**Table 2. Characteristics of included studies**

| Study | Participants (number, age, other important characteristics) | Prognostic factor(s) | Follow-up | Outcome measures | Comments | Risk of bias (per outcome measure)* |
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| *Individual studies* | | | | | | |
| Hackam, 2003 | <u>Country</u><br>USA<br><br><u>N at baseline</u><br>Down Syndrome group: 9<br>No Down Syndrome group: 57<br><br><u>Age at diagnosis (mean ± SEM)</u><br>Intervention: 24.7 ± 19 days<br>Control: 27 ± 30 days<br><br><u>Sex</u><br>Down Syndrome group: 88.9% male<br>No Down Syndrome Group:<br>80.7% male<br><br><u>Type of disease</u><br>Hirschprung's disease<br><br><u>Type of surgery</u><br><br>• Staged pull-through with a levelling colonoscopy: | Down Syndrome was the only prognostic factor, assessment was not described | <u>Duration or endpoint of follow-up:</u><br>22 months (average)<br><br>For how many participants were no complete outcome data available?<br>N (%): 0 (0%)<br><br>Reasons for incomplete outcome data: N/A | • **Enterocolitis**: if medical record indicated treatment for abdominal distension, feeding intolerance, explosive stools, or diarrhea with the possible inclusion of fever, leukocytosis, and distended bowel loops on abdominal radiographs<br>• **Constipation**: not defined<br>• **Incontinence**: not defined<br>• **Mortality** | • Funding: not reported<br>• Conflicts of interest: not reported | **All:** High |

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| | • 67% of patients with DS and 64% of patients with no DS<br>• Primary pull-through procedure: 33% of DS patients and 36% of no DS patients<br><br><u>Potential confounders or effect modifiers</u> not included in analyses | | | | | |
| Morabito, 2006 | <u>Country</u><br>UK<br><br><u>N at baseline</u><br>Down Syndrome group: 17<br>No Down Syndrome group: 156<br><br><u>Age (mean ± SD)</u><br>Down Syndrome group: 38.1 ± 1.7 weeks<br>No Down Syndrome group: 39.1 ± 2.7 weeks<br><br><u>Sex</u><br>Down Syndrome group: 94% male | Down Syndrome was the only prognostic factor, assessment by chromosomal analysis | <u>Duration or endpoint of follow-up:</u><br>1 to 10 years<br><br><u>For how many participants were no complete outcome data available?</u><br><u>N (%):</u><br>Down Syndrome group: 2 (12%) for outcomes soiling and incontinence.<br>No Down Syndrome group:<br>16 (10%) for outcomes soiling and incontinence | • **Enterocolitis**: A diagnosis of enterocolitis was based upon clinical evidence of sepsis, pyrexia above 38C, abdominal distension and foul smelling diarrhea<br>• **Soiling**: according to the modified Wingspread scoring system<br>• **Incontinence**: according to the modified Wingspread scoring system<br>• **Mortality** | • Funding: not reported<br>• Conflicts of interest: not reported | **All:** High |

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| | No Down Syndrome group: 80% male<br><br><u>Type of disease</u><br>Hirschprung's disease<br><u>Type of surgery</u><br>Down Syndrome group: 23.5% with primary pull-through without stoma, 76.5% had defunctioning stoma<br>No Down syndrome group: 43% had primary pull-through without colostomy, 37% had pull-through and defunctioning stoma, and 20% had a colostomy at birth followed by a delayed pull-through<br><br><u>Potential confounders or effect modifiers:</u><br>not included in analyses | | <u>Reasons for incomplete outcome data:</u><br>These children were not analyzed, because they were younger than 4. The decision was made to assess only children of 4 years and older for these outcomes. | | | |
| Travassos, 2011 | <u>Country</u><br>The Netherlands<br><br><u>N at baseline</u><br>Down Syndrome group: 20<br>No Down Syndrome group: 129 | Down Syndrome was the only prognostic factor, diagnosis was not described | <u>Duration or endpoint of follow-up</u><br>5.1 years mean (range: 0 to 13 years for Down Syndrome group and 0 to 18 years for no Down Syndrome group) | • **Enterocolitis**: criteria were whether the patient was hospitalized for episodes of diarrhea, generalized illness, sometimes accompanied by | • Funding: not reported<br>• Conflicts of interest: none | **All:** High |

