

## SUPPLEMENTAL MATERIAL

**Supplemental Figure 1** Directed acyclic graph for the association between maternal HBV infection in early pregnancy and risk of CHD in offspring.

**Supplemental Figure 2** Directed acyclic graph for the association between maternal coxsackievirus-B infection in early pregnancy and risk of CHD in offspring.

**Supplemental Figure 3** Directed acyclic graph for the association between maternal HCMV infection in early pregnancy and risk of CHD in offspring.

**Supplemental Figure 4** Directed acyclic graph for the association between maternal HSV infection in early pregnancy and risk of CHD in offspring.

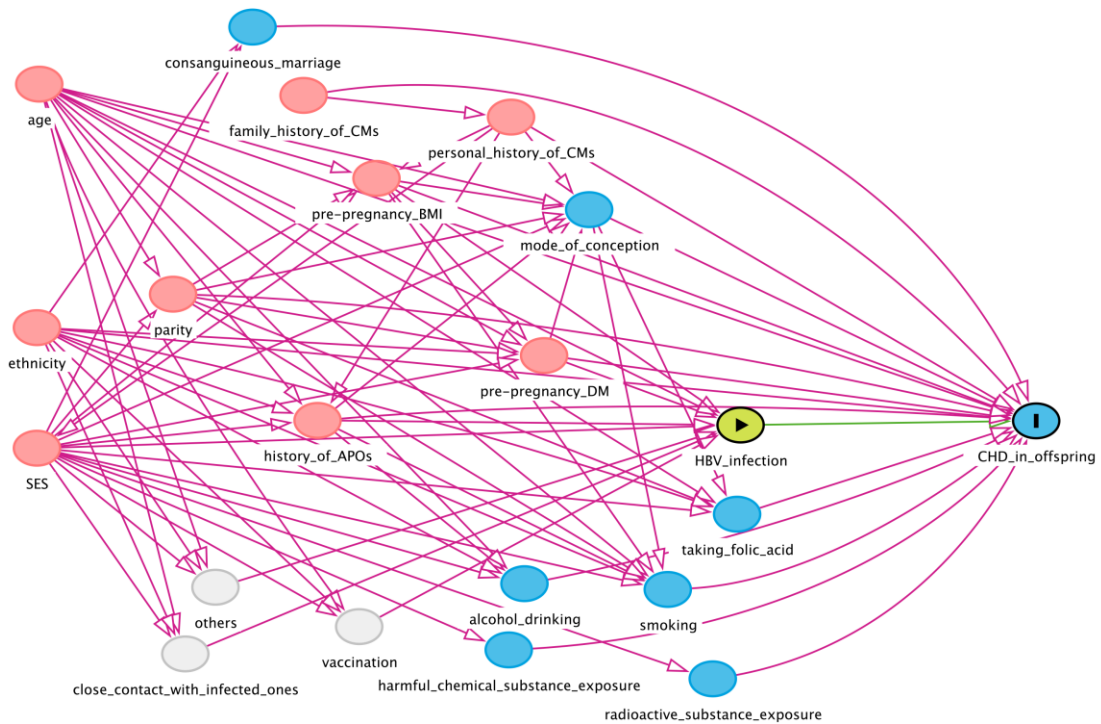
**Supplemental Figure 5** Directed acyclic graph for the association between maternal rubella virus infection in early pregnancy and risk of CHD in offspring.

**Supplemental Figure 6** The risks of CHD in offspring of pregnant women with viral infection in early pregnancy after excluding pregnant women whose children had non-cardiac defects.

