

Article

Ecological Analysis of Gastroschisis Incidence Decline in Liaoning, China, 2006-2016

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November 20, 2020

DOI:10.36316/gcatr.02.0036

ABSTRACT

Background: A gastroschisis incidence decline has recently been reported in Liaoning, China, from 2006 to 2015, we suspect that this decline could be associated with the fall in industrial manufacturing activities.

Methods: The outcome variable, gastroschisis incidence, was from a previous publication. The industrial manufacturing activities were measured by relative job participation and production in the primary and secondary economic sectors, and the corresponding data were collected in 14 cities from 2005 to 2015. The general linear model and a random-effect Poisson regression model were performed to assess the association and time-series trend of gastroschisis with the manufacturing activities.

Results: The relative job participation in the first economic sector was marginally associated with gastroschisis incidence in 2006 ($p=0.070$), but more significantly associated ($\text{Beta}=-0.040$; $p=0.014$) in the cross-sectional and time-series analysis with one-year lag in the outcome variable.

Conclusion: The gastroschisis incidence decline in Liaoning is likely due to the reduced job participation in manufacturing and heavy industry, which might be an indication of reduced risk exposure associated with the industrial manufacturing activities.

KEYWORDSGastroschisis incidence, ecological analysis, random-effect Poisson regression model, job participation

INTRODUCTION

Gastroschisis is a congenital abdominal wall defect manifested by the fetal intestine's evisceration through a defect in the paraumbilical anterior abdominal wall with herniation of gastrointestinal structures into the amniotic cavity (1, 2). The prevalence of gastroschisis has increased in the global populations over the past four decades (3). Based on the birth certificate and hospital discharge records in Washington State (USA), the prevalence was estimated to have increased by two- to four-fold from 1987 to 2006, particularly in teen mothers and smokers (4). In a large population-based sample of 4,713 cases identified by the National Birth Defects Prevention Network in 15 states of the United States from 1995-2005, gastroschisis incidence increased from 2.32 to 4.42 per 10,000 live births during

this period (5). This increase continued in a decade from 2005 to 2015 in some US areas (6, 7).

However, the cause of this increase in the incidence of gastroschisis is not yet clear. Younger maternal age, particularly maternal age below 20 (2, 6), is consistently established as a risk factor in multiple studies (8). Another possible risk factor is *in utero* exposure to opioids. An ecological analysis showed that gastroschisis prevalence was positively associated with the rate of opioid prescriptions, suggesting an association between opioid use during pregnancy and gastroschisis risk (7). Based on California's linked birth database from 1995 to 2012, a study showed a rapid increase in gastroschisis incidence, namely a threefold increase from 2005 to 5.3 cases per 10,000 births in 2012 (9). County-level statistics also showed some internal consistency that the gastroschisis

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incidence was increased in most counties within California. In addition, the study showed that the incidence of gastroschisis is positively associated with rural counties (OR=3.04) and partial rural counties (OR=1.60) compared to the metropolitan (9). The regional distribution of incidence closely mirrored cannabis consumption (10). In a follow-up study, fetal exposure to drugs (other than alcohol, cocaine, narcotics, or hallucinogenics) and other noxious substances are found to increase gastroschisis risk, which was still significant even after adjusting for rurality in multiple regression analyses (11).

In contrast to the reported increases in gastroschisis in various global regions, a recent study based on the centralized birth registry in Liaoning Province, China, showed that the overall incidence of gastroschisis in this province declined from seven cases per 10,000 births in 2006 to below two cases per 10,000 births in 2015, consistent across all 14 cities within the province (12). This observation provides an excellent opportunity to search for factors associated with the risk of gastroschisis. Over the past four decades, China has experienced rapid socio-economic development, particularly along the east coast and south China. However, the northeast region of China, including Liaoning Province, used to be the national manufacturing and heavy-industry centers and experienced a downfall in industrial production after the national reform and opening policy was implemented in the late 1970s². That changed in the provincial economy left a significant number of former state-owned industry employees out of work. Most of them switched to be engaged in the tertiary sectors (e.g., services). This was particularly relevant in the state-own enterprise (SOE)³ of manufacturing and heavy industry that belonged to the secondary economic sector, which consumed large quantities of energy and required factories and machinery to produce goods and products. Because the economic decline in manufacturing and heavy industry was coincident with the documented decline in gastroschisis incidence, we examined the association of job participation and production in the primary and secondary sectors with the incidence of gastroschisis in Liaoning province.

