ORIGINAL ARTICLE

Effect of trisomy 21 on long-term gastrointestinal outcomes in duodenal atresia

Anna Zrinyi[1] · Suyin A. Lum Min[1] · Emmanuel A. Bello[1] · Charanpal Singh[1] · Richard Keijzer[1]

Abstract

Purpose We aimed to determine if Trisomy 21 (T21) affected gastrointestinal outcomes for children with duodenal atresia (DA).

Methods We identified children born with DA between 1991 and 2017. Cases were divided into DA with T21 and DA without T21. Ten healthy controls per case were included. Esophageal, ulcerative, obstructive and stomach complaints were assessed. Risk ratios (RR), rate ratios (RaR) and Cox models were constructed. Analyses were performed for cases versus controls, and for T21 cases versus non-T21 cases.

Results DA cases totaled 52: 22 had T21 and 30 did not. There were 520 controls. DA cases had more gastrointestinal complaints than controls. T21 cases were at greater risk and frequency of esophageal disease than non-T21 cases ($RR = 4.08$, $p = 0.002$, $RaR = 69.8$, $p < 0.001$). T21 and non-T21 cases were equally likely to present with obstruction ($RR = 0.91$, $p = 1$), but T21 cases complained of obstructive symptoms less ($RaR = 0.57$, $p = 0.003$). T21 and non-T21 cases had the same risk of stomach diseases, but T21 cases complained more frequently ($RaR = 6.20$, $p < 0.001$). Cox models supported these observations. T21 did not affect ulcerative diseases.

Conclusion DA cases had more gastrointestinal problems than controls. T21 increased esophageal and gastric complaints in DA cases but did not affect ulcerative and obstructive complaints.

Keywords Duodenal atresia (DA) · Down syndrome · Trisomy 21 · Gastrointestinal

Introduction

Duodenal atresia is a congenital condition in which the small bowel distal to the pylorus and proximal to the ligament of Treitz is completely or partially obstructed. It is the most common site of congenital intestinal obstruction and occurs in 1 in 6000 to 10,000 live births [1]. Thirty to 40% of children with duodenal atresia have Trisomy 21 [2]. Studies have investigated activities of daily living, such as homecare and schooling, in children with Down syndrome. They found that Down syndrome children with duodenal atresia perform similar to children with Down syndrome but without duodenal atresia [3]. Vinycomb et al. concluded that after duodenal atresia repair, children have a quality of life comparable to the healthy population; however, children with both duodenal atresia and Trisomy 21 were more disposed to a reduced quality of life [4].

Vinycomb et al. also found no difference in the gastrointestinal quality of life between duodenal atresia cases with Down syndrome and without [5]. However, other comparisons of gastrointestinal outcomes in duodenal atresia with Trisomy 21 to duodenal atresia without Trisomy 21 are equivocal. Singh et al. concluded that despite a higher incidence of cardiac anomalies in the Trisomy 21 cases with duodenal atresia, Trisomy 21 did not influence morbidity and mortality [4]. However, Niramis et al. reported that in the absence of congenital heart disease, the overall survival of duodenal atresia cases with Trisomy 21 was worse than duodenal atresia without Trisomy 21 children. They postulated that the increased mortality was due to an increased risk of respiratory tract infections [6].

Trisomy 21 is one of the most common genetic disorders [7]. Almost 4% of children with Trisomy 21 have duodenal

✉ Richard Keijzer
    rkeijzer@hsc.mb.ca

1   Department of Surgery, Division of Pediatric Surgery, University of Manitoba, and Children's Hospital Research Institute of Manitoba, AE402-820 Sherbrook Street, Winnipeg, MB R3A 1S1, Canada

atresia [8]. It is unclear if, and how, management of duodenal atresia associated with Down syndrome should differ from duodenal atresia alone. Smith and Landman found that 82.4% of Trisomy 21 duodenal atresia patients had a gastrostomy [9]. Maassel et al. showed that the rate of delayed gastrostomy tube insertion at institutions that did not initially insert tubes was not greater than those that did [10]. They concluded that routine gastrostomy in Trisomy 21 patients may be unnecessary [10]. By comparing specific gastrointestinal outcomes in Down syndrome-duodenal atresia children, clinicians can make more informed decisions regarding treatment.

The aim of this case-control study was to perform a comparison of specific gastrointestinal outcomes, esophageal dysfunction, ulcerative diseases, intestinal obstruction, and gastric dysfunction for children with duodenal atresia and Trisomy 21 to children with duodenal atresia but without Trisomy 21.

Methods

After gaining approval by ethics [HS20964 (H2017:252)], we used a clinical database to identify all children born with duodenal atresia between 1991 and 2017. This database contains demographic information, treatment details, and follow-up after discharge for patients born with congenital surgical anomalies since 1991. For our study, we defined long-term as the time after discharge following the duodenal obstruction repair. The clinical database was linked to a government data repository using scrambled *Personal Health Information Numbers.* The data repository contains deidentified health, education, and socioeconomic data for all people living in the province. Cases were divided into two groups: duodenal atresia with Trisomy 21 and duodenal atresia without Trisomy 21.

A control cohort was obtained from the government data repository. Ten date-of-birth matched controls were randomly selected from the general population for each duodenal atresia patient. Scrambled *Personal Health Information Numbers* were used to access the control cohort's data. The cohort was created using SAS® statistical software then uploaded into R® for analysis.

Baseline characteristics for cases and controls were collected from the *Hospital Abstracts* dataset available from the government data repository. The baseline characteristics compared were: gestational age at birth, birth weight, sex, 1- and 5-min APGAR scores, and length of hospital stay after birth.

