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Epidemiological characteristics and risk factors of biliary atresia: a case–control study

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ABSTRACT

Objectives Biliary atresia (BA) is regarded as a serious neonatal hepatobiliary disease, and its aetiology and pathogenesis remain unclear. Epidemiological studies are limited, especially for the data from China. This study aims to explore risk factors of BA and provide new evidence to improve understanding of its aetiology.

Design This is a case–control study from 1 January 2015 to 31 December 2016.

Setting Cases were consecutively recruited from an urban tertiary care academic children's hospital in Shanghai, China, while the controls were recruited from a community hospital in Shanghai through a random sampling system.

Participants 721 patients suspected for BA who planned to take the diagnostic surgery were enrolled preoperatively. 613 were diagnosed with BA and recruited into the case group. Meanwhile, 688 infants without any observed major congenital anomalies or jaundice were enrolled. Finally, 594 valid questionnaires from the case group and 681 from the control group were obtained.

Primary and secondary outcome measures Standardised questionnaires were used for data collection. Multivariate logistic regression analysis was performed to evaluate associations reported as ORs and precision, by adjusting covariates.

Results Anxiety or stress during pregnancy was strongly associated with increased risk of BA (OR 8.36 (95% CI: 4.08 to 17.15); p<0.001), respectively. Lower birth weight, fathers from ethnic minorities of China, older age of fathers, lower income of parents, and exposure to infection, diseases and medication during pregnancy all made differences.

Conclusions Social factors including the educational and economic background and its related anxiety and stress during pregnancy might be noticed in the occurrence of BA. Maternal infections during pregnancy in the prevalence of BA were demonstrated.

Trial registration number ChiCTR-IPR-15005885.

Strengths and limitations of this study

- This is a case–control study regarding epidemiological factors of biliary atresia (BA) from China.
- Nearly 600 patients with BA were recruited within 2 years.
- A detailed questionnaire involving several aspects of exposure factors was administered.
- Subjects in the control group filled in the questionnaire at 42-day follow-up after birth to minimise the variation in the recall bias with the case group.
- The case and control groups were recruited in medical centres in Shanghai, which might introduce geographical bias.

INTRODUCTION

Biliary atresia (BA) is a neonatal disease, with most cases occurring within 1 month of birth. It is characterised by obstruction of the intrahepatic and extrahepatic bile duct system and progressive liver fibrosis.[1 2] The incidence is higher in the Asia-Pacific region (approximately 1.06 in 10 000 live births) than in the USA (4.47 in 100 000).[3 4] As far as the current research is concerned, BA is considered to be a serious neonatal hepatobiliary disease caused by multiple inducements. It is also the most common indication for liver transplantation in children with end-stage liver disease in various countries. However, unfortunately, its aetiology and pathogenesis are still unclear.[5–7]

Several studies exploring the aetiologies have been conducted on the epidemiology of BA, from region, ethnic group, preterm birth, birth weight and sex, to birth seasonality and viral infections.[8–15] As reported, infants of non-Hispanic black mothers were more likely to have BA than those of non-Hispanic white mothers.[9 11 12] The influence of other factors, mostly including the seasonality and maternal factors, has not achieved consensus.[3 12–15] This may be due to differences in the source of the data or the size of the sample. Most of the previous studies are retrospective using national databases from Europe or the USA. Such inconclusiveness reveals the necessity of prospective epidemiological investigations with larger sample sizes. Moreover, lack of data from mainland China, which accounts for the majority of patients

