NICOLAUS COPERNICUS UNIVERSITY IN TORUŃ

QUALITY IN SPORT

eISSN 2450-3118 · Open Access · Peer-reviewed

Vol. 55 (2026) · Article 70966 · Published 16 May 2026

apcz.umk.pl/QS · Nicolaus Copernicus University in Toruń

Cite as: Zielińska A, Kamińska ZZ, Blecharczyk M, et al. Maternal and environmental risk factors for congenital heart diseases in offspring: a review article. Quality in Sport 2026;55:70966. https://doi.org/10.12775/QS.2026.55.70966

ARTICLE TIMELINE

Received: 15.04.2026 **Revised:** 16.05.2026
Accepted: 16.05.2026 **Published:** 16.05.2026

INDEXING & EVALUATION

MEiN points: 20 **Unique ID:** 201398
Disciplines: Medical Sciences; Health Sciences

The journal has been awarded 20 points in the parametric evaluation by the Polish Ministry of Higher Education and Science (Annex to the announcement of 05.01.2024, No. 32553). Unique Journal Identifier: 201398. Scientific disciplines: Medical Sciences; Health Sciences.

Punkty Ministerialne z 2019 – aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Nauki medyczne; Nauki o zdrowiu.

REVIEW ARTICLE

Maternal and Environmental Risk Factors for Congenital Heart Diseases in Offspring: A Review Article

a review article

HIGHLIGHTS

- **Maternal diabetes, particularly poorly controlled pregestational diabetes, is the strongest non-genetic risk factor for congenital heart defects, with risk up to 8.5× higher when first-trimester HbA1c exceeds 8%.**
- **Maternal obesity shows a clear dose-response relationship with CHDs (OR 1.15 for moderate, up to 1.85 for class III obesity), independent of diabetes status.**

- **Active and passive maternal smoking, as well as paternal smoking, are consistently associated with elevated CHD risk; passive smoke exposure may carry the largest effect (RR up to 2.24).**
- **Environmental exposures — air pollutants (SO_2, ozone, cadmium) and toxic chemicals — contribute meaningfully to CHD risk and interact synergistically with parental behaviors.**
- **Folic acid and multivitamin supplementation attenuate CHD risk associated with environmental toxins, supporting modifiable preventive strategies during the periconceptional period.**

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ABSTRACT

BACKGROUND: Congenital heart diseases (CHDs) are the most common congenital anomalies and a leading cause of infant morbidity and mortality. Although genetic factors play an important role, many cases remain unexplained, highlighting the contribution of maternal and environmental exposures.

AIM: This review aims to provide a comprehensive and up-to-date synthesis of non-genetic maternal risk factors associated with CHDs in offspring.

MATERIALS AND METHODS: A literature review was conducted using PubMed, NCBI and Google Scholar, including studies published between 2010 and 2025. Systematic reviews, meta-analyses, cohort and case-control studies evaluating maternal and environmental exposures were analyzed.

RESULTS: Evidence indicates that maternal diabetes and obesity are key risk factors, with clear dose-response relationships. Additional contributors include smoking (active and passive), alcohol consumption, infections, fever, psychological stress and environmental pollutants. Protective effects of folic acid and multivitamin supplementation were also observed. Interaction effects between environmental exposures and parental behaviors further increase CHD risk.

CONCLUSIONS: CHD etiology is multifactorial, involving modifiable maternal and environmental factors. Identification and reduction of these exposures, particularly during early pregnancy, are essential for prevention. Further prospective and mechanistic studies are needed to clarify causal pathways and improve risk reduction strategies.

KEYWORDS congenital heart disease; maternal risk factors; diabetes; environmental exposure

1. INTRODUCTION

Congenital heart diseases are the most common congenital malformations, affecting approximately 8–10 per 1,000 live births globally. They encompass a broad spectrum of structural cardiac abnormalities, ranging from mild defects to complex malformations requiring surgical intervention. Despite advances in diagnosis and treatment, CHDs remain a major contributor to infant mortality and long-term morbidity.

The etiology of CHDs is complex and multifactorial. Although substantial progress has been made in identifying genetic determinants, including chromosomal abnormalities and single-gene mutations, these factors account for only a proportion of cases. Increasing evidence suggests that non-genetic factors, particularly maternal exposures during the periconceptional period and early pregnancy, play a critical role in cardiac development.

Environmental exposures, lifestyle behaviors, maternal health conditions, and psychosocial factors may all influence fetal cardiac morphogenesis through mechanisms such as oxidative stress, inflammation, epigenetic modification, and disruption of placental function. Moreover, emerging data highlight the importance of paternal factors and gene–environment interactions in modulating CHD risk.

