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2021-09

Davidson , J R , Kyrklund , K , Eaton , S , Pakarinen , M P , Thompson , D S , Cross , K , Blackburn , S C , De Coppi , P & Curry , J 2021 , ' Long-term surgical and patient-reported outcomes of Hirschsprung Disease ' , Journal of Pediatric Surgery , vol. 56 , no. 9 , pp. 1502-1511 . <https://doi.org/10.1016/j.jpedsurg.2021.01.043>

<http://hdl.handle.net/10138/341427>

<https://doi.org/10.1016/j.jpedsurg.2021.01.043>

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Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jped surg.org

Long-term surgical and patient-reported outcomes of Hirschsprung's Disease

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ARTICLE INFO

Article history:

Received 13 November 2020

Revised 7 January 2021

Accepted 26 January 2021

Available online xxx

Keywords:

Hirschsprung's

Duhamel

Long-term outcomes

Quality of life

Bowel function

ABSTRACT

Background: Information is needed regarding the complex relationships between long-term functional outcomes and health-related quality of life (HRQoL) in Hirschsprung's Disease (HSCR). We describe long-term outcomes across multiple domains, completing a core outcome set through to adulthood.

Methods: HSCR patients operated at a single center over a 35-year period (1978–2013) were studied. Patients completed detailed questionnaires on bowel and urologic function, and HRQoL. Patients with learning disability (LD) were excluded. Outcomes were compared to normative data. Data are reported as median [IQR] or mean (SD).

Results: 186 patients (median age 28 [18–32] years; 135 males) completed surveys. Bowel function was reduced (BFS 17 [14–19] vs. 19 [19–20], $p < 0.0001$; $\eta^2 = 0.22$). Prevalence and severity of fecal soiling and fecal awareness improved with age ($p < 0.05$ for both). Urinary incontinence was more frequent than controls, most of all in 13–26y females (65% vs. 31%, $p = 0.003$). In adults, this correlated independently with constipation symptoms (OR 3.18 [1.4–7.5], $p = 0.008$). HRQoL outcomes strongly correlated with functional outcome: 42% of children demonstrated clinically significant reductions in overall PedsQL score, and poor bowel outcome was strongly associated with impaired QOL ($B = 22.7$ [12.7–32.7], $p < 0.001$). In adults, GIQLI scores were more often impacted in patients with extended segment disease. SF-36 scores were reduced relative to population level data in most domains, with large effect sizes noted for females in General Health ($g = 1.19$) and Social Wellbeing ($g = 0.8$).

Conclusion: Functional impairment is common after pull-through, but bowel function improves with age. Clustering of poor functional outcomes across multiple domains identifies a need for early recognition and long-term support for these patients.

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1. Introduction

Hirschsprung's Disease (HSCR) is a neurocristopathy, characterized by the absence of ganglion cells along a continuous segment of distal bowel, leading to functional intestinal obstruction. Despite reconstructive surgery, disturbances in bowel function, including Hirschsprung's-associated enterocolitis (HAEC), may prevail to varying degrees long-term.

Most published studies have focused on surgical outcomes, bowel function and, more recently, health-related quality of life

(HRQoL), with similar functional outcomes reported between standardized surgical approaches such as the Duhamel and endorectal (ERPT) pull-through procedures [1,2]. Significant evidence gaps remain, however, in important long-term interaction between functional outcomes and quality of life [3]. This study aimed to describe detailed long-term operative and patient-reported outcomes for bowel and urologic function and HRQoL with comparison to previously published normative data, and included all domains of the recently developed core outcome set for HSCR [4].

Type of Study: Cross-sectional Study

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<https://doi.org/10.1016/j.jpedsurg.2021.01.043>

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Please cite this article as: J.R. Davidson, K. Kyrklund, S. Eaton et al., Long-term surgical and patient-reported outcomes of Hirschsprung's Disease, Journal of Pediatric Surgery, <https://doi.org/10.1016/j.jpedsurg.2021.01.043>

2. Methods

2.1. Ethical approval

Approval was obtained from the National Health Service Research and Ethics Committee (17/LO/1692).

2.2. Patients and data collection

All patients with histologically confirmed HSCR commencing treatment at Great Ormond Street Hospital (GOSH) between 1978 and 2013 were identified. Patients referred for redo surgery after primary pull-through in other hospitals were also invited to complete the outcomes survey. Clinical data were retrieved retrospectively. Post-operative complications were classified according to Clavien-Dindo [5], any complication requiring operative intervention (Grade 3b and above) were recorded as they could be reliably retrieved from the retrospective review of records, however we excluded simple examination under anesthesia from these "operative" complications as these were often performed routinely. Disease level was classified as rectosigmoid or extended segment, which in turn was analysed as long (extending past rectosigmoid) and TCA (total colonic aganglionosis +/- extension into small bowel; grouped here as TCA). Patients with documented learning disability (LD) were considered separately, excluded from this analysis and will be reported elsewhere.

2.2.1. Exclusion criteria

Patients who were living abroad, those who had died, and those unable to complete an English language questionnaire were excluded (Fig. 1). It was felt inappropriate to contact 4 patients who were in difficult personal circumstances.

2.3. Outcomes survey

All living, UK resident patients were contacted to take part in a cross-sectional outcomes survey. Recruitment was based on the STROBE (Strengthening The Reporting of OBservational studies in Epidemiology) statement [6]. The lead investigator was not involved in the clinical care of patients. Written consent was obtained from all patients, with patients under the age of 18 requiring a parent or guardian to consent to enter the study. Patients <16 years of age were assisted in responses by a proxy where necessary.

2.3.1. Assessment of functional outcomes

2.3.1.1. Bowel function. Bowel Function was assessed using the Rintala Bowel Function Score (BFS, 7-items, max. score 20) [7]. This instrument assesses fecal awareness and control along with stooling frequency, soiling, incontinence, constipation and social impact and has been used in multiple studies assessing patients with HSCR [8–10]. Patients with an end stoma or antegrade continence enema (ACE) conduit were not assessed with the instrument. A normal outcome was defined as BFS ≥ 17 , and a poor outcome a BFS < 12 or requiring stoma/ACE [11].