Gastrointestinal outcomes were identified through the *Medical Claims/Medical Services* data set available from the government data repository using the International Classification of Diseases version 9 (ICD-9) codes. The *Medical Claims/Medical Services* data set records all services provided in hospitals, clinics, and doctors' offices. We were able to classify complaints to three digits of the ICD-9 codes. The ICD-9 disease classifications studied were: esophageal (ICD-9 530), ulcerative (ICD-9 531-535 and 538), obstructive (ICD-9 560), and stomach (ICD-9 536 and 537) complaints. The ICD-9 code for esophageal diseases captured presentations for reflux, eosinophilia, and ulcers of esophagus, among other less common esophageal complaints in children. The ICD-9 code for ulcerative diseases included gastric, duodenal, peptic and gastrojejunal ulcers, gastritis, duodenitis, and gastrointestinal mucositis. The intestinal obstructive diseases relevant to our study were intussusception, volvulus, and post-operative adhesions or obstructions. The ICD-9 code for the disorders of the stomach included general gastrostomy complications, dyspepsia, and other functional disorders of the stomach.

Statistical analysis

Risk ratios (RR), rate ratios (RaR), Cox hazard ratio models, and Cox recurrent event ratio models were constructed for each disease. The results are reported as means with standard deviations. We defined the 'risk' as the number of individuals that were diagnosed with the ailment of interest; regardless of the number of times an individual complained they were only counted once. The 'rate' was defined as the number of times diagnosed individuals had a complaint, also referred to as the 'frequency' of the diagnoses. Analyses were performed for all duodenal atresia cases compared to the date-of-birth matched control group while controlling for the covariates sex, socioeconomic status and birth year. Relative risks were plotted for cases and controls using a control born in 2000 as the reference for the likelihood of being diagnosed with each outcome dependent on birth year and for the frequency of diagnosis dependent on birth year. Cases with duodenal atresia and Trisomy 21 were then compared to cases with duodenal atresia but without Trisomy 21. Covariates for this analysis were sex and socioeconomic status. The statistical analysis was performed using R® version 3.6.1. P-values < 0.05 were considered significant.

Results

A total of 52 cases of duodenal atresia were identified; 22 had Trisomy 21 and 30 did not have Trisomy 21. The control group consisted of 520 children without duodenal atresia. We have shown here examples of each type of analysis and summarized the results in Table 1 (cases versus controls) and Table 2 (Trisomy 21 cases versus no Trisomy 21 cases).

Table 1 Comparison of the gastrointestinal diseases between duodenal atresia cases compared to date-of-birth matched controls

Disease	Number of individuals diagnosed		Risk ratio			Total number of diagnoses		Poisson rate ratio			Cox hazard ratio			Cox recurrent hazard ratio		
	Cases	Controls	RR	95% CI	p	Cases	Controls	RaR	95% CI	p	HR	95% CI	p	RHR	95% CI	p
Esophageal																
Cases	16	33	4.85	2.87, 8.19	<0.001	229	96	1.88	0.93, 3.64	0.069	3.63*	0.55, 24.1	0.2	7.09*	2.11, 23.8	0.002
Case/birth year								29.0	9.17, 93.9	<0.001	0.30*	0.02, 4.30	0.4	3.48*	0.70, 17.3	0.13
Ulcerative																
Cases	8	29	2.76	1.33, 5.72	0.013	14	65	0.94	0.24, 3.01	>0.9	1.63*	0.29, 9.22	0.6	0.84*	0.16, 4.41	0.8
Case/birth year								0.21	0.01, 3.89	0.3	0.17*	0.00, 5.86	0.3	0.10*	0.00, 3.46	0.2
Obstructive																
Cases	20	**	100	24.04, 415.9	<0.001	132	24	4.40	1.91, 11.0	<0.001	21.4	1.28, 358	0.033	14.3	0.99, 206	0.051
Case/birth year								0.00	0.00, 0.01	<0.001	0.00	0.00, 188	0.3	0.00	0.00, 42.4	0.2
Stomach																
Cases	11	8	13.75	5.79, 32.66	<0.001	59	47	0.60	0.17, 1.80	0.4	6.12	0.69, 54.5	0.10	3.74	0.60, 23.2	0.2
Case/birth year								1.23	0.19, 8.46	0.8	0.28	0.00, 17.3	0.5	0.20	0.01, 6.12	0.4

The risk ratio (RR) and the Poisson rate ratio (RaR), Cox hazard ratio models (HR) and recurrent hazard ratios models (RHR) are shown. The 'interaction between cases and birth year' covariable is displayed but sex and socioeconomic factor are not

HR—Hazard ratio; *95% CI* 95% confidence interval; *p* *p*-value

*Failed Schoenfeld residuals assumption test

**Censored due to less than 5 individuals

Table 2 Comparison of gastrointestinal diseases between Trisomy 21 cases and those without Trisomy 21

Disease	Number of individuals diagnosed		Risk ratio			Total number of diagnoses		Poisson rate ratio			Cox hazard ratio			Cox recurrent hazard ratio		
	T21	No T21	Risk ratio	95% CI	p	T21	No T21	Rate ratio	95% CI	p	HR	95% CI	p	HR	95% CI	p
Esophageal	12	**	4.09	1.52, 10.1	0.002	224	5	69.8	32.1, 196	< 0.001	6.50	2.03, 20.8	0.002	12.1*	5.11, 31.5	< 0.001
Ulcerative	**	**	0.82	0.21, 3.07	1	7	7	1.38	0.47, 4.06	0.5	0.91*	2.24, 3.5	0.90	0.86*	0.20, 3.65	0.80
Obstructive	8	12	0.91	0.45, 1.84	1	39	93	0.57	0.39, 0.82	0.003	0.75	0.29, 1.93	0.55	0.39	0.16, 0.97	0.042
Stomach	7	**	2.39	0.80, 7.16	0.17	48	11	6.20	3.32, 12.7	< 0.001	2.61	0.86, 7.93	0.090	2.29	0.78, 6.79	0.13

