Annals of Surgery Publish Ahead of Print
DOI:10.1097/SLA.0000000000006615

OPEN

FERTILITY AND SEXUAL FUNCTION IN MALES WITH HIRSCHSPRUNG'S DISEASE: A NORDIC CROSS-SECTIONAL STUDY

Linnea Söderström MD*[1], Gustav Axelsson*[1], Annika Mutanen MD PhD[2], Pernilla Stenström MD PhD[3,4], Johan Danielsson MD PhD[5,6], Helena Borg MD PhD[7], Anders Telle Hoel MD PhD[8], Signe Olsbø MD[8], Mikko Pakarinen MD PhD[2], Niels Qvist MD PhD[9], Kristin Bjørnland MD PhD[8], Tomas Wester MD PhD[1,10], Anna Löf Granström MD PhD[1,10]

1. Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden.
2. Department of Pediatric Surgery, The New Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland.
3. Department of Pediatrics, Clinical Sciences, Lund University, Lund, Sweden.
4. Department of Pediatric Surgery, Skåne University Hospital Lund, Lund, Sweden
5. Institution of Women's and Children's Health, Uppsala University, Uppsala, Sweden.
6. Department of Pediatric Surgery, Akademiska sjukhuset, Uppsala, Sweden
7. Department of Pediatric Surgery, Drottning Silvia's Children's Hospital, Gothenburg, Sweden.
8. Department of Paediatric Surgery, Oslo University Hospital and University of Oslo, Oslo, Norway
9. Research Unit for Surgery, and Centre of Excellence in Gastrointestinal Diseases and Malformations in Infancy and Childhood (GAIN), Odense University Hospital, Odense, Denmark.
10. Unit of Pediatric Surgery, Karolinska University Hospital, Stockholm, Sweden

Corresponding author: Linnea Söderström
Email address: linnea.soderstrom@ki.se
Postal address: Unit of Pediatric Surgery, Karolinska University Hospital, S3:02, 171 76 Stockholm, Sweden

Competing interests: None to declare

Category of the manuscript: Original article
Previous communication: None

Funding sources: This study was supported by the H.K.H Kronprinessan Lovisas Förening för Barnasjukvård and Birgitta and Carl-Axel Rydbeck's Research Grant

Running head: Fertility-sexual function in HSCR males

Authorship contribution
A.LG, T.W, A.TH, P.S, A.M, H.B, M.P, N.Q, J.D and K.B took part in study conception and design. Data acquisition was performed by G.A, A.M, P.S, J.D, H.B, A.TH, S.O, M.P, N.Q and K.B. Statistical analysis was done by L.S and G.A. L.S, A.LG, T.W and G.A wrote the manuscript draft. All authors took part in critical revision and approval of the manuscript.

Mini-Abstract: We assessed fertility, sexual function, and sexual quality of life in males with Hirschsprung's in the Nordic countries through self-reported reported questionnaires. We did not observe lower fertility, erectile functioning or sexual quality of life compared to normative data. Poor bowel function was associated with impaired fertility and erectile dysfunction.

Abstract

Objective: The aim was to assess fertility, sexual function and sexual quality of life in males with Hirschsprung's disease (HSCR) in the Nordic countries with a cross-sectional study using self-reported validated questionnaires.

Summary Background Data: Data on fertility and sexual function in males with HSCR are limited.

Methods: This multi-center study targeted all males born between 1970-2003 who underwent pull-through surgery at a pediatric surgery center in Sweden, Denmark, Norway, or Finland. Participants completed a multi-domain questionnaire. Demographic data was collected retrospectively from the medical records. Patients with trisomy 21 and other syndromes associated with intellectual disability were excluded. Main outcomes were fertility, sexual function and sexual quality of life.

Results: A total of 169 patients (median age 32 years) were included. Of 63 individuals attempting to father a biological child, eight (12.7%) reported failure to conceive after one year and five (7.9%) reported failure to conceive after two years. Our cohort did not report impaired fertility, higher prevalence of erectile dysfunction or lower sexual quality of life scores compared to normative summary data. Poor bowel function was associated with impaired fertility and erectile dysfunction ($p=0.0278$ and $p=0.0026$, respectively). Length of the aganglionic segment and surgical method did not seem to affect fertility, sexual function, or sexual quality of life.

Conclusion: Males with HSCR that have undergone pull-through surgery do not seem to report an overall reduced fertility, higher prevalence of erectile dysfunction or reduced sexual quality of life compared to estimates from the general population. Impaired bowel function may correlate with erectile dysfunction and impaired fertility in affected individuals.

1. Introduction

Hirschsprung's Disease (HSCR) is a congenital bowel disorder characterized by an aganglionic segment in the distal hindgut[1]. The birth prevalence of HSCR is 1:5000 with a 4:1 male to female ratio[1]. The condition requires surgical treatment, usually within the first year of life. The goal of the reconstructive surgery, pull-through surgery, is to resect the aganglionic segment and create an anastomosis between the normally innervated bowel and the anal canal, preserving the sphincter complex[1, 2]. Despite a successful pull-through, impaired bowel function beyond childhood is common and might have a negative impact on quality of life[3-6].

