



# Maternal smoking during pregnancy and the risk of pediatric cardiovascular diseases of the offspring: A population-based cohort study with up to 18-years of follow up<sup>☆</sup>

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## ABSTRACT

**Background:** Cigarette smoke is a well-known reproductive toxicant. We aimed to study the long-term effect of cigarette smoking during pregnancy on the risk for childhood cardiovascular morbidity of the offspring.

**Methods:** A population-based cohort analysis was performed comparing total and subtypes of cardiovascular related pediatric hospitalizations among offspring of smoking mothers versus offspring of non-smoking mothers. The analysis included all singletons born between the years 1999–2014. A Kaplan-Meier survival curve was used to compare the cumulative cardiovascular morbidity, and a Cox proportional hazards model was constructed to adjust for confounders.

**Results:** The study population included 242,342 newborns which met inclusion criteria; among them 2861 were born to smoking mothers. Offspring of smoking mothers had higher rates of cardiovascular-related hospitalizations (1.3% vs. 0.6%, OR 2.1, 95% CI 1.5–2.9;  $p < 0.001$ ; Kaplan-Meier log-rank test  $p < 0.001$ ).

**Conclusion:** Smoking exposure during pregnancy is associated with an increased risk for long-term pediatric cardiovascular morbidity of the offspring.

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## 1. Introduction

A significant portion of mothers, approximately 10% in developed countries, smoke during pregnancy [1]. Cigarette smoke is a well-known reproductive toxicant, and maternal cigarette smoke exposure during gestation was shown to be associated with maternal cardiovascular morbidities and subfertility [2], as well as several pregnancy complications [3], including miscarriage, placental abruption, preterm premature rupture of membranes (PPROM), placenta previa, preterm labor, low birth weight (LBW), and ectopic pregnancy [4–7].

In addition, maternal smoking has been associated with deleterious effects on the offspring in the short term, such as: intrauterine fetal growth restriction (IUGR) and low birth weight [8], congenital malformations [9], prematurity [10] and perinatal mortality, including Sudden Infant Death Syndrome (SIDS). Pineless et al.

demonstrated an increased risk of neonatal death in smoking mothers (RR 1.22, 95% CI 1.1–1.3) [11].

Several mechanisms were proposed to explain the adverse pregnancy outcomes associated with maternal smoking; these include impaired fetal oxygenation, altered fetal development and toxin exposure. One of the hypotheses suggests smoking in pregnancy causes impaired oxygen delivery to the fetus. Structural changes were shown in placentas of smoking mothers, such as reduction in capillary volume and increased thickness of the villous membrane compared with non-smokers [12,13]. These may contribute to abnormal gas exchange within the placenta. Another suggested mechanism is nicotine-induced vasospasm which contributes to decreased intervillous perfusion [14]. In addition, carboxyhemoglobin which is formed as a result of smoking reduces maternal and fetal tissue oxygenation via competitive inhibition with oxyhemoglobin. Smoking also exposes the mother and fetus to multiple potential toxins which may cause direct damage to fetal genetic material [15].

In a case-control study, an increased risk of cardiac congenital malformations was reported for infants exposed to cigarette smoke during pregnancy [16]. These included pulmonary valve and artery

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**Table 1**  
Maternal, pregnancy, and neonatal characteristics in both study groups.

