Association of Offspring congenital heart disease with Maternal Autoimmune Diseases: A Retrospective Cohort Study with Real-world Evidence

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Abstract

Objectives Very few investigations have explored the association between CHDs in offspring and mothers with autoimmune disease. In this study, we aimed to explore whether maternal autoimmune disease increases the risk of CHDs in newborns. **Methods** We analyzed 4780 offspring with maternal autoimmune disease and 9416 offspring without maternal autoimmune disease matching 1:2 with age and sex between 2009 and 2016 from databases including the National Health Insurance program, birth certificate applications, cause of death data, and Maternal and Child Health Database, which is managed by the Health and Welfare Data Science Center (HWDC) in Taiwan. Birth year, birth weight, gestational age, the children's sex, mode of delivery, congenital defects, urbanization, insurance unit, maternal and paternal comorbidities, child or parents died within one year after birth and medication exposure during pregnancy were selected as covariates for further multivariate analysis. Also, multiple Cox regression analysis was performed to evaluate the adjusted hazard ratio (aHR) of CHDs. **Results** The incidence of CHDs was 5.35 per 10000 person-months in autoimmune mothers. The result of the multivariate Cox regression showed that the children whose mothers had autoimmune disease had a 1.57-fold risk of CHDs compared to children whose mothers did not have an autoimmune disease (crude hazard ratio: 1.57; 95% CI, 1.29-1.90, aHR: 1.51; 95% CI, 1.24-1.85). **Conclusion** Maternal autoimmune disease might be a risk factor for developing CHDs in offspring, especially in mothers with systemic lupus erythematosus or Sjogren's syndrome. Further research is warranted to investigate the possible pathogenesis mechanisms of this association.

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ABSTRACT

Objectives

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Methods

We analyzed 4780 offspring with maternal autoimmune disease and 9416 offspring without maternal autoimmune disease matching 1:2 with age and sex between 2009 and 2016 from databases including the National Health Insurance program, birth certificate applications, cause of death data, and Maternal and Child Health Database, which is managed by the Health and Welfare Data Science Center (HWDC) in Taiwan. Birth year, birth weight, gestational age, the children's sex, mode of delivery, congenital defects, urbanization, insurance unit, maternal and paternal comorbidities, child or parents died within one year after birth and medication exposure during pregnancy were selected as covariates for further multivariate analysis. Also, multiple Cox regression analysis was performed to evaluate the adjusted hazard ratio (aHR) of CHDs.

Results

The incidence of CHDs was 5.35 per 10000 person-months in autoimmune mothers. The result of the multivariate Cox regression showed that the children whose mothers had autoimmune disease had a 1.57-fold risk of CHDs compared to children whose mothers did not have an autoimmune disease (crude hazard ratio: 1.57; 95% CI, 1.29-1.90, aHR: 1.51; 95% CI, 1.24-1.85).

Conclusion

Maternal autoimmune disease might be a risk factor for developing CHDs in offspring, especially in mothers with systemic lupus erythematosus or Sjogren's syndrome. Further research is warranted to investigate the possible pathogenesis mechanisms of this association.

Trial Registration

ClinicalTrials.gov Identifier: CS19009

Keywords: autoimmune disease, congenital heart disease, longitudinal health insurance database

INTRODUCTION

Congenital heart diseases (CHDs) are a health burden, affecting approximately 15 million people worldwide [1-3]. The prevalence of CHDs varies, with a rate of 3 to 70 per 1,000 newborn infants depending on the methods

of diagnosis, severity of the disease, and population [4,5]. Additionally, CHDs are the major source of defects, accounting for one-third of congenital malformation[6,7] ; these diseases are associated with child morbidity, [6,8] and may be due to abnormalities during the conduction system and cardiac structures formation[9]. Although the treatment of CHDs and survival rate have been improved [10], there are still complications. Poor quality of life and poor performance in school affects some children with CHDs[11] . Children with severe CHDs require more than one surgery or may need a heart transplant[12]. Furthermore, CHDs can cause many cardiac complications even in adulthood and can reduce life expectancy[13,14].

Maternal illnesses due to autoimmunity or other in utero exposure to drugs are thought to be etiological factors related to CHDs.[15] There are very few studies in the literature on the association between CHDs in offspring and mothers with autoimmune disease. Notably, in a study of systemic lupus erythematosus (SLE) mothers, 7.5% of newborn children had a CHDs.[16] A recent investigation also reported higher incidence of CHDs in pregnant women with connective tissue disorders.[17] However, the investigators only included certain CHDs and autoimmune diseases so the results cannot be extrapolated to the general population.[18] The rate of CHDs were more than 5-fold compared with that seen in the general live birth population, although that is not a comparison group.[4] Investigators have observed prevalence rates of congenital heart block and CHDs between 20% to 40% in children born to pregnant women with SLE, after excluding newborns with CHDs that may have resulted in congenital heart block.[19-23] Although the incidence of CHDs, such as valve anomalies and septal defects, was slightly lower in newborn born to pregnant mother with SLE who did not have congenital heart block, the frequency was still higher compared to that in the general population.[19-23]

Whether maternal autoimmune disease increases the risk of CHDs in newborns has not been determined. In addition, there is still little evidence showed any correlation between maternal autoimmune disease and CHDs. Unfortunately, to date, no study with a large national longitudinal database has been employed to assess this correlation. In the present study, maternal autoimmune disease was hypothesized to increase the risk of CHDs in offspring. Accordingly, Taiwan's National Health Insurance Research Database (NHIRD) was employed to obtain a real-world, population-based retrospective cohort, which was analyzed to test our hypothesis.