DATA AND METHOD

The gastroschisis cases and all live births from 2006 to 2015 were from a published article (12) (**Table S1** and **Figure S1**). They were retrieved from the Maternal and Child Health Certificate Registry at the Liaoning Maternal and Child Hospital (12). All live births and stillbirth infants were included in this registry for follow-up. This registry covers all 14 cities (Shenyang, Dalian, Anshan, Fushun, Benxi, Dandong, Jinzhou, Yingkou, Fuxin, Liaoyang, Panjin, Tieling, Chaoyang, and Hulu Island) of the province, with a population of approximately 42 million residents. The maximal

time to diagnosis for a congenital malformation case was the seventh day after birth (13).

A previous study has indicated that rurality is a risk factor for gastroschisis (9, 11). We collected the data on the relative job participation and production in the primary and secondary sector, relative to the total three sectors, including the primary (raw materials), secondary (manufacturing) and tertiary (services), in all 14 cities from 2005 to 2015 (Liaoning Statistical Yearbook, 2006-2016), to examine if potential manufacturing-caused environmental exposure is associated with the decrease in the incidence of gastroschisis. The relative job participation was calculated in both rural and urban areas.

We performed a cross-sectional analysis in 2006 when the highest gastroschisis was observed and a cross-sectional and time-series analysis of 14 cities from 2006-2015, with and without a one-year lag in gastroschisis incidence, respectively. Because the number of cases was rare, a random-effect Poisson regression model simultaneously examined the association and temporality, a necessary condition for judging causality.

RESULTS

Job participation in the two sectors was suggestively associated with gastroschisis incidence in 2006. Relative job participation in the primary sector was negatively associated (Beta=-0.068, $p=0.0699$) with gastroschisis incidence. By contrast, job participation in the secondary sector was positively associated (Beta=0.094, $p=0.109$) with gastroschisis incidence (**Figure 1. a1-a2**). Both associations were marginally significant. In addition, a similar suggestive trend (**Figure 1. b1-b2**) was observed between the relative production of the primary and secondary sectors with gastroschisis incidence. However, they were not statistically significant ($p>0.2$).

The cross-sectional and time-series analysis showed a significant negative association between the primary sector production and gastroschisis incidence. Of the four models on relative job participation and production in the primary and secondary sectors, the best model was that the primary sector production was significantly associated with gastroschisis incidence (Beta=-0.066; $p=0.036$, **Table 1**). Of note, the model indicated a sizeable over-dispersion (Pearson-Chisq/df=1.22), indicating omitted variables or random-effect that might not have been considered in the model, although the temporal trend of decline in the incidence of gastroschisis was still very significant ($F=29.82$; $p<0.0001$).

We further analyzed the data with a year lag in gastroschisis incidence to capture the temporal causal effect. The best model was that the relative job participation in the primary economic sector was significantly associated with gastroschisis incidence (Beta=-0.040; $p=0.0139$; **Table 2**),

² Tianyu M Fang, Liaoning Province to Retirees: Start Your Own Business JULY 12, 2018. <https://supchina.com/2018/07/12/liaoning-province-to-retirees-start-your-own-business/>

³ Provincial Snapshot—Liaoning: How a Rust Belt Province Stagnated and why it Matters to China. <https://macropolo.org/provincial-snapshot-liaoning-rust-belt-province-stagnated-matters-china/>; Accessed April 8, 2019

in which the temporal trend of decline in the gastroschisis incidence was still very significant ($F=11.35$; $p<0.0001$). However, the primary sector production became not significantly associated with gastroschisis incidence ($\text{Beta} = -0.028$; $p=0.24$, detailed modeling not shown). Furthermore, the one-year lag in gastroschisis incidence fitted the model

better, as the estimate of the dispersion parameter (Pearson Chi-sq/DF) was reduced from 1.22 to close to 1.03 (**Table 2**), very close to 1. That the model fitted well was also indicated by the model diagnostics, in which the residuals appeared to be a normal distribution (**Figure S2**).

