy, the hospital databases covered the same region as the EUROCAT registry. Data on hospitalization and surgery for reference children and children with any congenital anomaly were obtained from previous EUROLINKCAT publications (Garne et al., 2023; Urhoj et al., 2022).

Surgical procedures were coded according to the coding systems used in the national health systems. Italy and Spain used ICD-9-CM (the International Classification of Diseases, 9th revision – Clinical Modification) for the study period, England and Wales used OPCS-4 (Classification of Interventions and Procedures), and Finland and Denmark used national adaptations of NCSP (NOMESCO Classification of Surgical Procedures). Three pediatricians from two European countries independently reviewed all the codes from the extensive lists of surgery and procedure codes from the six countries with the three different coding systems and reached consensus on which codes defined surgery. The surgery variables “any surgery,” “intestinal surgery,” and “stoma surgery” were defined in each of the coding systems.

2.1 | Statistical analysis

Registries were unable to share individual case data. Therefore, all the registries applied a common data model to the

linked data, which enabled the same Stata version 13 syntax script to be run by each registry. The aggregate tables and analytic results produced were then collated and meta-analytic techniques applied to obtain European estimates.

Analyses were performed on age groups (<1, 1–4, and 0–4 years) separately. All analyses were adjusted for region of birth and length of follow-up, which differed by registry. All children were followed up for a minimum of 1 year and in the first year of life the proportions of children having surgery out of the total number of live births was calculated for all types of surgery. In some registries not all children were followed up for 5 years and therefore Kaplan–Meier estimates of the proportions of children having surgery over the whole 5 years needed to be estimated within each registry. The overall proportion of children with surgeries was then calculated by combining the Kaplan–Meier registry estimates using the METAN command in Stata with the Freeman–Tukey double-arcsine transformation and the back-transformation based on the inverse-variance of the pooled transformed effects. The median and interquartile range of the number of days spent in hospital, the number of surgical procedures and age at first surgery by anomaly subgroup were reported by each registry. Details for the meta-analytic methods to combine medians across registries can be found in a previous publication (Urhoj et al., 2022).

3 | RESULTS

The analysis included 680 children diagnosed with Hirschsprung's disease and born in 1995–2014 in nine

TABLE 2 Surgical procedures in 680 children with Hirschsprung's disease, based on the codes for surgery in the hospital databases with overall percentages adjusted for registry and length of follow-up.

	Number of children	Adjusted percentage of children (95% CI)	Median age in days at first surgery (95% CI)
Total number of deaths in first year	15	2.3% (1.3–3.6)	
Children with any code for surgery <1 year	582	87% (84–89)	
Children with a code for intestinal surgery <1 year	570	85% (82–87)	24 days (95% CI: 9–40)
Children with a code for intestinal surgery up to 5 years	613	92% (90–94)	28 days (95% CI: 11–46)
Children with a code for intestinal surgery <28 days	345	50% (47–54)	
Children with a code for stoma surgery <28 days	123	17% (15–20)	

Note: Nine EUROCAT registries, birth years 1995–2014.

regions across Western Europe (Table 2). There were 15 deaths in the first year giving an overall registry adjusted 1-year survival of 97.7% (95% CI: 96.4–98.7).

Of the 680 children, we found that 582 (adjusted percentage: 87% [95% CI: 84–89]) had a procedure code for any surgery in the hospital databases in the first year of life and of these 570 children (adjusted percentage 85% [95% CI: 82–87]) had a code for a specified intestinal surgery. The adjusted median age at the first intestinal surgery in the first year of life was 24 days (95% CI: 9–40). Within the first 5 years of age 613 children had a code for an intestinal surgery (adjusted percentage 92% [95% CI: 90–94]). The adjusted median number of intestinal surgical procedures before age 5 years for the children with at least one surgical procedure was 3.5 (95% CI: 3.1–3.9). For children in Finland only 201 out of 251 children (81%) had a code for any surgery within the first year and thus accounting for the majority of children without codes for surgery in the hospital databases.

Mortality after neonatal surgery (within 28 days after birth) was analyzed after intestinal surgery and stoma surgery. There were 345 children (adjusted percentage 50%, [95% CI: 47–54]) with a code for intestinal surgery within the first 28 days after birth and 342 were alive 30 days after the surgery, corresponding to a 30-day post-operative mortality of 0.9% (95% CI: 0.2%–2.5%). Of the total 680 children, 123 (adjusted percentage 17%, [95% CI: 15–20]) had a specific code for stoma surgery within the first 28 days after birth and they were all alive 30 days after the surgery.