The surgical procedure involves operating in the small pelvis, posing a risk for postoperative scarring or adhesions in the area as well as structural damage to urogenital innervation and fertility-related structures that may impair sexual function and fertility. Patients with other bowel conditions, such as inflammatory bowel disease, frequently report a decreased sexual wellbeing and impaired fertility, with negative impact on their quality of life. Psychogenic factors, disease perception or structural damage following surgery may contribute to this[7-10].

There are few studies evaluating psychosexual wellbeing, sexual function, and fertility in HSCR patients. Limited evidence suggests that women with HSCR may have reduced fertility, whereas no impairment has been observed in men[11, 12]. Davidson et al. reported that 83% of HSCR men were successful in their attempt to father a child[11]. Males with HSCR have the same number of children compared to controls[12], suggesting unimpaired fertility. Current studies have failed to show an impact on sexual function or sexual quality of life in males with HSCR compared to normative data[11, 13]. In the study by Davidson et al. 97% of males reported an erection sufficient for penetration. In a smaller study only two out of 20 males reported moderate to severe erectile dysfunction (ED) [11, 13]. An important limitation to

previous studies is small cohorts, leading results to be severely underpowered with a risk of type II errors. Studied cohorts are also young with a risk of affecting external validity. Therefore, there is a need for larger studies evaluating fertility, sexual function, and sexual quality of life in males that have undergone pull-through surgery. Increased understanding would have a positive impact on clinical counseling and aid clinicians in identifying patients at risk of developing sexual dysfunction, thus paving the way for personalized treatment.

The primary aim of this study was to assess fertility, sexual function and sexual quality of life in males with HSCR in the Nordic countries using self-reported validated questionnaires. The secondary aim was to explore factors associated with impaired fertility, reduced sexual function, and reduced sexual quality of life.

2. Methods

2.1 Study design

This was a cross-sectional multi-center study set in the Nordic countries.

2.2 Study population

Inclusion criteria targeted all males born between 1970-2003 with accessible medical records that had biopsy-verified HSCR and had undergone pull-through surgery at one of the pediatric surgery centers in Sweden, Denmark, Norway, or Finland. Exclusion criteria were trisomy 21 or other syndromes causing intellectual disability, death, emigration and inability to answer the questionnaire in the reference country's language (Finland; Finnish or Swedish: Sweden; Swedish: Norway; Norwegian: Denmark; Danish).

2.3 Participating centers

The participating centers were: Karolinska University Hospital, Stockholm; Skåne University Hospital, Lund; University Children's Hospital, Uppsala; Queen Silvia's Children's Hospital,

Gothenburg; Helsinki University Children's Hospital, Helsinki; Odense University Hospital, Odense; and Oslo University Hospital, Oslo. Relevant data-sharing agreements were established prior to commencing the study. All statistical analysis was performed at the coordinating site at Karolinska University Hospital.

2.4 Data collection and measurements

Patients were invited to participate in the study via mail. Non-responders received one reminder. After written informed consent was obtained, study participants were asked to complete a validated questionnaire regarding bowel function (BFS), urinary tract function (IPSS), fertility and sexual function (IIEF-5), sexual quality of life (SQoL-M) and general quality of life (SF-36). Fertility was defined as the capacity to father a child and infertility was defined per the World Health Organization (WHO) as failure to conceive after 12 months despite regular (every 2-3 days) unprotected intercourse[14]. The questionnaire also included the following demographic parameters; age, body mass index (BMI), sexual orientation, marital status, educational level and occupation, smoking habits and previous abdominal and/or fertility organ related surgery. Disease-specific demographic data was collected retrospectively from the medical records. These included heredity, associated malformations and/or syndromes, age at diagnosis, length of aganglionic segment, presence of preoperative stoma, age at surgery, type of surgery, postoperative complications within 30 days and need of re-do pull-through. A flow chart for participant recruitment and inclusion in the study is shown in Figure 1.

2.5 Included questionnaires

Bowel function was assessed using the Rintala Bowel Function Score (BFS), a seven-item questionnaire for pediatric anorectal disorders. Scores range from 0-20, with ≥17 indicating normal bowel function[15-17]. The International Prostate Symptom Score (IPSS) evaluated lower

urinary tract symptoms (LUTS) across seven voiding-related questions, classifying severity as mild (0-7), moderate (8-19), or severe (20-35)[18]. Sexual quality of life was measured by the 11-item SQoL-M, transformed to a 0-100 scale, with higher scores indicating a higher level of sexual quality of life[19]. Erectile function was assessed using the IIEF-5, scored from 5-25, classifying ED as severe (5-7), moderate (8-11), mild to moderate (12-16), mild (17-21), and no ED (22-25)[20, 21]. Health related quality of life was assessed with the 36-item SF-36, covering eight health domains, with scores from 0-100[22].

2.6 Statistical analysis

Statistical analysis was performed using the R programming language (version 4.2.1) in RStudio (version 2022.07.01). Data wrangling was performed using dplyr, tables were created using tibble and gt, and diagrams were created using ggplot2 unless otherwise specified. Data are presented as frequencies and percentages for categorical variables as well as median and interquartile range (Q_1-Q_3) for numerical variables. SQoL-M and IIEF-5 are presented by age groups. Chi-square was used for comparative statistics of categorical data when applicable and Fishers exact test when assumptions of Chi-square were violated. For numerical data, Mann-Whitney U-test was used when comparing two independent groups and Kruskal-Wallis H test when comparing more than two groups. Statistical analysis of SF-36 was only performed in the Finnish and Norwegian population due to missing data from other centers. Age-specific dropout rates did not include Norwegian patients due to local ethical prohibitions. Statistical significance was set at $p \leq 0.05$.