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| | Age (median (range))<br>Down Syndrome group: 6 months (1-172)<br>No Down Syndrome 6 months (0-129)<br><br>Sex<br>Down Syndrome group: 70% male<br>No Down Syndrome Group: 83% male<br><br>Type of disease<br>Hirschsprung's disease<br><br>Type of surgery<br>Open (mostly prior to 1994) or laparoscopic Duhamel procedure<br><br>Potential confounders or effect modifiers<br>not included in analyses | | For how many participants were no complete outcome data available?<br>N (%)<br>• Outcome constipation:<br>- Down Syndrome group: 1 (5%)<br>- No Down Syndrome group: 6 (5%)<br>• Outcome incontinence:<br>- Down Syndrome group: 3 (15%)<br>- No Down Syndrome group: 20 (16%)<br><br>Reasons for incomplete outcome data<br>• Constipation: outcome was unknown, reason not stated (in no Down Syndrome group), death (1 in Down Syndrome Group) | fever, and abdominal distension<br>• **Constipation**: Krickenberg's grade<br>• **Incontinence**: Krickenberg's grade | | |

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| | | | • Incontinence: outcome was unknown, reason not stated, participants <4 years of age were not assessed for incontinence, death | | | |
| Menezes, 2005 | <u>Country</u><br>Ireland<br><br><u>N at baseline</u><br>Down Syndrome group: 39<br>No Down Syndrome group: 220<br><br><u>Age (mean ± SD)</u><br>Not provided<br><br><u>Sex</u><br>Not provided<br><br><u>Type of disease</u><br>Hirschsprung's disease<br><br><u>Type of surgery</u><br>Only reported for Down syndrome group<br>- 33 patients underwent definitive pull-through surgery (14 had primary | Down Syndrome was the only prognostic factor, diagnosis was not described | <u>Duration or endpoint of follow-up</u><br>6 months to 28 years<br><br><u>For how many participants were no complete outcome data available?</u><br><u>N (%)</u><br>• Down Syndrome group: 16 (41%)<br>• No Down Syndrome group: 59 (27%)<br><br><u>Reasons for incomplete outcome data</u><br>• Surgical intervention was refused<br>• Death<br>• Use of stoma | • **Soiling**: not defined, assessed by examination of patient's records and personal interviews/inquiries by telephone with patient's parents or guardians<br>• **Constipation**: not defined, assessed by examination of patient's records and personal interviews/inquiries by telephone with patient's parents or guardians | • Funding: not reported<br>• Conflicts of interest: not reported | **All:** High |

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| | pull-through surgery without colostomy and 19 had pull-through operation a few months after colostomy)<br><br><u>Potential confounders or effect modifiers</u><br>not included in analyses | | • Loss to follow-up<br>• Too young to be assessed for bowel control<br>• Having total colonic aganglionosis | | | |
| Pini Prato, 2019 | <u>Country</u><br>Italy<br><br><u>N at baseline</u><br>Down Syndrome group: 23<br>No Down Syndrome group: 362<br><br><u>Age (mean ± SD)</u><br>Not reported<br><br><u>Sex</u><br>Down Syndrome group: 65.2% male<br>No Down Syndrome group: 76.8% male<br><br><u>Type of disease</u><br>Hirschsprung's disease<br><br><u>Type of surgery</u><br>Total pull-through (endorectal, Duhamel, other), minimally | Down Syndrome was assessed chromosomally | <u>Duration or endpoint of follow-up</u><br>median 4 years (8 months to 16 years)<br><br><u>For how many participants were no complete outcome data available?</u><br><u>N (%)</u><br>• Constipation: 3 (13%) in DS group, and 121 (33%) in no DS group<br>• Enterocolitis: 4 (17%) in DS group and 57 (16%) in no DS group<br>• Incontinence: 8 (35%) in DS group and 146 (40%) in no DS group | • **Enterocolitis**: defined according to Elhalaby criteria and was graded into mild, moderate and severe<br>• **Constipation**: according to modified Rome criteria for functional constipation, in the absence of residual aganglionosis or hypoganglionosis or other anatomic, metabolic or iatrogenic issues<br>• **Incontinence**: assessed according to Wingspread classification in patients older than 4 years with at | • Funding: Italian Ministry of Health (MOH) Young Researchers Award, code WFR GR-2011-02347381<br>• Conflicts of interest: not reported | **All:** High |