2.3.1.2. Hirschsprung-associated enterocolitis (HAEC). Episodes of HAEC are difficult to define in a retrospective study, but were defined as per previous retrospective and outcome reporting studies [11,12]. Clinician-reported episodes were documented from records based on intention to treat. Patient-reported episodes were defined as "bowel inflammation related to Hirschsprung's requiring antibiotics." Recurrent HAEC was defined for the purposes of this study as ≥ 4 episodes within a 12-month period.

2.3.1.3. Lower Urinary Tract Symptoms (LUTS). LUTS were assessed using an 8-item questionnaire adapted from the Danish Prostatic Score [13], previously used in assessing HSCR patients. Given observed differences in symptom profile in adolescent and adult females [14], patients were grouped by age: 4–12 years, 13–26y and $\geq 27y$ and males and females $\geq 13y$ were analysed separately.

2.3.2. Assessment of Quality of Life (QoL)

pediatric quality of life was assessed with PedsQLv4.0, which assesses physical, emotional, social and schooling domains [15]. This was administered to participants <18 years. Participants ≥ 18 years of age completed the GI-symptoms specific Gastrointestinal Quality of Life Index (GIQLI) [16] and Short Form 36 (SF-36) survey, a more general quality of life assessment [17].

2.3.3. Controls and comparative data

BFS and LUTS questionnaire responses were compared to published normative data from the Finnish population using the same instruments [14,18]. Control data for LUTS did not extend to age >26 years, and as such we opted to use this as a cut-off to divide our adult cohort into older and younger groups for the purposes of assessment of functional outcome. PedsQL data were analysed using cut-offs for impairment derived from the KidCare evaluation ($n = 1745$) [19]. GIQLI outcomes were compared to pooled control data from published studies [12,20,21], a score of 105/144 defined significant impairment [16]. SF-36 data were reported relative to age and gender specific data from the United Kingdom general population ($n = 13,042$) [22]. No clinical cut-offs for the SF-36 have been defined; therefore comparison of study population to summary data was performed with scores more than 2 standard deviations (≤ -2 s.d.) below the population mean defined as significantly impaired; use of population level data as a comparator is established as an alternative to matched samples in observational studies [23].

2.4. Statistical analysis

Statistical analyses were performed using Prism 8.0 (GraphPad), SPSS 26.0 (IBM), and R (v3.6.2). Data are presented as median [IQR] or mean (SD). Distributions were compared with appropriate parametric and non-parametric tests, with correction for multiple comparisons where necessary. For analysis of bowel function domains, ordinal regression was performed to examine the association of age (as a continuous co-variate) and HSCR/control status and outcomes; these data were displayed graphically using the age brackets ≤ 12 years; 13–26 years; ≥ 27 years. Categorical data were compared using Fisher's Exact test or Chi-square for trend. $p < 0.05$ was considered statistically significant and reported to 3 significant figures. Effect sizes were calculated for outcomes: Odds Ratio (OR [95% CI]) for categorical and regression analyses. Parametric tests were accompanied with Hedge's g , using cut-offs: insignificant < 0.2 small < 0.5 moderate < 0.8 large, and non-parametric with eta-squared (η^2), cut offs: insignificant < 0.01 small < 0.06 moderate ≤ 0.14 large). Due to recognised differences in functional outcomes during childhood, in both patient and control populations [14,18], logistic regression was employed to demonstrate significant associations with bowel and urologic outcomes in adults only.

3. Results

3.1. Cohort characteristics: 35-year experience

Of 401 primary referrals, 379 (95%) underwent pull-through surgery, 320 (84%) with Duhamel approach (previously described

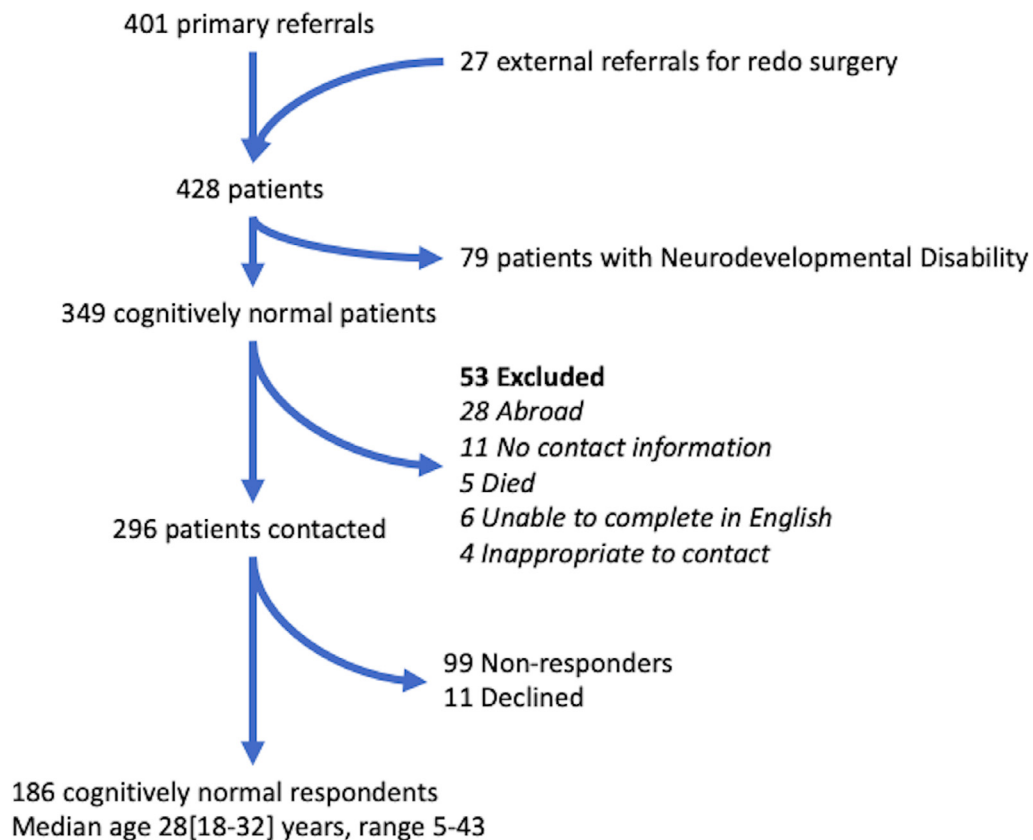


Fig. 1A. Study Inclusion Flowchart.