2.7 Ethics

The study was approved by the Swedish Ethical Review Authority for the Swedish centers and for the local ethical review boards at the other centers. All procedures were in accordance with the Helsinki declaration and its later amendments[23].

3. Results

3.1 Study population

A total of 461 individuals were found to meet the inclusion criteria. After invitation, 169 patients consented to participation and responded to the questionnaire, resulting in an overall response rate of 36.7%. Dropout rates per country did not differ significantly; Sweden (67.1%), Finland (65.8%), Norway (63%) and Denmark (52.7%) ($p = 0.11$). The dropout rate varied between each of the age groups: 15-19 years old (37.5%), 20-29 years old (71.9%), 30-39 years old (62,5%), 40-49 years old (59.3%), 50-59 years old (71.4%), and ≥60 years old (100%) ($p = 0.20$).

3.2 Patient characteristics

Demographic features of participating HSCR males are depicted in Table 1. Median age was 32 years. The largest age group was 20-29 years (63 individuals) and the smallest age group was 15-19 years (5 individuals). Active smoking was reported by 7.7% in the population. Associated malformations were present in 13 individuals (7.7%); five gastrointestinal, three musculoskeletal, three cardiovascular, two urogenital and four "other" malformations. Endorectal pull-through and Duhamel procedure were the most frequently performed procedures (32% and 23.1%, respectively). Thirty-three individuals had undergone other abdominal surgery than pull-through.

Median bowel function score was 18 (16-19). Impaired bowel function was found in 44 individuals (27.7%). Urinary tract symptoms were scored as following; mild (132, 80.5%), moderate (28, 17.1%) and severe (four, 2.4%). Thirty-nine complete and valid SF-36 scores were collected with a median score of 78.7 (69.7-88) in the population. Individual domains scored lowest to highest were as follows; Energy 65 (41.2-75), Perception of general health

75 (51.2-88.8), Emotional wellbeing 80 (69-88), Social functioning 87.5 (75-100), Pain 90 (71.9-100), Difficulties emotional role 100 (54.2-100), Physical functioning 100 (95-100), Difficulties physical role 100 (100-100).

3.3 Fertility, sexual function and sexual quality of life

In total 152 males (89.9%) had had sexual intercourse with a median age at sexual debut of 16.5 years (15-18 years) (table 2). Of 63 individuals attempting to father a biological child, eight (12.7%) reported failure to conceive after one year and five (7.9%) reported failure to conceive after two years. Eleven of these males had undergone a fertility investigation (17.5%) and six individuals reported need of medical assistance to conceive (9.5%). Overall, 63 males (37.3%) in our cohort had at least one child. Out of males that were successful in conceiving, the most common number of biological children for each male was two. A total of 124 children were conceived by the group leading cohort total fertility to be 0.743. Comparing individuals with impaired and normal bowel function showed no differences in sexual debut (81.8% vs. 92.2%; p=0.11), age at sexual debut (16 vs. 17; p=0.54) or relationship status (61.4% vs 68.7%; ongoing relationship; p=0.49). Thirteen males had undergone surgery on reproductive organs. In free text, two vasectomies, one orchidopexy, one preputioplasty, one intervention for hydrocele, one scrotal hernia repair, one intervention for testicular torsion and suture of scrotal laceration were reported.

Sexual function, as measured by IIEF-5, showed that median IIEF-5 score in the whole group was 24 (21-25) (Fig 2). Erectile dysfunction was reported by 40 (26.5%) individuals. Four individuals (2.7%) reported moderate to severe ED. The lowest median IIEF-5 score was found in the age group 15-19 years (19.5) and the highest IIEF-5 score in the age group 30-39 years (25).

The sexual quality of life (SQoL-M) questionnaire was completed by 157 individuals. Median score for all age groups was 95 (69-100). Individuals aged 15-19 had the lowest median SQoL-M score (75.5) and individuals aged 50-59 years the highest (100) (Fig 3). Eight individuals scored lower than 40 points. Out of these, six reported impaired bowel function, three reported major social/psychological problems related to bowel function and seven moderate to severe ED.

Factors associated with fertility status, erectile function and sexual quality of life are presented in Table 3. Poor bowel function was associated with impaired fertility and lower IIEF-5 scores (p=0.0278 and p=0.0026, respectively). Males with moderate to severe urinary tract symptoms reported lower IIEF-5 scores compared to males with mild symptoms (23 vs. 24, p=0.0089). Lower educational level was significantly associated with impaired fertility (p=0.0407), but not SQoL-M or IIEF-5. Young age was associated with both lower IIEF-5 and SQoL-M scores(p=0.0006 and p=0.0295). Low SQoL-M and IIEF-5 scores did not correlate with SF-36 significantly (p=0.0574 and p=0.0534). The relationship between SF-36 and impaired fertility could not be determined due to missing data. HSCR-type and type of surgery did not correlate with reported fertility, IIEF-5 or SQoL-M.