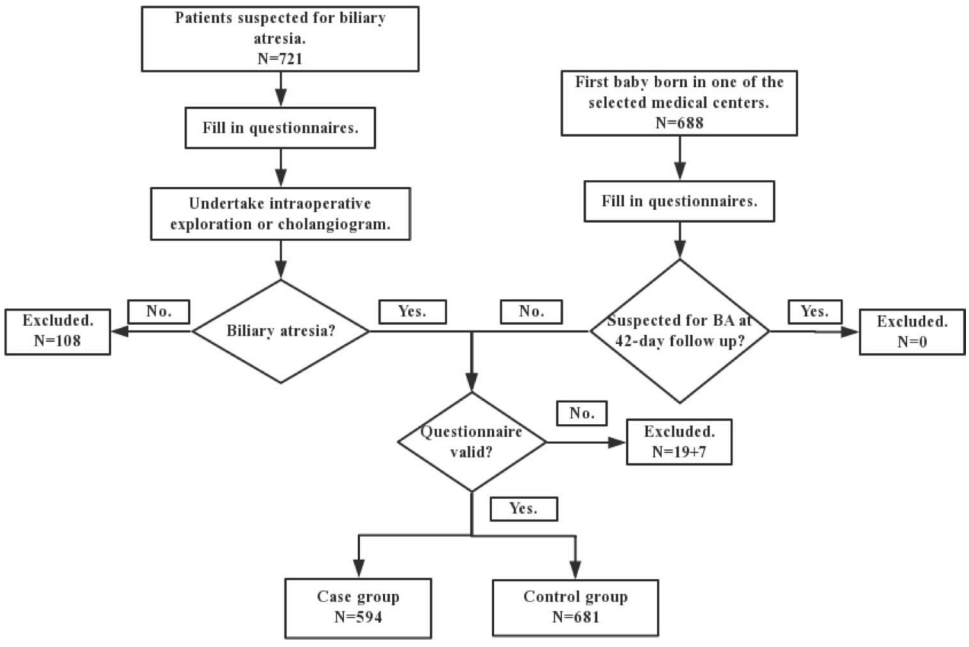

Figure 1 Flow chart of the study patients.

with BA annually, also confirms the need to conduct epidemiological studies on BA in China.

Therefore, this present case–control study aims to further explore the risk factors of BA with a large sample size, in order to better guide its aetiology research and provide new ideas for the screening, prevention and treatment of BA.

MATERIAL AND METHODS

Study design

This is a case–control study. A study protocol for recruitment plan and detailed data collection method was designed, and related medical professionals were trained before the study's start date.

Study subjects: the case group

Subjects of the case group were consecutively enrolled from 1 January 2015 to 31 December 2016 from Children's Hospital of Fudan University, an urban tertiary care academic children's hospital in Shanghai, China.

Paediatric patients suspected for BA who planned to take the diagnostic surgery were enrolled preoperatively. Intraoperative exploration and subsequent histological examination of liver biopsies were used to confirm the diagnosis of BA. Once the diagnosis of BA was confirmed, the patient was recruited into the case group. The rest were excluded.

Study subjects: the control group

The recruitment of controls was conducted parallel with the case recruitment. The control group was recruited using systematic random sampling, from Shanghai Pujiang Community Health Center.

Each day during the same study period with the case recruitment, the first baby born without any observed major congenital anomalies was enrolled. Babies were excluded if one was revealed to have signs of jaundice and suspected for BA at a 42-day revisit.

Data sources: questionnaire administration

A questionnaire was prospectively designed for data collection for the case and control groups, and the protocol was approved by a panel of experts before recruiting. Investigators were trained for recruiting subjects and implementation of data collection.

The questionnaire was administered by the newborn's guardian (online supplemental file 1). The information was filled in on the spot to reduce invalid answers. For the case group, the questionnaire was filled in at the admission, while for the control group, it was filled in at the 42-day revisit after birth in their home. The incomplete questionnaires were determined as invalid (less than 50% completion of all the items on the form), and the reasons were recorded on the cover of the questionnaire. The quality of the questionnaires was checked regularly.

The electronic input was consistent with the content of the paper questionnaire. The data entry interface was established through Microsoft Access V.2010.

Variables

Baseline assessments, involving demographic features, were performed for all cases enrolled.

Exposure factors mainly focused on the socioeconomic background of the family and the maternal part during pregnancy, including nutrition, infection or diseases, drugs or toxins, and life events.

Bias

In the selection of the control group, a community medical centre in Shanghai was selected since it is located in a district with a mixed population from all over China.

