## 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; $H B V$, 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.


Supplemental Figure 5 Directed acyclic graph for the association between maternal rubella virus 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.
a. Hepatitis B virus

c. Human cytomegalovirus

| Type of CHD | Negative ( $\mathrm{n}=40004$ ) | Positive ( $\mathrm{n}=2 \mathrm{328}$ ) | Model 1 |  | Model 2 |  | Model 3 |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Total CHD | 482 (12.05\%) | 82 (35.22\%) | 2.92 (2.32-3.68) | - | 3.23 (2.52-4.13) | - | 3.02 (2.24-4.07) | - |
| ASD | 148 (3.70\%) | 22 (9.45\%) | 2.55 (1.64-3.99) | -- | 2.77 (1.72-4.47) | -- | 3.03 (1.74-5.26) | - |
| VSD | 216 (5.40\%) | 30 (12.89\%) | 2.39 (1.63-3.49) | - | 2.62 (1.78-3.87) | -- | 2.18 (1.33-3.57) | - |
| AVSD | 46 (1.15\%) | 6 (2.58\%) | 2.24 (0.96-5.24) | - | 1.97 (0.82-4.76) | - | 2.02 (0.77-5.28) |  |
| PDA | 50 (1.25\%) | 34 (14.60\%) | 11.69 (7.57-18.03) | $\longmapsto$ | 11.12 (6.46-19.14) | $\longrightarrow$ | 13.35 (8.08-22.08) | $\rightarrow$ |
| TOF | 30 (0.75\%) | 6 (2.58\%) | 3.44 (1.43-8.25) | - | 7.57 (3.02-18.99) | $\cdots$ | 8.36 (3.34-20.9) | $\rightarrow$ |
| PS | 38 (0.95\%) | 6 (2.58\%) | 2.71 (1.15-6.41) | $\square$ | 2.27 (0.89-5.81) | - | 2.3 (0.76-6.94) |  |
| TGA | 28 (0.70\%) | 0 (0.00\%) | - |  | - |  | - |  |
|  |  |  |  | 01246810 <br> Risk ratio |  | 01246810 Risk ratio |  | 01246810 Risk ratio |

d. Herpes simplex virus

| Type of CHD | Negative ( $\mathrm{n}=41 \mathrm{768}$ ) | Positive ( $\mathrm{n}=564$ ) | Model 1 |  |
| :---: | :---: | :---: | :---: | :---: |
| Total CHD | 556 (13.31\%) | 8 (14.18\%) | 1.07 (0.53-2.13) |  |
| ASD | 166 (3.97\%) | 4 (7.09\%) | 1.78 (0.66-4.79) |  |
| VSD | 241 (5.77\%) | 5 (8.87\%) | 1.54 (0.64-3.71) | - |
| AVSD | 50 (1.20\%) | 2 (3.55\%) | 2.96 (0.72-12.14) |  |
| PDA | 82 (1.96\%) | 2 (3.55\%) | 1.81 (0.45-7.33) |  |
| TOF | 36 (0.86\%) | 0 (0.00\%) | - |  |
| PS | 44 (1.05\%) | 0 (0.00\%) | - |  |
| TGA | 28 (0.67\%) | 0 (0.00\%) | - |  |
|  |  |  |  | $\begin{array}{lllllll} \hline 1 & 1 & 1 & 1 & \\ 012 & 4 & 6 & 8 & 10 \\ \text { Risk ratio } \end{array}$ |