	Respondents (n=186)	Non-Respondents (n=110)	p-value
Age, years (median [IQR])	28 [18-32]	24 [17-31]	0.14
Gender (female: n, %)	51 (27)	14 (13)	0.003
Rectosigmoid (n, %)	141 (76)	83 (75)	1
Family History (n, %)	29 (16)	13 (12)	0.40
Duhamel PT (n, %)	154 (83)	90 (82)	0.87
Redo Surgery (n, %)	27 (15)	20 (18)	0.41

Figure 1B. Dropout Analysis.

by our center, [24]). A definitive stoma was performed in 18 patients (5%) due to associated anomalies or extent of aganglionosis. There was no surgical mortality. Overall survival during follow-up was 99% among non-syndromic patients and 82% among patients with a syndromic association or major concomitant anomaly (OR 16.3 [5.4–49.5], $p < 0.0001$). Four patients without syndrome died: 2 prior to pull-through surgery due to HAEC, both at 2 months of age, one patient with short bowel due to extensive aganglionosis died aged 7 years, and one of unknown causes aged 21 years. A further patient with no cognitive impairment died from complications of cystic fibrosis aged 24 years. None of the 17 deaths in syndromic patients were related to HSCR. Redo pull-through was performed 59 patients; this included 25 external referrals alongside 34 who had undergone primary pull-through at GOSH. Four patients of these and two further external referrals underwent a second redo procedure, totalling 65 redo procedures in the study period (60 using a Duhamel technique). Most prominent indications for redo surgery included transitional zone pull-through in 27(44%), and recalcitrant anastomotic stricture/spur in 12 (20%).

3.2. Outcomes survey

There were 186 cognitively normal respondents of 296 eligible patients (63% response rate, Inclusion Flowchart and drop out analysis: Fig. 1A+1B). Response rates varied by age in children, with higher response rate in children aged ≤ 12 y than those aged 13–18y; 32/46(70%) vs. 15/34(44%), $p = 0.04$. Overall there was a significantly higher response rate among females than males ($p = 0.003$), which was manifest exclusively in adult patients (41/51 (80%) adult women vs 91/165 (59%) adult men, $p = 0.007$). Otherwise participants were similar to non-respondents in terms of disease characteristics, operative management and need for redo surgery.

The clinical outcomes for the cohort are summarised in Table 1, but it is important to note inherent selection bias in that 7 patients referred in for redo surgery will all by definition have post-operative complications included. Bowel obstruction occurred less frequently in patients who had undergone single stage pull-through surgery: 4/56(7%) vs. 29/130(22%), OR 0.27 [0.1–0.8], $p = 0.02$.

Table 1

Patient demographics, disease characteristics and post-operative complications in the 186 respondents. Data provided are median and range unless specified.

Demographics and Disease Characteristics	
Total, n	186
Male / Female	135 / 51 (2.6:1)
Age at follow-up	28 [5–43]
Gestation, completed weeks	40 [27–42]
Birthweight, grams	3295 g [920–4800]
Family history of HSCR, n(%)	29 (16)
Level of disease, n(%)	
Rectosigmoid	141 (76)
Long segment	25 (13)
Total colonic	20 (11)
includes TCA + extending >10 cm into small bowel	4
Operative Management, n (%)	
Reconstruction	184 (99)
Single stage procedure	56 (30)
Age at pull-through, days	176 [7–3822]
Duhamel	154 (84)
Minimally Invasive Approach	17 (11)
Swenson	19 (10)
Minimally Invasive Approach	0 (0)
Soave	11 (6)
Minimally Invasive Approach	1 (9)
Definitive end stoma	2 (1)
Post-operative complications, n(%)	
Clavien-Dindo grade ≥ 3 ^{b,§}	75 (40)
Early	
Anastomotic leak	13 (7)
Intussusception (ileo-ileal)	1 (0.5)
Late	
Stricture	9 (5)
Duhamel Spur (requiring division)	18/154 (12)
Post-operative HAEC (patient-reported)	37 (20)
Bowel Obstruction (requiring emergency surgery)*	33 (18)
Redo pull-through §	27 (15)

* Cumulative incidence; § overall incidence, includes 7 external referrals.

3.2.1. Functional outcomes

3.2.1.4. Bowel function. At the time of study, among the 186 respondents, 1(0.5%) used an ACE and 7(5%) had a stoma. Five adult patients had previously used an ACE but had discontinued its use in adulthood. The median age at pull-through in those treated primarily at our center was 176 days. The age at pull-through was younger in patients treated in the more modern era (prior to 1990 vs. 1990–1999 vs. post 2000; 261 vs. 130 vs. 146 days, $p < 0.001$). We saw no relationship between age at pull-through and ultimate need for redo surgery ($p = 0.85$) or ultimate requirement for stoma ($p = 0.89$). In this data, there was no correlation between overall BFS and age at pull-through, $r^2 = 0.014$; $p = 0.12$.