Morbidity in the first year of life and 1–4 years of age for children with Hirschsprung's disease is compared with children with any congenital anomaly and to children without congenital anomalies in Figure 1. The

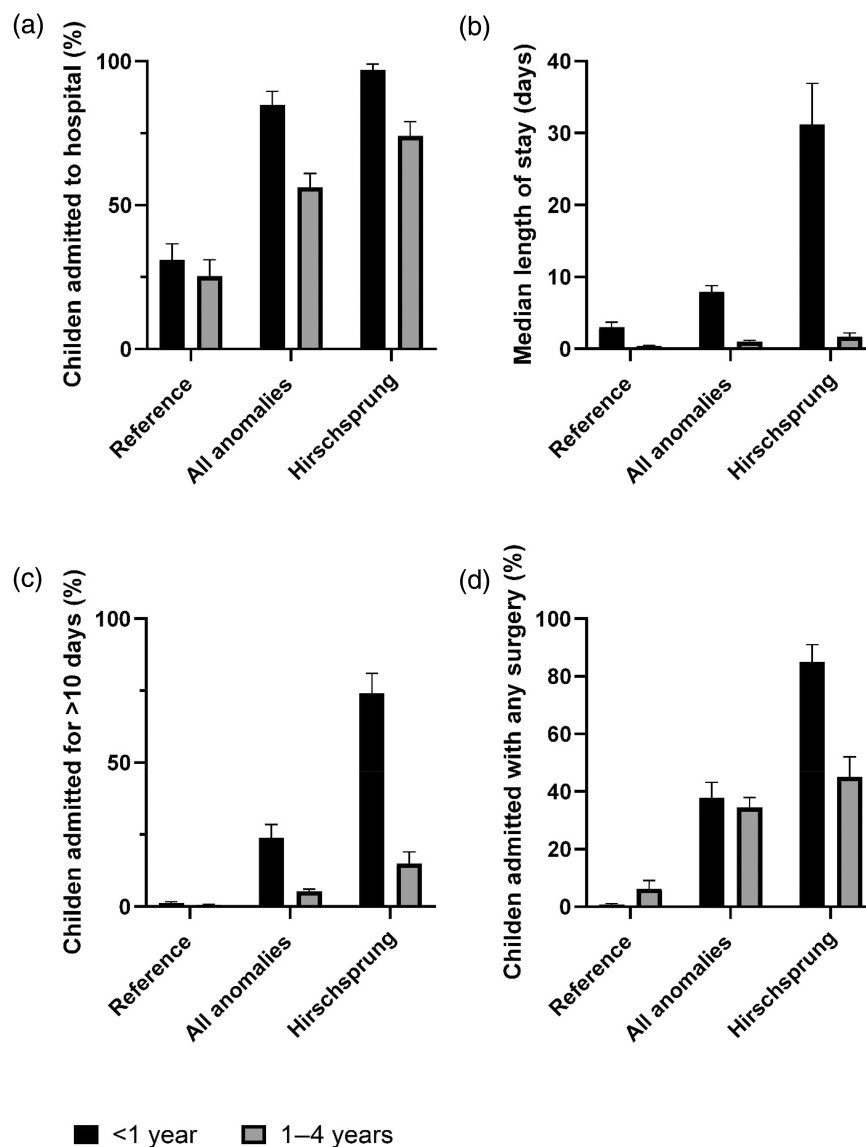
morbidity is measured as proportion hospitalized, proportion of term born children with at least one hospital stay of more than 10 days, median length of stay for all children and proportion having any surgery. For all four variables, morbidity is considerably higher for children with Hirschsprung's disease than for the children in the two other groups.

4 | DISCUSSION

Our results showed that most children born with Hirschsprung's disease were alive at age 1 year, although survival is lower than among the background population of children in the EU (EUROSTAT, 2021). In the original report by Harald Hirschsprung in 1888, in which he described a case series of infants with severe congenital bowel obstruction and megacolon, all the children died (Hirschsprung, 1888). A population-based study from Northern England including children with Hirschsprung's disease born in 1990–2008 found a higher mortality in the first year at 9% compared with the 2.3% in this study (Best et al., 2012). A EUROlinkCAT study including 13 registries showed a 1-year mortality of 2.9% (including the nine registries in this study) and a 5-year mortality of 3.4% (Coi et al., 2022). Although the children with Hirschsprung's disease had a high number of intestinal surgical procedures, undergoing a median of 3.5 intestinal surgical procedures in the first 5 years of life, 30 days mortality after neonatal surgery was low.

Our study included all children diagnosed with Hirschsprung's disease in the registry areas including those with genetic and chromosomal diagnoses and those with associated major congenital anomalies. Therefore,

FIGURE 1 The burden of hospitalizations in children with Hirschsprung's disease compared with all children with congenital anomalies (All anomalies) and to children without congenital anomalies (Reference). The data, covering nine population-based registries in five countries from 1995 to 2014, illustrates the percentage of children admitted to the hospital (a), the median length of hospital stay in days (b), the percentage of children with a hospital admission extending beyond 10 days (c), and the percentage of children undergoing any surgery (d).



some children may have died before the intestinal surgery for Hirschsprung, and a few may have received palliative care only. In a population-based epidemiological study from EUROCAT with data from 31 registries for the birth years 1980–2009 it was found that 283 of 1322 children (21%) with Hirschsprung's disease had associated genetic, chromosomal, and/or major congenital anomalies (Best et al., 2014).