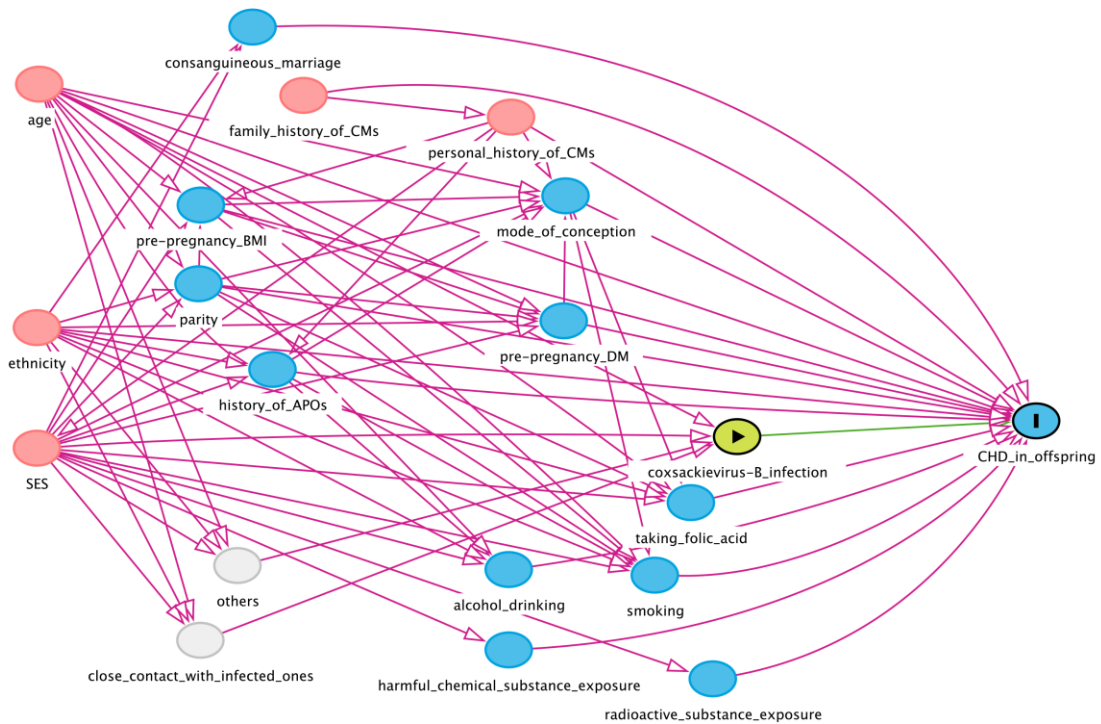
**Supplemental Figure 7** The risks of CHD in offspring of pregnant women with viral infection in early pregnancy after excluding pregnant women whose children were diagnosed with more than one CHD phenotypes.

**Supplemental Table 1** The distribution of maternal characteristics according to status of maternal HBV, coxsackievirus-B, and HCMV infection.

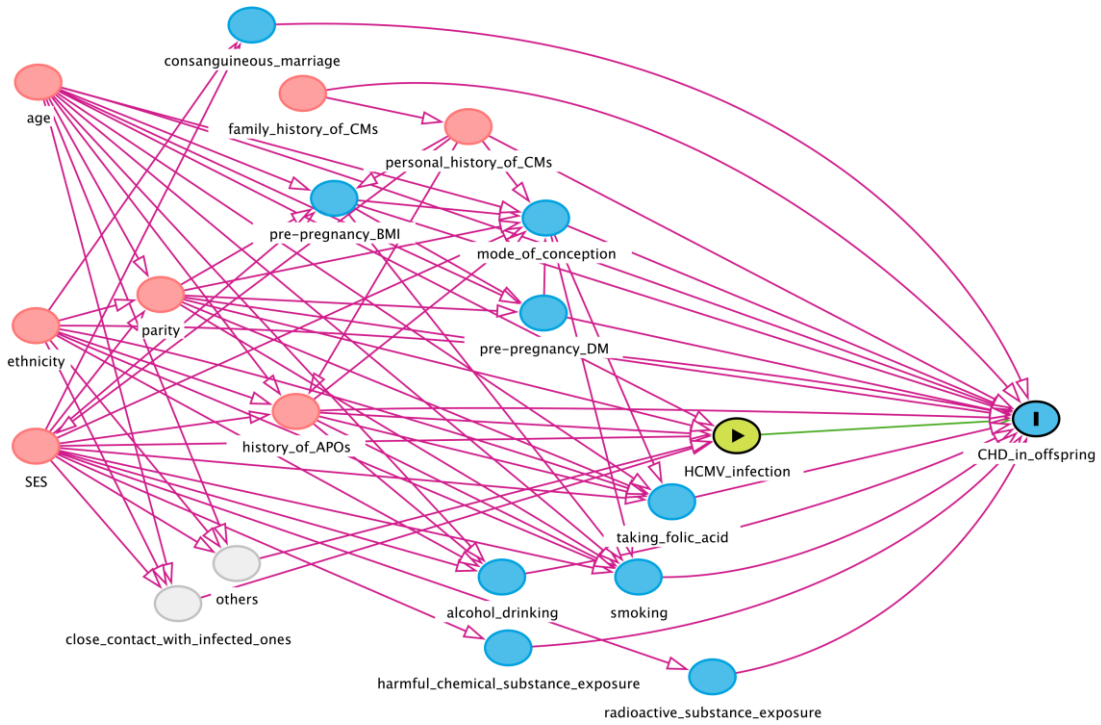
**Supplemental Table 2** The distribution of baseline characteristics according to status of maternal HSV and rubella virus infection.



