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Research Article

Changes in the Maternal Risk Factors of Congenital Heart Disease in Chinese Population: A Meta-analysis

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Abstract

Objective: To explore whether there were any changes in the maternal risk factors of congenital heart disease (CHD) in Chinese population between the ten years before 2008 (1999-2008) and the ten years after 2008 (2009-2018).

Methods: Databases including PubMed, Web of Science, Wanfang Data, China National Knowledge Infrastructure, Chinese Scientific and Technological Journal Database and China Biology Medicine disc were retrieved and reference lists of related articles were checked to collect relevant studies. Meta-analysis was conducted to calculate the pooled OR and 95%CI. Subgroup analyses, meta regression, sensitivity analysis and publication bias were further performed.

Results: A total of 44 studies were included in the meta-analysis. In the ten years before 2008, 6 risk factors including colds, infections, and medication use during pregnancy, exposure to chemical toxic substances during pregnancy, negative life events during pregnancy, and abnormal childbearing history were identified. While in the ten years after 2008, 12 factors were identified. The 6 new factors were periconceptional folic acid supplementation, vitamin supplementation, living near major traffic roads, living or working near factories, living in newly renovated rooms, and passive smoking during pregnancy.

Conclusion: The maternal risk factors of CHD in Chinese population has changed greatly between the ten years before 2008 and the ten years after 2008. People's concerns on living environments, lifestyles, and pregnancy care have been greatly increased in recent years. Notably, environmental pollution has become an important issue endangering maternal and fetal health in the ten years after 2008 in China.

Keywords: Congenital Heart Disease; Risk Factors; Maternal; Changes; Meta-Analysis

Introduction

Congenital heart disease (CHD) is one of the most common birth defects and one of the leading causes of infant death worldwide[1-3]. Although great advances in the surgical and medical treatment of CHD have led to a remarkable improvement in the survival rate of CHD neonates, due to the existence of complications such as heart failure, arrhythmia and pulmonary arterial hypertension, the life quality of CHD patients is still poorer and the mortality is much higher compared to general population, which exerts huge medical expenditures for both family and society [4, 5]. Obviously, the best solution towards this situation is to prevent CHD from happening. Therefore, to identify the risk factors of CHD, especially the modifiable factors such as maternal risk factors, and take corresponding measures is of vital importance. With the rapid development of China's modernization and industrialization in recent years, people's living standards and lifestyles have undergone dramatic changes, people's health care consciousness has been greatly enhanced, and more importantly, environmental pollution and ecological deterioration have been much aggravated, which may lead to changes in the maternal risk factors of CHD in Chinese population. Whether new maternal risk factors have emerged or whether the previous maternal risk factors have changed in recent years is unknown. Therefore, in the present meta-analysis, we made a comparison of the maternal risk factors of CHD in Chinese population between the ten years before 2008 (1999-2008) and the ten years after 2008 (2009-2018) to find whether there are any changes in the maternal risk factors of CHD, and to determine the current risk factors of CHD in Chinese population.

Methods

Literature selection

Literature selection was conducted in PubMed, Web of Science, China National Knowledge Infrastructure, Chinese Scientific and Technological Journal Database, China Biology Medicine disc and Wanfang Data to collect all Chinese and English relevant studies published in the ten years before 2008 and the ten years after 2008. The search strategy was as follows: ("congenital heart disease*" OR "congenital heart defect*" OR "heart abnormalit*" OR "malformation of heart" OR "congenital cardiovascular disease*" OR "CHD") AND ("risk" OR"etiology" OR "onset" OR "association" OR "connection" OR "relationship") AND ("Chinese" OR "China"). In addition, reference lists of the related original and review articles were checked manually to find additional studies that may meet the eligibility criteria. Literature selection was performed by two authors independently.

Eligibility Criteria

Eligible studies had to meet all of the following criteria: (1) relevant to the maternal risk factors of CHD in Chinese population; (2) were original epidemiological studies (i.e., case–control, cohort or RCT); (3) reported effect estimates and their 95% confidence intervals (CI), or provided sufficient data from which these measures could be calculated; (4) published in English or Chinese language. Studies was excluded if they: (1) were animal studies; (2) were of poor quality; (3) contained overlapped data; (4) reported incomplete data that cannot be obtained after contact with the author.

Titles and abstracts of retrieved studies were screened according to the above criteria by two authors independently, then full text of any potential relevant articles were assessed rigorously. Disagreements were resolved by discussion with the third author.

Data extraction

Data extraction was performed by two authors separately, and discrepancies were resolved by discussion with the third author. The following data were extracted from each eligible study: first author, geographical region, year of publication, study design, sample size, maternal risk factors and their adjusted estimates and corresponding 95% CI. If no effect estimate was provided in a given study, odds ratio (OR) or risk ratio (RR) and 95% CI would be calculated from the raw data presented in the study. And the authors would be contacted for further information if necessary.