Table 1 General characteristics of the subjects and parents

Variable	Case group	Control group	OR	95% CI	P value
Subjects					
Sex			0.78	0.63 to 0.98	0.03
Male	336 (56.6)	342 (50.2)			
Female	258 (43.4)	339 (49.8)			
Ethnicity			2.62	1.38 to 4.98	0.002
Han	563 (94.8)	667 (97.9)			
Minority	31 (5.2)	14 (2.1)			
Birth weight (kg)	3.2 (2.9, 3.5)	3.4 (3.1, 3.6)	0.46	0.36 to 0.58	<0.001
Season of birth			1.02	0.93 to 1.13	0.64
Spring	177 (29.8)	158 (23.2)			
Summer	110 (18.5)	185 (27.2)			
Autumn	129 (21.7)	185 (27.2)			
Winter	178 (30.0)	153 (22.4)			
Preterm birth			7.76	3.25 to 18.53	<0.001
No	533 (93.5)	671 (99.1)			
Yes	37 (6.5)	6 (0.9)			
Delivery modes			0.89	0.72 to 1.10	0.28
Natural labour	316 (54.8)	346 (51.1)			
Caesarean	255 (44.2)	329 (48.5)			
Other	6 (1.0)	3 (0.4)			
Feeding patterns			4.28	3.48 to 5.27	<0.001
Breast feeding	166 (28.9)	476 (70.3)			
Mixed feeding	316 (55.1)	180 (26.6)			
Formula	91 (15.8)	21 (3.1)			
Other	1 (0.2)	0 (0)			
Mothers					
Age (years)			1.04	0.84 to 1.28	0.71
15–24	157 (26.5)	176 (25.9)			
25–35	296 (66.9)	471 (69.3)			
>35	39 (6.6)	33 (4.8)			
Ethnicity			1.47	0.8 to 2.63	0.19
Han	566 (95.5)	647 (96.9)			
Minority	27 (4.5)	21 (3.1)			
Height (metre)	1.6 (1.6, 1.6)	1.6 (1.6, 1.6)	2.29	0.22 to 24.20	0.49
Highest weight (kg)	68.3 (61, 75)	67.7 (62, 72)	1.01	1.0 to 1.02	0.12
BMI	26.2 (24.0, 28.9)	26.2 (24.4, 27.5)	1.03	0.98 to 1.06	0.17
Fathers					
Age (years)			1.37	1.08 to 1.73	0.008
15–24	77 (13.2)	103 (15.2)			
25–35	435 (74.9)	530 (78.2)			
>35	69 (11.9)	45 (6.6)			
Ethnicity			2.53	1.26 to 5.05	0.009
Han	562 (95.6)	655 (98.2)			
Minority	26 (4.4)	12 (1.8)			
Height (metre)	1.72 (1.7, 1.75)	1.74 (1.7, 1.75)	0.02	0.001 to 0.18	0.001
Weight (kg)	70 (60, 75)	70 (65, 76)	0.99	0.98 to 1.00	0.04
BMI	21.2 (19.8, 22.2)	25.0 (23.9, 26.4)	1	—	<0.001

BMI, body mass index.

Table 2 Socioeconomic factors of parents

Variable	Case group	Control group	OR	95% CI	P value
Maternal factors					
Education and occupation					
Academic degree			0.83	0.73 to 0.94	0.004
Primary school	30 (5.1)	15 (2.2)			
High school	281 (48.1)	330 (49.0)			
Technical school	154 (26.3)	125 (18.6)			
University or above	120 (20.5)	203 (30.2)			
Occupation			1.17	1.09 to 1.25	<0.001
Manager/cadre	30 (5.0)	8 (1.2)			
Technician	26 (4.4)	20 (3.0)			
Business owner	4 (0.7)	4 (0.6)			
Worker	91 (15.5)	403 (59.8)			
Farmer	169 (28.9)	13 (1.9)			
Self-employed	68 (11.6)	18 (2.7)			
Other	199 (33.9)	208 (30.8)			
Income					
10 000	2 (0, 4)	5 (0, 10)	0.85	0.83 to 0.88	<0.001
Paternal factors					
Education and occupation					
Academic degree			0.89	0.78 to 1.00	0.06
Primary school	21 (3.7)	12 (1.8)			
High school	266 (46.8)	329 (49.5)			
Technical school	145 (25.5)	107 (16.1)			
University or above	136 (24.0)	217 (32.6)			
Occupation			1.12	1.04 to 1.21	0.002
Manager/cadre	37 (6.3)	14 (2.1)			
Technician	77 (13.1)	37 (5.5)			
Business owner	12 (2.0)	6 (0.9)			
Worker	149 (25.3)	479 (71.2)			
Farmer	121 (20.6)	6 (0.9)			
Self-employed	82 (14.0)	72 (10.7)			
Other	110 (18.7)	59 (8.7)			
Income					
10 000	4 (2.5, 6)	8 (5, 12)	0.86	0.84 to 0.89	<0.001