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| | invasive surgery (MIS, mostly since 2003)<br><br><u>Potential confounders or effect modifiers</u><br>Not included in analyses | | <u>Reasons for incomplete outcome data</u><br>• Lack of reliable data<br>• Patients <4 years of age for assessment of incontinence | least 6 months of follow-up<br>• **Mortality** | | |

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| Niramis, 2010 | <u>Country</u><br>Thailand<br><br><u>N at baseline</u><br>Down Syndrome group: 86<br>No Down Syndrome group: 141<br><br><u>Age (mean ± SD)</u><br>Down Syndrome group: 12.9 ± 15.7 days<br>No Down Syndrome: 9.5 ± 40.4 days<br><br><u>Sex</u><br>Down Syndrome group: 53% male<br>No Down Syndrome group:<br>44% male<br><br><u>Type of disease</u><br>Congenital intrinsic duodenal obstruction (CIDO), including duodenal atresia, duodenal stenosis, and duodenal web or diaphragm<br><br><u>Type of surgery</u><br>duodenoduedenostomy, duodenoplasty, web excision and duodenoplasty, duodenojejunostomy | • Down Syndrome<br>• Congenital heart diseases (CHD), including (among others) patent ductus arteriosus, atrial septal defects, and ventricular septal defects | <u>Duration or endpoint of follow-up</u><br>Down Syndrome group: 4.6 ± 2.2 years<br>No Down Syndrome group: 4.8 ± 5.2 years<br><br><u>For how many participants were no complete outcome data available?</u><br>N (%)<br>Down Syndrome group: 5 (14%)<br>No Down Syndrome group: 4 (3%)<br><br><u>Reasons for incomplete outcome data</u><br>Early mortality (within 30 days post-surgery) | • **Mortality** | • Funding: not reported<br>• Conflicts of interest: not reported | **All:** High |

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| | Potential confounders or effect modifiers<br>not included in multivariate analysis, but data for CHD subgroups are provided | | | | | |
| Bethell, 2020 | Country<br>UK<br><br>N at baseline<br>Down Syndrome group: 33<br>No Down Syndrome group: 64<br><br>Age (median (range))<br>Down Syndrome group: 2 (0-14) days<br>No Down Syndrome group: 3 (0-75) days<br><br>Sex<br>Down Syndrome Group: 55% male<br>No Down Syndrome Group: 55% male<br><br>Type of disease<br>Congenital duodenal obstruction (CDO)<br><br>Type of surgery<br>duodenoduodenostomy, duodenojejunostomy, | Down Syndrome, diagnosis not described | Duration or endpoint of follow-up<br>1 year post-surgery<br><br>For how many participants were no complete outcome data available?[1]<br>N (%)<br>Down Syndrome group: 5 (15%)<br>No Down Syndrome group: 15 (23%)<br><br>Reasons for incomplete outcome data<br>Event status unknown at 1-year follow-up, infant died before 1-year post-surgical repair, missing data or missing 1-year follow-up | • **Mortality**<br>• **Feeding difficulties**: having achieved full enteral feed | • Funding: This project was funded through a National Institute for Health Research (NIHR) Professorship award to Marian Knight (NIHR RP-011-032). George Bethell is funded by the National Institute of Heath Research Academic Clinical Fellow programme.<br>• Conflicts of interest: none | **All:** High |