Cases with Trisomy 21 were more likely than cases without Trisomy 21 to have esophageal dysfunction (risk ratio) and more frequently report esophageal and stomach complaints (rate ratio). There was no difference regarding the presentation of obstructive diseases, but Trisomy 21 cases had fewer complaints. Ulcerative disease was unaffected by the presentation of Trisomy 21

HR Hazard ratio, *95% CI* 95% confidence interval, *p* p-value

*Failed Schoenfeld assumption test

**Censored due < 5 individuals

Esophageal dysfunction

Duodenal atresia patients were at greater risk of developing esophageal disease than controls (RR = 4.85, $p < 0.001$) as shown in Table 1. There was a small increase in the frequency with which cases complained of esophageal symptoms but it failed to reach significance (RaR = 1.88, $p = 0.069$). The plot of the cumulative incidence, shown in Fig. 1, showed that throughout childhood and adolescence cases were more likely to be diagnosed with esophageal disease, and most diagnoses occurred within the first few years of life. The plot of the cumulative events demonstrated that throughout childhood and adolescence cases presented more frequently with esophageal complaints and most complaints occurred in the first ten years of life (Fig. 2). The case-birth year interaction variable was significant in the Poisson analysis, as seen in Table 1, suggesting the rate of esophageal complains for cases born in later years was greater than controls born in later years. The plot of the relative risk of being diagnosed with esophageal disease based on birth year suggested that the birth year affected the risk of having an esophageal diagnosis (Fig. 3). Cases born in 2003 appeared to be at the greatest relative risk. The Cox proportional hazard model suggested that neither duodenal atresia alone or interacting with birth year affected the risk of being diagnosed with esophageal disease (Table 1). However, the assumption of a proportional hazard failed based on the test of Schoenfeld residuals making the Cox proportional hazard model suspect as shown in Fig. 4. The plot of the relative frequency of esophageal diagnoses based on birth year again suggested an effect of birth year (Fig. 5). Cases born in 2009 appeared to have the greatest relative frequency. The Cox proportional hazard model of recurrent events suggested that duodenal atresia was associated with an increased rate of complaints at all ages, but the case-birth year interaction had no effect. Again, the assumption of a proportional hazard failed based on the Schoenfeld residuals test making the model suspect. Therefore, we could not conclude that birth year affected the esophageal complaints but the weight of evidence suggests it did.