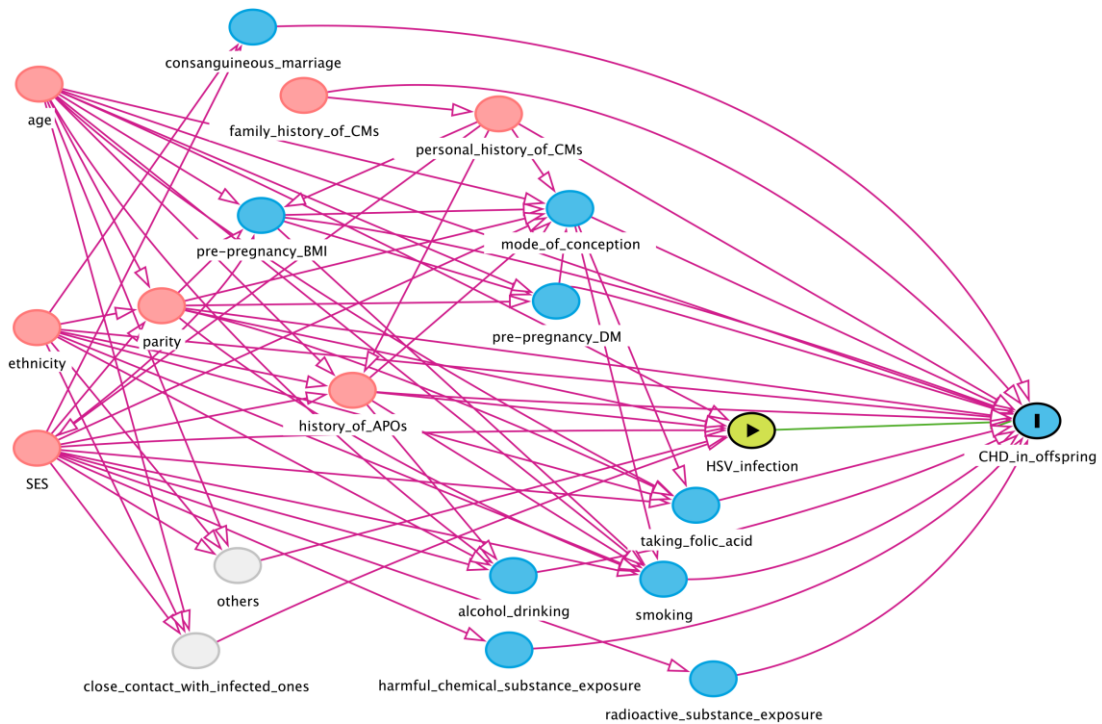
**Supplemental Figure 1** Directed acyclic graph for the association between maternal HBV infection in early pregnancy and risk of CHD in offspring. Red arrows indicate biasing paths, green arrows indicate causal paths. APOs, adverse pregnancy outcomes; BMI, body mass index; CHD, congenital heart disease; CMs, congenital malformations; DM, diabetes mellitus; HBV, hepatitis B virus.



**Supplemental Figure 2** Directed acyclic graph for the association between maternal coxsackievirus-B infection in early pregnancy and risk of CHD in offspring. Red arrows indicate biasing paths, green arrows indicate causal paths. APOs, adverse pregnancy outcomes; BMI, body mass index; CHD, congenital heart disease; CMs, congenital malformations; DM, diabetes mellitus.



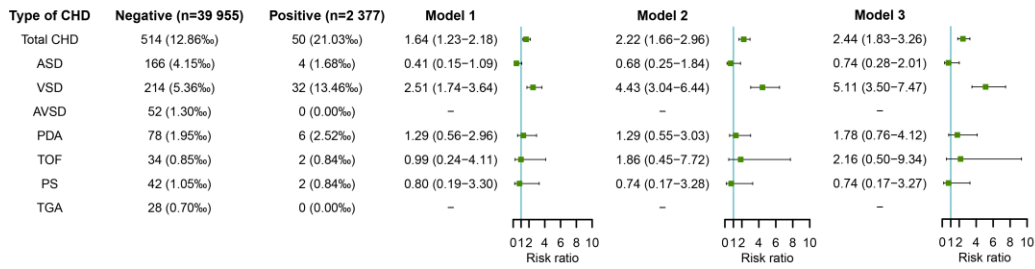
**Supplemental Figure 3** Directed acyclic graph for the association between maternal HCMV infection in early pregnancy and risk of CHD in offspring. Red arrows indicate biasing paths, green arrows indicate causal paths. APOs, adverse pregnancy outcomes; BMI, body mass index; CHD, congenital heart disease; CMs, congenital malformations; DM, diabetes mellitus; HCMV, human cytomegalovirus.



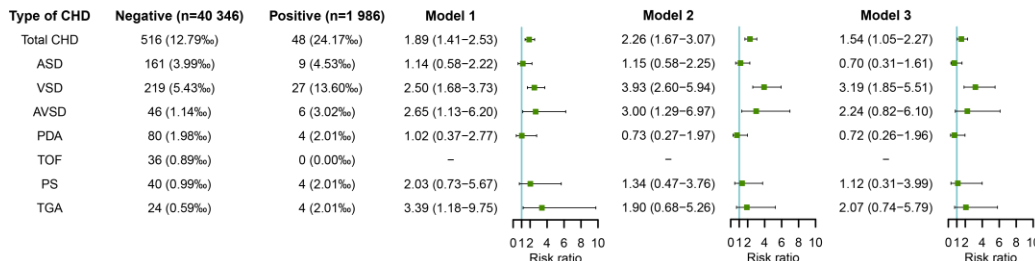
**Supplemental Figure 4** Directed acyclic graph for the association between maternal HSV infection in early pregnancy and risk of CHD in offspring. Red arrows indicate biasing paths, green arrows indicate causal paths. APOs, adverse pregnancy outcomes; BMI, body mass index; CHD, congenital heart disease; CMs, congenital malformations; DM, diabetes mellitus; HSV, herpes simplex virus.