Given the potentially modifiable nature of many of these exposures, a better understanding of maternal risk factors is essential for effective prevention strategies. Therefore, this review aims to comprehensively summarize current evidence on maternal and parental non-genetic risk factors associated with CHDs in offspring, with a particular focus on recent epidemiological findings and their clinical implications.

2. MATERIALS AND METHODS

This review article was conducted to synthesize current evidence on maternal risk factors associated with congenital heart diseases in offspring. A comprehensive literature search was performed using platforms such as PubMed, NCBI and Google Scholar. The search included studies published in years 2010–2025 and was performed in April 2026.

Keywords used in the search strategy included combinations of terms such as “congenital heart disease,” “maternal risk factors,” “obesity,” “environmental exposure,” “smoking,” “alcohol,” “infection,” “fever,” “psychological stress,” and “air pollution.”

We included systematic reviews, meta-analyses, cohort studies, and case-control studies that evaluated associations between maternal or parental exposures and CHD risk in offspring. Studies focusing exclusively on genetic causes or lacking relevant outcome measures were excluded.

Data extraction focused on study design, population characteristics, exposure definitions, and reported effect estimates (e.g., odds ratios, risk ratios, confidence intervals). Particular emphasis was placed on high-quality meta-analyses and large population-based studies.

3. RESULTS

3.1. Maternal Obesity and BMI

Maternal body mass index (BMI) before and during early pregnancy has been consistently identified as an important, modifiable risk factor for congenital heart defects (CHDs). Numerous large cohort studies and meta-analyses demonstrate a positive association between increasing maternal BMI and the risk of CHDs in offspring, often with a clear dose-response relationship.

A large meta-analysis (Salmeri et al., 2024) including over 4.8 million pregnancies showed that the risk of CHDs increases progressively with the severity of maternal obesity. Moderate obesity was associated with an increased risk (OR 1.15; 95% CI 1.11–1.20), while severe obesity further elevated the risk (OR 1.39; 95% CI 1.27–1.53). For severe CHDs, the risk was even higher (OR up to 1.48), and specific defects such as tetralogy of Fallot, pulmonary valve stenosis, and atrial septal defects showed odds ratios approaching or exceeding 1.7–1.8 in women with severe obesity. Importantly, these associations persisted independently of maternal diabetes status.

Meta-analyses further support these findings. One analysis of over 2.4 million participants (Liu et al., 2019) showed that being overweight (RR 1.08; 95% CI 1.03–1.13) and obesity (RR 1.23; 95% CI 1.17–1.29) were associated with increased CHD risk. Additionally, each 5 kg/m² increase in maternal BMI raised the risk by approximately 7%, indicating a continuous relationship. Another meta-analysis (Zheng et al., 2018) confirmed this trend, reporting increasing risk across obesity classes, from OR 1.15 in class I obesity to OR 1.42 in class III obesity.

However, not all studies show uniform results. Some analyses suggest that being overweight alone may not significantly increase overall CHD risk, while obesity does. For example, a large case-control study by Mills (2010) found no increased risk in overweight women (OR 1.00), but a significant increase in obese (OR 1.15) and morbidly obese women (OR 1.33). Additionally, some studies reported no association between BMI and overall CHDs after adjustment, although associations persisted for specific subtypes such as outflow tract defects and complex CHDs (Turunen et al., 2024).

Experimental data (McMullan et al., 2025) indicate that maternal obesity may directly affect fetal cardiac development. Animal studies demonstrate that obesity alone, independent of diabetes, can disrupt oxidative phosphorylation, increase oxidative stress and alter gene expression involved in cardiac morphogenesis, leading to structural heart defects.

Despite some heterogeneity across studies, the overall body of evidence strongly supports maternal obesity, particularly moderate and severe obesity, as a significant risk factor for CHDs. Umbrella reviews (Nie et al., 2022) classify maternal obesity as having convincing to highly suggestive evidence for association with CHDs. These findings highlight the importance of preconception weight optimization as a potential strategy for reducing the risk of congenital heart defects.

3.2. Maternal Diabetes

Maternal diabetes is one of the most well-established non-genetic risk factors for congenital heart defects and is associated with a substantially higher risk compared to maternal obesity alone. The strength of this association varies depending on the type of diabetes and the level of glycemic control, particularly during early pregnancy.

These findings emphasize that early pregnancy, particularly the first trimester, is a critical period, as cardiac development occurs primarily during weeks 7–8 of gestation. Poor glycemic control during this period appears to be a key teratogenic mechanism.

