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Intestinal Atresia in Finland: Maternal Risk Factors, Prevalence, Associated Anomalies and Survival

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ABSTRACT

Aim: We aimed to investigate prevalence, associated anomalies and survival of congenital intestinal atresia and to examine maternal risk factors for jejunoileal atresia (JIA).

Methods: All children born with, or pregnancies terminated because of, JIA or colonic atresia (CA) in Finland during 1987–2019 were identified from the Finnish Register of Congenital Malformations. Clinical information was obtained from national health registers. Maternal risk factors were assessed using all JIA cases from 2004 to 2017 ($n = 101$). For each case, five appropriately matched live-born controls were selected.

Results: We identified 175 JIA and 48 CA cases. About half were isolated anomalies. Gastrointestinal anomalies were the most common associated defects (26% in JIA, 35% in CA), followed by cardiac anomalies in JIA (13%) and urinary tract anomalies in CA (19%). Survival was 88% in JIA and 94% in CA. Only two of 224 patients died directly due to intestinal atresia. Maternal insulin use (adjusted odds ratio [aOR] 8.4, 95% CI 1.4–51.0) and propionic acid derivatives (aOR 4.6, 95% CI 1.5–14.8) were associated with increased JIA risk.

Conclusion: Although associated anomalies were frequent, mortality in intestinal atresia remained low. Maternal insulin and propionic acid derivative use may meaningfully contribute to JIA risk.

Level of Evidence: IV.

Abbreviations: aOR, adjusted odds ratio; ASD, atrial septal defect; ATC, Anatomical Therapeutic Chemical; AWD, abdominal wall defect; BMI, body mass index; CA, colonic atresia; CFTR, cystic fibrosis transmembrane conductance regulator; CI, confidence interval; HD, Hirschsprung disease; IA, intestinal atresia; ICD, International Classification of Diseases; JIA, jejunoileal atresia; NSAID, non-steroidal anti-inflammatory drug; OR, odds ratio; PDA, patent ductus arteriosus; THL, Finnish Institute for Health and Welfare; VSD, ventricular septal defect.

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Summary

- This study was needed to improve knowledge of the prevalence, associated anomalies, survival and maternal risk factors of intestinal atresia.
- The study found that associated anomalies were common, mortality was low and maternal use of insulin and propionic acid derivatives was associated with intestinal atresia.
- The findings highlight the need for systematic screening for associated anomalies and further research on maternal risk factors due to limited case numbers.

1 | Introduction

The term intestinal atresia (IA) refers to congenital obstruction of the intestine between the duodeno-jejunal flexure and the rectum [1]. Jejunioleal atresia (JIA) is clearly more common compared to colonic atresia (CA) [1, 2]. JIA occurs in approximately 0.7–2.0 and CA in 0.15–1.0 per 10000 live births [3–5]. The pathophysiology of JIA and CA remains unclear but is thought to be related to intrauterine disruption of bowel circulation [6]. Both JIA and CA necessitate surgical management, which entails typically primary anastomosis in JIA and colostomy in CA [7, 8]. About half of the children with JIA or CA have at least one associated anomaly [8, 9]. Currently, in the era of sophisticated parenteral nutrition, overall survival of children with intestinal atresia is excellent, and the small remaining mortality is usually related to associated anomalies rather than to atresia itself [8, 10]. Due to rarity of intestinal atresia, there are only few previous population-based studies on IA while maternal risk factors for JIA remain little studied.

In this population-based study, we analysed the prevalence, associated anomalies, survival and causes of death among children born with JIA or CA in Finland during 1987–2019. In addition, for all the JIA cases from 2004 to 2017, we performed case–control study to find possible maternal risk factors for JIA.

2 | Patients and Methods

This was a retrospective, population-based and partly case–control (maternal risk factors for JIA) register study. The utilised registries are maintained by the Finnish Institute Health and Welfare (THL) and Statistics Finland, and the Social Insurance Institution of Finland (Kela). The ICD-9 Atlanta and ICD-10 codes of World Health Organization were used to identify patients and classify cases.