Patients without ACE or stoma were compared to control data for BFS using ordinal regression (data are portrayed, grouped by age in Fig. 2). Compared to controls [18], HSCR patients had inferior overall BFS (17 [14–19] vs. 19 [19–20], $p < 0.0001$; $\eta^2 = 0.22$), while scores for all subdomains were also inferior ($p < 0.0005$ for all; Fig. 2). Among patients, fecal awareness ($p = 0.01$) and fecal soiling ($p = 0.048$) both improved with age; there were no statistically significant effects regarding the ability to hold back stool ($p = 0.68$); frequency of fecal accidents ($p = 0.941$) which both appear to improve with age or social impact of bowel function ($p = 0.244$) which appeared to become worse.

By BFS, 97 patients (52%) had a good outcome (BFS ≥ 17), 67 (36%) moderate (BFS 12–16), and 22(12%) a poor functional outcome (BFS < 12 or patients with ACE/stoma). Constipation was reported by 68 patients (38%). No patient reported using rectal enemas for management of constipation management was either with medication or dietary modification. Patients managing with medication ($n = 23$) were younger than those managing with dietary modification alone ($n = 45$); age 20 [12–26]y vs. 27 [22–36.5]y,

$p = 0.003$. The median bowel movement frequency was twice per day; abnormally frequent bowel movements (3–8/day) were present in 65 patients (37%), this included 5 patients taking medication for constipation and 15 on dietary modification. Seven patients (4%) reported bowel movements less often than every other day.

3.2.1.5. Impact of segment length and redo surgery. Patients with extended segment ($n = 45$) were compared to those with rectosigmoid disease ($n = 141$). BFS was lower overall in extended segment (16 [13.5–18] vs. 17 [15–19], $p = 0.036$; $\eta^2 = 0.02$), with increased stooling frequency (more than twice daily) in 27(65%) vs. 38(28%); OR 5 [2.4–10.6], $p < 0.0001$. There was higher prevalence of stoma in the extended segment group (4/45(8.9%) vs. 4/141(2.1%), $p = 0.09$) and need for redo pull-through was also higher (8/45(18%) vs 19/141(13%), $p = 0.6$).

Twenty seven respondents (15%) had undergone redo surgery, including 7 referred for redo surgery from external centres. Two of the patients who had undergone redo surgery had a stoma (7.4%). The overall BFS score was 16 [14–17] (vs. (17 [14–19], $p = 0.06$). Stooling frequency >2/day was more common (16/25 [64%] vs. 49/153 [32%], OR 3.8 [1.6–9.1], $p = 0.003$) and social restrictions were more prevalent (23 [92%] vs 82(54%), OR 10 [2.3–43.7], $p = 0.0002$).

3.2.1.6. Hirschsprung's associated enterocolitis. Patient and clinician reported incidences of HAEC were comparable, 37(20%) and 32(17%) respectively. HAEC in the preceding year occurred in 6(3.2%) patients, and 13(7%) patients reported previous recurrent HAEC. On univariate analysis, extended segment disease was associated with both recurrent HAEC (18% vs. 3.5%, OR 5.9 [1.8–19.0], $p = 0.003$) and HAEC within the past year (11% vs. 0.7%, OR 17.5 [2.0–154] $p = 0.003$). This remained significant on multivariate analysis for recurrent HAEC (OR 5.7 [1.7–19], $p = 0.005$). HAEC within the past year was associated with both extended segment (OR 25.7 [2.4–277], $p = 0.007$) and Age ≤ 12 y (OR 12.4 [1.7–89], $p = 0.01$) on multivariate analysis.

3.2.1.7. Predictors of bowel functional outcome in adults. Given the observed symptom improvements through childhood, multivariate analysis was performed to assess predictors of good outcome (BFS ≥ 17) and poor outcome (BFS < 12 or stoma/ACE) in adults only ($n = 139$).

Poor outcome was independently associated with a history of emergency abdominal surgery (OR 3.5 [1.0–12.5], $p = 0.05$), but not with age, sex, redo surgery, segment length or patient-reported HAEC. Good outcome was independently, inversely associated with patient reported HAEC (OR 4.7 [1.4–16.0], $p = 0.013$) but not with patient sex, age, redo surgery, segment length or a history of emergency surgery.

3.2.2. Lower Urinary Tract Symptoms (LUTS)

185/186 (99.5%) cognitively normal patients (median age 26 [18–32] years) returned questionnaires on LUTS and were compared to normative data up to 26 years: 4–12y (31 patients vs. 292 controls) and 13–26y (62 patients vs. 302 controls). There were no controls to compare patients >27 years.

Significant LUTS (weekly/daily) were more common in HSCR patients in childhood (4–12y: 7 [23%] vs. 12 [4.1%], OR 6.8 [2.5–18.9], $p = 0.0008$) and also in adolescents and adults (13–26y: 12(18%) vs. 11(3.6%) OR 5.9 [2.5–14], $p = 0.0001$). Urinary frequency (>8 times daily) was reported in 21 patients (11%), most commonly in female patients ≥ 27 years (8/26 (31%)). Urinary incontinence was more frequently reported in patients of both sexes 13–26 years ($p < 0.02$). Nocturnal enuresis was reported infrequently, no difference between patients and controls (4/185(2.2%)