As shown in Table 2, cases with Trisomy 21 and duodenal atresia had a higher risk and frequency of esophageal disease compared to cases without Trisomy 21 (RR = 4.09, $p = 0.002$; RaR = 69.8, $p < 0.001$). The plot of the cumulative incidence, shown in Fig. 6, showed that Trisomy 21 children were more likely to be diagnosed with esophageal disease, the proportional hazard assumption appeared valid, and most diagnoses occurred within the first few years of life. The Cox proportional hazard model passed the Schoenfeld residuals test as shown in Fig. 7 and showed that the hazard ratio for Trisomy 21 cases was greater than no Trisomy 21 cases (HR = 6.50, $p = 0.002$). The plot of the cumulative events of esophageal
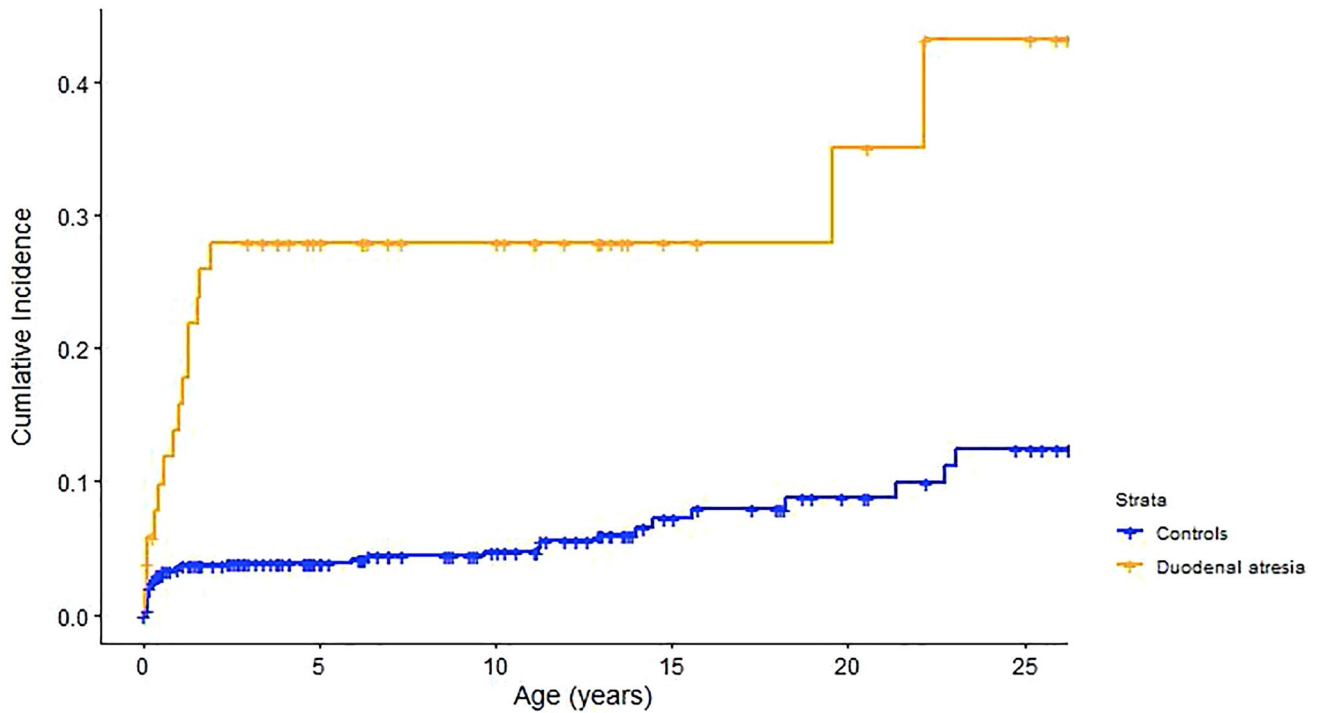
Fig. 1 Cumulative incidence of individuals with esophageal diseases for cases and controls. Cases were more likely to be diagnosed with an esophageal disease. The diagnoses were more likely to occur within the first 5 years of life
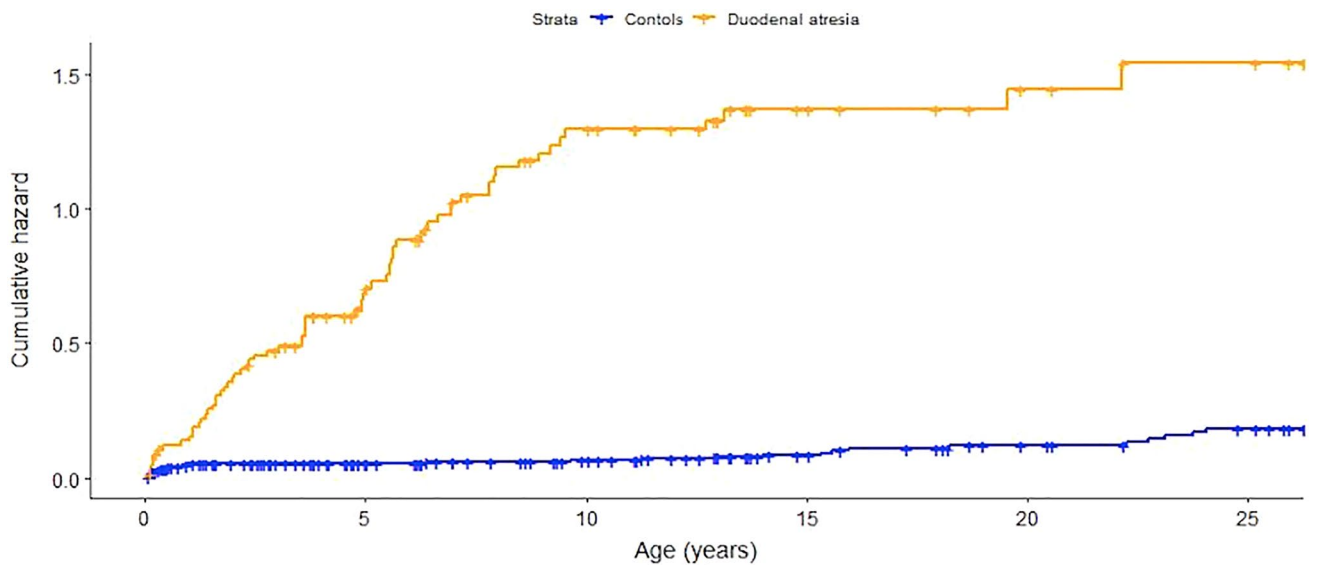

Fig. 2 Cumulative events of esophageal presentations for duodenal atresia patients and controls. Cases with esophageal disease complained more frequently than controls. The complaints were more likely to occur within the first 10 years of life