In order to match the population composition of the case group and to eliminate the selection bias as much as possible, the main population of Pujiang Hospital consists of those from other regions of China including remote areas. In addition, we chose to select the first-born neonate each morning as a control to mostly achieve equidistant sampling (system sampling).

Furthermore, because the questionnaire was a retrospective survey, in order to ensure the balance of recall bias between the case group and the control group, the questionnaire was filled in at a 42-day revisit for the control group. Due to the clinical characteristics of BA, most of the case group consulted at 30–60 days of age.

Study size

The sample size calculation was based on the hypothesis to identify any risk factors of BA. A sample size of 500 cases and 500 controls was sufficient to identify a risk factor with prevalence over 10% and OR over 1.8 after adjustment of covariates, at α of 5% and a power of 0.85. PS (power and sample size calculations) software V.2.1.31 was used to calculate the sample size.

Statistical analysis

The characteristics of subjects in the case and control groups were summarised using frequency distributions and descriptive statistics. Categorical variables were described by n (%). Numerical variables were expressed as median (Q1, Q3). The X^2 test with univariate analysis was conducted for categorical variables, whereas the t-test was performed for all continuous variables of normal distribution. Otherwise, the Mann-Whitney U test was performed. To adjust covariates, multivariate logistic regression was further performed using the stepwise method with a p value less than 0.05. The ORs and 95% CI were presented.

Statistically significant differences were defined as a p value less than 0.05. STATA V.14 software (StataCorp, College Station, Texas, USA) was used for all the analyses.

Patient and public involvement

Patients and their guardians were not involved in the study design and were not consulted to develop patients' relevant diagnoses and outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy. We intend to disseminate the main results to the families of the trial participants and will pursue patient and public involvement when developing an appropriate method of dissemination.

RESULTS

Participants

Six hundred thirteen subjects were enrolled in the case group, and 594 questionnaires were valid, accounting for 96.90%. Six hundred eighty-eight subjects were enrolled in the control group, and 681 questionnaires were valid, accounting for 98.98% (figure 1).

The baseline characteristics of the subjects were significantly different in several aspects, including sex distribution, the rate of preterm birth, birth weight and feeding patterns. There were 336 males and 258 females in the case group and 342 males and 339 females in the control group (p=0.030), with a higher proportion of subjects from ethnic minorities of China (p=0.002). Also, the case group had 6.5% of preterm infants, and the control group had 0.9% (p<0.0001), leading to lower average birth weight (3.2±0.5 kg vs 3.4±0.4 kg, p<0.0001) and higher mixed or formula feeding (p<0.0001) in the case group. Further, it was demonstrated that almost 60% of the patients with BA were born in spring or winter (table 1).

General characteristics of parents

The height, weight, body mass index (BMI), age and ethnic factors from the maternal part were not significantly different (p>0.05), while there were significant differences from the paternal part. In terms of age, the results suggested that the case group's fathers were of older age (>35 years old: 11.9% vs 6.6%, p=0.008). Also, more ethnic minorities were observed in the case group (4.4% vs 1.8%, p=0.009), which was consistent with the proportion of subjects (table 1).

Exposure factors: socioeconomic characteristics of parents

In the case group, a higher proportion was seen in the occupation of 'other' (mostly referred to no work) and farmers in mothers, accounting for 33.9% and 28.9%, respectively. Worker referred to blue-collar class worker including factory worker, construction worker, courier, sanitation worker and so on. Similarly, among fathers' occupations, farmers also ranked higher, accounting for 20.6%. This was consistent with the family's income. The median annual incomes for the mothers in the case group and the control group were ¥20 000 and ¥50 000, respectively (p<0.001), and ¥40 000 vs ¥80 000 for the fathers (p<0.001). A higher proportion of mothers in the control group obtained the degree of university or above, while those in the case group mostly only graduated from primary school, high school or a technical school (p=0.004) (table 2).