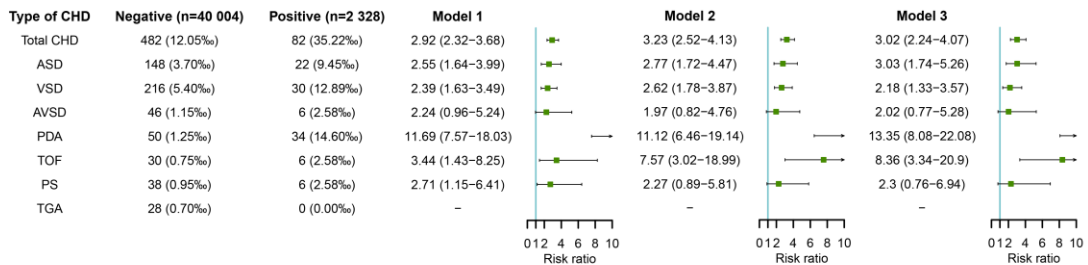
**a. Hepatitis B virus**



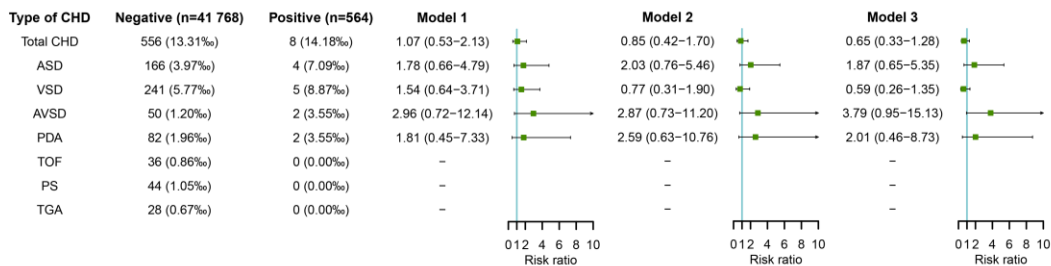
**b. Coxsackievirus-B**



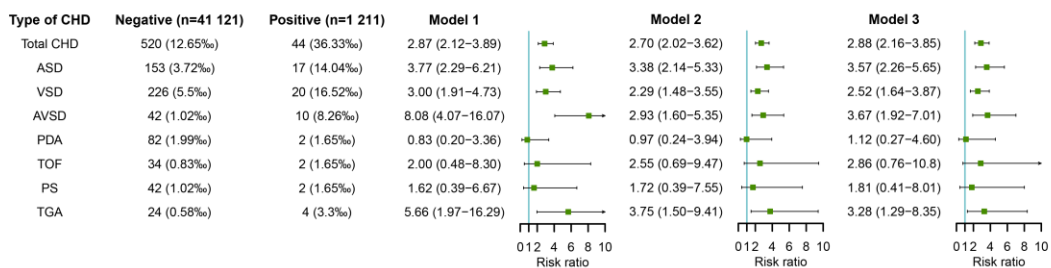
**c. Human cytomegalovirus**



**d. Herpes simplex virus**



**e. Rubella virus**

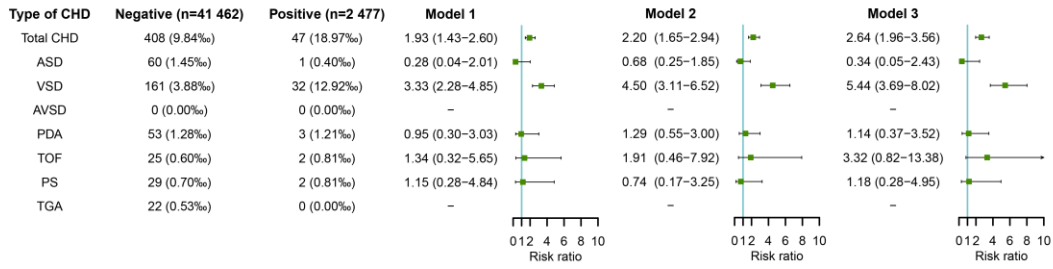


**Supplemental Figure 6** The risks of CHD in offspring of pregnant women with viral infection in early pregnancy after excluding pregnant women whose children had non-cardiac defects. For the five viruses analyzed, model 1 was a crude model without any variable adjusted. For HBV (a), model 2 adjusted for educational level, age, ethnicity, history of adverse pregnancy