presentations for cases with Trisomy 21, shown in Fig. 8, showed that Trisomy 21 children are more likely to have recurrent presentations than cases with Trisomy 21. Most presentations occurred within the first ten years of life. The Cox recurrent hazard model suggested that the effect of Trisomy 21 on the frequency of esophageal complaints was significant, but the model failed the test of proportional hazards. Therefore, we can only suggest that although Trisomy 21 increases esophageal complaints, the effect may not persist over all ages.
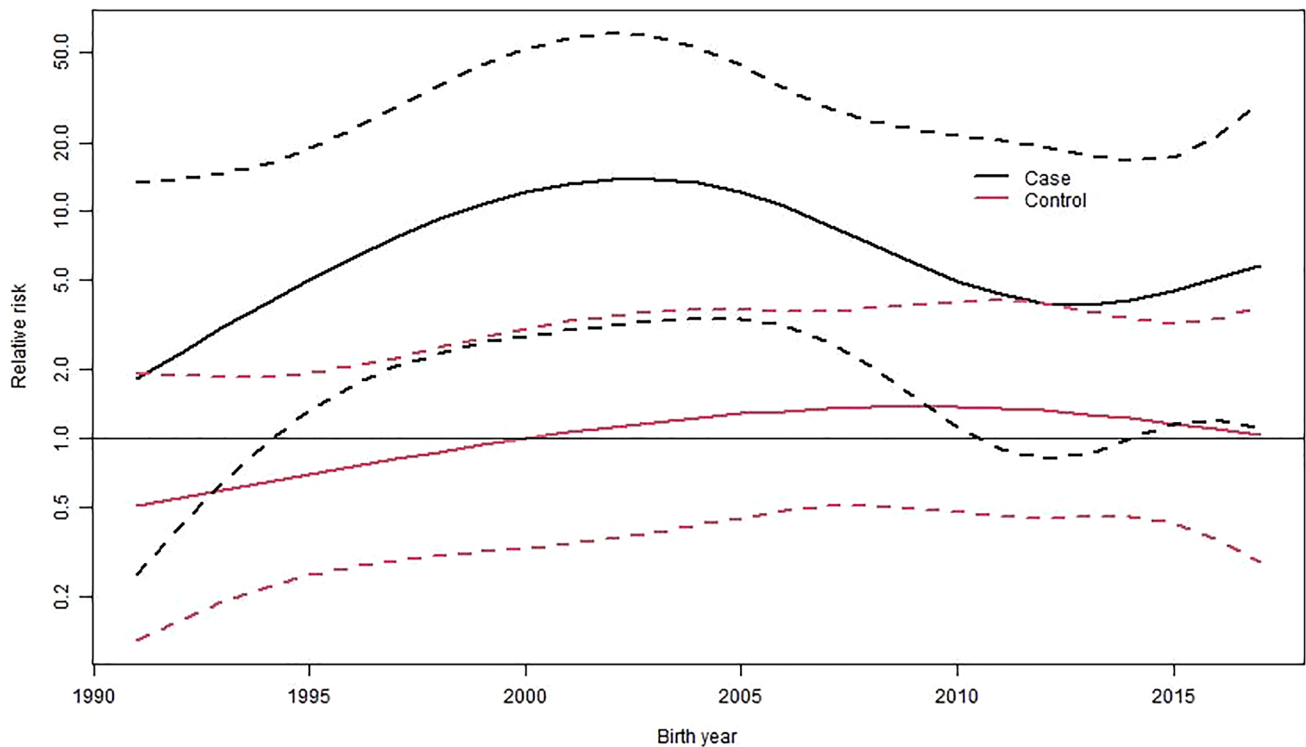
Fig. 3 Plot of the relative risk for duodenal atresia cases and controls using a control born in the year 2000 as the reference suggested an effect of birth year for esophageal disease
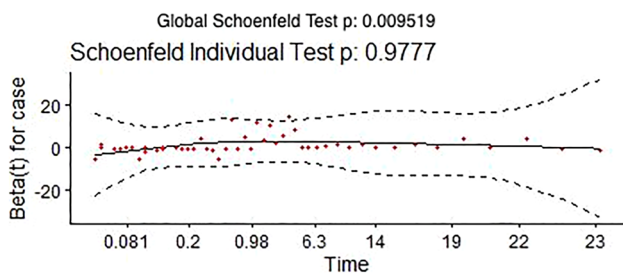
Fig. 4 Schoenfeld residuals test for the Cox proportional hazard plots for the duodenal atresia cases compared to controls examining esophageal diseases

Ulcerative diseases

The risk of ulcerative disease was higher for duodenal atresia patients than for controls (RR = 2.76, $p = 0.013$). However, the frequency with which cases were diagnosed was not different (RaR = 0.94, $p > 0.9$). The case-birth year interaction variable was not significant in the Poisson analysis. The Cox models predicted no effect for cases or cases interacting with birth year but did not meet the assumption of proportional hazards and were therefore suspect.

The risk and rate of ulcerative disease for cases with Trisomy 21 and cases without were similar (RR = 0.82, $p = 1$; RaR = 1.38, $p = 0.5$). Both Cox proportional hazard models failed the Schoenfeld residuals test so the results of the models were suspect.

Intestinal obstruction

Duodenal atresia patients were more likely to have an intestinal obstruction than healthy controls, and the rate of presenting with obstructive complaints was higher (RR = 100, $p < 0.001$, RaR = 4.40, $p < 0.001$) as seen in Table 1. The case-birth year interaction was significant in the Poisson analysis suggesting that cases born in later years were less likely to have recurrent events than controls born in later years. The Cox hazard ratio and Cox recurrent hazard ratio predicted an effect for cases, but birth year had no effect of. Both Cox proportional hazard models passed the Schoenfeld residual test suggesting that these results persisted at all ages.