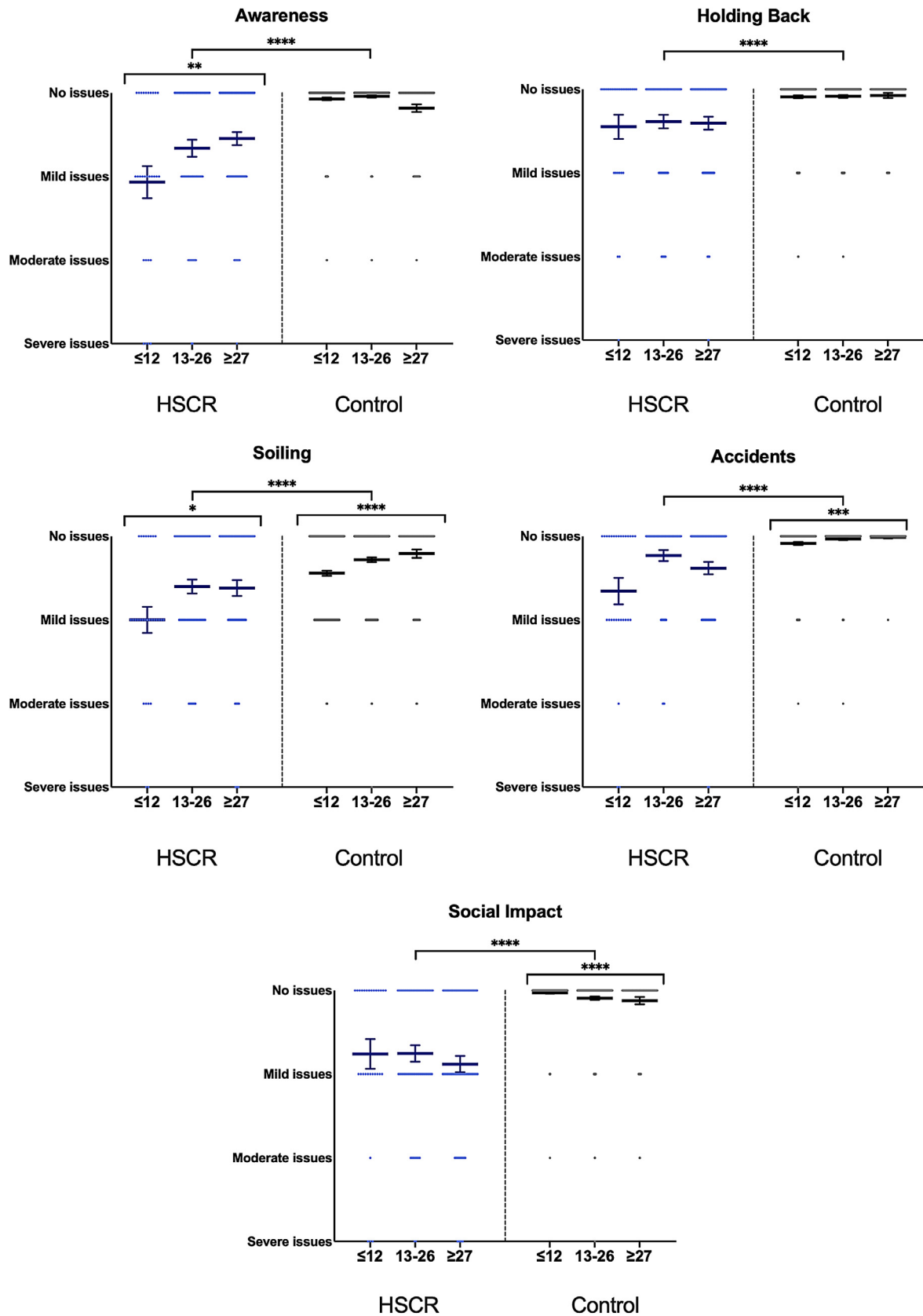


Fig. 2. Individual items from BFS across age groups and with comparison to control data [11,18]. Age grouping, depicted mean + Standard Error of the Mean are depicted for illustrative purposes; analysis performed with ordinal regression.
 * $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$, **** $p < 0.0005$.

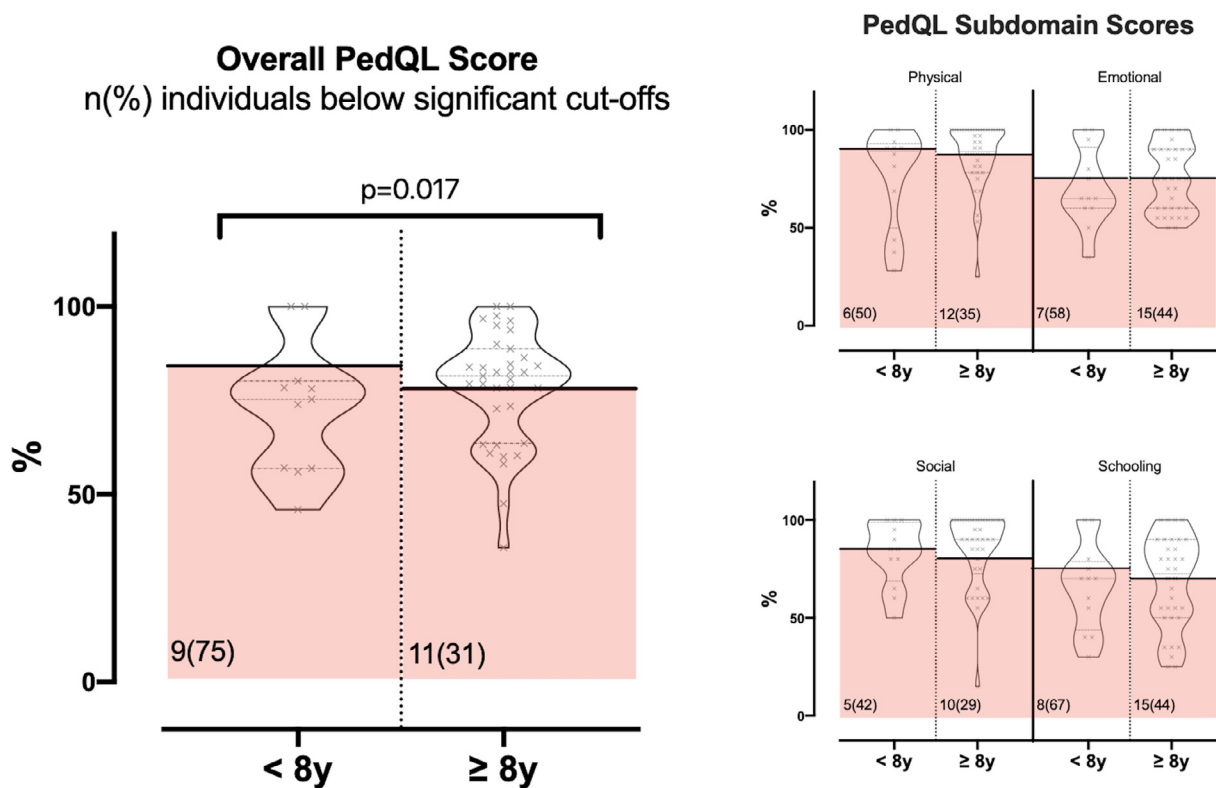


Fig. 3. PedsQL Total Scores for cognitively normal children ($n = 46$) with clinically significant cut-offs for significant impairment $<8y$ and $\geq 8y$ [19], comparison of proportion with impaired score between $<8y$ and $\geq 8y$ ($p = NS$ unless stated). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

vs. 12/594(2%), $p = 1.0$). Overall, 5 patients (2.7%) declared social problems related to urinary incontinence.