Quality assessment

The quality of the eligible studies were assessed by the 9-star Newcastle-Ottawa Scale (NOS), which evaluates a study based on three major aspects: selection, comparability, and exposure or outcome [6]. Quality assessment was performed by two authors independently. If differences of opinion arose, these would be settled by discussion with the third author.

Statistical analysis

Where maternal risk factors had consistent definitions across studies (at least 3 studies) and effect estimates were presented in a similar fashion, meta-analysis would be performed to calculate the pooled OR and corresponding 95% CI. Cochran's Q and I^2 statistics were calculated to test for the heterogeneity among studies. If no evidence of heterogeneity was presented ($p>0.1$, $I^2<50\%$), a fixed effect model would be used. Otherwise, a random effect model would be adopted, and meta regression analyses would be further conducted based on year of publication, quality of study, geographical region and number of cases to explore the source of heterogeneity. Meta regression analyses would be conducted only when there were no fewer than 10 studies. Then subgroup analyses were performed based on the potential sources of heterogeneity. Sensitivity analysis was performed by omitting one study at a time to determine whether the results of meta-analysis were stable. Publication bias would be conducted only when there were no fewer than 10 studies, via Egger's linear regression method. Probability value $P<0.05$ was considered statistically significant. All statistical analyses were performed using STATA software (version 14.0; Stata Corporation, College Station, Texas, USA).

Results

Literature selection

A total of 4686 studies were obtained initially, of which 4508 studies were obtained through database searching, 178 studies were obtained by reference lists checking. After the duplicate studies were removed, titles and abstracts of the remaining 2516 studies were further screened for eligibility. Full text of the 516 potentially relevant studies were assessed rigorously, and a total of 472 studies were then excluded. Finally, 44 studies were included in the meta-

analysis (Figure 1).

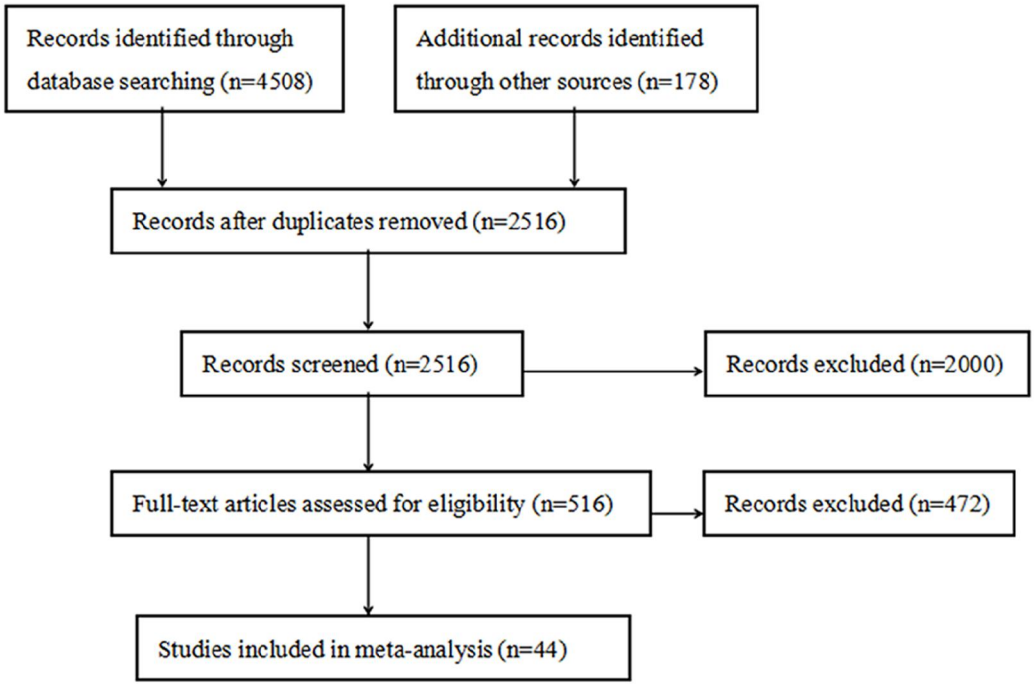

Figure 1: Flow diagram of literature selection

Study characteristics and quality evaluation

A total of 44 case-control studies, covering 19 provinces (or municipalities) nationwide, were included in this meta-analysis. Of these studies, 12 [7-18] were published during the ten years before 2008, involving 3436 cases and 4157 controls; 32 studies [19-50] were published during the ten years after 2008, involving 10341 cases and 14289 controls. All of these studies were published in Chinese except for 2 studies published in English. After quality assessment by the Newcastle-Ottawa Scale, 15 studies got a score of 5, 21 studies got a score of 6, and 7 studies got a score of 7, 1 study got a score of 8. The main characteristics of the included studies are showed in Table 1.