Children with both Trisomy 21 and duodenal atresia had the same risk of an obstructive disorder as cases without Trisomy 21 (RR = 0.91, $p = 1$). However, the frequency with which Trisomy 21 cases presented with obstructive complaints was lower (RaR = 0.57, $p = 0.003$). These results were supported by the modeling of diagnosis over age. The hazard model confirmed that the cumulative incidence was not different for Trisomy 21 versus no Trisomy 21 (HR = 0.75, $p = 0.6$). And, the recurrent hazard model was significant
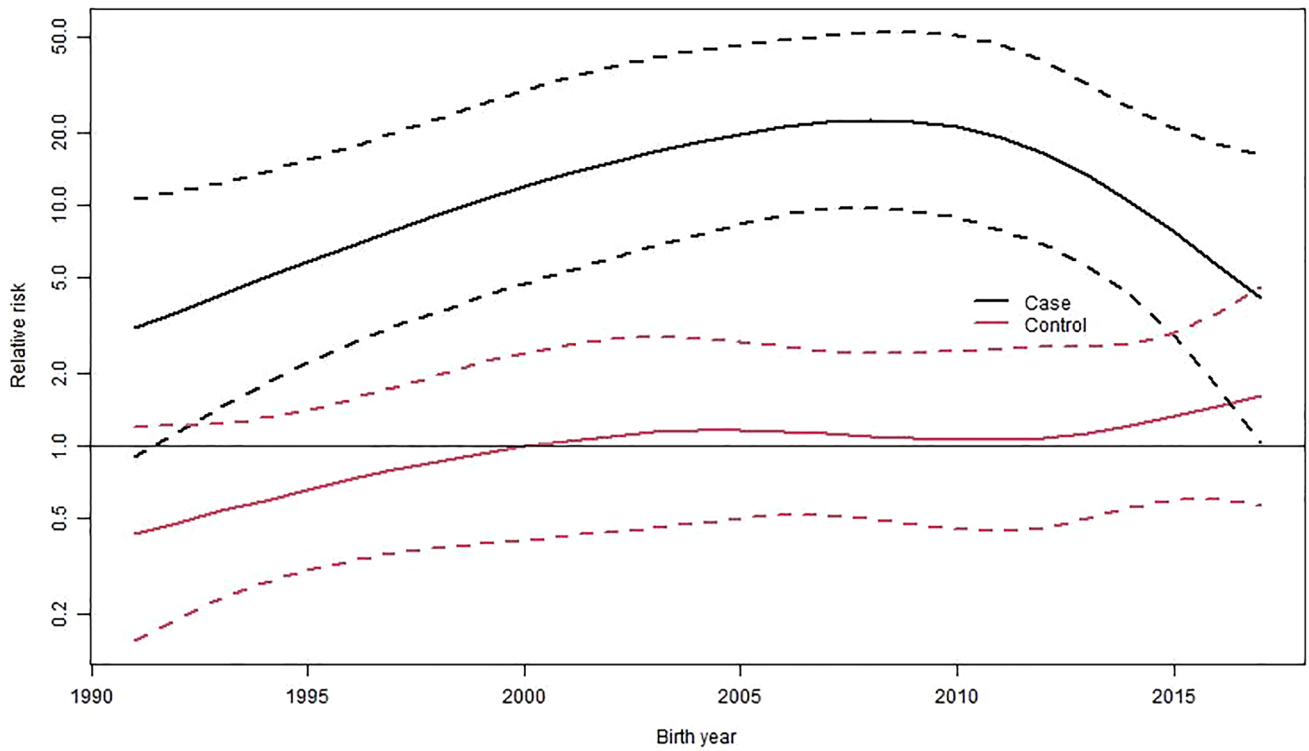
Fig. 5 Plot of the relative frequency for esophageal disease cases and controls using a control born in the year 2000 as the reference suggested an effect of birth year
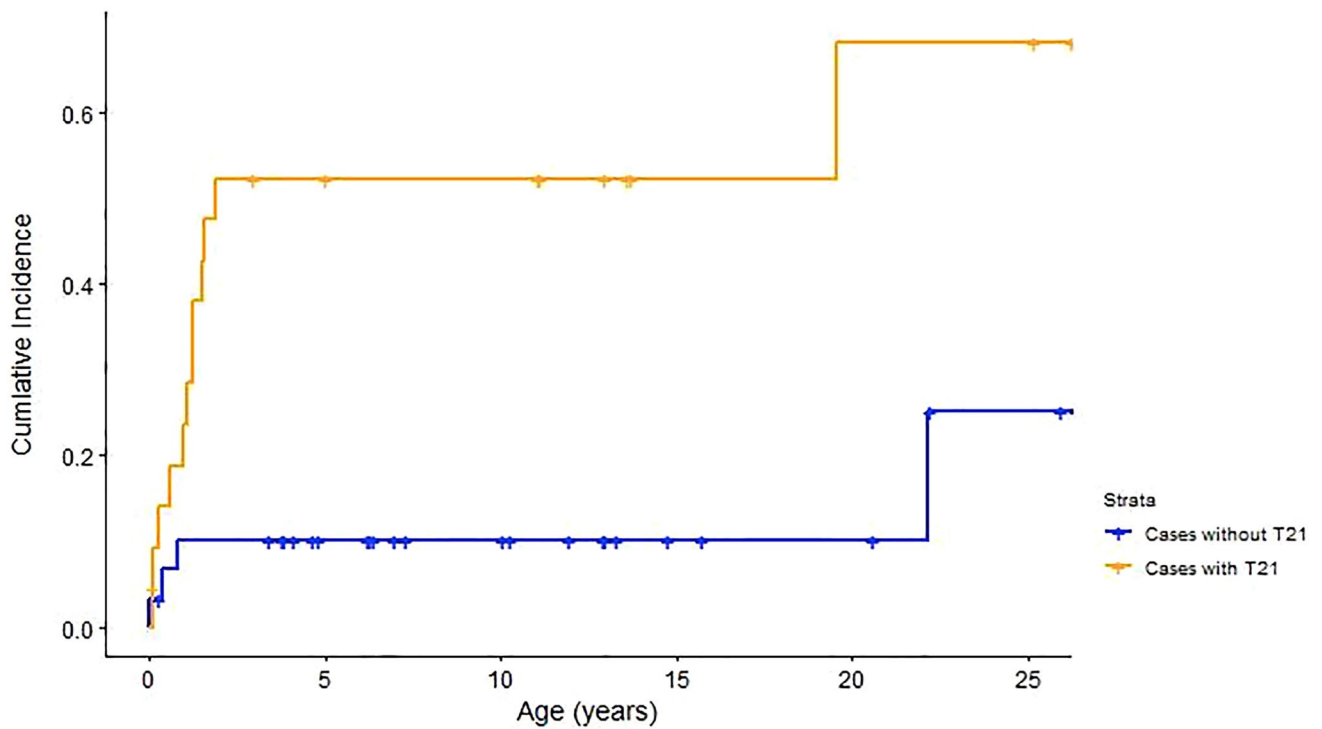