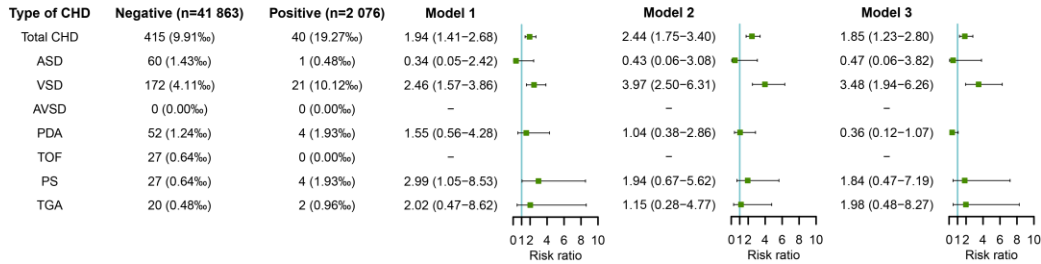
outcomes, pre-pregnancy BMI, and pre-pregnancy diabetes mellitus, while model 3 adjusted for the variables in model 2 plus other virus infection including coxsackievirus-B, HCMV, HSV, and rubella virus. For coxsackievirus-B (b), model 2 adjusted for educational level, age, and ethnicity, while model 3 adjusted for the variables in model 2 plus other virus infection including HBV, HCMV, HSV, and rubella virus. For HCMV (c), model 2 adjusted for educational level, age, ethnicity, parity, and history of adverse pregnancy outcomes, while model 3 adjusted for the variables in model 2 plus other virus infection including HBV, coxsackievirus-B, HSV, and rubella virus. For HSV (d), model 2 adjusted for educational level, age, ethnicity, parity, and history of adverse pregnancy outcomes, while model 3 adjusted for the variables in model 2 plus other virus infection including HBV, coxsackievirus-B, HCMV, and rubella virus. For rubella virus (e), model 2 adjusted for educational level, age, ethnicity, parity, history of adverse pregnancy outcomes, and pre-pregnancy BMI, while model 3 adjusted for the variables in model 2 plus other virus infection including HBV, coxsackievirus-B, HCMV, and HSV. BMI, body mass index; CHD, congenital heart disease; HBV, hepatitis B virus; HCMV, human cytomegalovirus; HSV, herpes simplex virus.