METHODS

Data sources

The dataset analyzed in this study included the National Health Insurance program in Taiwan, birth certificate applications, cause of death data, and Maternal and Child Health Database, which is managed by the Health and Welfare Data Science Center (HWDC) in Taiwan. The National Health Insurance program contains all outpatient and inpatient medical claims, including drug medications, medical operations, procedures and fees. The birth certificate applications contained the following information: birth weight, gestational weeks, delivery type, live birth, stillbirth, multiple birth, and nationality of mother. The identification numbers of mothers and their children in the Maternal and Child Health Database were de-identified in accordance with privacy protocol. By linking these databases, we were able to trace the mother's comorbidities and medications during pregnancy. Our study was approved by the ethical review board of the Chung Shan Medical University Hospital (approval No. CS19009).

Study group and outcome

This study employed a retrospective cohort study design. There were 1459093 birth certifications in the database from 2009 to 2016. After excluding missing data on mother's identity and child's nationality as well as foreign nationality, multiple births, and stillbirth, there were 1246129 children in this study. The exposure group was offspring with maternal autoimmune disease. The definition of autoimmune disease was a diagnosis of any of the following: rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, ankylosing spondylitis, and psoriasis, which had been entered with their respective ICD-9-CM codes (714, 710, 710.2, 720, 696, and 696.1) and ICD-10-CM codes (M05, M06, M07, M09, M32, M35, M45, and L40) in at least two outpatient visits or at least one hospitalization during pregnancy or one year before pregnancy. The comparison group had never been diagnosed with an autoimmune disease during pregnancy or one year

before pregnancy. The index date was set as the birth date.

The outcome variable was defined as a diagnosis of CHD, including common truncus (ICD-CM=745.0, Q20.0), transposition of the great arteries (ICD-CM= 745.1, Q20.3, Q20.8, Q20.2, Q20.5), double outlet right ventricle (ICD-CM= 745.1, Q20.1), Tetralogy of Fallot (ICD-CM= 745.2, Q21.3), single ventricle (ICD-CM= 745.3, Q20.4), endocardial cushion defect or ostium primum atrial septal defect (ASD) (ICD-CM= 745.6, Q21.2), tricuspid atresia, stenosis, or absence (ICD-CM= 746.1, Q22.4, Q22.6, Q22.8, Q22.9), hypoplastic left heart syndrome (ICD-CM= 746.7, Q23.4), ventricular septal defect (ICD-CM= 745.4, Q21.0), secundum ASD or patent foramen ovale (ICD-CM= 745.5, Q21.1), patent ductus arteriosus (ICD-CM= 747.0, Q25.0), anomalies of pulmonary valve (ICD-CM= 746.0, Q22.0, Q22.3, Q22.2, Q22.1), Ebstein anomaly (ICD-CM= 746.2, Q22.5), aortic valve stenosis (ICD-CM= 746.3, Q23.0), aortic insufficiency or bicuspid, unicuspid aortic valve (ICD-CM= 746.4, Q23.1), mitral valve abnormalities (ICD-CM=746.5, 746.6, Q23.2, Q23.3), anomalies of pulmonary artery (ICD-CM= 747.3, Q25.5, Q25.6, Q25.7), subaortic stenosis (ICD-CM= 746.81, Q24.4), cor triatrium (ICD-CM=746.82, Q24.2), infundibular or subvalvar pulmonary stenosis (ICD-CM=746.83, Q24.3), coronary artery anomaly (ICD-CM= 746.85, Q24.5), malposition of heart or apex (ICD-CM=746.87, Q24.0, Q24.1, Q24.8), anomaly of the aorta (coarctation of aorta, interrupted aortic arch) (ICD-CM=747.2, 747.1, Q25.3, Q25.8, Q25.4, Q25.9, Q25.2, Q25.1), anomalies of great veins (TAPVR, PAPVR) (ICD-CM= 747.4, Q26.2, Q26.9, Q26.0, Q26.1, Q26.8, Q26.2, Q26.3, Q26.4), and at least three outpatient visits or at least one hospitalization during the observational period. Among CHDs, patent foramen ovale, atrial septal defect, and patent ductus arteriosus were only included after1 year old as they are common condition in newborn infant. Both groups were followed up until the onset of CHDs, death, or 31 December 2019, whichever occurred first.