In a Finnish population-based study (Turunen et al., 2024) of over 620,000 births, maternal type 1 diabetes was associated with a nearly fourfold increase in CHD risk (OR 3.77; 95% CI 3.26–4.36), with significantly elevated risks across multiple CHD subtypes, including transposition of the great arteries and septal defects. Type 2 diabetes also increased risk, although to a lesser extent (OR ~1.9).

Gestational diabetes mellitus (GDM) appears to have a weaker and less consistent association with CHDs. Studies including Turunen et al. (2024) and Nagasawa et al. (2024) report a modest increase in risk (e.g., OR 1.08–1.77), while others find no significant association after adjustment. This discrepancy is likely explained by the timing of hyperglycemia onset — GDM is typically diagnosed later in pregnancy, after the critical window of cardiac development has passed.

Comparative analyses suggest that maternal diabetes has a stronger and more consistent association with CHDs than maternal obesity. While obesity is associated with modest increases in risk (typically OR 1.1–1.8), pregestational diabetes mellitus can increase risk several-fold through oxidative stress, altered metabolic pathways, and disrupted embryonic development.

An umbrella review by Nie et al. (2022) classified maternal diabetes (both pregestational and gestational) as having highly suggestive evidence for association with CHDs. In summary, maternal diabetes, especially pregestational diabetes with poor glycemic control, is a major risk factor for congenital heart defects. Effective preconception care and strict glycemic control in early pregnancy are critical components of CHD prevention.

3.3. Maternal Smoking

Maternal smoking during the periconceptional period and pregnancy has been consistently identified as a significant modifiable risk factor for congenital heart defects. Both active and passive exposure to tobacco smoke are associated with increased risk.

A comprehensive meta-analysis (Zhao et al., 2020) including 125 studies and over 8.7 million participants demonstrated that maternal active smoking was associated with a 25% increase in CHD risk (RR = 1.25; 95% CI: 1.16–1.34). Even stronger associations were observed for maternal passive smoking (RR = 2.24; 95% CI: 1.81–2.77), suggesting that second-hand smoke exposure may represent a particularly harmful but often underestimated risk factor. Additionally, paternal smoking was also associated with increased CHD risk (RR = 1.74; 95% CI: 1.48–2.06).

In a case–control study by Li et al. (2020), maternal exposure to second-hand smoke was associated with a more than threefold increase in CHD risk (OR = 3.32; 95% CI: 2.41–4.56), with a dose-response relationship (OR = 2.75 for 1–3 days/week vs. OR = 3.62 for >3 days/week).

Maternal smoking has been linked to increased risk of atrial septal defects (RR = 1.27) and right ventricular outflow tract obstruction (RR = 1.43) (Zhao et al., 2020). Overall, smoking cessation and avoidance of second-hand smoke during the preconception and pregnancy periods should be strongly emphasized.

3.4. Maternal Alcohol Consumption

Maternal alcohol consumption during the periconceptional period and pregnancy has been associated with an increased risk of congenital heart defects, although the strength of this association is generally weaker and more heterogeneous compared to other risk factors.

A meta-analysis by Zhang et al. (2020) including 55 studies (over 41,000 CHD cases) demonstrated that maternal alcohol exposure was associated with a modest but statistically significant increase in CHD risk (OR = 1.16; 95% CI: 1.05–1.27). Paternal alcohol consumption was also associated with increased risk (OR = 1.44; 95% CI: 1.19–1.74). A nonlinear dose-response relationship was identified.

Maternal alcohol consumption has been significantly associated with tetralogy of Fallot (OR = 1.20; 95% CI: 1.08–1.33). Complete abstinence from alcohol during preconception and pregnancy remains the safest recommendation.

3.5. Maternal Infections and Fever

Maternal infections and fever during early pregnancy, particularly during the critical period of cardiac development, have been increasingly recognized as important environmental risk factors for congenital heart defects.

A meta-analysis of 16 studies including over 31,000 CHD cases (Yang et al., 2021) demonstrated that maternal fever during the preconception and conception periods was associated with a significantly increased risk of CHDs (OR = 1.45; 95% CI: 1.21–1.73). The association was stronger when fever occurred during the first trimester (OR = 1.79; 95% CI: 1.32–2.44).

Maternal fever was also associated with increased risk of specific CHD phenotypes, including:

conotruncal defects (OR = 1.38; 95% CI: 1.01–1.89),

atrial septal defects (OR = 1.48; 95% CI: 1.01–2.17),

transposition of the great arteries (OR = 1.81; 95% CI: 1.14–2.88),

right ventricular outflow tract obstruction (OR = 1.66; 95% CI: 1.04–2.65).