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| | membrane incision, membrane resection, duodenoplasty<br><br>Potential confounders or effect modifiers: not included in statistical analyses | | | | | |
| Balela, 2023 | <u>Country</u><br>Indonesia<br><br><u>N at baseline</u><br>Down Syndrome group:<br>No Down Syndrome group:<br><br><u>Age[2] (n (%))</u><br><1 year: 68 (60%)<br>≥1 year: 46 (40%)<br><br><u>Sex[2]</u><br>69% male<br><br><u>Type of disease</u><br>Hirschsprung's disease<br><br><u>Type of surgery</u><br>Transanal endorectal pull-through (TEPT), Swenson-like pull-through, and Duhamel pull-through<br><br><u>Potential confounders or effect modifiers</u> | • Down Syndrome<br>• Type of surgery: transanal endorectal pull-through (TEPT), Swenson-like pull-through, and Duhamel pull-through<br>• Sex<br>• Age<br>• Aganglionosis type (short, long, total colon aganglionosis)<br>• Global developmental delay: not defined, presented as yes or no | <u>Duration or endpoint of follow-up</u><br>At least 6 months<br><br><u>For how many participants were no complete outcome data available?</u><br><u>N (%)</u><br>0 (0%)<br><br><u>Reasons for incomplete outcome data</u><br>N/A | **Other abdominal complications**: abdominal distension, bloating, borborygmi, vomiting, or severe constipation following pull-through | • Funding: no specific funding was received<br>• Conflicts of interest: none | **All:** Low |



Table 2. Characteristics of included studies bij module Gastro-enterologie
Richtlijn Medische begeleiding van kinderen met downsyndroom 2025

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| | • Type of surgery<br>• Sex<br>• Age<br>• Aganglionosis type<br>• Global developmental delay | | | | | |
| Kwendakwema, 2016 | Country<br>USA<br><br>N at baseline<br>Down Syndrome group: 26<br>No Down Syndrome group: 181<br><br>Age (median)<br>Down Syndrome group: 8.4 months<br>No Down Syndrome: 7.2 months<br><br>Sex<br>Down Syndrome group: 81% male<br>No Down Syndrome group: 75% male<br><br>Type of disease<br>Hirschsprung's disease<br><br>Type of surgery<br>Primary pull-through and two-stage pull-through surgery | Down Syndrome, diagnosis not described | Duration or endpoint of follow-up<br>2 years<br><br>For how many participants were no complete outcome data available?<br>N (%)<br>0 (0%)<br><br>Reasons for incomplete outcome data<br>N/A | **Enterocolitis**: clinically diagnosed attacks within the first two years of the primary surgery | • Funding: this investigation was supported by the University of Utah Study Design and Biostatistics Center, with funding in part from the National Center for Research Resources and the National Center for advancing Translational Sciences, National Institutes of Health, through grant 5UL1TR001067-02 (formerly 8UL1TR000105 and UL1RR025764) | **All:** High |

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| | Potential confounders or effect modifiers<br>Not assessed | | | | • Conflicts of interest: not reported | |
| Le-Nguyen, 2019 | Country<br>Canada<br><br>N at baseline<br>Down Syndrome group: 9<br>No Down Syndrome group: 161<br><br>Age at surgery (median (IQR))[2]<br>7 (3, 19) weeks<br><br>Sex[2]<br>75% male<br><br>Type of disease<br>Hirschsprung's disease<br><br>Type of surgery<br>Pull-through (Soave, Duhamel, Swenson, sphincterectomy)<br><br>Potential confounders or effect modifiers<br>Sveral were included, but association between Down Syndrome and enterocolitis was not assessed multivariately, | • Down Syndrome, diagnosis not described<br>• Sex<br>• Gestational age<br>• Age at diagnosis<br>• Age at first surgery<br>• Weight at birth<br>• Weight at first surgery<br>• Type of Hirschsprung's disease (long, short)<br>• Associated malformations<br>• Type of surgery<br>• Preoperative antibiotics<br>• Preoperative enterocolitis<br>• Postoperative intestinal obstruction | Duration or endpoint of follow-up<br>Not reported<br><br>For how many participants were no complete outcome data available?<br>N (%)<br>21 (11%)<br><br>Reasons for incomplete outcome data<br>Death, missing data | **Enterocolitis**: defined as a clinical diagnosis made by the surgeons as documented in the charts. Children who presented fever in addition to obstructive symptoms were diagnosed with enterocolitis rather than bowel obstruction. | • Funding: no funding was received<br>• Conflicts of interest: none | High |