Covariates and matching

The baseline characteristics were birth year, child's sex, birth weight (<2500; 2500-3499; [?]3500 gram), gestational weeks (<37; 37-40; [?]40 weeks), delivery (normal spontaneous delivery, NSD; cesarean section, C/S), Apgar score (less than 5 at 1 minute, less than 5 at 5 minutes), parents' ages, congenital defects, urbanization, insurance unit, maternal and paternal comorbidities, children or parents died within one year after birth, medication exposure during pregnancy, and maternal comorbidities, including asthma (ICD-CM=493, J44, J45), hypertension (ICD-CM=401-405, I10-I15), diabetes mellitus (ICD-CM=250, E10, E11, E12, E13, E14), hyperlipidemia (ICD-CM= 272, E78), gestational diabetes (ICD-CM= 648.8, O99.81, O24.41, O24.42, O24.43), preeclampsia or eclampsia (ICD-CM= 6424.4, 642.5, 642.6, 642.7, O11, O14,O15), urinary tract infection (ICD-CM=599, N39), endometriosis (ICD-CM=617.0-617.9, 621.3, N80), sleep disorder (ICD-CM=327, 780.5, G47), and depression (ICD-CM= 293.83, 296.2, 296.3,300.4, 311, F06.3, F32.0-F32.5, F32.9-F33.4, F33.9, F34.1). The comorbidities were defined as those that occurred two years before the index date and were observed during at least two outpatient visits or one hospitalization. In addition, paternal comorbidities including asthma, hypertension, diabetes mellitus, hyperlipidemia, urinary tract infection, sleep disorder, and depression, were also included in the multivariate analysis.

Statistical analysis

The relative risk (RR) and the 95% confidence intervals (CI) were calculated via the Poisson regression model. Kaplan-Meier analysis was used to calculate the cumulative incidence of CHDs among the two groups. The log-rank test was used to test the significance. Independent risk (hazard ratio) of the maternal autoimmune disease group was calculated using a multivariate Cox proportional hazard model. The statistical software used was SAS version 9.4 (SAS Institute Inc, NC, USA).

RESULTS

After exclusion of individuals with missing ID, foreign citizenship of mother, and stillbirth,

there were 4708 offspring with maternal autoimmune disease and 9416 offspring without maternal autoimmune disease matching 1:2 with age and sex (Supplement 1). Among the demographic characteristics of both cohorts, the maternal autoimmune disease group had a higher prevalence of maternal comorbidity such

as hypertension (4.61% vs.1.68%, with P < 0.0001), hyperlipidemia (1.59% vs. 0.52%, with P < 0.0001), preeclampsia or eclampsia (6.63% vs. 3.90%, with P < 0.0001), sleep disorder (9.47% vs. 5.11%, with P < 0.0001), depression (6.52% vs. 2.57%, with P < 0.0001), asthma (2.06% vs. 1.22%, with P = 0.0001), and urinary tract infection (16.46% vs. 11.68%, with P < 0.0001) when compared with that of the without maternal autoimmune disease group; whereas the other comorbidities and risk factors, including birth year, child's sex, congenital defects, diabetes mellitus, gestational diabetes, urbanization, and insurance unit were not different between the maternal autoimmune disease and without maternal autoimmune groups. (Table 1). The incidence rate of CHDs was significantly higher among autoimmune disease mothers than that of the non-autoimmune disease mothers (5.35 vs. 3.39 per 10000 person-months). Children whose mothers had autoimmune disease had a 1.57-fold risk of CHDs compared to children whose mothers did not have an autoimmune disease (crude hazard ratio: 1.57; 95% CI, 1.29-1.90). We adjusted for child's birth year, child's sex, mother's age, urbanization, insurance unit, mother's comorbidity, and father 's age in model one (aHR: 1.51; 95% CI, 1.24-1.85) and adjusted for all variables in model two (aHR: 1.25; 95% CI, 1.01-1.54) (Table 2). Furthermore, the CHDs risk was higher in male patients than in females though the CI was wide. In table 3, patients with low body weight (< 2500 gm) were at a higher risk of CHDs (aHR: 1.46; 95% CI, 1.06-2.01). Preterm (aHR: 1.74; 95% CI, 1.28-2.37) and caesarean section (aHR: 1.40; 95% CI, 1.14-1.72) were also significantly associated with a higher risk of CHDs (as summarized in supplementary Table 3). Furthermore, the stratified analysis revealed that offspring with maternal systemic lupus erythematosus (aHR: 2.01, 95% CI, 1.55-2.60), and Sjogren's syndrome (aHR: 1.47, 95% CI, 1.10-1.96) had a significantly higher risk of CHDs. (Figure 1) The cumulative risk of CHDs in the maternal autoimmune group was significantly higher than that of the comparison group, with the log-rank test in the Kaplan–Meier curve analysis indicating statistical significance, p < 0.001 (Figure 2).

DISCUSSION

In this study, the infants born to pregnant women with autoimmune disease had a 1.57-fold higher risk of developing CHDs than those whose mothers did not have an autoimmune disease, regardless of child's birth year, child's sex, mother's age, urbanization, insurance unit, mother's comorbidity, and father 's age. This is the first study to analyze the association between maternal autoimmune disease and offspring with CHDs in Taiwan. To the best of our knowledge, this is the largest epidemiological research to probe these associations by employing a nationwide longitudinal population-based dataset. The risk of CHDs should be explained to pregnant women with autoimmune disease, and this patient group should be provided appropriate management for CHDs as required.

Our finding showed an association between CHDs and hydroxychloroquine exposure in utero, although the CI was wide. (Supplement 2) Several studies have found an association between hydroxychloroquine exposure and specific types of congenital anomalies.[24] In the present study, the effect of in utero hydroxychloroquine exposure on CHDs might explained the disease severity. Moreover, if maternal autoimmune disease itself has a potential effect on CHDs, mothers with more severe autoimmune disease might be more likely to flare up during pregnancy, requiring hydroxychloroquine for disease control. Therefore, disease severity may have accounted for the apparent effect of hydroxychloroquine exposure.