First author (year)	Region	Study design	No. of cases/controls	Quality
Qiu (1999)	Guangxi, China	Case-control	1286 / 1286	5
Zhang (1999)	Zhejiang, China	Case-control	351 / 351	6
Lai (2001)	Chongqing, China	Case-control	761 / 761	6
Liu (2004)	Shandong, China	Case-control	72 / 144	5
Gao (2005)	Shandong, China	Case-control	73 / 146	6

Tan (2006)	Hunan, China	Case-control	230 / 230	5
Yuan (2006)	Beijing, China	Case-control	63 / 126	7
Hou (2007)	Shanghai, China	Case-control	207 / 414	5
Zhong (2007)	Guangxi, China	Case-control	132 / 132	5
Wang (2007)	Shandong, China	Case-control	100 / 200	5
Wu (2008)	Zhejiang, China	Case-control	45 / 135	7
Liu (2008)	Anhui, China	Case-control	116 / 232	6
Gong (2009)	Shaanxi, China	Case-control	80 / 80	5
Li (2009)	Ningxia, China	Case-control	113 / 113	5
Mi (2010)	Anhui, China	Case-control	86 / 86	7
Mei (2010)	Zhejiang, China	Case-control	459 / 977	6
Chen (2010)	Anhui, China	Case-control	65 / 130	7
Chen (2011)	Fujian, China	Case-control	76 / 152	6
Ou (2011)	Hunan, China	Case-control	123 / 246	6
Guo (2011)	Shaanxi, China	Case-control	98 / 196	6
Yang (2012)	Shaanxi, China	Case-control	42 / 221	5
Zhu (2013)	Zhejiang, China	Case-control	108 / 108	6
Liu (2013)	Jiangsu, China	Case-control	70 / 140	6
Zhang (2013)	Shanxi, China	Case-control	203 / 406	5
Li (2013)	Guangdong, China	Case-control	358 / 422	6
Chen (2014)	Hebei, China	Case-control	110 / 297	6
Lin (2014)	Fujian, China	Case-control	69 / 69	6
Dong (2014)	Hebei, China	Case-control	815 / 1630	7
Hu (2014)	Shenzhen, China	Case-control	364 / 364	6
Ou (2015)	Guangdong, China	Case-control	4034 / 4034	6
Yang(2016)	Beijing, China	Case-control	117 / 117	6
Bing (2016)	Jiangsu, China	Case-control	48 / 48	7

Lv (2016)	Fujian, China	Case-control	149 / 149	5
Zhang (2016)	Henan, China	Case-control	728 / 728	6
Jiang (2016)	Guangdong, China	Case-control	30 / 30	5
Xiang (2017)	Zhejiang, China	Case-control	500 / 500	6
Li (2017)	Fujian, China	Case-control	61 / 61	6
Li (2017)	Fujian, China	Case-control	187 / 374	5
Zhang (2017)	Shaanxi, China	Case-control	270 / 1633	5
Li (2017)	Shandong, China	Case-control	160 / 160	5
Li (2017)	Fujian, China	Case-control	72 / 72	6
Chen (2017)	Sichuan, China	Case-control	250 / 250	6
Zhang (2017)	Henan, China	Case-control	165 / 165	8
Xu (2018)	Qinghai, China	Case-control	331 / 331	7

Table1: The main characteristics of the included studies

The major maternal risk factors in the ten years before 2008 (1999-2008)

1. Colds during pregnancy

Seven of the 12 studies investigated colds during pregnancy as a potential risk factor for the onset of CHD. No evidence of heterogeneity was found among the 7 studies ($p=0.126$, $I^2=39.9\%$), therefore a fixed effect model was performed. The overall results of this meta-analysis showed that colds during pregnancy significantly increased the risk of CHD (OR=3.54, 95%CI:2.90-4.32, $p<0.001$, Figure 2a). After sequentially omitting each included study in sensitivity analysis, the result remained largely unchanged, indicating the results were stable.

2. Exposure to chemical toxic substances during pregnancy

Six studies assessed exposure to chemical toxic substances (such as pesticides, organic solvents, etc.) during pregnancy as a possible risk factor. No evidence of heterogeneity was found ($p=0.248$, $I^2=24.8\%$), thus a fixed effect model was conducted. The overall results of this meta-analysis showed that exposure to chemical toxic substances during pregnancy significantly increased the risk of CHD (OR=4.67, 95%CI: 3.44-6.34, $p<0.001$, Figure 2b). No obvious change was found in sensitivity analysis, suggesting the results were stable.