Exposure factors during pregnancy for BA

For the history of gestation, mothers in the case group had a higher percentage of history of abnormal pregnancy (37.2% vs 24.7%, p<0.001).

Exposure factors during pregnancy were analysed in four sections: nutrition, infections and diseases, drugs and toxins, and life events.

For the maternal nutrients, taking vitamins or other nutritional supplements before pregnancy was not associated with the occurrence of BA (p>0.05). However, taking vitamins or other nutritional supplements during pregnancy was associated with BA (p<0.001). Nutritional supplements included calcium and iron.

For infections and diseases, fever, respiratory infections, gastrointestinal infections, other infections, cytomegalovirus (CMV) and gestational hypertension occurrence all had a certain correlation (p<0.05). Other infections involved urinary tract infection or vaginitis.

Additionally, mothers who were exposed to medication, illicit drugs, toxins, alcohol and secondhand smoking during pregnancy made up a higher percentage of the case group (p<0.001). Most medications, like paracetamol, were for colds, some were antibiotics, and others were Chinese-patented medicine for colds or miscarriage prevention. Chemical toxins are scientifically confirmed to harm people's health such as insecticide, formaldehyde, heavy metals and some poisonous plants. We would also confirm with the parents if they had worked in an environment that had exposure to chemical hazards or toxic substances.

In the daily life events of individuals, we first compared the number of family members living together with the mothers during pregnancy. The mothers in the case group lived with more members than those in the control group (5 vs 4, p<0.001). More mothers in the case group used electronic devices and stayed up at night (p<0.001). Electronic devices referred to TV, computer, mobile

Table 3 Exposure factors during pregnancy

Variables	Case group	Control group	OR	95% CI	P value
History of gestation					
Gravidity	2 (1, 3)	2 (1, 2)	1.21	1.09 to 1.34	<0.001
Parity	1 (1, 2)	1 (1, 2)	1.14	0.93 to 1.40	0.20
History of abnormal pregnancy					
No	354 (62.8)	484 (75.3)	1.81	1.41 to 2.31	<0.001
Yes	210 (37.2)	159 (24.7)			
Nutrition					
Vitamins and other nutritional supplements before pregnancy			0.97	0.75 to 1.26	0.82
No	408 (74.9)	503 (74.3)			
Yes	137 (25.1)	174 (25.7)			
Vitamins and other nutritional supplements during pregnancy			1.72	1.37 to 2.16	<0.001
No	239 (44.5)	392 (58.0)			
Yes	298 (55.5)	284 (42.0)			
Infection or diseases					
Fever			5.64	3.42 to 9.30	<0.001
No	504 (85.4)	661 (97.1)			
Yes	86 (14.6)	20 (2.9)			
Respiratory infection			2.85	2.04 to 3.98	<0.001
No	464 (79.1)	623 (91.5)			
Yes	123 (20.9)	58 (8.5)			
Gastrointestinal infection			2.01	1.17 to 3.45	0.01
No	551 (93.7)	658 (96.8)			
Yes	37 (6.3)	22 (3.2)			
Other infection			48.66	6.66 to 355.31	<0.001
No	545 (93.3)	680 (99.9)			
Yes	39 (6.7)	1 (0.1)			
Rubella virus			—	—	0.06*
No	580 (99.5)	681 (100.0)			
Yes	3 (0.5)	0 (0.0)			
HSV			—	—	0.28*
No	583 (99.8)	681 (100.0)			
Yes	1 (0.2)	0 (0.0)			
CMV			—	—	0.001*
No	574 (98.3)	681 (100.0)			
Yes	10 (1.7)	0 (0.0)			
Gestational diabetes			1.36	0.81 to 2.27	0.24
No	531 (94.2)	634 (95.6)			
Yes	33 (5.8)	29 (4.4)			
Gestational hypertension			2.58	1.29 to 5.16	0.007
No	553 (95.5)	659 (98.2)			
Yes	26 (4.5)	12 (1.8)			
Drugs or toxins					
Medication			7.50	4.91 to 11.45	<0.001
No	438 (75.7)	652 (95.9)			
Yes	141 (24.3)	28 (4.1)			