We observed that gestational diabetes mellitus (GDM) was a predictor of CHDs, although the CI was wide. Major congenital anomalies, such as CHDs, may be cause by diabetic embryopathy due to maternal hyperglycemia in the first trimester.[25] The most common type of congenital anomalies in women with GDM were CHDs.[25] In the previous study, the risk of CHDs in the women with GDM was 1.5 fold greater compared to healthy women.[26,27] Our observation was similar and consistent with other published literature.

The mechanisms of maternal autoimmune disease that may underlie the physiopathology of CHDs in newborn infants include cytokine imbalance and autoantibody-mediated damage. Transplacental transfer of maternal autoantibodies, such as immunoglobulin G, might affect the fetus in some CHDs and congenital heart block[21,28,29]. It has been hypothesized that maternal autoimmune disease might play a critical role in structural CHD [30,31].

Children born to mothers with autoimmune disease have an increased incidence of CHDs compared to children born to the general population. Circulating levels in the fetus reach maternal levels during the second trimester via active transport of maternal IgG antibodies cross the placenta.[32] Antibodies, such as Anti-SSA/Ro, are associated with neonatal lupus, and may progress to a cardiac manifestation. Some research has demonstrated that the release of profibrosing and proinflammatory cytokines and scarring are due to the binding of maternal antibodies and apoptotic fetal cardiocytes.[33] This process may extend to valves, endocardium, and myocardium. Cardiac histological damage beyond the conduction system was observed in a retrospective study of autopsies from neonatal lupus cases.[22] In particular note, one case showed a lymphohistiocytic infiltrate in the ventricular septum, and another showed foci of calcification in the atrial septum. Nevertheless, 40% of deaths caused by congenital heart block had pathology findings, including calcification of the aortic, pulmonary, tricuspid, or mitral valves.[22] Furthermore, macrophages, a crucial component of the innate immune system, have been reported to play an important role in cardiac structure formation[34] . However, muscular VSDs are thought to be associated with cellular death within a formed ventricular septum during active cardiac remodeling.[35] Moreover, maternal autoantibodies might prohibit closure of septal defects possibly explaining the risk of ASD and VSD in offspring of autoimmune pregnant women in comparison with the general population.[6]

Antiphospholipid antibodies (APLs), one of the types of autoantibodies found in women with autoimmune disease, can cross the placenta. Moreover, 40% of newborns tested positive for APLs in cord blood in a study of neonates born to mothers with antiphospholipid syndrome.[36] APLs are associated with some valvular diseases (e.g., valvular regurgitation, nodules, and verrucous endocarditis.)[37] Deposits of APLs are thought to play a significant pathogenic role in the valvular disease.[37] Although other studies have showed perinatal thrombotic events in children born to APLs (+) mothers, the relationship with the prevalence of CHDs remained unclear in these patients.[38] Therefore, it has been hypothesized that APLs may play an important role in congenital valve anomalies in fetuses due to their involvement in valvular damage and their ability to cross the placenta.

Transforming growth factor beta (TGF-β) also plays a role in endocardial cushion formation. It plays an important role in cardiac septation during cardiac embryogenesis, requiring expression of cytokines, such as TGF-β. [39] It has been demonstrated in animal models that both fetal and maternal TGF-β in cardiac embryogenesis are important.[39] The mice born to mothers with TGF-β-1 non-expression had more severe CHDs compare to those born to mothers with normal TGF-β-1 expression. Investigators hypothesized that transplacental transfer of maternal TGF-β-1 occurring from mother to fetus might rescue potential heart defects in the offspring.[39] The levels of TGF-β-1 in autoimmune disease patients are lower than in controls, inversely correlating with the activity of disease.[40] Maternal TGF-β-induced rescue or heart defect in defective TGF-β fetuses might not happen in autoimmune pregnant women, leading to an increased risk of CHDs.

Our study still had some limitations. First, the subgroup analysis of relevant medication exposures during pregnancy did not precisely estimate the association between CHDs in offspring and maternal autoimmune disease. The medication exposures in our research were based on prescriptions, and the patients might not have actually taken the medicine. Regardless of this limitation, this is still the largest study assessing the potential risk of CHDs in maternal autoimmune disease offspring. Second, our study did not adjust for multivitamin and folic acid exposures during pregnancy. Multivitamin and folic acid may have been obtained without a formal prescription in a proportion of the women. Nevertheless, our study excluded stillbirths because a proportion of stillbirths result from termination, and no information on the reason or outcome was recorded.[41] Another potential limitation that is common to all observational studies is that there may have been poorly measured or unmeasured confounders. We used defined proxies precisely for certain variables: for example, urbanization, socioeconomic status. However, the administrative databases in our study do not contain information on certain variables (e.g., alcohol use, obesity, and smoking) that are knowen to increase the risk of CHDs in children born to mothers with these risk factors. [42]Furthermore, the NHIRD does not record any individual serological data. This might have shed light on the role of certain types of autoantibodies, such as antiphospholipid antibodies and anti-Ro/SSA, in mothers with autoimmune disease in the subsequent development of CHDs in their newborn infants. The association between CHDs

and utero autoimmune disease exposure, as well as the role of maternal cytokines and autoantibodies in the pathogenesis of CHDs still needs to be established in further research.

CONCLUSION

In conclusion, newborns born to mothers with autoimmune disease had a significantly increased risk of CHDs, in comparison with the control group. Further research is need on the role of maternal cytokines and autoantibodies, which might increase the risk of CHDs in newborn born to mothers with autoimmune disease.