3. Negative life events during pregnancy

Six studies explored the association between negative life events during pregnancy and the risk of CHD. As there was heterogeneity between the 6 studies ($p=0.015$, $I^2=64.5\%$), a random effect model was used. The overall results of this

meta-analysis showed that negative life events during pregnancy significantly increased the risk of CHD (OR=3.71, 95%CI: 2.16-6.37, p<0.001, Figure 2c). No significant change was found in sensitivity analysis, showing the results were stable.

4. Medication use during pregnancy

Five studies reported the association between medication use during pregnancy and the risk of CHD. No evidence of heterogeneity was found (p=0.182, I^2=35.8%), therefore a fixed effect model was used. The overall results of this meta-analysis showed that medication use during pregnancy significantly increased the risk of CHD (OR=2.10, 95%CI: 1.60-2.76, p<0.001, Figure 2d). No obvious change was found in sensitivity analysis, indicating the results were stable.

5. Infection during pregnancy

Four studies assessed the association between infection during pregnancy and the risk of CHD. No evidence of heterogeneity was found (p=0.217, I^2=32.5%), therefore a fixed effect model was used. The overall results of this meta-analysis showed that infection during pregnancy significantly increased the risk of CHD (OR=3.74, 95%CI: 2.69-5.21, p<0.001, Figure 2e). No significant change was found in sensitivity analysis, suggesting the results were stable.

6. Abnormal childbearing history

Three studies assessed the association between abnormal childbearing history (such as abortion, stillbirth, etc.) and the risk of CHD. No evidence of heterogeneity was found (p=0.320, I^2=12.2%), therefore a fixed effect model was used. The overall results of this meta-analysis showed that abnormal childbearing history significantly increased the risk of CHD (OR=1.73, 95%CI: 1.28-2.34, p<0.001, Figure 2f). No significant change was found in sensitivity analysis, suggesting the results were stable.

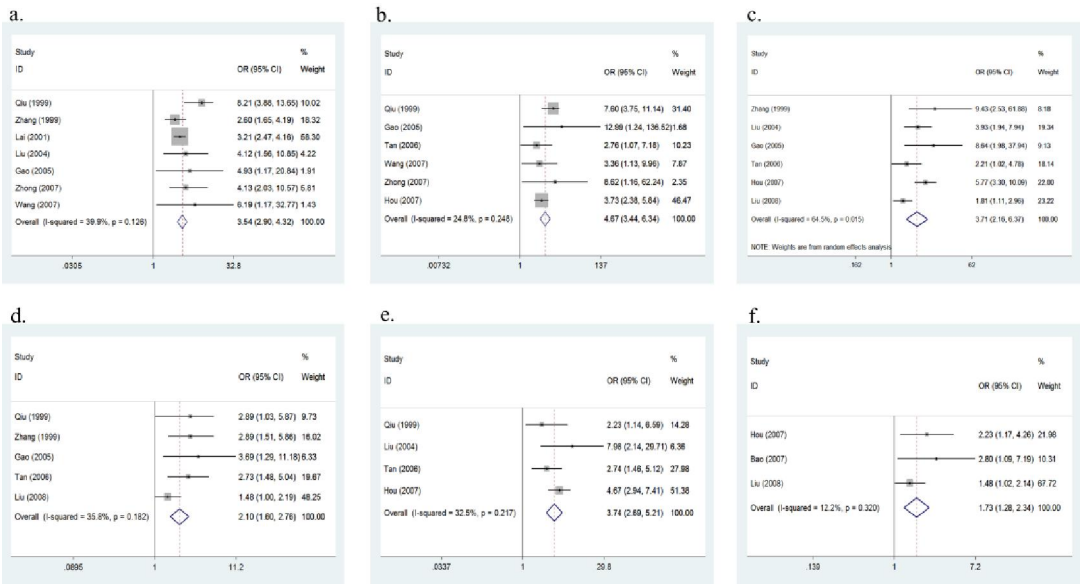

Figure 2: The major maternal risk factors in the ten years before 2008 (1999-2008)

Figure 2a: forest plot for the association between colds during pregnancy and CHD risk.

Figure 2b: forest plot for the association between exposure to chemical toxic substances during pregnancy and CHD risk.

Figure 2c: forest plot for the association between negative life events during pregnancy and CHD risk.

Figure 2d: forest plot for the association between medication use during pregnancy and CHD risk.

Figure 2e: forest plot for the association between infection during pregnancy and CHD risk.

Figure 2f: forest plot for the association between abnormal childbearing history and CHD risk.

The major maternal risk factors in the ten years after 2008 (2009-2018)

The same risk factors as ten years before 2008

1. Colds during pregnancy

Sixteen of the 32 studies investigated colds during pregnancy as a potential risk factor for the onset of CHD. As there was heterogeneity between the 16 studies ($p<0.001$, $I^2=85.2\%$), a random effect model was adopted. The overall results of this meta-analysis showed that colds during pregnancy significantly increased the risk of CHD (OR=2.75, 95%CI: 1.97-3.83, $p<0.001$, Figure 3a). To explore the source of heterogeneity, meta regression analyses were conducted based on year of publication, quality of study, geographical region and number of cases. However, no significant results were derived. No significant change was found in sensitivity analysis, suggesting the results were stable. No publication bias was found in this meta-analysis (Egger's test $p=0.870$).