A meta-analysis by Ye et al. (2019) found that maternal viral infection in early pregnancy was associated with significantly higher odds of CHDs (OR = 2.28; 95% CI: 1.54–3.36). The association was particularly strong for rubella virus (OR = 3.49) and cytomegalovirus (OR = 3.95). Preventive strategies should include infection control, vaccination (e.g., rubella), and prompt management of febrile illnesses.

3.6. Psychological Stress

Maternal psychological stress during pregnancy has been increasingly investigated as a potential risk factor for CHDs. A systematic review and meta-analysis (Gu & Guan, 2021) demonstrated that maternal stress exposure is associated with a significantly increased risk of CHDs (OR = 2.11; 95% CI: 1.62–2.74). Exposure to stressful life events was also associated with elevated risk (OR = 1.86; 95% CI: 1.29–2.68).

Maternal exposure to negative life events during pregnancy was associated with a 62% increased risk (OR = 1.62; 95% CI: 1.29–2.03), with a clear dose-response relationship (Li et al., 2021). Conversely, positive life events appeared to exert a protective effect (OR = 0.38; 95% CI: 0.30–0.48).

Biologically, maternal stress may influence fetal cardiac development through dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, increased cortisol levels, placental dysfunction, and altered uteroplacental blood flow.

3.7. Environmental Exposure

Environmental exposures represent an important and increasingly investigated group of non-genetic risk factors for CHDs. It is estimated that only approximately one-third of CHD cases can be attributed to single-gene causes, highlighting the substantial contribution of environmental mechanisms.

A large population-based study including over 1.1 million births demonstrated that prenatal exposure to air pollutants during weeks 3–8 of gestation was associated with increased CHD risk (Jin et al., 2024). Sulfur dioxide (SO_2) exposure was strongly associated with ventricular septal defects (OR = 6.843, 95% CI: 5.746–8.149), while cadmium exposure also showed a significant association (OR = 1.513, 95% CI: 1.187–1.930).

Air pollutants and heavy metals are known to induce oxidative stress, systemic inflammation, and epigenetic modifications, all of which may disrupt normal cardiac development. Additionally, these exposures may interfere with placental function, supporting the concept of the heart-placenta axis (Jin et al., 2024).

Other environmental exposures, including volatile organic compounds, occupational hazards and noise, have also been implicated (Nie et al., 2022). Further high-quality prospective studies are needed to clarify exposure thresholds and critical windows of vulnerability.

3.8. Interaction Effects

The etiology of CHDs is increasingly understood as the result of complex interactions between genetic predisposition and environmental exposures, as well as interactions among multiple environmental and behavioral factors.

A large multicenter study (Wang et al., 2024) demonstrated that maternal ozone (O_3) exposure during early pregnancy was associated with increased CHD risk (OR per 10 μg/m³ = 1.17, 95% CI: 1.14–1.20). The combined presence of high ozone exposure and paternal smoking resulted in a substantially higher risk (OR = 2.23, 95% CI: 1.84–2.71).

A case-control study by Ruan et al. (2024) demonstrated that high indoor exposure to total volatile organic compounds (TVOCs) significantly increased CHD risk (OR = 9.23, 95% CI: 3.78–22.53), while regular multivitamin supplementation attenuated this association.

CHDs are increasingly recognized as multifactorial conditions involving gene–environment interactions (Boyd et al., 2022). Understanding these interactions is essential for developing targeted prevention strategies.

Table 1. Summary of Included Studies Investigating Maternal and Environmental Risk Factors for Congenital Heart Defects (CHDs) in Offspring

Risk factor	Exposure definition	Effect estimate (OR/RR)	95% CI	Key source
Maternal obesity	Moderate obesity	OR 1.15	1.11–1.20	*Salmeri et al., 2024*
	Severe obesity	OR 1.39	1.27–1.53	*Salmeri et al., 2024*
		~2.0 (selected defects)	—	*Persson et al., 2019*
	Class III obesity	aOR 1.85	1.54–2.21	*Hedermann et al., 2024*
	+5 kg/m² BMI increase	RR 1.07	—	*Liu et al., 2019*
Maternal diabetes	Pregestational diabetes	RR 2.8	2.1–3.7	*He et al., 2024*