What is already known on this topic –Maternal illnesses due to autoimmunity or other in utero exposure to drugs are thought to be etiological factors related to CHDs

What this study adds – Newborns born to mothers with autoimmune disease had a significantly increased risk of CHDs, in comparison with the control group.

How this study might affect research, practice or policy – Further research is need on the role of maternal cytokines and autoantibodies, which might increase the risk of CHDs in newborn born to mothers with autoimmune disease.

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FIGURE LEGENDS:

Figure 1. aHRs for CHDs in offspring by subtype of maternal autoimmune disease

Figure 2. KM curves for cumulative probability of CHDs in offspring

Supplement 1. Study flow chart

Supplement 2. Incidence of congenital heart disease

Supplement 1. Study flow chart

Figure 1. aHRs for CHDs in offspring by subtype of maternal autoimmune disease

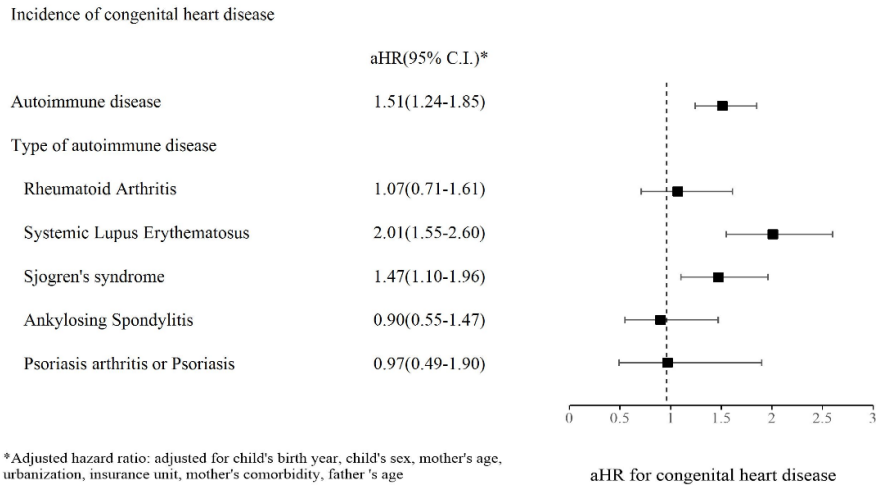


Figure 2. KM curves for cumulative probability of CHDs in offspring

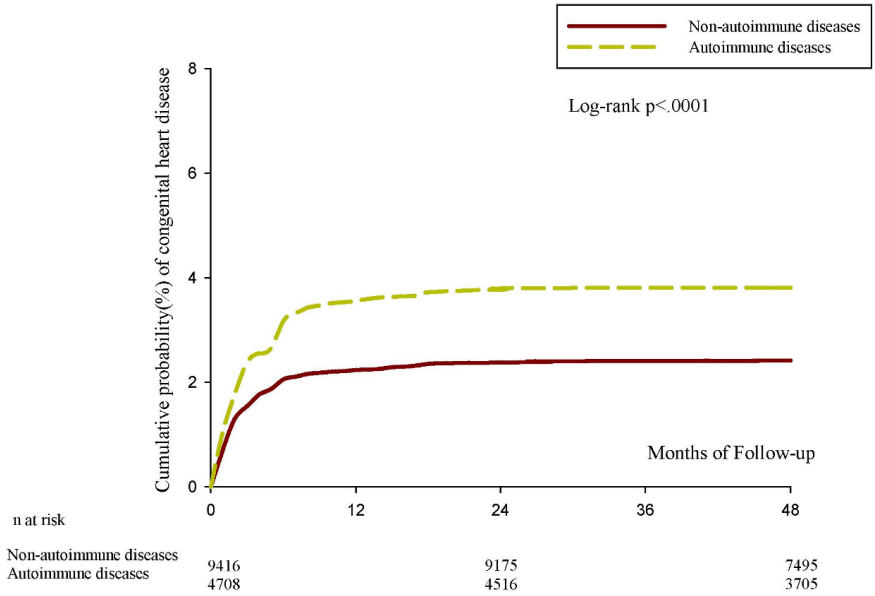


Table 1. Baseline characteristics

	After matching	After matching	After matching
Variable	Non-autoimmune diseases	Autoimmune diseases	p-value
N	9416	4708	
Child characteristics			
Birth year			0.7738
2009	212(2.25%)	128(2.72%)	
2010	847(9%)	425(9.03%)	
2011	1144(12.15%)	548(11.64%)	
2012	1311(13.92%)	651(13.83%)	