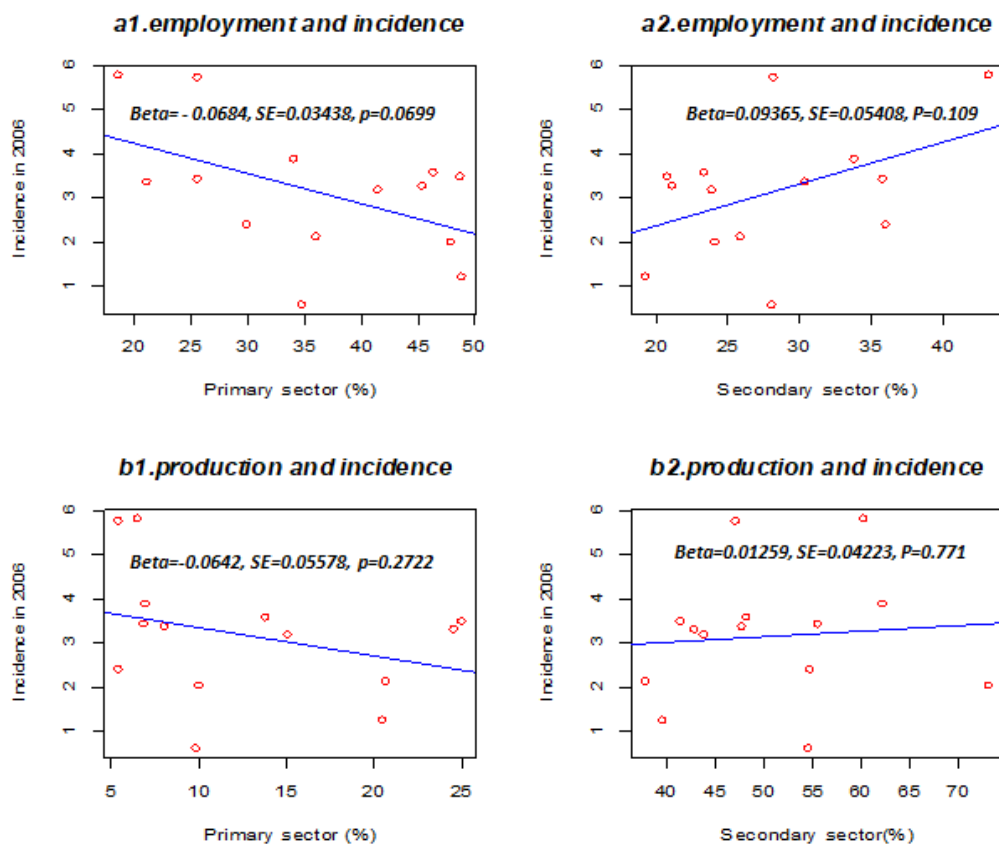


Figure 1. Simple linear regression analysis of cross-sectional gastroschisis incidence in 14 cities of Liaoning, China, 2006. Relative job participation (employment) in a1) primary sector and a2) secondary sector, and relative production in b1) primary sector and b2) secondary sector.

Table 1. Association of primary sector production with gastroschisis incidence in 14 cities of Liaoning, China, 2006 to 2015.

	Beta	RR	SE	DF	t Value	Pr > t	F	P
Year							29.82	<.0001
2006(ref)	0.000	1.000						
2007	-0.153	0.858	0.083	125	-1.85	0.0669		
2008	-0.420	0.657	0.091	125	-4.62	<.0001		
2009	-0.787	0.455	0.103	125	-7.64	<.0001		
2010	-1.031	0.357	0.114	125	-9.04	<.0001		
2011	-0.951	0.386	0.113	125	-8.39	<.0001		
2012	-0.956	0.385	0.112	125	-8.54	<.0001		
2013	-1.112	0.329	0.122	125	-9.14	<.0001		
2014	-1.303	0.272	0.129	125	-10.08	<.0001		
2015	-1.957	0.141	0.160	125	-12.25	<.0001		
Primary sector production	-0.066		0.031	125	-2.12	0.0359		
Pearson Chi-Sq/DF	1.220							

Note, the best model for job participation and production in the primary and secondary sectors.

Table 2. Association of primary sector job participation with gastroschisis incidence in 14 cities of Liaoning, China, 2006 to 2015.

Year	Beta	RR	SE	DF	t Value	Pr > t	F	P
2006(ref)	0.000	1.000					11.35	<.0001
2007	0.271	1.312	0.131	116	2.08	0.0400		
2008	-0.007	0.993	0.139	116	-0.05	0.9574		
2009	-0.365	0.694	0.153	116	-2.38	0.0187		
2010	-0.636	0.529	0.168	116	-3.8	0.0002		
2011	-0.559	0.572	0.165	116	-3.39	0.0010		
2012	-0.595	0.551	0.169	116	-3.53	0.0006		
2013	-0.766	0.465	0.181	116	-4.23	<.0001		
2014	-1.012	0.363	0.201	116	-5.03	<.0001		
2015	-1.712	0.181	0.249	116	-6.89	<.0001		
Primary sector employment	-0.040		0.016	116	-2.50	0.0139	**	
Pearson Chi-Sq/DF	1.030							

Note, the best model for job participation and production in the primary and secondary sectors, with gastroschisis incidence, lagged for one year from the economic data (i.e., 2005-2014); P, p-value for assessing the statistical significance of gastroschisis decline by year.