Patients were gathered in two cohorts. First, to analyse prevalence, associated anomalies and survival, all live born children with JIA ($n=175$) or CA ($n=48$) from 1987 to 2019 were identified from the Finnish Register of Congenital Malformations. To ensure accuracy, all data in these registers undergo verification by a medical geneticist. Multiple national and international investigations have validated the accuracy and high degree or coverage of these data [11–13]. All registered congenital malformations were reviewed and classified based on the Eurocat

criteria [14]. Anomalies in single organ system are classified as isolated, whereas an anomaly in two or more organ systems lead to multiple congenital anomaly-classification. However, all anomalies occurring in the context of known genetic or chromosomal disorder are classified as syndromic. All recorded deaths in JIA ($n=21$) and CA ($n=3$) groups were identified up to year 2019 and reviewed in terms of cause and timing of death.

Second, to analyse maternal risk factors, all JIA cases from 2004 to 2017 ($n=101$) were separately identified. For each case, five live-born controls with no congenital gastrointestinal anomalies matched for geographic area, maternal age and year of birth or termination of pregnancy (within 1 year) were randomly selected from the Medical Birth Register. Analysed maternal risk factors included prescription medications dispensed during the time window of 1 month before the last menstrual period until the end of the first trimester of pregnancy, body mass index, smoking, reproductive history and chronic maternal diseases. Regarding maternal medication and chronic diseases, groups with five or more exposed fetuses among cases or controls were selected for analysis. Data on reimbursed maternal prescription medicine purchases were obtained from the Reimbursement for Medicine Expenses Register and the Long-Term Illnesses Register, both maintained by Social Insurance Institution of Finland (Kela).

Conditional logistic regression was utilised in the assessment of different risk factors. Before creating a multivariable model, univariate models and Fisher exact test were used to identify potential risk factors. Odds ratios (ORs) and adjusted odds ratios (aORs) with 95% confidence intervals were calculated. Linear regression was used to assess the change in prevalence rate over time. All statistical tests were executed as two-sided. A significance level was set at $p < 0.05$. The analysis also included non-significant variables previously recognised as risk factors for multiple other congenital anomalies. The analysis was performed with SAS System, version 9.4 for Windows (SAS Institute Inc., Cary, NC).

3 | Results

3.1 | Prevalence

The total prevalence for JIA was 0.9 per 10000 births and for CA 0.25 per 10000 births, including both live births and terminated pregnancies. Live birth prevalence for years 1987–2019 is shown in Figure 1A,B.

3.2 | Associated Syndromes and Anomalies

Overall, 49% of the JIA and 58% of the CA were isolated. On the other hand, 7% of JIA and 4% of CA cases were syndromic (Table 1). In both groups, the main associated anomalies were gastrointestinal (26% in JIA and 35% in CA), followed by cardiac anomalies (13%) and abdominal wall defects (AWD) (9%) in JIA group and urinary tract anomalies (19%), cardiac defects (13%) and AWDs (13%) in CA group (Table 2). Among gastrointestinal anomalies, malrotation was common in both groups, covering 20% ($n=13$) in JIA and 16% ($n=4$) in CA. In JIA, associated large

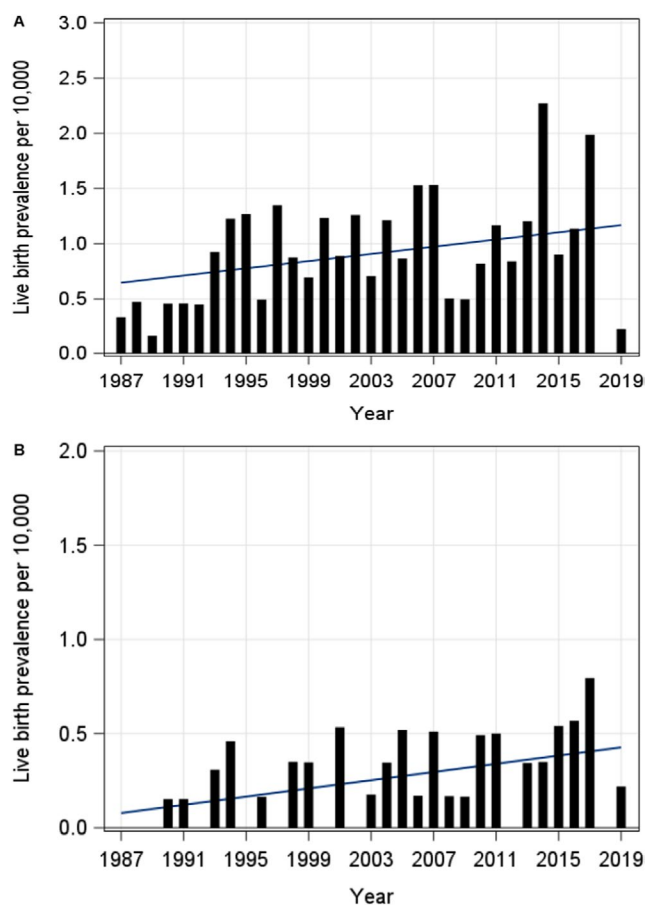


FIGURE 1 | (A) Live birth prevalence of JIA 1987–2019. (B) Live birth prevalence of CA 1987–2019.