2. Exposure to chemical toxic substances during pregnancy

Thirteen studies assessed exposure to chemical toxic substances during pregnancy as a possible risk factor. As there was heterogeneity between the 13 studies ($p<0.001$, $I^2=86.2\%$), a random effect model was adopted. The overall results of this meta-analysis showed that exposure to chemical toxic substances during pregnancy significantly increased the risk of CHD (OR=3.43, 95% CI: 2.05-5.74, $p<0.001$, Figure 3b). To explore the source of heterogeneity, meta regression analyses were conducted and number of cases was found to be the possible source ($p=0.018$). Subgroup analysis by number of cases was further performed, in the subgroup of cases ≤ 200, the pooled OR was 2.13 (95% CI: 1.53-2.94), with no evidence of heterogeneity ($p=0.061$, $I^2=46.3\%$); in the subgroup of cases > 200, the pooled OR was 7.72 (95% CI: 5.64-10.56), with no evidence of heterogeneity either ($p=0.766$, $I^2=0.0\%$). No significant change was found in sensitivity analysis, suggesting the results were stable. No publication bias was found in this meta-analysis (Egger's test $p=0.152$).

3. Negative life events during pregnancy

Five studies explored the association between negative life events during pregnancy and the risk of CHD. No evidence of heterogeneity was found ($p=0.557$, $I^2=0.0\%$), therefore a fixed effect model was used. The overall results of this meta-analysis showed that negative life events during pregnancy significantly increased the risk of CHD (OR=2.27, 95%CI: 1.75-2.95, $p<0.001$, Figure 3c). No significant change was found in sensitivity analysis, showing the results were stable.

4. Medication use during pregnancy

Thirteen studies reported the association between medication use during pregnancy and the risk of CHD. No evidence of heterogeneity was found (p=0.110, I^2=34.0%), therefore a fixed effect model was used. The overall results of this meta-analysis showed that medication use during pregnancy significantly increased the risk of CHD (OR=2.77, 95%CI: 2.31-3.33, p<0.001, Figure 3d). No publication bias was found in this meta-analysis (Egger's test p=0.557). No obvious change was found in sensitivity analysis, indicating the results were stable.

5. Infection during pregnancy

Four studies assessed the association between infection during pregnancy and the risk of CHD. No evidence of heterogeneity was found (p=0.319, I^2=14.5%), therefore a fixed effect model was used. The overall results of this meta-analysis showed that infection during pregnancy significantly increased the risk of CHD (OR=1.74, 95%CI: 1.35-2.23, p<0.001, Figure 3e). No significant change was found in sensitivity analysis, suggesting the results were stable.

6. Abnormal childbearing history

Four studies assessed the association between abnormal childbearing history and the risk of CHD. No evidence of heterogeneity was found (p=0.112, I^2=50.0%), therefore a fixed effect model was used. The overall results of this meta-analysis showed that abnormal childbearing history significantly increased the risk of CHD (OR=2.16, 95%CI: 1.78-2.62, p<0.001, Figure 3f). No significant change was found in sensitivity analysis, suggesting the results were stable.