4. Discussion

4.1 Key findings

With the largest cohort to date, this cross-sectional multi-center study aimed to describe fertility, sexual function, and sexual quality of life in males that had undergone surgery for HSCR. The patients did not report impaired fertility, higher prevalence of ED or lower SQoL-M scores compared to normative summary data[14, 19, 24-27]. Poor bowel function was associated with impaired fertility and lower IIEF-5 scores whereas the length of the aganglionic segment

and the type of surgical method did not seem to impact fertility, sexual function, or sexual quality of life.

4.2 Interpretation

Our study showed that 12.7% of males with HSCR that attempted to father a biological child were unsuccessful within the first year. This is lower than the 17% reported by Davidson et. al. as well as global population estimates by WHO (16.5% lifetime prevalence of infertility in the European region and 17.8% in high income countries)[11, 14]. Overall, 37.3% of males in our cohort had at least one child, with a cohort total fertility of 0.743. This can be compared to the estimated cohort total fertility between 1.59 to 1.84 in males aged 45 in the Nordic countries (born 1965-1969)[28]. The considerably low median age in our cohort, 32 years, may provide a possible explanation for the lower prevalence of infertility and low cohort total fertility as the average age at birth of first child ranges from 30.9 to 32.3 for fathers in the Nordic countries [28, 29]. Recent data from Byström et al corroborates this, reporting 35.3% of Swedish males, median age 29.8 years, to have at least one child within normative population data (n=2255)[12].

Erectile functioning, measured by IIEF-5, indicated any form of ED in 26.5% of the population and moderate-severe ED in 2.7%. Prevalence rates of ED vary significantly in literature, partially due to differences in methodological approach. Incoherent definitions of ED ranging from non-validated single questions to a plethora of questionnaires often hamper the direct comparison of prevalence rates[30]. In a systematic review by Prins et al. the prevalence of ED ranged from 2 to 9% in males <40 years, however only three of the 23

included studies used a validated instrument for evaluating ED[30]. A large survey-based study by Mark et al. in the US reported an overall ED prevalence, defined by IIEF-5, of 24.2% (age ≥18, n=1882)[27]. Another study by Ponholzer et al. reported IIEF-5 scores in 2869 men aged 20–80 years participating in a health-screening project in Vienna. They found an overall ED prevalence of 32.2% with a stable prevalence of ED from 20–30 years until 41–50 years (25.5%–28.9%)[24]. By comparison to normative results of Mark and Ponholzer, our study does suggest a higher prevalence of ED within our cohort.

Males in our study reported a median SQoL-M score of 95, which is slightly higher than the mean score of 88.2 observed by Davidson et al[11]. In the validation study of the SQoL-M for premature ejaculation and ED, 101 controls had a mean score of 87.13, while reference data from Roserira et al., involving 398 patients, reported a mean score of 83.83 [19, 25]. Although the SQoL-M questionnaire does not define a cutoff score for impaired sexual quality of life, our data does not imply a lower sexual quality of life compared to normative reference data[19, 25].

Even though our results may not suggest an impaired fertility, sexual function, or sexual quality of life in males with HSCR on a group level, it is important to note that individuals with impaired bowel function may be at risk. Males with poor bowel function reported failure to conceive more frequently than those with normal bowel function (31.2% vs 7%) as well as a lower grade of erectile functioning (24 vs 25). As hypothesized in inflammatory bowel disease patients, we considered psychogenic factors, disease perception and structural damage following surgery as possible causes. We could not find any association to type of surgical treatment nor length of aganglionic segment. To explore psychosocial elements of sexual

behavior and relationship formation in patients with impaired bowel function, we analyzed proportion of sexually debuted individuals, age at sexual debut and relationship status with no significant differences. Even though impaired bowel function does not seem to hinder relationship development and intimate relations, the concern that social and self-stigma may affect psychosexual wellbeing remains. Although not statistically significant, it is noteworthy that patients with poor bowel function reported a median SQoL-M score of 90.9 compared to 96.4 in those with normal bowel function.

Another interesting aspect is that the lowest IIEF-5 and SQoL-M scores were reported in the youngest age group (15-19 years), with an improving trend until 30-39 years. It is well established that bowel function after pull through surgery improves with age[31-36]. Evidence also suggests that young adults with chronic diseases report lower life satisfaction, more mental health problems and lower peer support[37]. Considering this, both higher disease burden and psychological vulnerability may put this cohort at specific risk of decreased psychosexual wellbeing.

4.3 Limitations

There are several limitations in this study that need to be addressed. Firstly, the median age in our cohort is young, causing data to be more representative towards this age group. Consequently, a significant proportion of our cohort may not have attempted to conceive at time of the study. Secondly, the motivation of patients to participate in the study was

unknown. It could be argued that participants who do experience problems related to fertility or sexual function are more inclined to participate as it would benefit them further on. It could also be argued that sexual dysfunction and reduced fertility is linked to certain stigma, leading patients who experience such problems to be reluctant to participate. Thirdly, as medical records span prior to the digitalized era, many patients eligible for inclusion might have been lost to follow up or have incomplete medical record affecting the quality of retrospectively collected variables. Lastly, this study does not have a control group making the nature of the study more descriptive.