As Hirschsprung's disease is very rare and there are several types of surgery for the anomaly, evidence-based treatment is difficult to obtain, and consensus-based guidelines are needed (Kyrklund et al., 2020). We were not able to compare the outcome of different surgical methods as this information was not available in the hospital procedure codes. For those having surgery in the neonatal period, 36% (95% CI: 31–41) had a code for stoma surgery. This is a minimum estimate as some children may have had a non-specific code for intestinal

surgery in the hospital databases. Our study also documented the need for surgical treatment early in life for children born with Hirschsprung's disease. Half of the children underwent anesthesia and surgery in the neonatal period which carries significantly higher risks for complications than later in life (Kuan & Shaw, 2020).

In terms of long-term outcomes, quality of life for children with Hirschsprung's disease may be affected by fecal incontinence and the presence of a permanent stoma (Allin et al., 2017; Oltean et al., 2022). Core outcome sets are groups of standardized outcomes that have been identified by key stakeholders as being the most important in determining the success of an intervention or treatment for a disease. Ten core outcomes have been agreed for Hirschsprung's disease (Allin et al., 2017). Most of them require questionnaires and/or access to text in medical records, but three of them may be answered using public databases including hospital discharge

databases: death with a cause specified, unplanned reoperation with indication specified, and need for a permanent stoma with indication specified. However, as some children had unspecified codes for the surgical procedures during our study period 1995–2014, it will take some time before the evidence for treatment methods of Hirschsprung's disease can be found through these discharge databases.

Parents of children with Hirschsprung's disease may also worry about other long-term outcomes besides those related to the intestine, as studies have shown an association between exposure to anesthesia and surgery in young children and later academic performance (Glatz et al., 2017; Rosenblatt et al., 2019). A systematic review of the developmental outcomes of children with gastrointestinal anomalies including children with Hirschsprung's disease found that these children had impaired developmental outcomes with minor cognitive impairments and more serious motor and language impairments (Roorda et al., 2021). These impairments were found to be associated with the length of hospital stays and number of surgical procedures. Prenatal diagnosis of Hirschsprung's disease is difficult as most fetuses have no visible abnormalities (Jakobson-Setton et al., 2015). Therefore, parents will only be informed about the diagnosis after the birth of their child and cannot be prepared for the expected long hospital stays. The long hospital stays in the first year for these children have an impact on family life and siblings (Toledano-Toledano & Luna, 2020). Families should therefore be supported by both health care professionals and social care professionals.

The main strength of our study is the population-based cohort of children from five European countries registering all children born with Hirschsprung's disease and the standardized case classification and registration of the congenital anomalies in the EUROCAT registries. Another strength of the study is, as part of the EUROlinkCAT study, the creation of standardized hospital data and syntax scripts, enabling a common data model and the possibility of combining analytical results. The linkage success to the hospital databases was very high (97.5% of the EUROCAT children, Urhoj et al., 2022). However, during the data cleaning for this study, it was found that seven children from one registry had to be excluded as they did not have a final diagnosis of Hirschsprung's disease. This indicates that follow-up after the first year of life is needed for the complete and correct registration of this congenital anomaly. Using codes for surgery from hospital databases instead of reviewing text descriptions of the surgical procedures is another limitation for this study. Another limitation of the study is that we were not able to analyze outcomes separately by registry and by presence of

associated anomalies due to the use of aggregate data in combination with small numbers of each outcome in most of the participating registries.

5 | CONCLUSION

This extensive population-based study, encompassing data from nine EUROCAT registries across five European countries, has provided valuable insights into the morbidity and mortality associated with Hirschsprung's disease in the first 5 years of life. Our findings underscore the high morbidity burden in children with Hirschsprung's disease, as evidenced by the significant number of surgical interventions required within this period. The majority of these children underwent their first intestinal surgery within the first month of life, with a median of 3.5 surgical procedures by the age of 5. This high frequency of surgical interventions highlights the complex and ongoing medical needs of these children, pointing to the necessity for specialized and continuous pediatric care.

FUNDING INFORMATION

This study has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 733001.

CONFLICT OF INTEREST STATEMENT

The authors have no relevant financial or non-financial interests to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the participating registries of congenital anomalies, but restrictions apply to the availability of these data, which were used under license for the current study. These data are available for scientifically valid requests and with permission of the participating registries of congenital anomalies. To apply for the data please contact the corresponding author.

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How to cite this article: Damkjær, M., Tan, J., Morris, J. K., Loane, M., Given, J., Caverro-Carbonell, C., Gissler, M., Neville, A. J., Pierini, A., Rissmann, A., Tucker, D., & Garne, E. (2024). Children with Hirschsprung's disease have high morbidity in the first 5 years of life. *Birth Defects Research*, 116(5), e2338. <https://doi.org/10.1002/bdr2.2338>