Fig. 6 Cumulative incidence of individuals with esophageal diseases for cases with Trisomy 21 and cases without Trisomy 21. Cases with Trisomy 21 were more likely to be diagnosed with an esophageal disease. The diagnoses are more likely to occur within the first few years of life
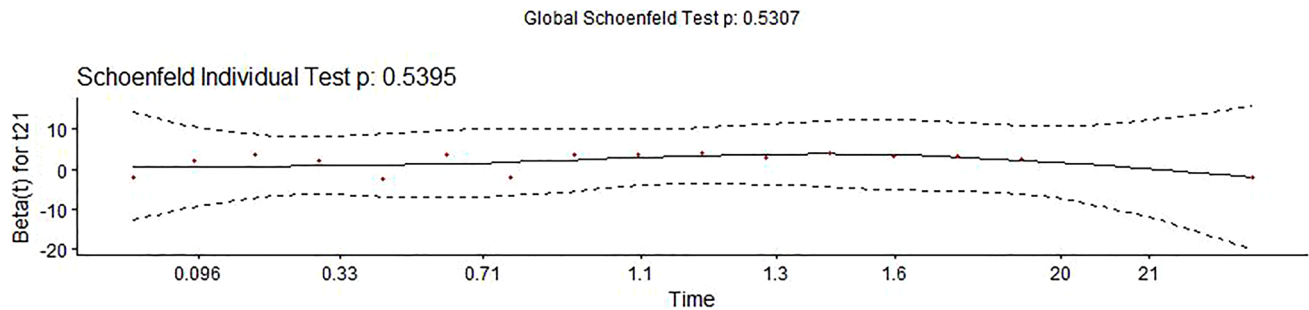
Global Schoenfeld Test p: 0.5307

Fig. 7 Global Schoenfeld residuals test for the Cox proportional hazard model of esophageal dysfunction for cases with and without Trisomy 21. The model appears valid and the residuals for the case variable are minimal
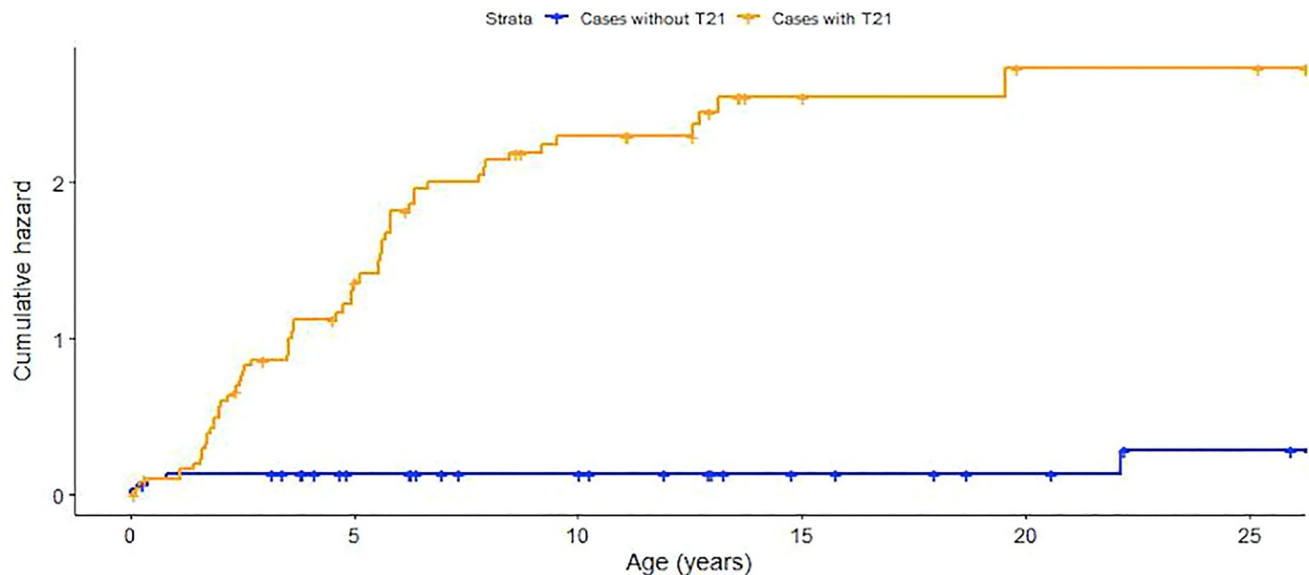
Fig. 8 Cumulative events of esophageal presentations for cases with Trisomy 21 patients and cases without Trisomy 21. Cases with Trisomy 21 and esophageal disease complained more frequently than cases without Trisomy 21

(RHR = 0.39, $p = 0.042$) as seen on Table 2 indicating that the frequency of obstruction was lower in Trisomy 21 cases at all ages. The risk of obstruction was not affected by Trisomy 21 but rate of complaint was lower for Trisomy 21.

Gastric dysfunction

Duodenal atresia patients were at greater risk of stomach disorders than controls (RR = 13.75, $p < 0.001$). However, the frequency with which cases complained of stomach issues was not different from controls as seen in Table 1 (RaR = 0.60, $p = 0.4$). The case-birth year interaction variable was not significant in the Poisson analysis. The Cox proportional hazard and recurrent hazard models failed to reach significance (HR = 6.12, $p = 0.10$, RHR = 3.74 $p = 0.4$). Cox models may have been hampered by attempting to model small numbers over many years.