e. Rubella virus

| Type of CHD | Negative ( $\mathrm{n}=41$ 121) | Positive ( $\mathrm{n}=1$ 211) | Model 1 |  | Model 2 | Model 3 |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Total CHD | 520 (12.65\%) | 44 (36.33\%) | 2.87 (2.12-3.89) | -- | 2.70 (2.02-3.62) | - | 2.88 (2.16-3.85) | - |
| ASD | 153 (3.72\%) | 17 (14.04\%) | 3.77 (2.29-6.21) | $\cdots$ | 3.38 (2.14-5.33) | $\cdots$ | 3.57 (2.26-5.65) | - |
| VSD | 226 (5.5\%) | 20 (16.52\%) | 3.00 (1.91-4.73) | -- | 2.29 (1.48-3.55) | - | 2.52 (1.64-3.87) | -- |
| AVSD | 42 (1.02\%) | 10 (8.26\%) | 8.08 (4.07-16.07) | $\cdots$ | 2.93 (1.60-5.35) | -- | 3.67 (1.92-7.01) | -- |
| PDA | 82 (1.99\%) | 2 (1.65\%) | 0.83 (0.20-3.36) |  | 0.97 (0.24-3.94) |  | 1.12 (0.27-4.60) |  |
| TOF | 34 (0.83\%) | 2 (1.65\%) | 2.00 (0.48-8.30) |  | 2.55 (0.69-9.47) |  | 2.86 (0.76-10.8) |  |
| PS | 42 (1.02\%) | 2 (1.65\%) | 1.62 (0.39-6.67) |  | 1.72 (0.39-7.55) |  | 1.81 (0.41-8.01) |  |
| TGA | 24 (0.58\%) | 4 (3.3\%) | 5.66 (1.97-16.29) | $\stackrel{\square}{\square 1,}$ | 3.75 (1.50-9.41) | $\stackrel{\pi}{\pi 11}$ | 3.28 (1.29-8.35) | $\stackrel{\square}{\pi 111}$ |
|  |  |  |  | $\begin{aligned} & 01246810 \\ & \text { Risk ratio } \end{aligned}$ |  | $01246810$ Risk ratio |  | $\begin{gathered} 01246810 \\ \text { Risk ratio } \end{gathered}$ |

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.

d. Herpes simplex virus


| Type of CHD | Negative ( $\mathrm{n}=42 \mathrm{660}$ ) | Positive ( $\mathrm{n}=1$ 279) | Model 1 |  | Model 2 |  | Model 3 |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Total CHD | 422 (9.89\%) | 33 (25.80\%) | 2.61 (1.84-3.70) | - | 2.47 (1.76-3.48) | - | 2.65 (1.89-3.71) | - |
| ASD | 55 (1.29\%) | 6 (4.69\%) | 3.64 (1.57-8.44) | $\square$ | 4.55 (2.07-10.01) | $\square$ | 4.51 (2.06-9.87) | $\square$ |
| VSD | 183 (4.29\%) | 12 (9.38\%) | 2.19 (1.22-3.91) | - | 1.86 (1.06-3.29) | - | 1.94 (1.14-3.29) | - |
| AVSD | 0 (0.00\%) | 0 (0.00\%) | - |  | - |  | - |  |
| PDA | 54 (1.27\%) | 2 (1.56\%) | 1.24 (0.30-5.06) |  | 1.47 (0.36-6.02) |  | 1.89 (0.46-7.75) |  |
| TOF | 25 (0.59\%) | 2 (1.56\%) | 2.67 (0.63-11.25) |  | 3.25 (0.84-12.51) | $\xrightarrow{\longrightarrow}$ | 3.61 (0.92-14.20) |  |
| PS | 30 (0.70\%) | 1 (0.78\%) | 1.11 (0.15-8.15) |  | 1.26 (0.16-9.95) |  | 1.28 (0.16-10.46) |  |
| TGA | 18 (0.42\%) | 4 (3.13\%) | 7.41 (2.51-21.87) | $\rightarrow$ | 4.65 (1.73-12.5) | $\square$ | 4.07 (1.51-10.96) | $\square$ |
|  |  |  |  |  |  | 11 1 1 1 <br> 12 4 6 8 <br> 10    |  | $\begin{array}{llllll} \hline 1 & 1 & 1 & 1 & \\ 12 & 4 & 6 & 8 & 10 \end{array}$ |
|  |  |  |  | Risk ratio |  | Risk ratio |  | Risk ratio |

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 |
| Sociodemographic characteristics |  |  |  |  |  |  |  |  |  |
| Age (years) |  |  | < 0.001 |  |  | < 0.001 |  |  | $<0.001$ |
| <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\%) |  |
| $\geq 35$ | 4,868 (11.7\%) | 284 (11.5\%) |  | 5,066 (12.1\%) | 86 (4.1\%) |  | 4,952 (11.9\%) | 200 (8.1\%) |  |
| Ethnicity |  |  | < 0.001 |  |  | < 0.001 |  |  | $<0.001$ |
| 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 |  |  | < 0.001 |  |  | < 0.001 |  |  | < 0.001 |
| 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\%) |  |
| Obstetric, clinical, and genetic characteristics |  |  |  |  |  |  |  |  |  |
| Mode of conception |  |  | < 0.001 |  |  | < 0.001 |  |  | $<0.001$ |
| 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\%) | < 0.001 | 158 (0.4\%) | 26 (1.1\%) | < 0.001 |