Multivariate regression identified that symptoms of urinary incontinence in adults (at any frequency) were significantly associated with female sex (OR 7.05 [2.8–17.5], $p < 0.001$) and presence of constipation (OR 3.18 [1.4–7.5], $p = 0.008$). There was no independent association with age, extended segment disease, history of emergency abdominal surgery or redo pull-through.

3.2.3. Quality of life outcomes

3.2.3.1. PedsQL. Child-reported scores correlated with proxy-reported scores in all domains ($R^2 = 0.6-0.8$, $p < 0.0001$ for all). Cognitively normal children ($n = 46$) were analysed with defined cut-offs for significant impairment for children $<8y$ and children $\geq 8y$ of age [19] (Fig. 3). Impaired overall scores were noted in 20/46 children (42%), more so in younger children ($<8y$ vs. $\geq 8y$; 9/12 (75%) vs. 11/34 (31%), $p = 0.017$). All subdomains were affected. Overall scores were lower in the 9 children with poor bowel outcome (defined as a binary outcome, 56 [36–84] vs. 91 [83–100], $p < 0.001$; $\eta^2 = 0.25$). On multivariate linear regression analysis, poor bowel outcome was an independent predictor of a lower overall score ($B = 22.7$ [12.7–32.7], $p < 0.001$). Age, sex and segment length were not significant predictors.

3.2.3.2. Gastrointestinal Quality of Life (GIQLI). GIQLI was completed by all 139 cognitively normal adults and compared to a pooled control population [12,20,21], overall scores were reduced (123.4(14.6) vs. 113.7(23.4), $g = 0.5$, $p < 0.00,001$) with all subdomains affected ($g = 0.28-0.50$, $p < 0.005$ for all). An ‘impaired’ GIQLI score (<105) was found in 25% (35/139) and as shown in Fig. 4A, the proportion of patients increased with longer segment disease. Scores in all subdomains were reduced in long segment and total colonic disease, with largest differences observed

in GI symptoms ($g = 0.58$, $p = 0.002$, Fig. 4B) and Physical QOL ($g = 0.67$, $p = 0.0004$, Fig. 4C).

On multivariate analysis, extended segment ($B = 8.52$ [3.48–13.55], $p < 0.001$) remained independently associated with lower overall GIQLI scores; female sex was also associated with lower scores ($B = 13.25$ [5.6–20.9], $p < 0.001$).

3.2.3.3. SF-36. Cognitively normal patients ($n = 139$, 100%) were compared to gender specific scores for the UK population. Differences from population mean were observed in all domains except physical function (Fig. 5). Female patients reported lower scores than males across all domains of SF-36 and effect sizes of comparison to normative data were also larger for all domains. Multivariate analysis demonstrated lower emotional wellbeing scores in patients with poor bowel function ($B = 26.2$ [16–40], $p < 0.001$). Lower social wellbeing scores were observed in patients with poor bowel function ($B = 34$ [20–49], $p < 0.001$) and urinary incontinence symptoms ($B = 11$ [1.0–20], $p = 0.03$).

4. Discussion

Here we describe a detailed complete core outcome set through to adulthood in HSCR patients. Our results suggest that outcomes for bowel function are similar to the normal population in over half of cases, with a low requirement for long-term bowel management with ACE or enterostomy in cognitively normal patients. The differences we observe across our data compared to controls are not only statistically significant, but large effect sizes derived from the statistical analysis performed would suggest that these translate to clinically meaningful differences of importance to patients.

We observed better functional outcomes in adult patients compared to the children within our cohort, as suggested by studies