DISCUSSION

In this study, we found that the primary sector job participation was negatively associated with gastroschisis risk. The association was consistent in analyzing cross-sectional data in 2006 alone and the simultaneous analysis of cross-sectional and time-series data from 2006-2015 with a one-year lag from the relative job participation.

Our findings seemed contrary to a previous study that found rurality to be a risk factor for the rising gastroschisis incidence in the United States (10). Further analysis suggested that additional factors might contribute to the rise in gastroschisis incidence after adjusting for rurality (11). Previous studies have also shown that the increased risk of gastroschisis was associated with opioid prescriptions and cannabis use in the United States (7, 10). However, these drugs were rarely accessible to the public or even illegal for personal use in China. Drug use could not be a causal factor for gastroschisis in Liaoning Province. Our observations do not rule out the potential role of opioid and cannabis use in the rising gastroschisis incidence in the United States.

In addition, the gastroschisis decline in Liaoning may be less likely due to the introduction of the folic acid supplement. While assessing the data regarding gastroschisis in Liaoning Province from 2005-2015, we noted that in the same period, there was a significant decline in some congenital disabilities such as neural tube defects, anencephaly, spina bifida, and congenital hydrocephalus in Liaoning (8), which might be related to the institution of a folic acid supplement program. However, geographically within Liaoning, the areas (e.g., Hulu Island, Chaoyang, and Fuxin) with a higher prevalence of neural tube defects (NTDs) were not the same (e.g., Shenyang, Fushun, Benxi) with a higher prevalence of gastroschisis (14). Furthermore, more than 20 years of observations in California showed that folic acid fortification has a slower decline in the prevalence of NTDs, an emergence of a decline in orofacial clefts, but a slower increase in gastroschisis incidence (15).

The decline of the secondary sector job participation in Liaoning Province could contribute to the decline of gastroschisis through reducing the possible personal exposure to the risk factors such as industrial pollutions from manufacturing industrials. Liaoning had been one of China's largest manufacturing and heavy-industry centers, mostly state-own enterprises (SOE). It is inevitable that labor-intensive industries such as manufacturing and heavy industry have a huge consumption of non-renewable resources and produce environmental pollution, which could affect the health of the employed workers and their children or the residents living close to manufacturing factories. In recent decades, the industrial sector in Liaoning has been stagnating. The production output and the relative job participation in the SOE sectors have significantly declined. According to Liaoning statistics, there was a rapid decline in relative job participation in the secondary sector from 1999 to 2003 (16), likely driven by the continuing job participation shifting to the tertiary sector.

Interestingly, there was a gap of about 12-16 years between the declines in secondary sector job participation and the gastroschisis incidence. Likely, the job participation decline in the early years ahead of gastroschisis could have contributed to the later decline in the gastroschisis incidence. Parents may have experienced reduced exposure to some industrial pollutants while in their childhood and teenage years. This conjecture is consistent with many observations that mothers' younger age (age < 20 years) is a risk factor for gastroschisis (2).

In summary, we found consistent evidence that the primary sector job participation is associated with a decline in gastroschisis incidence in cross-sectional and time-series data when analyzed with one year lagged in the incidence. Even so, the ecological analysis may not provide a causal inference on individual risk. Our findings warrant a further study of environmental and workplace factors in the etiology of gastroschisis. We encourage investigators to seek some definable subpopulations to search for some

specific risk factors and characterize possible cause-effect relationships for this devastating disorder of newborns. In combining with previous studies in the US, our findings may indicate the etiological heterogeneity of gastroschisis.

CONFLICT OF INTEREST

The authors declare no conflict of interest regarding the publication of this paper

ARTICLE INFORMATION

Received October 9, 2020; accepted November 14, 2020; published November 20, 2020.

DOI:10.36316/gcatr.02.0036.

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How to cite this article:

Liu R, Zhang F, C Hughes C, Li J. Ecological Analysis of Gastroschisis Incidence Decline in Liaoning, China, 2006 to 2015. *Glob Clin Transl Res*. 2020; 2 (4):100-106. DOI:10.36316/gcatr.02.0036.