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| | as there was no statistically significant univariate association | | | | | |
| Surana, 1994 | Country<br>Ireland<br><br>N at baseline<br>Down Syndrome group: 17<br>No Down Syndrome group: 118<br><br>Age (mean ± SD)<br>not reported<br><br>Sex[2]<br>79% male<br><br>Type of disease<br>Hirschsprung's disease<br><br>Type of surgery<br>pull-through (Swenson, Boley-Soave, Duhamel, Lester Martin), undefined surgery<br>Potential confounders or effect modifiers<br>Several were included, see prognostic factors, but were not included in analyses | • Down Syndrome: assessment not described<br>• Type of pull-through surgery<br>• Level of aganglionosis | Duration or endpoint of follow-up<br>Not defined<br><br>For how many participants were no complete outcome data available?<br>N (%)<br>Not reported<br><br>Reasons for incomplete outcome data<br>N/A | **Enterocolitis**: diagnosed on the clinical findings of abdominal distension, diarrhea and/or bloody stools, vomiting, and fever | • Funding: not reported<br>• Conflicts of interest: not reported | High |
| Sakurai, 2020 | Country<br>Japan | • Down Syndrome: | Duration or endpoint of follow-up (median (range)) | **Enterocolitis**: | • Funding: not reported | High |

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| | N at baseline<br>Down Syndrome group: 5<br>No Down Syndrome group: 30<br><br>Age at surgery (median (range))[2]<br>Children without enterocolitis: 1.47 (0.6 to 6.1) months<br>Children with enterocolitis: 2.73 (0.73 to 10.77) months<br><br>Sex<br>Children without enterocolitis: 73% male<br>Children with enterocolitis: 76% male<br><br>Type of disease<br>Hirschsprung's disease<br><br>Type of surgery<br>Rectoplasty with a posterior triangular colonic flap (RPTCF) or transanal endorectal pull-through with rectoanal myotony rectoplasty (TEPTRAM)<br><br>Potential confounders or effect modifiers | assessment not described<br>• Demographic variables<br>• Malformations<br>• Type of HD<br>• Preoperative enterocolitis<br>• Type of surgery and duration<br>• Postoperative stenosis<br>• Postoperative enema duration<br>• Postoperative dilatations duration | Not reported<br><br>For how many participants were no complete outcome data available?<br>N (%)<br>0 (0%)<br><br>Reasons for incomplete outcome data<br>N/A | a score of at least four for Frykman et al. and a need for hospitalization | • Conflicts of interest: none | |

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| | not included in multivariate statistical analyses | | | | | |
| Singh, 2004 | Country<br>UK<br><br>N at baseline<br>Down Syndrome group: 28<br>No Down Syndrome group: 48<br><br>Age at surgery (mean (range))[2]<br>2 days (1 day-3 years)<br><br>Sex[2]<br>58% male<br><br>Type of disease<br>Congenital duodenal obstruction<br><br>Type of surgery<br>Duodeno-duodenostumy, duodeno-jejunostomy, duodenoplasty, gastroduodenostomy, duodeo—ileostomy<br><br>Potential confounders or effect modifiers<br>Not included in analyses | • Down Syndrome: assessment not described | Duration or endpoint of follow-up (median (range))<br>No specific follow-up duration reported, but at least 3 years<br><br>For how many participants were no complete outcome data available?<br>N (%)<br>0 (0%) (if only including patients who were operated and survived surgery)<br><br>Reasons for incomplete outcome data<br>N/A | • **Mortality**<br>• **Other abdominal complications:** Not predefined, but the following were found: (adhesive)intestinal obstruction, anastomotic leak, subacute obstruction, intra-abdominal abscess, ileal atresia, | • Funding: not reported<br>• Conflicts of interest: not reported | **All**: High |

*For further details, see risk of bias table in the appendix

[1]N estimated based on percentages provided
[2]Only provided for total study population or other subgroups as specified