Continued

Table 3 Continued

Variables	Case group	Control group	OR	95% CI	P value
Illicit drugs			0.23	0.09 to 0.55	0.001
No	573 (99.0)	651 (95.6)			
Yes	6 (1.0)	30 (4.4)			
Toxins			—	—	<0.001*
No	550 (95.5)	671 (100.0)			
Yes	26 (4.5)	0 (0.0)			
Alcohol			2.87	1.49 to 5.53	0.002
No	555 (94.7)	668 (98.1)			
Yes	31 (5.3)	13 (1.9)			
Smoking			0.70	0.17 to 2.96	0.63
No	575 (99.5)	675 (99.3)			
Yes	3 (0.5)	5 (0.7)			
Secondhand smoking			2.69	1.98 to 3.64	<0.001
No	421 (73.9)	577 (88.4)			
Yes	149 (26.1)	76 (11.6)			
Life events					
Family members living together	5 (4, 6)	4 (4, 5)	1.50	1.35 to 1.66	<0.001
Exposure to electronic devices			6.32	4.87 to 8.21	<0.001
No	264 (45.1)	570 (83.8)			
Yes	322 (54.9)	110 (16.2)			
Stay up			4.87	3.25 to 7.29	<0.001
No	475 (80.1)	647 (95.2)			
Yes	118 (19.9)	33 (4.8)			
Negative events			12.54	3.81 to 41.24	<0.001
No	557 (94.7)	676 (99.6)			
Yes	31 (5.3)	3 (0.4)			
Anxiety and stress			15.33	8.74 to 26.87	<0.001
No	447 (75.6)	666 (97.9)			
Yes	144 (34.4)	14 (2.1)			

*Based on X^2 tests. The rest were all based on univariate logistic regression analysis.
CMV, cytomegalovirus; HSV, herpes simplex virus.

phone and other devices for entertainment, and exposure to electronic devices was defined as continuous use for more than 2 hours. Staying up at night was defined as sleeping after 23:00 often during the pregnancy. Negative life events referred to divorce, job loss, death of important family members or other severe adverse life events that could cause negative emotions or depression in life. The mothers' negative life events were significantly different between the case group and the control group (p<0.001) (table 3).

Multivariate logistic regression analysis for BA

Several factors were identified as risk factors for BA by adjusting covariates, among which stress during pregnancy played the most important role, with OR of 8.36 (95% CI: 4.08 to 17.15, p<0.001). Moreover, lower birth weight, older fathers from ethnic minorities of China, lower income of parents, and exposure to infection, diseases and medication during pregnancy all made differences (table 4).

DISCUSSION

BA is considered to be a serious neonatal hepatobiliary disease with a pathogenesis that is still unknown. Limited studies have been focused on its epidemiology, especially in mainland China where the incidence and case loads are regarded as one of the highest across the globe.

Thus, we conducted this case–control study in the largest medical centre for BA in China, expecting to recognise some risk factors for the occurrence of BA. This is the largest study so far. Finally, 594 valid questionnaires from the case group and 681 from the control group were obtained. The aetiology of BA has not arrived at consensus yet for whether it is a prenatal disease or perinatal disease. Thus, exposure during the entire pregnancy was studied,

Table 4 Multivariate logistic regression analysis of risk factors of biliary atresia

Variables	OR	95% CI	z	P>z
Birth weight (kg)	0.39	0.26 to 0.58	−4.70	<0.001
Age of father				
<25	1.0	–	–	–
25–35	1.80	1.08 to 2.97	2.28	0.023
>35	3.59	1.71 to 7.52	3.38	0.001
Ethnicity of father	5.54	2.20 to 13.92	3.64	<0.001
Annual income of father (¥10 000)	0.93	0.90 to 0.97	−3.75	<0.001
Annual income of mother (¥10 000)	0.88	0.83 to 0.94	−3.75	<0.001
Respiratory infection	1.80	1.11 to 2.92	2.36	0.018
Gestational diabetes	2.44	1.15 to 5.20	2.32	0.02
Medication	4.91	2.75 to 8.75	5.40	<0.001
Number of family members living together	1.76	1.50 to 2.06	7.02	<0.001
Exposure to electronic devices	3.86	2.64 to 5.64	6.97	<0.001
Anxiety and stress	8.36	4.08 to 17.14	5.80	<0.001
_constant	0.02	0.00 to 0.11	−4.21	<0.001