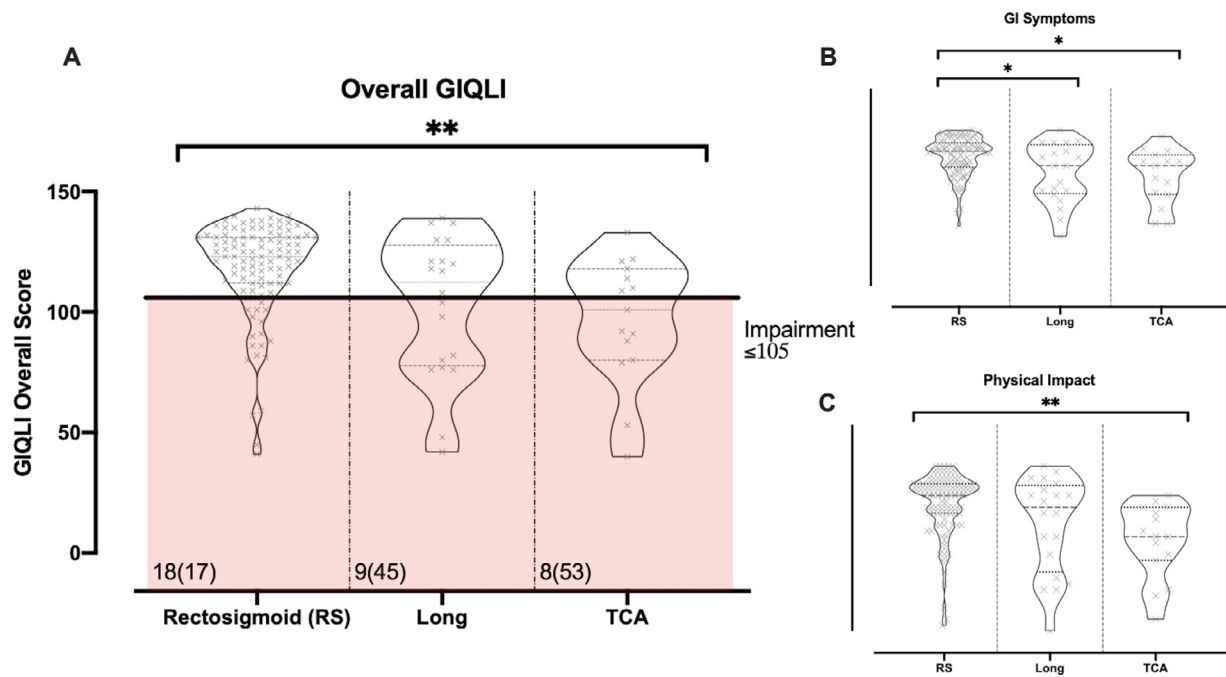


Fig. 4. A: GIQLI Overall scores by segment length with proportion of impaired scores displayed as n(%). B GI Symptoms by segment. C Physical Impact on QOL. Kruskal-Wallis for all: $p < 0.005$. Pairwise comparison and adjusted p -values labelled * $p < 0.05$, ** $p < 0.01$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

that have shown better bowel functional outcome and/or quality of life with age in HSCR, [2,9,12,25–27], although none of these papers have reported bowel and urological function and quality of life in the same patients, and none have reported data from childhood to adulthood in the same study. While neither our data nor any of these referenced studies, are longitudinal assessments, it remains encouraging to see that older patients demonstrate good outcomes comparable if not better than those in adolescence. This would align somewhat to those studies where serial assessments have been performed on patients; where little change is seen between childhood assessments [28,29], but improvements are noted in the transition to adulthood [8]. Improvements through adolescence in soiling and accidents would correspond to social changes such as starting secondary education and the development of adaptive behaviours in adulthood. This is further supported by the observation of increased social restrictions and the fact that fewer adults report using medication to manage constipation despite a similar prevalence of symptoms. It is noteworthy that 7 patients had discontinued use of their ACE; which has been observed in a group of mixed diagnoses previously in long-term follow-up [30].

The 38% prevalence of constipation in our cohort compares similarly to other series after Duhamel pull-through using the same instrument [11], but is higher than reported in a meta-analysis of studies describing outcomes after ERPT (8%) [31]. Small numbers of patients who had pull-through techniques other than Duhamel meant that there was too little statistical power for any meaningful comparison, although we acknowledge the importance of being able to reliably compare the Duhamel with other currently popular techniques such as endorectal pullthrough. The higher rate of constipation may explain the higher observed incidence of urologic dysfunction in this study, not found after ERPT [3]; indeed we found constipation symptoms were more prevalent in those patients with urinary incontinence on multivariate analysis, although clearly impaction and constipation must not be regarded as synonymous. That only 5 patients reported social issues related to their urinary symptoms, suggests that most symptoms were min-

imally intrusive. The only available control data for urologic outcomes spanned a younger age range; this is particularly relevant in adult women – where age, BMI and gravidity may affect the prevalence of LUTS, particularly urinary incontinence. Information was unavailable on gravidity and BMI of the control population, therefore it was not possible to factor these into a multivariate analysis.

Outcomes in extended segment have been recognised as inferior [32], with these patients often requiring ongoing management into adulthood [33]. Despite limited numbers of patients with long-segment or total colonic disease, our results support this, as patients with extended segment had increased stooling frequency (68% vs. 28%) and were also more likely to have experienced recent or recurrent HAEC. Multivariate analysis of outcomes in adulthood suggested that these patients are less likely to obtain a normal bowel outcome. Great Ormond Street Hospital has long been a regional referral center for children across the south of the United Kingdom, indeed this would explain the high number of redo procedures that were performed over the study period. Many of these were necessary as a result of transition zone pull-through which we have recently attempted to reduce with intra-operative frozen sections from the complete distal margin of the pull-through [34]. The redo procedure of choice at our center is a Duhamel, and we evidence good functional results in our cohort. Importantly we did not find Redo surgery to be an independent predictor of poor outcome. While redo surgery is generally felt to be associated with a worse outcome in HSCR, our results align with other large institutional series [35,36], and would support the notion that these challenging cases are centralised to high-volume centres.

Although bowel functional outcomes between males and females were comparable, female patients had lower scores across all quality of life metrics, most markedly in areas of emotional wellbeing. This finding has been documented previously in females with HSCR [12], female patients with enterostomy [37], and more generally in HRQoL surveys [22], and these discrepant outcomes should be considered in the long-term support offered to patients. As part of the same study reported here, we also performed objec-