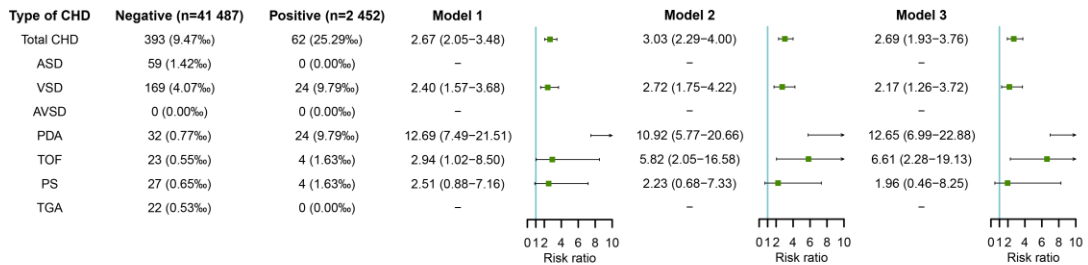
**a. Hepatitis B virus**



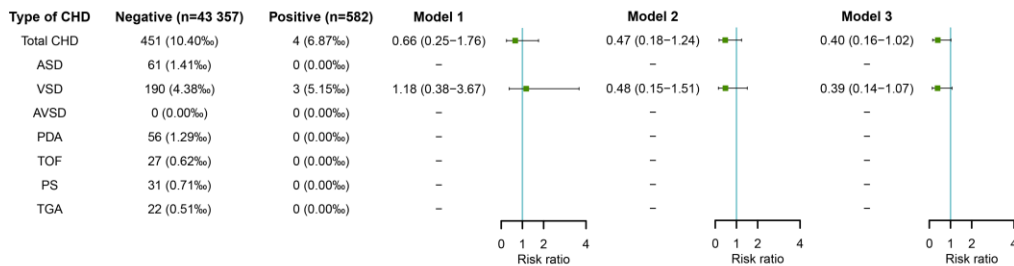
**b. Coxsackievirus-B**



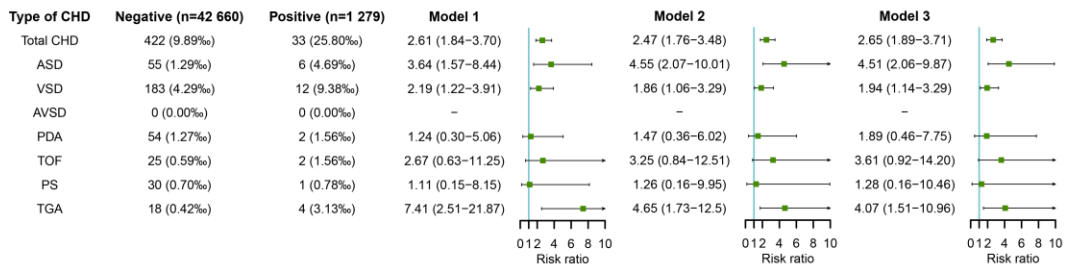
**c. Human cytomegalovirus**



**d. Herpes simplex virus**



**e. Rubella virus**



**Supplemental Figure 7** The risks of CHD in offspring of pregnant women with viral infection in early pregnancy after excluding pregnant women whose children were diagnosed with more than one CHD phenotypes. For the five viruses analyzed, model 1 was a crude model without any variable adjusted. For HBV (a), model 2 adjusted for educational level, age, ethnicity,

history of adverse pregnancy outcomes, pre-pregnancy BMI, and pre-pregnancy diabetes mellitus, while model 3 adjusted for the variables in model 2 plus other virus infection including coxsackievirus-B, HCMV, HSV, and rubella virus. For coxsackievirus-B (b), model 2 adjusted for educational level, age, and ethnicity, while model 3 adjusted for the variables in model 2 plus other virus infection including HBV, HCMV, HSV, and rubella virus. For HCMV (c), model 2 adjusted for educational level, age, ethnicity, parity and history of adverse pregnancy outcomes, while model 3 adjusted for the variables in model 2 plus other virus infection including HBV, coxsackievirus-B, HSV, and rubella virus. For HSV (d), model 2 adjusted for educational level, age, ethnicity, parity and history of adverse pregnancy outcomes, while model 3 adjusted for the variables in model 2 plus other virus infection including HBV, coxsackievirus-B, HCMV, and rubella virus. For rubella virus (e), model 2 adjusted for educational level, age, ethnicity, parity, history of adverse pregnancy outcomes, and pre-pregnancy BMI, while model 3 adjusted for the variables in model 2 plus other virus infection including HBV, coxsackievirus-B, HCMV, and HSV. BMI, body mass index; CHD, congenital heart disease; HBV, hepatitis B virus; HCMV, human cytomegalovirus; HSV, herpes simplex virus.

**Supplemental Table 1 The distribution of maternal characteristics according to status of maternal HBV, coxsackievirus-B, and HCMV infection.**

Baseline characteristics	HBV			Coxsackievirus-B			HCMV		
	Negative (n, %)	Positive (n, %)	p-value	Negative (n, %)	Positive (n, %)	p-value	Negative (n, %)	Positive (n, %)	p-value
<b>Sociodemographic characteristics</b>									
Age (years)			<b>&lt; 0.001</b>			<b>&lt; 0.001</b>			<b>&lt; 0.001</b>
<25	4,666 (11.2%)	314 (12.7%)		4,668 (11.1%)	312 (15.0%)		4,658 (11.2%)	322 (13.0%)	
25-29.9	18,442 (44.4%)	1,282 (51.7%)		18,530 (44.2%)	1,194 (57.3%)		18,292 (44.0%)	1,432 (57.9%)	
30-34.9	13,592 (32.7%)	600 (24.2%)		13,700 (32.6%)	492 (23.6%)		13,674 (32.9%)	518 (21.0%)	
≥35	4,868 (11.7%)	284 (11.5%)		5,066 (12.1%)	86 (4.1%)		4,952 (11.9%)	200 (8.1%)	
Ethnicity			<b>&lt; 0.001</b>			<b>&lt; 0.001</b>			<b>&lt; 0.001</b>
Han	39,350 (94.7%)	2,468 (99.5%)		39,700 (94.8%)	2,048 (98.3%)		39,428 (94.8%)	2,390 (96.7%)	
Minority	2,281 (5.3%)	12 (0.5%)		2,194 (5.2%)	36 (1.7%)		2,148 (5.2%)	82 (3.3%)	
Educational level			<b>&lt; 0.001</b>			<b>&lt; 0.001</b>			<b>&lt; 0.001</b>
Junior high school or below	6,783 (16.3%)	116 (4.7%)		6,814 (16.2%)	86 (4.1%)		6,648 (16.0%)	252 (10.2%)	
Senior middle school	22,276 (53.6%)	888 (35.8%)		21,826 (52.0%)	1,338 (64.2%)		21,704 (52.2%)	1,460 (59.1%)	
College	9,426 (22.7%)	1,394 (56.2%)		10,318 (24.6%)	502 (24.1%)		10,206 (24.5%)	614 (24.8%)	
Master or above	3,082 (7.4%)	82 (3.3%)		3,006 (7.2%)	158 (7.6%)		3,018 (7.3%)	146 (5.9%)	
<b>Obstetric, clinical, and genetic characteristics</b>									
Mode of conception			<b>&lt; 0.001</b>			<b>&lt; 0.001</b>			<b>&lt; 0.001</b>
Spontaneous conception	32,638 (78.5%)	1,466 (59.1%)		32,072 (76.4%)	2,032 (97.5%)		32,012 (77.0%)	2,092 (84.6%)	
Assisted conception	8,930 (21.5%)	1,014 (40.9%)		9,892 (23.6%)	52 (2.5%)		9,564 (23.0%)	380 (15.4%)	
Consanguineous marriage (yes)	170 (0.4%)	14 (0.6%)	0.243	152 (0.4%)	32 (1.5%)	<b>&lt; 0.001</b>	158 (0.4%)	26 (1.1%)	<b>&lt; 0.001</b>