4.4 Generalizability and clinical implications

This study is the largest of its kind addressing male fertility, sexual function, and sexual quality of life in individuals with HSCR that have undergone pull through surgery. It provides the most reliable cohort to date and considers many potential risk stratifiers, paving the way for personalized treatment and follow up. However, the setting is limited to the Nordic countries, colored by its unique prerequisites regarding high age at family formation and relatively low cohort total fertility. Additionally, prevailing cultural beliefs and stigma may affect psychological burden of disease differently between countries.

Contrary to current evidence regarding women with HSCR, the results of our study suggest that males with HSCR as a group do not seem to report reduced fertility, sexual function or sexual quality of life compared to normative data. However, a subset of individuals with

impaired bowel function and/or young age may be at risk. We believe this aspect important to consider when developing the transitional care from adolescence to adulthood. As fertility and intimacy are important aspects to many young adults, it is likely advantageous to address these subjects as part of the disease-related education. Not only to increase knowledge for affected individuals but as a screening measure to identify patients at risk.

4.5 Conclusion

Males with HSCR that have undergone pull-through surgery do not seem to report reduced fertility, sexual functioning or reduced sexual quality of life compared to the general population. Impaired bowel function may correlate with erectile dysfunction and impaired fertility.

4.6 Acknowledgements

This work is generated within ERNICA: the European Reference Network for rare Inherited and Congenital (digestive and gastrointestinal) Anomalies.

References

1. Montalva L, Cheng LS, Kapur R, et al. Hirschsprung disease. *Nat Rev Dis Primers* 2023; 9(1):54.
2. Calkins CM. Hirschsprung Disease beyond Infancy. *Clin Colon Rectal Surg* 2018; 31(2):51-60.
3. Wester T, Granstrom AL. Hirschsprung disease-Bowel function beyond childhood. *Semin Pediatr Surg* 2017; 26(5):322-327.
4. Khalil M. Long-term health-related quality of life for patients with Hirschsprung's disease at 5 years after transanal endorectal pull-through operation. *Qual Life Res* 2015; 24(11):2733-8.
5. Hartman EE, Oort FJ, Aronson DC, et al. Quality of life and disease-specific functioning of patients with anorectal malformations or Hirschsprung's disease: a review. *Arch Dis Child* 2011; 96(4):398-406.
6. Hartman EE, Oort FJ, Sprangers MA, et al. Factors affecting quality of life of children and adolescents with anorectal malformations or Hirschsprung disease. *J Pediatr Gastroenterol Nutr* 2008; 47(4):463-71.
7. Leenhardt R, Riviere P, Papazian P, et al. Sexual health and fertility for individuals with inflammatory bowel disease. *World J Gastroenterol* 2019; 25(36):5423-5433.
8. Riviere P, Zallot C, Desobry P, et al. Frequency of and Factors Associated With Sexual Dysfunction in Patients With Inflammatory Bowel Disease. *J Crohns Colitis* 2017; 11(11):1347-1352.
9. Bel LG, Vollebregt AM, Van der Meulen-de Jong AE, et al. Sexual Dysfunctions in Men and Women with Inflammatory Bowel Disease: The Influence of IBD-Related Clinical Factors and Depression on Sexual Function. *J Sex Med* 2015; 12(7):1557-67.
10. Marin L, Manosa M, Garcia-Planella E, et al. Sexual function and patients' perceptions in inflammatory bowel disease: a case-control survey. *J Gastroenterol* 2013; 48(6):713-20.
11. Davidson JR, Kyrklund K, Eaton S, et al. Sexual function, quality of life, and fertility in women who had surgery for neonatal Hirschsprung's disease. *Br J Surg* 2021; 108(2):e79-e80.
12. Bystrom C, Ortqvist L, Gunnarsdottir A, et al. Fertility in patients with Hirschsprung's disease: population-based cohort study. *BJS Open* 2023; 7(3).
13. van den Hondel D, Sloots CE, Bolt JM, et al. Psychosexual Well-Being after Childhood Surgery for Anorectal Malformation or Hirschsprung's Disease. *J Sex Med* 2015; 12(7):1616-25.
14. Organization WH. Infertility prevalence estimates, 1990–2021. License: CC BY-NC-SA 3.0 IGO. 2023.
15. Rintala RJ, Lindahl H. Is normal bowel function possible after repair of intermediate and high anorectal malformations? *J Pediatr Surg* 1995; 30(3):491-4.
16. Rintala RJ, Lindahl HG, Rasanen M. Do children with repaired low anorectal malformations have normal bowel function? *J Pediatr Surg* 1997; 32(6):823-6.
17. Pakarinen MP, Goyal A, Koivusalo A, et al. Functional outcome in correction of perineal fistula in boys with anoplasty versus posterior sagittal anorectoplasty. *Pediatr Surg Int* 2006; 22(12):961-5.
18. Barry MJ, Fowler FJ, Jr., O'Leary M P, et al. The American Urological Association Symptom Index for Benign Prostatic Hyperplasia. *J Urol* 2017; 197(2S):S189-S197.