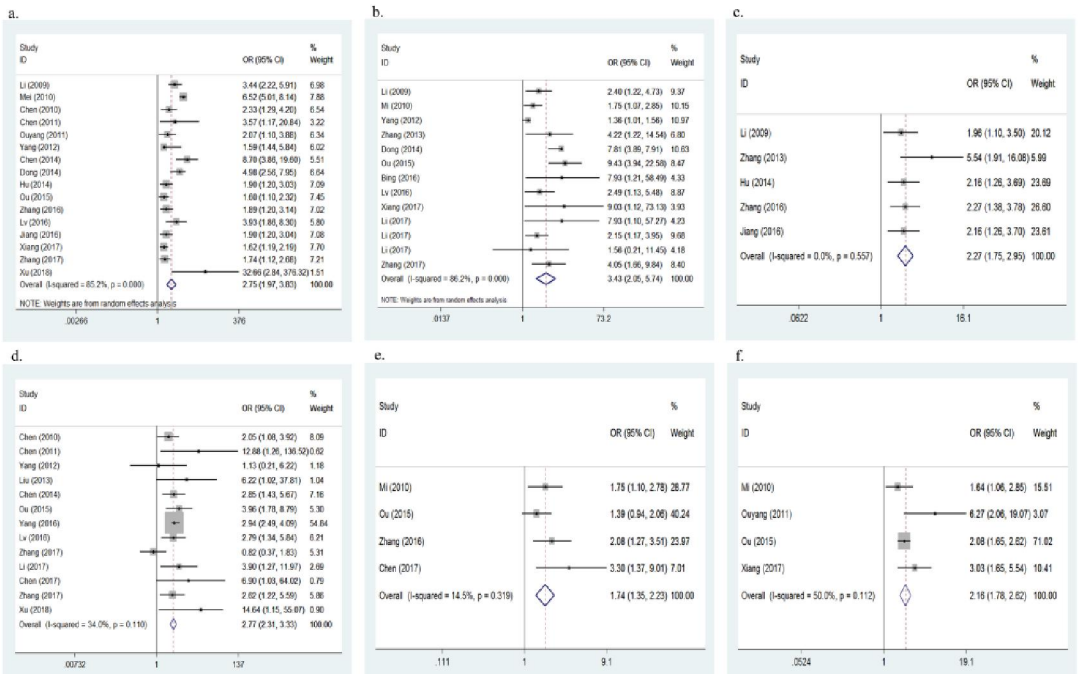

Figure 3: The same risk factors as ten years before 2008 (2009-2018)

Figure 3a: forest plot for the association between colds during pregnancy and CHD risk.

Figure 3b: forest plot for the association between exposure to chemical toxic substances during pregnancy and CHD

risk.

Figure 3c: forest plot for the association between negative life events during pregnancy and CHD risk.

Figure 3d: forest plot for the association between medication use during pregnancy and CHD risk.

Figure 3e: forest plot for the association between infection during pregnancy and CHD risk.

Figure 3f: forest plot for the association between abnormal childbearing history and CHD risk.

New risk factors in the ten years after 2008

1. Passive smoking during pregnancy

Nine studies investigated passive smoking during pregnancy as a potential risk factor for the onset of CHD. As there was heterogeneity between the 9 studies ($p<0.001$, $I^2=85.2\%$), a random effect model was adopted. The overall results of this meta-analysis showed that passive smoking during pregnancy significantly increased the risk of CHD (OR=2.90, 95%CI: 1.83-4.62, $p<0.001$, Figure 4a). No significant change was found in sensitivity analysis, suggesting the results were stable.

2. Periconceptional folic acid supplementation

Nine studies assessed the association between periconceptional folic acid supplementation and the risk of CHD. No evidence of heterogeneity was found ($p=0.968$, $I^2=0.0\%$), therefore a fixed effect model was used. The overall results of this meta-analysis showed that periconceptional folic acid supplementation significantly decreased the risk of CHD (OR=0.50, 95%CI: 0.43-0.59, $p<0.001$, Figure 4b). No significant change was found in sensitivity analysis, suggesting the results were stable.

3. Periconceptional vitamin supplementation

Six studies assessed the association between periconceptional vitamin supplementation and the risk of CHD. No evidence of heterogeneity was found ($p=0.311$, $I^2=16.0\%$), therefore a fixed effect model was used. The overall results of this meta-analysis showed that periconceptional vitamin supplementation significantly decreased the risk of CHD (OR=0.45, 95%CI: 0.36-0.58, $p<0.001$, Figure 4c). No significant change was found in sensitivity analysis, indicating the results were stable.

4. Living or working near factories during pregnancy

Six studies assessed the association between living or working near factories during pregnancy and the risk of CHD. No evidence of heterogeneity was found ($p=0.153$, $I^2=38.0\%$), therefore a fixed effect model was adopted. The overall results of this meta-analysis showed that living or working near factories during pregnancy significantly increased the risk of CHD (OR=2.10, 95%CI: 1.64-2.69, $p<0.001$, Figure 4d). No significant change was found in sensitivity analysis, indicating the results were stable.

5. Living in newly renovated rooms during pregnancy

Six studies explored the association between living in newly renovated rooms during pregnancy and the risk of CHD. As there was heterogeneity between the 6 studies ($p<0.001$, $I^2=81.0\%$), a random effect model was used. The overall

results of this meta-analysis showed that living in newly renovated rooms during pregnancy significantly increased the risk of CHD (OR=4.32, 95%CI: 2.58-7.24, p<0.001, Figure 4e). No significant change was found in sensitivity analysis, showing the results were stable.

6. Living near major traffic roads (<50m) during pregnancy

Four studies reported the association between living near major traffic roads during pregnancy and the risk of CHD. No evidence of heterogeneity was found (p=0.200, I^2=35.4%), therefore a fixed effect model was adopted. The overall results of this meta-analysis showed that living near major traffic roads during pregnancy significantly increased the risk of CHD (OR=2.19, 95%CI: 1.78-2.70, p<0.001, Figure 4f). No obvious change was found in sensitivity analysis, indicating the results were stable.