	After matching	After matching	After matching
2013	1197(12.71%)	614(13.04%)	
2014	1366(14.51%)	668(14.19%)	
2015	1618(17.18%)	813(17.27%)	
2016	1721(18.28%)	861(18.29%)	
Children's sex			1.0000
Male	4936(52.42%)	2468(52.42%)	
Female	4480(47.58%)	2240(47.58%)	
Gestational age, weeks			<.0001
<37	693(7.36%)	785(16.67%)	
37-40	6863(72.89%)	3275(69.56%)	
>=40	1860(19.75%)	648(13.76%)	
Birth weight, g			<.0001
<2500	605(6.43%)	829(17.61%)	
2500-3500	7405(78.64%)	3481(73.94%)	
>=3500	1406(14.93%)	398(8.45%)	
Apgar score at 1 min <5	46(0.49%)	68(1.44%)	<.0001
Apgar score at 5 min <5	10(0.11%)	12(0.25%)	0.0347
Infant died within 1 year of birth	22(0.23%)	14(0.3%)	0.4789
Maternal characteristics			
Mother's age			0.7586
<30	1902(20.2%)	944(20.05%)	
30-40	7082(75.21%)	3535(75.08%)	
>=40	432(4.59%)	229(4.86%)	
Urbanization			0.3064
Urban	6220(66.06%)	3057(64.93%)	
Sub-urban	2763(29.34%)	1414(30.03%)	
Rural	433(4.6%)	237(5.03%)	
Insurance unit			0.0002
Government	641(6.81%)	415(8.81%)	
Privately held company	7321(77.75%)	3614(76.76%)	
Agricultural organizations	421(4.47%)	191(4.06%)	
Others	1033(10.97%)	488(10.37%)	
Delivery mode			<.0001
NSD	6060(64.36%)	2678(56.88%)	
C/S	3356(35.64%)	2030(43.12%)	
Mother died within 1 year of delivery	7(0.07%)	8(0.17%)	0.1002
Maternal comorbidity			
Diabetes mellitus	234(2.49%)	135(2.87%)	0.1793
Hypertension	158(1.68%)	217(4.61%)	<.0001
Gestational diabetes	615(6.53%)	269(5.71%)	0.0586
preeclampsia	367(3.9%)	312(6.63%)	<.0001
Depression	242(2.57%)	307(6.52%)	<.0001
Sleep disorder	481(5.11%)	446(9.47%)	<.0001
Asthma	115(1.22%)	97(2.06%)	0.0001

	After matching	After matching	After matching
Hyperlipidemia	49(0.52%)	75(1.59%)	<.0001
Urinary tract infection	1100(11.68%)	775(16.46%)	<.0001
endometriosis	127(1.35%)	87(1.85%)	0.0221
Congenital defects	50(0.53%)	41(0.87%)	0.0173
Father's age			0.0933
miss	395(4.19%)	157(3.33%)	
<30	1124(11.94%)	572(12.15%)	
30-40	6612(70.22%)	3319(70.5%)	
>=40	1285(13.65%)	660(14.02%)	
Father died within 1 year of delivery	8(0.08%)	3(0.06%)	0.6697

Table 2 Incidence of congenital heart disease

	Non-autoimmune diseases	Autoimmune diseases
N	9416	4708
Observed person-month	678712	334344
Event of outcome	230	179
Incidence rate*(95% C.I.)	3.39(2.98-3.86)	5.35(4.62-6.20)
Crude Relative risk (95% C.I.)	reference	1.57(1.29-1.90)
Model 1 : aHR(95% C.I.)*	reference	1.51(1.24-1.85)
Model 2 : aHR(95% C.I.)*	reference	1.25(1.01-1.54)

* Incidence rate, per 10,000 person months

aHR(95% C.I.), Adjusted hazard ratio(aHR)

* Model 1: adjusted for child's birth year, child's sex, mother's age, Urbanization, Insurance unit, mother's comorbidity, father 's age

* Model 2: adjusted for all variable.

Table 3. Cox proportional hazard model analysis for risk of congenital heart disease

		After matching	After matching	After matching
		HR (95% C.I.)	Model 1 aHR (95% C.I.)	Model 2 aHR (95% C.I.)
	Study group			
	Non-autoimmune diseases	reference	reference	reference
	Autoimmune diseases	1.57(1.29-1.9)	1.51(1.24-1.85)	1.25(1.01-1.54)
	Birth year			
	2009	reference	reference	reference
	2010	0.6(0.33-1.07)	0.57(0.32-1.04)	0.56(0.31-1.01)
	2011	0.48(0.27-0.86)	0.48(0.27-0.86)	0.48(0.27-0.86)
	2012	0.55(0.31-0.96)	0.53(0.3-0.93)	0.55(0.31-0.98)
	2013	0.54(0.3-0.95)	0.49(0.27-0.87)	0.5(0.28-0.89)
	2014	0.58(0.33-1.01)	0.55(0.31-0.97)	0.58(0.33-1.02)