Parity			<b>&lt; 0.001</b>			<b>&lt; 0.001</b>			<b>&lt; 0.001</b>
Nulliparous	17,954 (43.2%)	1,608 (64.8%)		19,356 (46.1%)	206 (9.9%)		18,938 (45.6%)	624 (25.2%)	
Multiparous	23,614 (56.8%)	872 (35.2%)		22,608 (53.9%)	1,878 (90.1%)		22,638 (54.4%)	1,848 (74.8%)	
History of adverse pregnancy outcomes (yes)	16,708 (40.2%)	1,000 (42.3%)	<b>0.034</b>	17,046 (40.6%)	712 (34.2%)	<b>&lt; 0.001</b>	16,832 (40.5%)	926 (37.5%)	<b>0.003</b>
Family history of congenital malformations (yes)	62 (0.1%)	0 (0.0%)	0.054	50 (0.1%)	12 (0.6%)	<b>&lt; 0.001</b>	42 (0.1%)	20 (0.8%)	<b>&lt; 0.001</b>
<b>Health-related factors</b>									
Pre-pregnancy BMI (kg/m <sup>2</sup> )			<b>&lt; 0.001</b>			<b>&lt; 0.001</b>			<b>&lt; 0.001</b>
<18.5	7154 (17.2%)	378 (15.2%)		6,998 (16.7%)	534 (25.6%)		7,070 (17.0%)	462 (18.7%)	
18.5-23.9	27,336 (65.8%)	1,988 (80.2%)		28,018 (66.8%)	1,306 (62.7%)		27,626 (66.4%)	1,698 (68.7%)	
24-27.9	5,990 (14.4%)	72 (2.9%)		5,902 (14.1%)	160 (7.7%)		5,818 (14.0%)	244 (9.9%)	
≥28	1,088 (2.6%)	42 (1.7%)		1,046 (2.5%)	84 (4.0%)		1,062 (2.6%)	68 (2.8%)	
Pre-pregnancy diabetes mellitus (yes)	298 (0.7%)	34 (1.4%)	0.152	332 (0.8%)	0 (0.0%)	<b>&lt; 0.001</b>	318 (0.8%)	14 (0.6%)	0.268
Personal history of congenital malformations (yes)	394 (0.9%)	72 (2.9%)	<b>&lt; 0.001</b>	466 (1.1%)	0 (0.0%)	<b>&lt; 0.001</b>	426 (1.0%)	40 (1.6%)	<b>0.005</b>
Taking folic acid in 3 months before pregnancy or in early pregnancy (yes)	39,754 (95.6%)	2,318 (93.5%)	<b>&lt; 0.001</b>	40 088 (95.5%)	1,984 (95.2%)	0.480	39,740 (95.6%)	2,332 (94.3%)	<b>0.004</b>
Smoking in early	558 (1.3%)	46 (1.9%)	<b>0.033</b>	566 (1.3%)	38 (1.8%)	0.069	562 (1.4%)	42 (1.7%)	0.149

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pregnancy (yes)									
Drinking in early pregnancy (yes)	556 (1.3%)	8 (0.3%)	<b>&lt; 0.001</b>	560 (1.3%)	4 (0.2%)	<b>&lt; 0.001</b>	546 (1.3%)	18 (0.7%)	<b>0.012</b>
Environmental pollution around the dwelling place in three months before pregnancy or in early pregnancy (yes)	880 (2.1%)	40 (1.6%)	0.088	892 (2.1%)	28 (1.3%)	<b>0.015</b>	884 (2.1%)	36 (1.5%)	<b>0.024</b>
Exposure to radioactive hazardous while at work in three months before pregnancy or in early pregnancy (yes)	1,326 (3.2%)	106 (4.3%)	<b>0.003</b>	1,328 (3.2%)	104 (5.0%)	<b>&lt; 0.001</b>	1,372 (3.3%)	60 (2.4%)	<b>0.017</b>

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BMI, body mass index; HBV, hepatitis B virus; HCMV, human cytomegalovirus.