TABLE 1 | Syndromes and associations related to intestinal atresias.

Syndrome/association	n (%)
Jejunioleal atresia	175 (100)
Trisomy 21	4 (2.3)
VATER/VACTERL	3 (1.7)
Trisomy 18	< 3
CATCH-22	< 3
Cartilage-hair hypoplasia	< 3
Alagille's syndrome	< 3
Colonic atresia	48 (100)
VATER/VACTERL	< 3
Nager syndrome type 2	< 3

Note: Due to Finnish legislation, frequencies under three are not reported.

bowel atresia covered 14% ($n=9$) of associated gastrointestinal anomalies. Duodenal atresia was also found in 14% ($n=9$) of JIA patients. Other significant associated gastrointestinal anomalies in JIA group were anorectal malformations ($n=5$), oesophageal atresia ($n=4$), biliary atresia ($n=4$) and Hirschsprung's disease (HD) ($n=1$). In CA group, jejunioleal atresia presented in 8 cases and anorectal malformation in 4 cases. There were no cases of HD in CA group.

TABLE 2 | Associated anomalies in patients with jejunioleal and colonic atresia. N (%).

	JIA ($n=175$)	CA ($n=48$)	p
Syndrome	12 (7)	2 (2)	0.9
Multiple congenital anomalies	73 (42)	25 (52)	0.8
Isolated	89 (51)	20 (42)	0.8
Gastrointestinal	46 (26)	17 (35)	0.8
Cardiac	23 (13)	6 (13)	1
Abdominal wall defect	16 (9)	6 (13)	0.9
Urinary	10 (6)	9 (19)	0.3
Ear-face-neck	11 (6)	4 (8)	0.9
Nervous system	9 (5)	3 (6)	1
Respiratory	9 (5)	3 (6)	1
Limb	7 (4)	< 3	1
Genital	4 (2)	4 (8)	0.6
Spine	< 3	< 3	0.9
Eye	< 3	< 3	0.9
Oro-facial cleft	< 3	0 (0)	1
Other	11 (6)	4 (8)	0.9

Note: Due to Finnish legislation, frequencies under three are not reported.

Only one of the AWDs was exomphalos (in CA group), the rest being all gastroschisis. Almost half of the cardiac anomalies (10/23 in JIA and 3/6 in CA group) consisted of either ventral septal defect (VSD), atrial septal defect (ASD) or patent ductus arteriosus (PDA). VSD was the leading cardiac anomaly in both groups. In CA group, where urinary tract anomalies were more common, over half of the patients (5/9) had one or two dysplastic kidney(s).

3.3 | Survival

In total, there were 21 (12%) deaths in JIA and three (6%) deaths in CA group. In JIA group, the median age at the time of death was 49 days. Ten (48%) of the babies died as neonates, before day 30 of life. Only one neonatal death was a direct consequence of intestinal atresia—intestinal perforation in a preterm baby, who died in day one of life. In addition, one neonate died of sepsis—a cause of death that could be explained also by intestinal atresia and/or its treatment. Three neonates died due to cardiovascular abnormalities, two due to genetic abnormalities, one due to meconium aspiration, one due to twin-to-twin transfusion syndrome and one due to malformation of the pancreas.

After the neonatal period, just one death resulted directly from intestinal atresia—a 3-month-old baby, who had developed hepatic fibrosis as a contributing factor for death. One case was a premature, extremely low birth weight child with respiratory distress syndrome and suspected bacterial sepsis, who died at the age of 48 days. Two patients died from congenital

gastrointestinal abnormalities (biliary atresia and gastroschisis); two children from infectious diseases; one from a neurological disorder; and one from a cardiac abnormality. Three additional deaths were attributable to other causes unrelated to intestinal atresia.

In CA group, two of the three deaths were related to kidney abnormalities and occurred on during the first day of life. The third died of ‘undefined ear, head or neck-abnormality’ during the second day of life.