The risk of gastric dysfunction in Trisomy 21 cases compared to non-Trisomy 21 cases was higher but failed to reach significance (RR = 2.39, $p = 0.17$). Trisomy 21 cases had a greater frequency of diagnoses than non-Trisomy 21 as seen on Table 2 (RaR = 6.20, $p < 0.001$). The Cox proportional hazard model approached but did not meet the threshold for significance (HR = 2.61, $p = 0.09$). The recurrent hazard ratio model also approached but failed to reach significance (RHR = 2.29, $p = 0.13$) as seen on Table 2. It appeared that gastric complaints were more frequent in Trisomy 21 cases.

Discussion

As expected, and demonstrated in this study, individuals with duodenal atresia have more bowel related problems compared to healthy controls. More importantly, our study

showed that the gastrointestinal outcomes of cases with Trisomy 21 differed from cases without Trisomy 21. Esophageal, obstructive and gastric complaints were more common in cases with Trisomy 21 but ulcerative complaints were similar.

According to our findings, duodenal atresia patients are more prone to esophageal diseases than the general population. Spigland and Yazbeck reviewed 33 patients who underwent surgery for duodenal atresia and found that 17% had gastroesophageal reflex [11]. Our study further explored this difference and found that individuals with Trisomy 21 and duodenal atresia may account for the difference between cases and controls. Children with Down syndrome are more likely to have esophageal disorders than a healthy population [12, 13]. Comparison of esophageal diseases in Trisomy 21 with duodenal atresia to those without duodenal atresia may help to determine if the symptoms are due to the Trisomy 21 or duodenal atresia. Our study also suggested an effect of birth year on the rate and frequency of esophageal dysfunction. This may reflect a change in diagnosis and/or treatment patterns over time.

Ulcerative diseases typically present in adulthood. However, peptic ulcer disease is a common complication associated with duodenal atresia [1, 14]. Our study confirmed that cases were more likely to develop an ulcerative disease than healthy controls. Our study also found no difference in the risk or frequency of ulcerative diseases between Trisomy 21 and non-Trisomy 21 cases. Because ulcerative diseases typically present later in life, longitudinal studies on ulcerative diseases in duodenal atresia and Trisomy 21 patients are recommended.

Not surprisingly, cases were at greater risk of intestinal obstruction compared to controls. Post-operative obstructive complications manifesting as motility disorders, blind-loop syndrome and anastomotic strictures are common after repair of duodenal obstruction [14]. Niramis et al. identified 11 intestinal obstructions and one anastomotic stricture in 227 cases of duodenal obstruction followed for more than 4 years [6]. We reported that duodenal atresia and Trisomy 21 patients were not more likely to develop an obstructive disease compared to cases with duodenal atresia only, but the frequency with which obstructive complaints were made was lower in children with associated Trisomy 21. The lower rate of obstructive complaints in Trisomy 21 patients in our study may be due to clinician's interpretation of the patients' presentation. Note that Trisomy 21 cases had a higher frequency of stomach complaints than non-Trisomy 21 cases.

The risk of developing gastric dysfunction was higher in cases compared to controls. We found no difference in the risk of developing gastric dysfunction between Trisomy 21 and non-Trisomy 21 cases. The frequency with which Trisomy 21 patients complained of stomach disease was higher than patients without Trisomy 21. Bairdain et al.

reported the short-term outcomes in enteral feeding in children with duodenal atresia. They found that children with Down syndrome took longer to reach full enteral feeds [15]. The increased frequency of gastric dysfunction may be due to the higher rate of gastrostomy insertion in Trisomy 21 cases or to gastric issues common to children with Trisomy 21 but unrelated to duodenal atresia or its complications. By comparing the gastric complaints of children with Trisomy 21 and duodenal atresia to children with Trisomy 21 uncomplicated by duodenal atresia, the relative contribution of each condition may be determined.

There are several limitations to this study. We could only use ICD-9 codes up to three digits; therefore, we could not be more specific with respect to the outcomes. Our study would have benefitted from having another control group consisting of children with Trisomy 21 but without duodenal atresia. Another limitation was the small sample size. This meant that we could not account for an interaction between case and birth year, and the Cox proportional hazard modeling was suspect in several analyses.

Conclusion

This study investigated the prevalence of specific gastrointestinal diseases in children with duodenal atresia and Trisomy 21 compared to children with duodenal atresia without Trisomy 21. We found Trisomy 21 cases had a higher risk of esophageal disease and the number of esophageal complaints for Trisomy 21 cases was greater than cases without Trisomy 21. Birth year appeared to affect the risk and rate of esophageal diagnoses more than controls suggesting changes in diagnosis or treatment patterns. Ulcerative disease was not affected by Trisomy 21. The number of children with an obstructive complaint was the same for Trisomy 21 and non-Trisomy 21 cases. However, Trisomy 21 children with obstructions complained less frequently than non-Trisomy cases. Stomach diseases occurred slightly more commonly in Trisomy 21 cases, and frequency with which Trisomy 21 cases complained of stomach issues was greater than non-Trisomy 21 cases. Overall, Trisomy 21 cases had more long-term gastrointestinal complications.

Author contributions SLM and RK designed the study AZ, SLM, EB and CS collected and analyzed the data AZ and SLM wrote the main manuscript EB, CS and RK critically reviewed the manuscript.

Declarations

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