**Supplemental Table 2 The distribution of baseline characteristics according to status of maternal HSV and rubella virus infection.**

Baseline characteristics	HSV			Rubella virus		
	Negative (n, %)	Positive (n, %)	p-value	Negative (n, %)	Positive (n, %)	p-value
<b>Sociodemographic characteristics</b>						
Age (years)			<b>&lt; 0.001</b>			<b>&lt; 0.001</b>
<25	4,824 (11.1%)	156 (26.6%)		4,796 (11.2%)	184 (14.3%)	
25-29.9	19,522 (44.9%)	202 (34.5%)		19,206 (44.9%)	518 (40.2%)	
30-34.9	14,108 (32.5%)	84 (14.3%)		13,784 (32.2%)	408 (31.6%)	
≥35	5,008 (11.5%)	144 (24.6%)		4,972 (11.6%)	180 (14.0%)	
Ethnicity			<b>&lt; 0.001</b>			0.388
Han	41,232 (94.9%)	586 (100%)		40,600 (95.0%)	1,218 (94.4%)	
Minority	2,230 (5.1%)	0 (0.0%)		2,158 (5.0%)	72 (5.6%)	
Educational level			<b>&lt; 0.001</b>			0.677
Junior high school or below	6,718 (15.5%)	182 (31.1%)		6,684 (15.6%)	216 (16.7%)	
Senior middle school	22,932 (52.8%)	232 (39.6%)		22,502 (52.6%)	662 (51.3%)	
College	10,664 (24.5%)	156 (26.6%)		10,504 (24.6%)	316 (24.5%)	
Master or above	3,148 (7.2%)	16 (2.7%)		3,068 (7.2%)	96 (7.4%)	
<b>Obstetric, clinical, and genetic characteristics</b>						
Mode of conception			<b>0.005</b>			<b>0.025</b>
Spontaneous conception	33,622 (77.4%)	482 (82.3%)		33,072 (77.3%)	1,032 (80.0%)	
Assisted conception	9,840 (22.6%)	104 (17.7%)		9,686 (22.7%)	258 (20.0%)	
Consanguineous marriage (yes)	180 (0.4%)	4 (0.7%)	0.317	178 (0.4%)	6 (0.5%)	0.789
Parity			<b>&lt; 0.001</b>			<b>&lt; 0.001</b>
Nulliparous	19,498 (44.9%)	64 (10.9 %)		19,234 (45.0%)	328 (25.4%)	

Multiparous	23,964 (55.1%)	522 (89.1%)		23,524 (55.0%)	962 (74.6%)	
History of adverse pregnancy outcomes (yes)	17,506 (40.3%)	252 (43.0%)	0.182	17,188 (40.2%)	570 (44.2%)	<b>0.004</b>
Family history of congenital malformations (yes)	62 (0.1%)	0 (0.0%)	0.360	62 (0.1%)	0 (0.0%)	0.171
<b>Health-related factors</b>						
Pre-pregnancy BMI (kg/m <sup>2</sup> )			<b>&lt; 0.001</b>			<b>&lt; 0.001</b>
<18.5	7,450 (17.1%)	82 (14.0%)		7,290 (17.0%)	242 (18.8%)	
18.5-23.9	28,846 (66.4%)	478 (81.6%)		28,506 (66.7%)	818 (63.4%)	
24-27.9	6,040 (13.9%)	22 (3.8%)		5,888 (13.8%)	174 (13.5%)	
≥28	1,126 (2.6%)	4 (0.7%)		1,074 (2.5%)	56 (4.3%)	
Pre-pregnancy diabetes mellitus (yes)	332 (0.8%)	0 (0.0%)	<b>0.034</b>	322 (0.8%)	10 (0.8%)	0.928
Personal history of congenital malformations (yes)	466 (1.1%)	0 (0.0%)	<b>0.012</b>	456 (1.1%)	10 (0.8%)	0.314
Taking folic acid in 3 months before pregnancy or in early pregnancy (yes)	41,492 (95.5%)	580 (99.0%)	<b>&lt; 0.001</b>	1,926 (4.5%)	50 (3.9%)	0.283
Smoking in early pregnancy (yes)	600 (1.4%)	4 (0.7%)	0.149	590 (1.4%)	14 (1.1%)	0.370
Drinking in early pregnancy (yes)	560 (1.3%)	4 (0.7%)	0.195	538 (1.3%)	26 (2.0%)	<b>0.017</b>
Environmental pollution around the dwelling place in three months before pregnancy or in early pregnancy (yes)	908 (2.1%)	12 (2.0%)	0.945	894 (2.1%)	26 (2.0%)	0.852
Exposure to radioactive hazardous while at work in three months before	1,406 (3.2%)	26 (4.4%)	0.103	1,398 (3.3%)	34 (2.6%)	0.206

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pregnancy or in early pregnancy

(yes)

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BMI, body mass index; HSV, herpes simplex virus.