3.4 | Maternal Risk Factors for JIA

For analysis of risk factors, 101 JIA patients were identified (90 livebirths, 6 stillbirths and 5 terminations of pregnancy). After the exclusion of syndromic cases, there were 95 cases and 475 matched controls. In univariate analysis, maternal use of insulin (ATC code A10A) (odds ratio [OR] 7.7, 95% confidence interval [CI] 1.3–46.8) and propionic acid derivatives (M01AE) (OR 3.9, 95% CI 1.3–11.6) increased the risk of JIA. This group of propionic acid derivatives includes common non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, ketoprofen and naproxen. There was no association with BMI, smoking, chronic diseases or use of other drugs during the pregnancy and the risk of JIA. In multivariable analysis, insulin and propionic acid derivatives were both associated with an increased risk of JIA—adjusted odds ratio (aOR) 8.4, 95% CI 1.4–51.0 and aOR 4.6, 95% CI 1.5–14.8, respectively. Results of univariate and multivariable analysis are shown in Table 3.

4 | Discussion

In this study, we retrospectively analysed patients with intestinal atresia born in Finland between 1987 and 2019 and

conducted a case–control study involving 95 patients with jejunoileal atresia (JIA) to identify potential maternal risk factors.

Given the limited understanding of the aetiology of intestinal atresia, our findings—particularly the observed association between JIA and maternal use of insulin and propionic acid derivatives—are notable. Although risk factors for intestinal atresia have not been extensively studied, a few prior publications do exist. In 1987, Seashore et al. reported five families with more than one child affected by apple peel atresia (APA), suggesting a complex genetic background [15]. Chen et al. identified *TTC7A* gene mutations as a cause of combined immunodeficiency with multiple intestinal atresias [16], and Bilodeau et al. also described hereditary multiple intestinal atresia [17]. In addition, a link between jejunoileal atresia and cystic fibrosis, resulting from *CFTR* gene mutations, has been documented in several studies [18–20]. Moreover, inherited thrombophilia has been proposed as a contributing factor to foetal mesenteric thrombotic events leading to intestinal atresia [21]. Gastroschisis is a well-known risk factor for intestinal atresia, as documented in earlier studies [22–24].

When it comes to maternal risk factors, available literature is scarce. A systematic review and meta-analysis by Chen et al. suggest NSAIDs exposure in early pregnancy increases the risk of major birth defects, congenital heart defects and gastroschisis [25]. An American study reported that maternal use of vasoconstrictive drugs and cigarette smoking during early pregnancy—especially in combination—increased the risk of both gastroschisis and small intestinal atresia [26]. Although the effects of NSAIDs are likely multifactorial, their vasoconstrictive properties could potentially represent one of the mechanisms contributing to the increased risk of JIA observed in this study. However, we did not observe similar signal for other vasoconstrictive medicines. Lin et al. found no association between maternal periconceptional use of asthma

TABLE 3 | Unadjusted and adjusted analysis for maternal risk factors.

	Cases (total number of cases)	Controls (total number of controls)	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Insulin	3 (92)	< 3 (475)	7.5 (1.3–44.9)	8.40 (1.38–51.04)
Propionic acid derivatives	6 (89)	8 (475)	4.3 (1.4–13.6)	4.64 (1.45–14.80)
BMI < 18.5	3 (83)	14 (450)	1.03 (0.27–3.88)	
BMI 18.5–24.99	53 (83)	262 (450)	Reference	
BMI ≥ 25	27 (83)	174 (450)	0.77 (0.46–1.27)	
Smoking	12 (91)	85 (461)	0.65 (0.33–1.28)	
Multiparity	55 (92)	275 (474)	1.11 (0.69–1.80)	
No miscarriages	66 (92)	377 (474)	Reference	
One miscarriage	19 (92)	69 (474)	1.59 (0.90–2.80)	
Two or more miscarriages	7 (92)	28 (474)	1.46 (0.58–3.67)	

Note: The total number of cases and controls varies due to missing data. BMI is not applicable in terminated pregnancies due to foetal anomaly. Due to Finnish legislation, frequencies under three are not reported.

medication and small intestinal atresia [27]. A Hungarian study suggested that maternal glomerulonephritis may be a potential risk factor for isolated intestinal atresia or stenosis [28]. A population-based study from Hawaii observed a higher incidence of small intestinal atresia among individuals of Far East Asian descent compared to Caucasians and reported a U-shaped risk distribution in relation to maternal age [29]. Pregestational diabetes is a well-established risk factor for multiple congenital anomalies [30–33], and substantial evidence indicates that periconceptional hyperglycaemia is a major diabetic teratogen [34, 35]. However, the observed associations with insulin use may reflect not only glycaemic exposure but also disease severity, treatment intensity or other diabetes-related factors.