		After matching	After matching	After matching
	2015	0.73(0.43-1.25)	0.69(0.4-1.18)	0.72(0.42-1.23)
	2016	0.75(0.44-1.29)	0.7(0.41-1.19)	0.73(0.43-1.25)
	Children's sex			
	Male	1.07(0.88-1.29)	0.94(0.77-1.14)	0.95(0.77-1.15)
	Female	reference	reference	reference
	Gestational weeks			
	<37	2.93(2.33-3.68)		1.74(1.28-2.37)
	37-40	reference		reference
	>=40	0.85(0.63-1.14)		1.04(0.77-1.41)
	Birth weight (g)			
	<2500	2.73(2.17-3.44)		1.46(1.06-2.01)
	2500-3500	reference		reference
	>=3500	0.62(0.42-0.91)		0.62(0.42-0.93)
	Apgar score at 1 min <5	0.12(0.08-0.19)		0.3(0.17-0.51)
	Apgar score at 5 min <5	0.08(0.03-0.17)		0.47(0.18-1.22)
	Mother's age			
	<30	0.99(0.77-1.27)	1.11(0.83-1.48)	1.15(0.86-1.54)
	30-40	reference	reference	reference
	>=40	0.97(0.6-1.58)	0.93(0.55-1.56)	0.86(0.51-1.46)
	Urbanization			
	Urban	reference	reference	reference
	Sub-urban	1.02(0.82-1.26)	0.96(0.77-1.2)	0.97(0.78-1.21)
	Rural	0.47(0.24-0.92)	0.4(0.2-0.82)	0.39(0.19-0.8)
	Insurance unit			
	Government	0.84(0.56-1.25)	0.85(0.57-1.27)	0.88(0.59-1.31)
	Privately held company	reference	reference	reference
	Agricultural organizations	1.08(0.68-1.71)	1.5(0.91-2.48)	1.49(0.9-2.47)
	Others	0.9(0.63-1.29)	0.95(0.67-1.36)	0.96(0.67-1.37)
	Delivery mode			
	NSD	reference		reference
	C/S	1.65(1.35-2.01)		1.4(1.14-1.72)
	Maternal comorbidity			
	Diabetes mellitus	1.62(0.98-2.67)	1.57(0.94-2.63)	1.66(0.99-2.78)
	Hypertension	2.3(1.5-3.53)	1.59(0.98-2.56)	1.12(0.69-1.84)
	Gestational diabetes	0.76(0.48-1.2)	0.72(0.45-1.14)	0.74(0.47-1.19)
	Preeclampsia or eclampsia	2.04(1.45-2.88)	1.68(1.15-2.45)	1.2(0.81-1.78)
	Depression	1.09(0.66-1.8)	0.9(0.53-1.52)	0.82(0.48-1.39)
	Sleep disorder	1.21(0.83-1.76)	1.12(0.75-1.65)	1.09(0.73-1.63)
	Asthma	0.52(0.17-1.63)	0.47(0.15-1.48)	0.5(0.16-1.57)
	Hyperlipidemia	1.45(0.6-3.49)	1.07(0.44-2.63)	1.04(0.42-2.55)
	Urinary tract infection	1.08(0.82-1.44)	1.03(0.77-1.37)	0.99(0.74-1.32)
	endometriosis	1.87(1.03-3.41)	1.79(0.98-3.27)	1.67(0.91-3.05)
	Father's age			

		After matching	After matching	After matching
	<30	0.82(0.6-1.14)	0.8(0.55-1.15)	0.81(0.56-1.17)
	30-40	reference	reference	reference
	>=40	0.95(0.71-1.26)	0.94(0.69-1.29)	0.93(0.68-1.26)

* Model 1: adjusted for child's birth year, child's sex, mother's age, Urbanization, Insurance unit, mother's comorbidity, father 's age

* Model 2: adjusted for all variable.