and the main findings are as follows: (1) socioeconomic factors of parents may play a significant role, since those from lower income families have a higher risk of BA; (2) babies from ethnic minorities of China are more likely to get BA; (3) exposure to infection or diseases and medication used accordingly during pregnancy may increase the risk of offspring with BA; and (4) birth seasonality may have an effect, for those born in winter and spring accounted for the majority of the case group.

The present study shows that the prevalence of BA is higher in families with lower educational backgrounds and lower income. On the one hand, this is related to the difference in regional economic development. A higher prevalence of BA was noticed in rural areas.[16] Most of the people from ethnic minorities of China (not Han) live in remote or even underdeveloped areas. Some studies revealed that there may be some association between economic development and BA.[17] The overall socioeconomic improvement may result in better health services, better public health policies and possibly fewer exposures to infections during pregnancy, thereby reducing the incidence. On the other hand, it may also be related to the anxiety and stress brought on by the economy. A significant relationship between the prenatal maternal emotional factors and development of the fetus has been confirmed, especially for neurodevelopment.[18 19] However, the parents of the case group may be affected by their children's illness when filling in the questionnaires, so there is a certain bias of recall.

Another study showed that colder climate is likely to have a decisive impact on the incidence of BA.[20] Epidemiological studies in some areas also found that the incidence of BA in autumn and winter is higher, which is consistent with our findings.[12 21] This is probably related to virus exposure during pregnancy, including rotavirus and CMV. Animal experiments also confirmed that the success rate of the rotavirus animal model was higher in colder months.[22]

However, many studies have not found any seasonal and geographical variations in the incidence of BA.[9 10 15 17 21 23–25] In our study, we did not make a detailed division of the patients' ethnicity or region, and the seasonal variation cannot be compared with the control group due to the study design. Besides, date of conception instead of date of birth is more accurate. Therefore, further surveys based on nationwide population are needed.

In the case group, there are eight cases whose parents or relatives were once diagnosed with BA. Since there are no relevant cases in the control group, this variable is not included in the multivariate regression analysis. However, its relationship with BA is obvious, and a higher prevalence in those whose relatives have other hepatobiliary diseases, including hepatitis B, liver cancer and gallstones, is also noticed (online supplemental table 1). This may be due to some family genes related to liver disease. At present, there is limited research on the susceptible genes of BA, including interleukin-8, glutathione metabolism-related genes and so forth.[26 27] Further basic research on the pathogenesis of BA is warranted.

However, our study still has some limitations. First, the case group was recruited in a single centre; however, with a large sample size, the study spanning 2 years and patients coming from different regions of China, the geographical bias could not be ignored. Further, the control group was chosen from one medical centre in Shanghai. We had already considered the geographical factors, so the centre selected was in a suburb where most residents are from other provinces of China, but the mothers may have stayed in Shanghai during the pregnancy. Therefore, it is not entirely clear yet how geographical factors impact

the incidence of BA. More studies based on nationwide population are necessary. Second, due to the design of the retrospective study, there might be recall bias in questionnaire filling. However, the control mothers were interviewed at the 42-day revisit after birth in order to minimise the recall bias with the case group, since most of the babies with BA consulted at the age between 30 and 60 days.

CONCLUSION

Social factors including educational and economic background and relevant anxiety and stress during pregnancy might be noticed in the occurrence of BA. Seasonal variation in the prevalence of BA was demonstrated. Further studies based on nationwide population are necessary to confirm the geographical effect in China.

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Competing interests None declared.

Patient consent for publication Parental/guardian consent obtained.

Ethics approval This study protocol was reviewed and approved by the Ethics Committee of Children's Hospital of Fudan University, Shanghai, China (No. (2015) 45), and it was performed in compliance with the Declaration of Helsinki and other relevant regulations. Written informed consent was obtained from the parent or legal guardian of each subject before data collection.

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