| Parity |  |  | < 0.001 |  |  | < 0.001 |  |  | < 0.001 |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 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\%) | 0.034 | 17,046 (40.6\%) | 712 (34.2\%) | < 0.001 | 16,832 (40.5\%) | 926 (37.5\%) | 0.003 |
| Family history of congenital malformations (yes) | 62 (0.1\%) | 0 (0.0\%) | 0.054 | 50 (0.1\%) | 12 (0.6\%) | < 0.001 | 42 (0.1\%) | 20 (0.8\%) | < 0.001 |
| Health-related factors |  |  |  |  |  |  |  |  |  |
| Pre-pregnancy BMI (kg/m²) |  |  | < 0.001 |  |  | < 0.001 |  |  | < 0.001 |
| <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\%) |  |
| $\geq 28$ | 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\%) | < 0.001 | 318 (0.8\%) | 14 (0.6\%) | 0.268 |
| Personal history of congenital malformations (yes) | 394 (0.9\%) | 72 (2.9\%) | < 0.001 | 466 (1.1\%) | 0 (0.0\%) | < 0.001 | 426 (1.0\%) | 40 (1.6\%) | 0.005 |
| Taking folic acid in 3 months before pregnancy or in early pregnancy (yes) | 39,754 (95.6\%) | 2,318 (93.5\%) | < 0.001 | 40088 (95.5\%) | 1,984 (95.2\%) | 0.480 | 39,740 (95.6\%) | 2,332 (94.3\%) | 0.004 |
| Smoking in early | 558 (1.3\%) | 46 (1.9\%) | 0.033 | 566 (1.3\%) | 38 (1.8\%) | 0.069 | 562 (1.4\%) | 42 (1.7\%) | 0.149 |


| pregnancy (yes) |  |  |  |  |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Drinking in early pregnancy (yes) | 556 (1.3\%) | 8 (0.3\%) | < 0.001 | 560 (1.3\%) | 4 (0.2\%) | < 0.001 | 546 (1.3\%) | 18 (0.7\%) | 0.012 |
| 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\%) | 0.015 | 884 (2.1\%) | 36 (1.5\%) | 0.024 |
| Exposure to radioactive hazardous while at work |  |  |  |  |  |  |  |  |  |
| in three months before pregnancy or in early pregnancy (yes) | 1,326 (3.2\%) | 106 (4.3\%) | 0.003 | 1,328 (3.2\%) | 104 (5.0\%) | < 0.001 | 1,372 (3.3\%) | 60 (2.4\%) | 0.017 |

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 |
| Sociodemographic characteristics |  |  |  |  |  |  |
| Age (years) |  |  | < 0.001 |  |  | < 0.001 |
| <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\%) |  |
| $\geq 35$ | 5,008 (11.5\%) | 144 (24.6\%) |  | 4,972 (11.6\%) | 180 (14.0\%) |  |
| Ethnicity |  |  | < 0.001 |  |  | 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 |  |  | < 0.001 |  |  | 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\%) |  |
| Obstetric, clinical, and genetic characteristics |  |  |  |  |  |  |
| Mode of conception |  |  | 0.005 |  |  | 0.025 |
| 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 |  |  | < 0.001 |  |  | < 0.001 |
| 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\%) | 0.004 |
| Family history of congenital malformations (yes) | 62 (0.1\%) | 0 (0.0\%) | 0.360 | 62 (0.1\%) | 0 (0.0\%) | 0.171 |
| Health-related factors |  |  |  |  |  |  |
| Pre-pregnancy $\mathrm{BMI}\left(\mathrm{kg} / \mathrm{m}^{2}\right)$ |  |  | $<0.001$ |  |  | $<0.001$ |
| <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\%) |  |
| $\geq 28$ | 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\%) | 0.034 | 322 (0.8\%) | 10 (0.8\%) | 0.928 |
| Personal history of congenital malformations (yes) | 466 (1.1\%) | 0 (0.0\%) | 0.012 | 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\%) | < 0.001 | 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\%) | 0.017 |
| 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 |

pregnancy or in early pregnancy
(yes)
BMI, body mass index; HSV, herpes simplex virus.