Supplement 2. Incidence of congenital heart disease

Mother with autoimmune diseases used medication

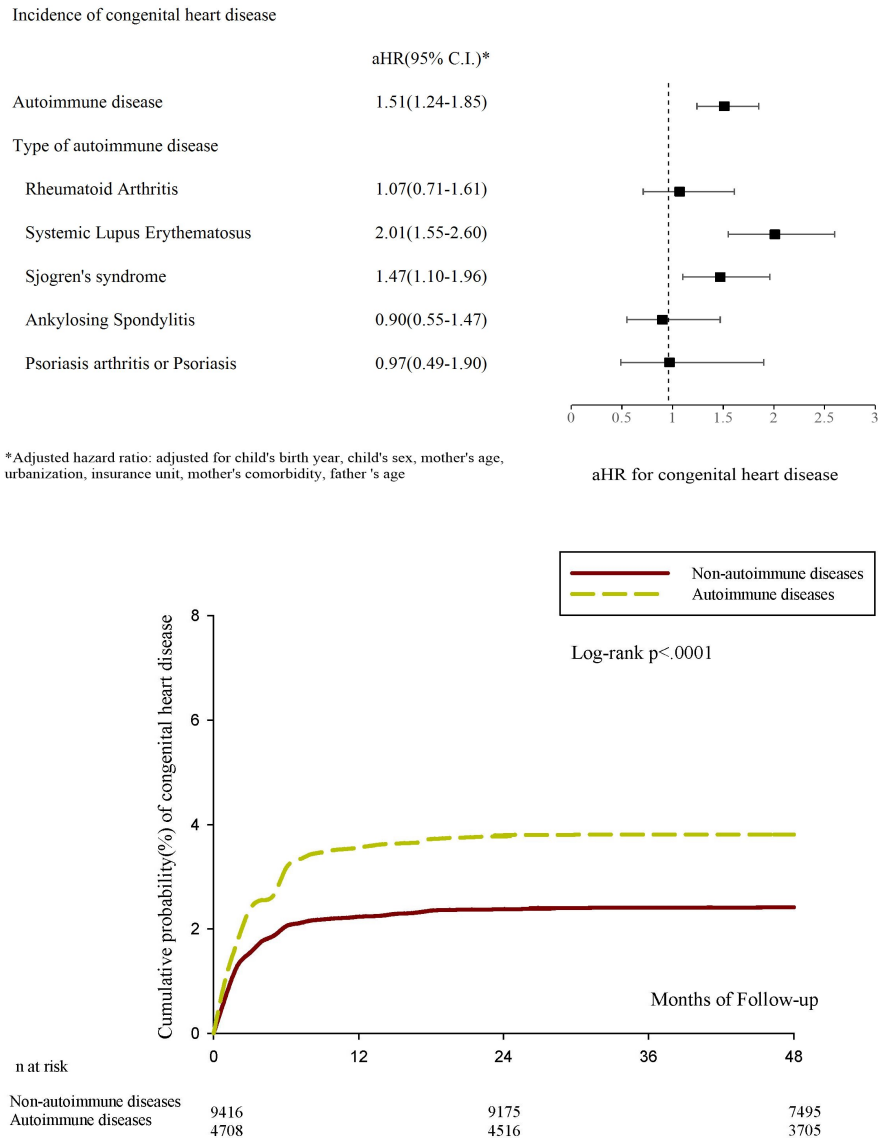
	pre-pregnancy	First Trimester	Second Trimester	Third Trimester
NSAID				
Crude Relative risk (95% C.I.)	1.01(0.63-1.62)	0.82(0.6-1.11)	0.94(0.67-1.32)	0.77(0.57-1.05)
Model 1 : aHR(95% C.I.)*	0.97(0.6-1.57)	0.8(0.58-1.1)	0.97(0.68-1.37)	0.73(0.54-1.01)
Model 2 : aHR(95% C.I.)*	1.06(0.66-1.72)	0.85(0.62-1.17)	0.94(0.66-1.35)	0.77(0.56-1.07)
DMARDs				
Crude Relative risk (95% C.I.)	1.29(0.92-1.82)	1.64(1.22-2.22)	1.35(1.01-1.82)	1.3(0.97-1.75)
Model 1 : aHR(95% C.I.)*	1.25(0.88-1.78)	1.56(1.15-2.13)	1.3(0.96-1.75)	1.2(0.88-1.63)
Model 2 : aHR(95% C.I.)*	1.1(0.77-1.56)	1.32(0.96-1.81)	1.07(0.78-1.46)	1.02(0.75-1.4)
DMARDs Hydroxychloroquine				
Crude Relative risk (95% C.I.)	1.55(1.14-2.1)	1.65(1.23-2.22)	1.39(1.04-1.87)	1.33(0.99-1.8)
Model 1 : aHR(95% C.I.)*	1.51(1.1-2.06)	1.55(1.15-2.1)	1.32(0.97-1.78)	1.21(0.89-1.65)
Model 2 : aHR(95% C.I.)*	1.29(0.94-1.77)	1.28(0.94-1.75)	1.07(0.79-1.47)	1.02(0.74-1.4)
Leflunomide				
Crude Relative risk (95% C.I.)	NA	NA	NA	NA
Model 1 : aHR(95% C.I.)*	NA	NA	NA	NA
Model 2 : aHR(95% C.I.)*	NA	NA	NA	NA
Methotrexate				
Crude Relative risk (95% C.I.)	0.8(0.45-1.4)	NA	NA	NA
Model 1 : aHR(95% C.I.)*	0.87(0.49-1.53)	NA	NA	NA
Model 2 : aHR(95% C.I.)*	0.89(0.5-1.58)	NA	NA	NA

	pre-pregnancy	First Trimester	Second Trimester	Third Trimester
Azathioprine				
Crude Relative risk (95% C.I.)	1.15(0.74-1.77)	1.21(0.73-2.03)	1.26(0.72-2.21)	1.1(0.6-2.02)
Model 1 : aHR(95% C.I.)*	1.07(0.68-1.68)	1.15(0.69-1.94)	1.21(0.67-2.19)	1.07(0.56-2.04)
Model 2 : aHR(95% C.I.)*	0.85(0.54-1.35)	0.88(0.52-1.49)	0.84(0.46-1.54)	0.79(0.41-1.52)
Ciclosporin				
Crude Relative risk (95% C.I.)	0.98(0.4-2.37)	NA	NA	NA
Model 1 : aHR(95% C.I.)*	0.77(0.28-2.08)	NA	NA	NA
Model 2 : aHR(95% C.I.)*	0.63(0.23-1.72)	NA	NA	NA
Sulfasalazine				
Crude Relative risk (95% C.I.)	0.65(0.41-1.03)	1.01(0.57-1.77)	1.16(0.57-2.35)	1.31(0.62-2.8)
Model 1 : aHR(95% C.I.)*	0.68(0.43-1.09)	1.13(0.64-1.99)	1.27(0.62-2.59)	1.48(0.69-3.16)
Model 2 : aHR(95% C.I.)*	0.8(0.5-1.28)	1.28(0.72-2.26)	1.35(0.66-2.76)	1.58(0.74-3.39)
Minocycline				
Crude Relative risk (95% C.I.)	0.72(0.27-1.94)	NA	NA	NA
Model 1 : aHR(95% C.I.)*	0.73(0.27-1.97)	NA	NA	NA
Model 2 : aHR(95% C.I.)*	0.8(0.29-2.16)	NA	NA	NA
bDMARDs-TNFi				
Crude Relative risk (95% C.I.)	NA	NA	NA	NA
Model 1 : aHR(95% C.I.)*	NA	NA	NA	NA
Model 2 : aHR(95% C.I.)*	NA	NA	NA	NA

* Model 1: adjusted for child's birth year, child's sex, mother's age, Urbanization, Insurance unit, mother's comorbidity, father 's age

* Model 2: adjusted for all variable.

NA= not applicable



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