19. Abraham L, Symonds T, Morris MF. Psychometric validation of a sexual quality of life questionnaire for use in men with premature ejaculation or erectile dysfunction. *J Sex Med* 2008; 5(3):595-601.
20. Rosen RC, Cappelleri JC, Smith MD, et al. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. *Int J Impot Res* 1999; 11(6):319-26.
21. Rosen RC, Riley A, Wagner G, et al. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 1997; 49(6):822-30.
22. Brazier JE, Harper R, Jones NM, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ* 1992; 305(6846):160-4.
23. World Medical A. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Participants. *JAMA* 2024.
24. Ponholzer A, Temml C, Mock K, et al. Prevalence and risk factors for erectile dysfunction in 2869 men using a validated questionnaire. *Eur Urol* 2005; 47(1):80-5; discussion 85-6.
25. Roseira J, Magro F, Fernandes S, et al. Sexual Quality of Life in Inflammatory Bowel Disease: A Multicenter, National-Level Study. *Inflamm Bowel Dis* 2020; 26(5):746-755.
26. Gerbild H, Larsen CM, Graugaard C, et al. Physical Activity to Improve Erectile Function: A Systematic Review of Intervention Studies. *Sex Med* 2018; 6(2):75-89.
27. Mark KP, Arenella K, Girard A, et al. Erectile dysfunction prevalence in the United States: report from the 2021 National Survey of Sexual Wellbeing. *J Sex Med* 2024; 21(4):296-303.
28. Jalovaara M, Neyer G, Andersson G, et al. Education, Gender, and Cohort Fertility in the Nordic Countries. *Eur J Popul* 2019; 35(3):563-586.
29. Parents age at birth of first child by reporting country, parent and time [database online]. *Insert City of Publication Here see notes*; 2022.
30. Prins J, Blanker MH, Bohnen AM, et al. Prevalence of erectile dysfunction: a systematic review of population-based studies. *Int J Impot Res* 2002; 14(6):422-32.
31. Reding R, de Ville de Goyet J, Gosseye S, et al. Hirschsprung's disease: a 20-year experience. *J Pediatr Surg* 1997; 32(8):1221-5.
32. Bai Y, Chen H, Hao J, et al. Long-term outcome and quality of life after the Swenson procedure for Hirschsprung's disease. *J Pediatr Surg* 2002; 37(4):639-42.
33. Baillie CT, Kenny SE, Rintala RJ, et al. Long-term outcome and colonic motility after the Duhamel procedure for Hirschsprung's disease. *J Pediatr Surg* 1999; 34(2):325-9.
34. Rescorla FJ, Morrison AM, Engles D, et al. Hirschsprung's disease. Evaluation of mortality and long-term function in 260 cases. *Arch Surg* 1992; 127(8):934-41; discussion 941-2.
35. Yanchar NL, Soucy P. Long-term outcome after Hirschsprung's disease: patients' perspectives. *J Pediatr Surg* 1999; 34(7):1152-60.
36. Moore SW, Albertyn R, Cywes S. Clinical outcome and long-term quality of life after surgical correction of Hirschsprung's disease. *J Pediatr Surg* 1996; 31(11):1496-502.
37. Berkelbach van der Sprenkel EE, Nijhof SL, Dalmeijer GW, et al. Psychosocial functioning in adolescents growing up with chronic disease: The Dutch HBSC study. *Eur J Pediatr* 2022; 181(2):763-773.