There is more extensive data on maternal risk factors for other congenital anomalies. Maternal obesity, smoking during pregnancy, diabetes and exposure to organic solvents have been associated with congenital heart disease [36]. Additional risk factors include the maternal use of vitamin A supplements, valproic acid and antihypertensive medications [37]. Congenital vertebral anomalies have been linked to maternal pregestational diabetes and rheumatoid arthritis [38]. Interestingly, the use of extended-spectrum penicillin during early pregnancy may reduce the risk of omphalocele [32]. In the future, further research into the risk factors of intestinal atresia and other congenital anomalies is essential. For clinicians, better knowledge of these factors can support prenatal and postnatal diagnostics. In some cases, avoidance of specific medications during pregnancy could potentially reduce the incidence of certain congenital anomalies. However, it should be noted that prescribed medications may act as a proxy for other underlying clinical or contextual factors rather than representing a direct causal effect. Also, we have no information on the possible stockpiling of prescription drugs or on over-the-counter medication, foreign online pharmacies, herbal medicines or illicit drugs.

In our cohort, overall survival was 88% for JIA and 94% for colonic atresia (CA). Among JIA patients, the mortality rate was higher than in more recent studies [39, 40], yet slightly lower than in older studies [1, 41], reflecting the advancements in the care of patients with intestinal atresia that we previously reported [8]. For CA, the survival rate was lower than in some prior studies [1, 41]. However, it is important to note that most of the deaths (19/21 in JIA and 3/3 in CA) were due to causes unrelated to intestinal atresia itself.

Based on our results, approximately half of JIA cases are isolated, whereas about half of CA cases involve multiple congenital anomalies. Approximately one in twenty intestinal atresia cases is syndromic. Cardiac and gastrointestinal anomalies, along with abdominal wall defects (AWDs), were commonly associated with both JIA and CA. This is consistent with previous literature. In JIA, Dalla Vecchia et al. found AWDs to be even more prevalent, with cardiac and gastrointestinal malformations among the most common associated anomalies [1]. Despite differences in anomaly classification, similar patterns were observed in a German study [42]. Although the number of CA patients in many studies is limited, associations with AWDs and gastrointestinal anomalies have also been reported elsewhere [1, 43, 44]. Notably, nearly 20% of our CA patients had

associated urinary tract anomalies—higher than previously reported [1, 43, 44]. Despite a known association between CA and HD, we did not identify any HD cases among CA patients in our cohort. One HD case was found in a JIA patient.

This study has several limitations. Despite Finland's high-quality medical registries [32], our dataset may not include all cases of intestinal atresia from the study period. For example, a mild intestinal atresia (stenosis) without apparent symptoms or clinical findings might not be recorded, as the Finnish Register of Congenital Malformations covers only the first year of life. Conversely, there may be cases included that do not correspond to true jejunoileal or colonic atresia, even though the Finnish register does confirm all major congenital anomalies (THL: Register of Congenital malformations <https://thl.fi/en/statistics-and-data/data-and-services/register-descriptions/register-of-congenital-malformations>). Retrospective registry-based studies inherently carry the risk of missing or misclassifying data. It is also noteworthy that not all possible risk factors are recorded. We attempted to mitigate these issues by carefully selecting diagnostic codes used for case screening and rigorously reviewing registry data. Whenever possible, we used free-text information to confirm and refine ICD coding.

In conclusion, our findings suggest an association between maternal use of insulin and propionic acid derivatives and the occurrence of JIA. To our knowledge, this is the first study to report such an association. Both JIA and CA are frequently accompanied by other anomalies, although associated anomalies are more prevalent in CA. Survival among patients with intestinal atresia is generally excellent, and mortality is mainly from associated conditions rather than the atresia itself.

Author Contributions

Esko Tahkola: writing – original draft, conceptualization, investigation, methodology, visualization, writing – review and editing, data curation. **Mika Gissler:** methodology, validation, writing – review and editing, data curation.

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Conflicts of Interest

Author M.P.P. declares no conflicts of interest for this article. Authors E.T., A.R., T.L., T.K., E.L., M.G. and M.K.L. declare no conflicts of interest. Author J.S. has received a lecture honorarium from Bonali. Author I.H. serves as a consultant for Medtronic International.

Data Availability Statement

Research data are not shared.

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