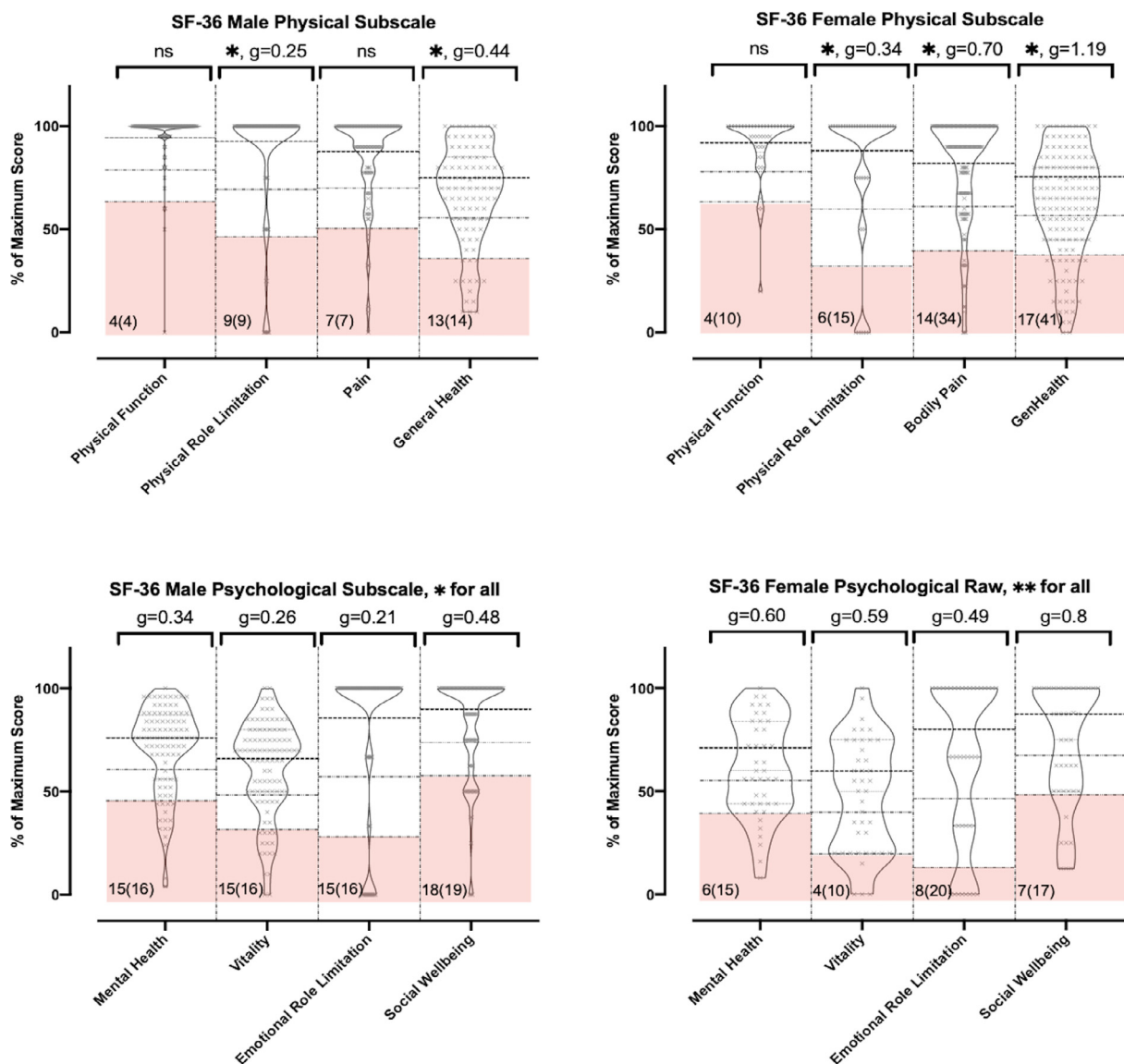


Fig. 5. Male and Female SF-36 Responses for Physical and Psychological Subscales, reference of mean and -1 s.d. and -2 s.d. drawn from UK-general population derived data [17]. Comparison to summary values with unpaired t -test. $*p < 0.05$ $**p < 0.005$.

tive assessment of sexual function, fertility and sexual quality of life in adult patients and have reported significantly inferior outcomes in females across these domains [38]. It would be important to factor into the analysis of these data that the higher proportion of female respondents limits the likelihood of confounding reporting bias in females specifically, however this remains a possible factor in the male participants. This discrepancy has been reported previously in many studies with similar methodology [2,12,20].

A limitation of this study was that control data was not available from the population of the United Kingdom; it is possible that despite consideration for age and gender, demographic or language influences may have influenced results. The comparative outcomes to the general population in HSCR are well documented and echoed by the data presented here; however the integration of multiple functional and QOL domains to explore composite outcomes has not, to our knowledge, previously been performed. The data reported herein include the outcomes prioritised in core outcome set developed for HSCR [4] (demonstrated in Supplemental Data), and thus provide age-specific cross-sectional core outcomes that may be useful for comparison with other studies. Although

age-grouped analysis has been performed, it may not be suitable to accurately predict long-term outcomes in younger patients because of the cross-sectional nature of the study. Longitudinal assessment will be necessary in order to demonstrate functional changes related to age, as confounding factors such as modifications to operative techniques over time cannot be accounted for retrospectively. Prospective patient registries will give new information regarding function in older adults in whom outcomes are sparsely described. The relatively small number of younger patients represented within this cross-sectional study is also a limitation to consider, and the numbers overall may produce type 2 statistical error for low-frequency events such as requirement of stoma or redo surgery. Furthermore, it is not possible to factor into the analysis any effect of new developments in management, including the adoption of minimally invasive techniques, increasing use of intersphincteric botulinum toxin for the treatment of anal outlet obstruction, and a introduction of the formal transitional care service. Our evidence aligns high-resolution qualitative research that there should be a clear transition pathway for all patients with HSCR [39].

5. Conclusions

The demonstrated independent associations between poor functional outcomes with a significant impact on HRQOL have not been reported previously. These are seen in children as well as adults and support early active enquiry of symptoms in a systematic and formalised follow-up clinic. The observed clustering of functional impairments continuing into adulthood support the notion that a multi-disciplinary follow-up should be offered long-term to patients with HSCR.

Financial statement

This study was not performed with any additional funding. PDC holds an NIHR Professorship. All research at Great Ormond Street Hospital NHS Foundation Trust and UCL Great Ormond Street Institute of Child Health is made possible by the NIHR Great Ormond Street Hospital Biomedical Research center. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health

Level of Evidence: II

(Prognosis: Prospective cohort study, <80% follow-up, patients enrolled at different time points of disease)

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jpedsurg.2021.01.043](https://doi.org/10.1016/j.jpedsurg.2021.01.043).

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