Figure 1. Flow chart for participant recruitment

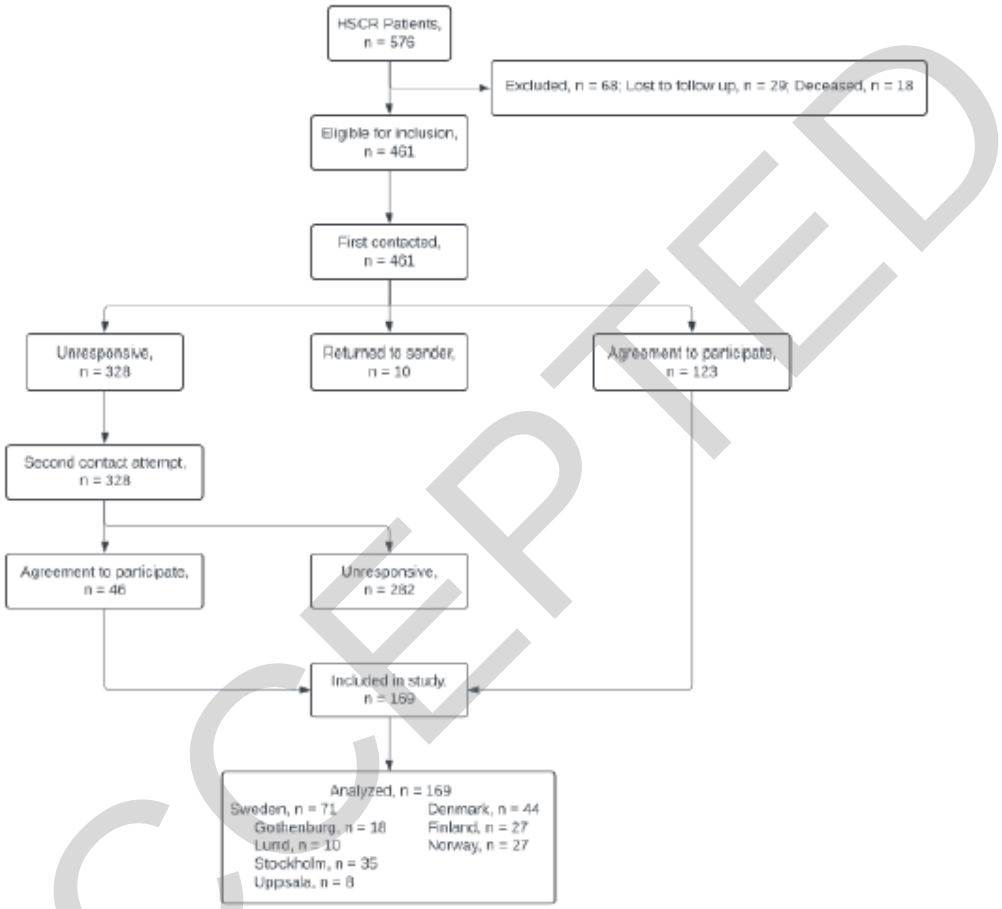

Figure 2. Prevalence of erectile dysfunction by age group in men with HSCR

Prevalence of erectile dysfunction (ED) and severity of ED, divided into 10-year age intervals. Number below bar indicating total number of individuals within the age group that has responded to the IIEF-5 questionnaire. Normative values from published data indicated by dashed bar (the groups mild to moderate ED and moderate ED were combined to one moderate ED group) [24].

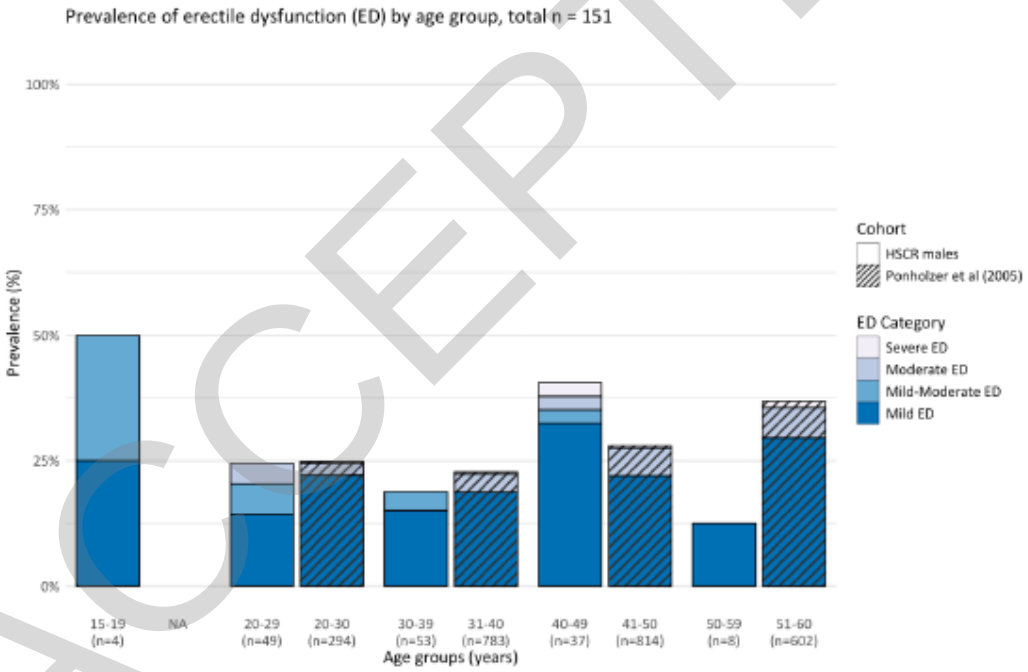

Figure 3. Sexual quality of life by age group in men with HSCR

SQoL-M scores by age group visualized by boxplots. Width of box indicating number of individuals within the group. Dots represent individual values recorded. Normative values from published data indicated by background color: white= mean ± 1 s.d; light blue= 1 s.d to 2 s.d; dark blue > 2.s.d[19].