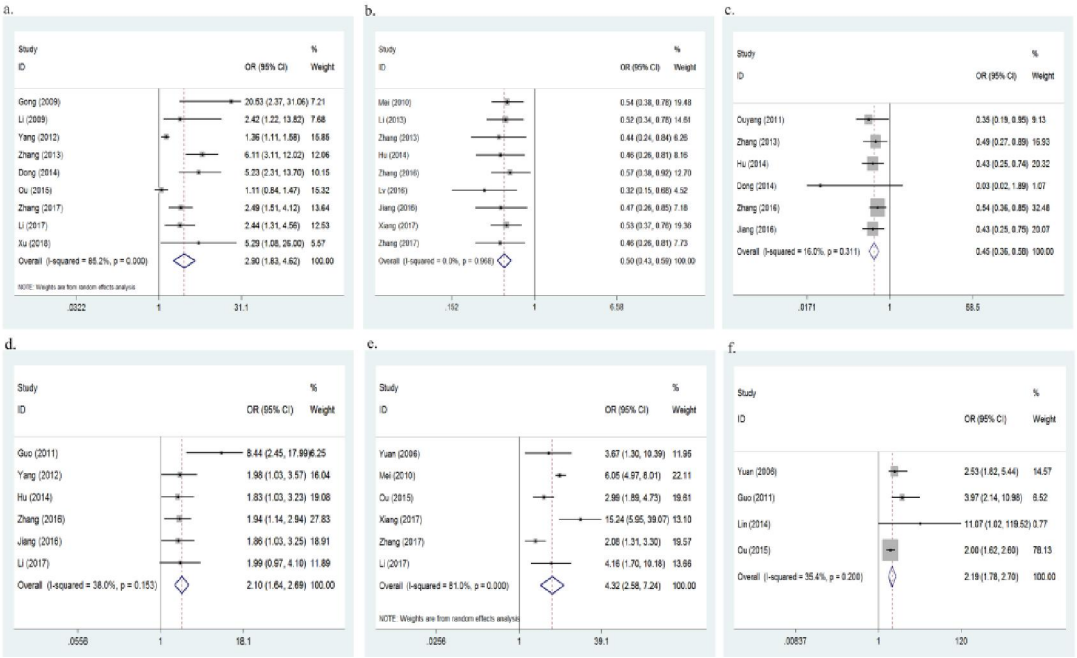

Figure 4: The new risk factors in the ten years after 2008 (2009-2018)

Figure 4a: forest plot for the association between passive smoking during pregnancy and CHD risk.

Figure 4b: forest plot for the association between periconceptional folic acid supplementation and CHD risk.

Figure 4c: forest plot for the association between periconceptional vitamin supplementation and CHD risk.

Figure 4d. forest plot for the association between living or working near factories during pregnancy and CHD risk.

Figure 4e: forest plot for the association between living in newly renovated rooms during pregnancy and CHD risk.

Figure 4f: forest plot for the association between living near major traffic roads during pregnancy and CHD risk.

Discussion

According to the present meta-analysis, the major maternal risk factors of CHD in Chinese population has changed greatly, and a total of 12 risk factors were identified as the current risk factors of CHD in Chinese population. In the ten years before 2008, 6 major risk factors were identified. Exposure to chemical toxic substances during pregnancy was found to have the highest risk for the onset of CHD, with a 4.67-fold increase in risk. While in the ten years after 2008 (2009-2018), the number of studies exploring the risk factors of CHD has greatly increased, and a total of 12 major risk factors were identified. Apart from the 6 risk factors identified ten years ago, 6 newly emerged risk factors concerning the living environments, lifestyles and pregnancy care were further identified. Living in newly renovated rooms during pregnancy was observed to have the highest risk for the onset of CHD (OR=4.32, 95%CI: 2.58-7.24).

Among the 6 same risk factors, the OR value of infection during pregnancy has changed significantly from 3.74 (95%CI: 2.69-5.21) in the ten years before 2008 to 1.74 (95%CI: 1.35-2.23) in the ten years after 2008, which may be due to the gradual popularization of pre-pregnancy and prenatal examinations, as well as to the improvement of people's pregnancy care consciousness. However, there were no significant change in the OR values of exposure to chemical toxic substances during pregnancy, negative life events during pregnancy, colds during pregnancy, medication use during pregnancy as well as abnormal childbearing history between the ten years before 2008 and the ten years after 2008, indicating that these 5 risk factors may have an stable effect on the onset of CHD.

Of the 6 new factors emerged in the ten years after 2008, 2 factors were protective factors of CHD (periconceptional folic acid supplementation and periconceptional vitamin supplementation) and 4 factors were risk factors of CHD (living near major traffic roads (<50m) during pregnancy, living or working near factories during pregnancy, living in newly renovated rooms during pregnancy, and passive smoking during pregnancy). All the 6 new factors focus on the the living environments, lifestyles, and health care during pregnancy, which shows that people's concerns on these aspects have been greatly increased. More importantly, it may also indicate that environmental pollution and ecological deterioration has become an important issue endangering maternal and fetal health in the ten years after 2008.