Supplementary Information

Table S1. Relative job participation in primary economic sector by the city in Liaoning, 2005 to 2015.

City	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Liaoning, overall	34.1	33.7	32.4	31.9	30.6	30.3	29.6	28.7	27.1	26.8	28.6
Shenyang	24.9	25.5	25.0	26.1	24.3	22.6	22	21.5	18.8	18.4	18.5
Dalian	22.1	21.1	19.9	19	17.8	17.2	15.5	14.2	13.1	12.4	18.0
Anshan	30.0	29.9	29.9	30.7	27.1	29.9	29.2	27.9	26.8	27.0	27.7
Fushun	25.8	25.6	25.6	27.6	27.4	26.8	27.6	27.3	28	26.6	27.3
Benxi	20.5	18.5	19.4	19.4	19.6	19.1	20.4	20.0	19	19.0	18.4
Dandong	41.4	41.4	40.4	39	38.9	37.8	35.9	35.9	33.5	34.4	35.6
Jinzhou	47.2	48.8	43.1	44.2	41.6	42.5	42.4	41.2	38.5	38.4	38.2
Yingkou	35.4	34.8	29.2	27.6	25.8	26.7	24.5	23.9	23.9	22.1	19.4
Fuxin	39.7	36.0	37.8	33.8	34.8	34.9	36.3	33.3	33.5	35.4	35.4
Liaoyang	33.7	34.0	33.5	34.8	35.1	34.9	35.1	30.3	34.6	34.4	35.2
Panjin	46.5	47.8	46.7	43.2	39	41	41.9	41.6	38.8	36.3	38.1
Tieling	45.2	45.4	44.1	40.6	42.6	41.1	41	41.6	40	41.7	41.4
Chaoyang	49.5	48.7	45.6	45.2	42.9	43.2	42.7	40.9	39.6	41.5	41.0
Hulu Island	46.2	46.3	44.2	43.1	42.3	41.8	41.8	41.6	38.4	38.5	39.1

Figure S1. Cross-sectional and time-series trend of gastroschisis incidence in 14 cities of Liaoning, 2006-2015 (Plot was made based on the annual number of live birth and gastroschisis incidence; detailed data can be found at Li et al. Scientific Reports, 2016, doi:10.1038/srep33333).

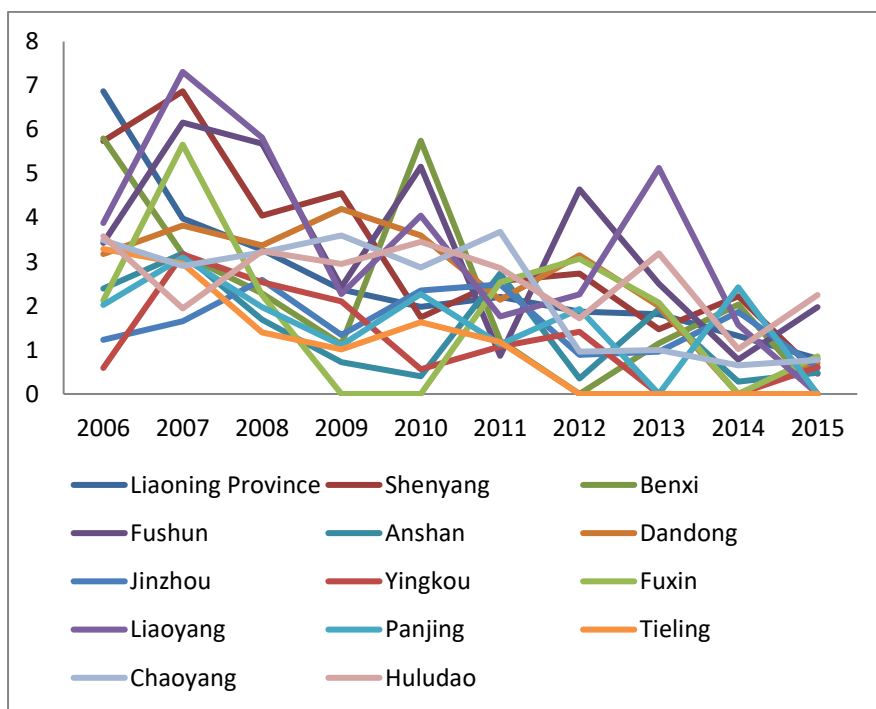


Figure S2. Model diagnosis on primary sector job participation and gastroschisis incidence in cross-sectional and time-series analysis in 14 cities of Liaoning, 2006 to 2015.