	Poor glycemic control (HbA1c >8%)	RR up to 8.5	—	*He et al., 2024*
	Type 1 diabetes	OR 3.77	3.26–4.36	*Turunen et al., 2024*
	Gestational diabetes	OR 1.08–1.77	—	*Nagasawa et al., 2024*
Maternal smoking	Active smoking	RR 1.25	1.16–1.34	*Zhao et al., 2020*
	Passive smoking	RR 2.24	1.81–2.77	*Zhao et al., 2020*
	Passive smoking (high exposure)	OR 3.62	—	*Li et al., 2020*
	Paternal smoking	RR 1.74	1.48–2.06	*Zhao et al., 2020*
Alcohol consumption	Maternal alcohol exposure	OR 1.16	1.05–1.27	*Zhang et al., 2020*
	Paternal alcohol exposure	OR 1.44	1.19–1.74	*Zhang et al., 2020*
	Tetralogy of Fallot	OR 1.20	1.08–1.33	*Zhang et al., 2020*
Maternal fever	Periconceptional fever	OR 1.45	1.21–1.73	*Yang et al., 2021*
	First trimester fever	OR 1.79	1.32–2.44	*Yang et al., 2021*
Maternal infections	Viral infection (overall)	OR 2.28	1.54–3.36	*Ye et al., 2019*
	Rubella infection	OR 3.49	—	*Ye et al., 2019*
	Cytomegalovirus	OR 3.95	—	*Ye et al., 2019*
Psychological stress	General stress exposure	OR 2.11	1.62–2.74	*Gu & Guan, 2021*
	Stressful life events	OR 1.86	1.29–2.68	*Gu & Guan, 2021*
		OR >3.0	—	*Li et al., 2021*
Environmental exposure	SO_2 exposure (VSD)	OR 6.84	5.75–8.15	*Jin et al., 2024*
	Cadmium exposure	OR 1.51	1.19–1.93	*Jin et al., 2024*
	Ozone (per 10 μg/m³)	OR 1.17	1.14–1.20	*Wang et al., 2024*
Interaction effects	Ozone + paternal smoking	OR 2.23	1.84–2.71	*Wang et al., 2024*
Protective factors	Multivitamin supplementation (TVOCs)	—	—	*Ruan et al., 2024*
	Positive life events	OR 0.38	0.30–0.48	*Li et al., 2021*

4. DISCUSSION

This review highlights that congenital heart diseases arise from a complex interplay of maternal, paternal and environmental factors, with multiple modifiable exposures contributing to risk. Among these, maternal diabetes, particularly pregestational diabetes with poor glycemic control, shows the strongest and most consistent association. Maternal obesity also demonstrates a clear dose-response relationship and may further amplify risk when coexisting with diabetes.

Lifestyle factors such as smoking and alcohol consumption contribute to CHD risk to varying degrees. The evidence for smoking, especially passive exposure, is relatively consistent and supported by dose-response relationships. Infections and fever during early pregnancy, as well as environmental exposures such as air pollution and toxic substances, further underscore the importance of early gestational vulnerability.

Psychological stress appears to be associated with increased CHD risk, particularly in the context of significant life stressors. Interaction effects, such as those between environmental pollutants and parental behaviors or nutritional status, indicate that CHD risk is driven by combined and potentially synergistic effects.

Despite growing evidence, most findings are based on observational studies and are subject to residual confounding and exposure misclassification. Further prospective and mechanistic research is needed to better establish causality and clarify underlying biological pathways.

5. CONCLUSIONS

Congenital heart diseases are influenced by a range of modifiable maternal and environmental factors, with maternal diabetes and obesity playing a central role. Additional contributors include smoking, alcohol consumption, infections, psychological stress and environmental exposures.

The presence of dose-response relationships and interaction effects supports a multifactorial model of CHD pathogenesis and highlights opportunities for prevention. Optimizing maternal health before and during early pregnancy, reducing harmful exposures and promoting protective behaviors such as folic acid supplementation are key strategies.

Future research should focus on high-quality prospective studies and mechanistic investigations to improve understanding of causal pathways and support the development of targeted preventive interventions.

DISCLOSURE

Authors' Contributions

Conceptualization, A. Zielińska; methodology, I. Zydlewski and Z. Kamińska; software, A. Jakimowicz; check, A. Malcher and M. Blecharczyk; formal analysis, M. Pacanowska-Trawnicka and M. Mrozek; investigation, M. Pacanowska-Trawnicka, A. Zielińska; resources, I. Zydlewski; data curation, A. Malcher and M. Blecharczyk; writing – original draft preparation, A. Zielińska; writing – review and editing, M. Mrozek; visualization, Z. Kamińska; supervision, A. Zielińska; project administration, A. Zielińska.

All authors have read and agreed with the published version of the manuscript.

Financing statement

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Conflict of interest

The authors deny any conflict of interest.

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