Although the clear biological mechanisms underlying the relationship between these risk factors and the onset of CHD remain to be determined, some relevant hypotheses have been proposed. Living in newly renovated rooms, living or working near factories, living near major traffic roads, exposure to chemical toxic substances, as well as passive smoking during pregnancy, all of them will expose pregnant women to environmental teratogens such as formaldehyde, benzene, organic solvents, heavy metals, carbon monoxide, ozone, pesticides, herbicides, and cigarette smoke etc., which may induce congenital malformations through the induction of oxidative stress [36, 51]. As for infections and colds during pregnancy, many pathogens of infections and colds could be transmitted vertically to fetus through placenta and increase the risk of congenital malformations. In addition, fever caused by infections and colds may lead to abnormal cell apoptosis during embryonic heart development and hence cause cardiac dysplasia [52-55]. The possible mechanism between medication use during pregnancy and CHD risk may be that, many medications have the ability to cross placental and blood-brain barriers, which may directly affect embryonic development and increase the risk of congenital malformations [56, 57]. Maternal stress caused by negative life events during pregnancy would

lead to increased secretion of plasma adrenocorticotrophin, β-endorphin, glucocorticoids, and catecholamines, which may lead to changes in the fetal neurotransmitter systems and transcriptional mechanisms [40, 58]. Abnormal childbearing history, such as previous abortions, may result in some residual effects that may affect the development of subsequent embryo [59, 60]. In addition, the causes of previous abnormal pregnancies, such as genetic factors, uterine factors, maternal chronic diseases, etc., if not removed, will still affect subsequent embryonic development [60]. Moreover, having an abnormal childbearing history may lead to an increased use of medications, which may increase the possibility of congenital malformations induced by medications [36]. Periconceptional folic acid supplementation was found as an protective factor for CHD. It has been hypothesized that deficiency of folic acid during pregnancy would impair folate and/or homocysteine metabolism, result in hyperhomocysteinemia and impair methionine formation in the embryo, which may increase the risk of congenital malformations [2, 3, 60-62]. Periconceptional vitamin supplementation was another protective factor for CHD. Many vitamins play important roles during embryonic development. For example, vitamin B_{12} works as a coenzyme with folates in methionine, purine, and thymine synthesis, and one-carbon metabolism, vitamin C may protect embryos from oxygen free radical damages due to their antioxidant properties [62, 63].

There are some limitations in this meta-analysis. Firstly, all the 44 studies included in the final meta-analysis were case-control studies, which were susceptible to selection bias and information bias. Therefore, we evaluated the quality of each eligible study rigorously and eliminated studies with poor quality to increase the credibility of our results. Secondly, although significant heterogeneity were found in negative life events during pregnancy (the ten years before 2008), passive smoking during pregnancy, and living in newly renovated rooms during pregnancy, we did not carry out further analysis to clarify the source of heterogeneity due to the lack of enough studies. Thirdly, there were limited evidence regarding these newly emerged factors such as living near major traffic roads (<50m) during pregnancy, living in newly renovated rooms during pregnancy, etc., thus only several studies were included in our meta-analysis to explore the association between these new factors and the risk of CHD. Therefore, further studies should focus on these new risk factors, rather than those for which considerable evidence already exists.

Despite the limitations mentioned above, there are also some strengths in this meta-analysis. Firstly, to our best knowledge, this is the first meta-analysis comparing the major maternal risk factors of CHD in Chinese population between the ten years before 2008 and the ten years after 2008. And 6 new risk factors, focusing on the living environments, lifestyles, and health care during pregnancy, were further identified in this meta-analysis. Secondly, this meta-analysis covered a total of 12 risk factors of the onset of CHD, and each of them was analyzed carefully in our paper.

Conclusions

The major maternal risk factors of CHD in Chinese population has changed greatly between the ten years before 2008 and the ten years after 2008. And a total of 12 factors were identified as the current risk factors of CHD in Chinese population. Among these two periods, there are 6 same risk factors and 6 newly emerged risk factors of CHD. Of the 6 same risk factors, the OR value of infection during pregnancy has significantly changed, which may be due to the

gradual popularization of pre-pregnancy and prenatal examinations and the improvement of people's pregnancy care consciousness in recent years. And all the 6 new risk factors that emerged in the ten years after 2008 focus on the living environments, lifestyles, and health care during pregnancy. This shows that people's concerns on these aspects have been greatly increased in recent years. More importantly, this may also indicate that environmental pollution and ecological deterioration has become an important issue endangering maternal and fetal health in the ten years after 2008.

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Conflicts of interest

The authors report no conflicts of interest.

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