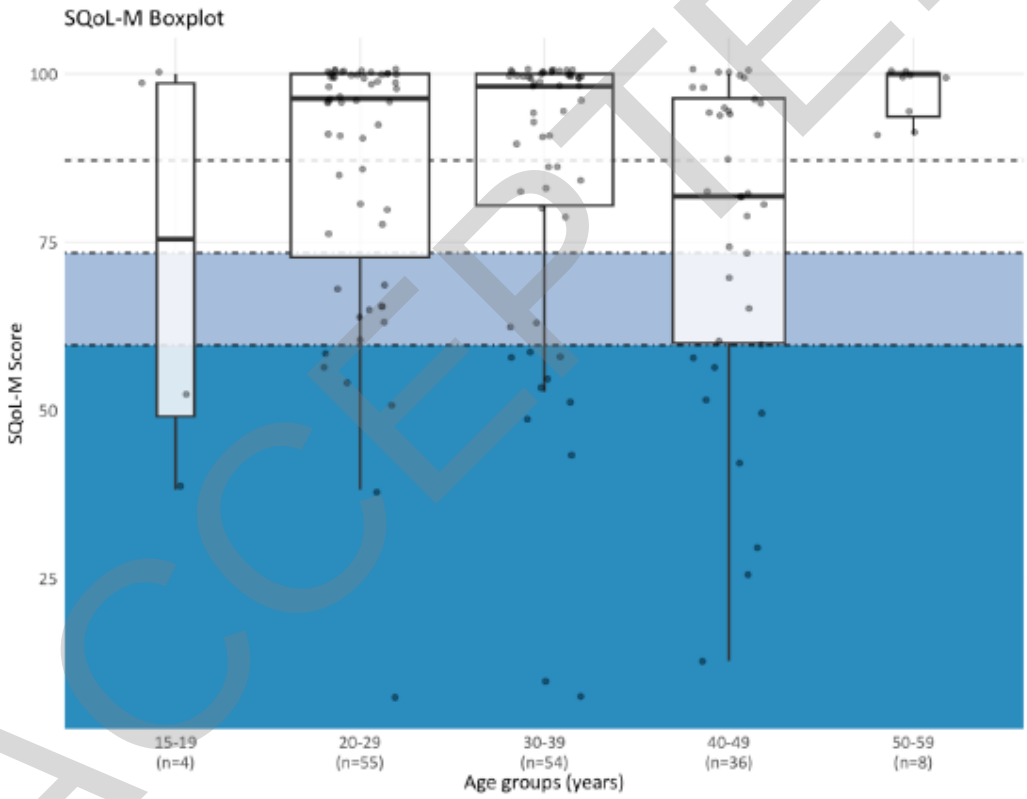

Table 1. Demographic data for males with Hirschsprung's disease

Patient characteristics	n=169
Age median (Q_1-Q_3), years	32 (25-41)
Associated malformations n (%)	13 (7.7%)
Other abdominal surgery n (%)	33 (19.5)
Extent of aganglionosis n (%)	
Rectosigmoid	101 (59.8)
Long segment	16 (9.5)
Total colonic aganglionosis	6 (3.6)
Other/unknown	46 (27.2)
Surgery n (%)	
Endorectal pull-through	54 (32)
Swenson	6 (3.6)
Duhamel	39 (23.1)
Rehbein	21 (12.4)
Ileoanal anastomosis with J-pouch	1 (0.6)
Posterior sagittal ano-recto-plasty	1 (0.6)
Other/unknown	47 (27.8)
Sexual orientation n (%)	
Heterosexual	157 (92.9)
Homosexual	3 (1.8)
Bisexual	6 (3.6)
Other/unknown	3 (1.8)
Marital status n (%)	
Married/living together	82 (48.5)
Divorced	2 (1.2)
In a relationship	32 (18.9)
Single	51 (30.2)
Unknown/other	2 (1.2)

Table 2. Fertility status in males with Hirschsprung's Disease

Fertility status	n=169
	n (%)
Sexually debuted	152 (89.9)
Attempt to conceive	63 (41.4)
Failure to conceive (>1 yr)*	8 (12.7)
Failure to conceive (>2yr)*	5 (7.9)
Undergone fertility investigation*	11 (17.5)
Partner examined for fertility issues *	9 (14.3)
Need of medical assistance to conceive*	6 (9.5)

*Out of individuals that have attempted to conceive

Table 3. Factors associated with sexual quality of life, sexual function and fertility

	Bowel function (BFS)			**Urinary tract function (IPSS)**			**Extent of aganglionosis***				**Surgery**			**Educational level**				
	Normal (BFS≥17)	Poor (BFS<17)	p-value	Normal/mild (IPSS ≤7)	Moderate/Severe (IPSS>7)	p-value	RS	LS	TCA	p-value	TERP	Duhamel	Rehbein	p-value	Primary	Secondary	Folk high school	Tertiary	p-value
SQoL-M median (Q1-Q3)	96.4 (78.2-100)	90.9 (59.1-100)	0.1026$_{\delta}$	96.4 (80-100)	82.7 (55-100)	0.0547$_{\delta}$	92.7 (63.6-100)	94.5 (79.1-100)	100 (93.2-100)	0.1799$_{\gamma}$	93.6 (69.5-100)	82.7 (60-98.2)	98.2 (80-100)	0.1504$_{\gamma}$	96.4 (70.9-99.1)	98.2 (84.5-100)	92.7 (59.1-99.1)	94.5 (67.7-100)	0.3947$_{\gamma}$
IIEF-5 median (Q1-Q3)	24 (22-25)	23 (18-24)	**0.0026$_{\delta}$**	24 (22-25)	23 (20-24)	**0.0089$_{\delta}$**	24 (20-25)	23 (22-25)	25 (25-25)	0.0679$_{\gamma}$	24 (22-25)	24 (20-25)	24 (20-25)	0.5229$_{\gamma}$	23 (22-24.5)	24 (21-25)	24 (18.5-24.5)	24 (23-25)	0.1394$_{\gamma}$
Impaired fertility n (%)	3 (7)	5 (31.2)	**0.0278$_{\phi}$**	6 (11.8)	2 (18.2)	0.623 3$_{\phi}$	6 (17.1)	0	1 (33.3)	0.5101$_{\phi}$	5 (26.3)	1 (5.9)	0	0.1719$_{\phi}$	3 (50)	3 (15)	0	2 (5.7)	**0.0407$_{\phi}$**

P-values ≤0.05 marked in bold. Statistical test indicated by δ=Mann-Whitney U test,

ϕ=Fischer's exact test, γ=Kruskal Wallis H test

*RS=rectosigmoid, LS=Long segment, TCA=Total colonic aganglionosis