	Smoking mothers%(n = 2861)	Non-smoking mothers%(n = 239,481)	OR (95% CI)	P Value
<b>Follow-up time (years, mean ± SD)</b>	9.8 ± 3.9	10.3 ± 5.9	–	<0.001
<b>Maternal characteristics</b>				
<b>Age at delivery (years, mean ± SD)</b>	29.7 ± 5.8	28.1 ± 5.8	–	0.69
<b>In Vitro Fertilization</b>	1.5 (44)	1.1 (2560)	–	0.03
<b>Parity</b>				
<b>1</b>	22.1 (633)	23.6 (56533)		
<b>2–4</b>	63.6 (1819)	51 (122123)	–	<0.001
<b>5+</b>	14.3 (409)	25.4 (60772)		
<b>Diabetes<sup>a</sup></b>	5.9 (169)	5 (11941)	1.2 (1.0–1.4)	0.025
<b>Chronic Hypertension</b>	5 (143)	5 (11967)	1.0 (0.8–1.2)	0.998
<b>PET</b>	4.1 (118)	3.9 (9383)	1.1 (0.9–1.3)	0.57
<b>Fetal and delivery characteristics</b>				
<b>Gender</b>				
<b>Male</b>	50.8 (1452)	50.8 (121729)	1.0 (0.9–1.1)	0.933
<b>Female</b>	49.2 (1409)	49.2 (117752)		
<b>Preterm labor (&lt;37 Weeks)</b>	9.8 (279)	6.5 (15537)	1.6 (1.4–1.8)	<0.001
<b>Preterm labor (&lt;34 Weeks)</b>	1.6 (47)	1.1 (2548)	1.6 (1.2–2.1)	0.003
<b>Induced labor</b>	35.9 (1027)	25.9 (62129)	1.6 (1.5–1.7)	<0.001
<b>Pathological presentation</b>	5.9 (170)	4.7 (11294)	1.3 (1.1–1.5)	0.002
<b>Non-reassuring fetal heart rate monitoring</b>	5 (144)	5 (11861)	1.0 (0.8–1.2)	0.84
<b>Nuchal cord</b>	14.6 (419)	14.4 (34386)	1.0 (0.9–1.1)	0.67
<b>% Cesarean delivery</b>	21.7 (620)	13.4 (32134)	1.8 (1.6–1.9)	<0.001
<b>SGA<sup>b</sup></b>	6.3 (181)	4.4 (10817)	1.4 (1.2–1.7)	<0.001
<b>LBW<sup>c</sup></b>	12.4 (354)	6.3 (15110)	2.1 (1.9–2.3)	<0.001
<b>VLBW<sup>d</sup></b>	0.6 (17)	0.3 (791)	1.8 (1.1–2.9)	0.015
<b>Apgar 1 min &lt;7</b>	3.8 (108)	4.9 (11628)	0.8 (0.6–0.9)	0.007
<b>Apgar 5 min &lt;7</b>	0.9 (25)	1.8 (4303)	0.5 (0.3–0.7)	<0.001

<sup>a</sup> Including all types of gestational diabetes and pre-gestational diabetes.

<sup>b</sup> Small for gestational age, defined as less than the 5th centile for gestational age.

<sup>c</sup> Low birth weight, defined as birth weight ≤2500 gr.

<sup>d</sup> Very low birth weight, defined as birth weight ≤1500 gr.

abnormalities and atrial septal defects, specifically. Few childhood morbidities have been associated with maternal smoking, such as: respiratory infections, asthma, atopy, hyperactivity and decreased school performance [17,18].

However, the understanding of the effect of in utero exposure on long term childhood cardiovascular morbidity is limited. Therefore, we aimed to study the long term effects of cigarette smoking during gestational period on the risk of childhood cardiovascular morbidity of the offspring.

## 2. Methods

This is a population-based retrospective cohort study included all singletons born between the years 1999–2014 at the Soroka University Medical Center (SUMC), the sole tertiary medical center in the region of southern Israel, serving 14.4% of Israel's population [19].

We studied the long term cardiovascular morbidity among offspring of smoking mothers in comparison to offspring of non-smoking mothers. The outcome assessed included hospitalizations with different subtypes of cardiovascular morbidity in the offspring up to the age of 18 years. Cardiovascular related morbidity included hospitalizations involving a pre-defined set of ICD-9 codes, as recorded in the hospital computerized medical files, detailed in the Supplemental Table.

Exclusion criteria from the analysis were: newborns with congenital malformations, as well as cardiac malformations, multiple gestations, and all perinatal deaths.

Follow up time was defined as time to a cardiovascular related hospitalization (time to an event), or until censored in case of death or at age 18 years. Only the first cardiovascular related hospitalization for each offspring was included in the analyses. Separate analyses were also conducted for the two main ethnic populations

in the Negev, Jewish and Bedouin Arabs, as well as separate analyses of the different subgroups of cardiovascular diagnoses.

For the analyses two databases were cross-linked and merged: the computerized perinatal database of the Obstetrics and Gynecology department and the computerized hospitalization database of SUMC (“Demog-ICD9”). The Demog-ICD9 database includes demographic information and ICD-9 codes for all medical diagnoses made during hospitalizations at SUMC. The perinatal database consists of information recorded immediately following delivery by an obstetrician and includes perinatal assessments, maternal morbidities and maternal and fetal outcome and complications. Records were anonymized prior to analysis. The study received the approval of the Institutional Review Board Committee of the Soroka University Medical Center (SUMC IRB).

Statistical analysis was performed using the SPSS package 23rd ed. (IBM/SPSS, Chicago, IL). Differences in categorical data were assessed by chi-square for general association. T-test was used for comparison of continuous variables with normal distribution. Kaplan-Meier survival curves were used to compare cumulative cardiovascular related hospitalization incidences over time according to smoking exposure. The differences between the two cumulative morbidity curves were assessed using the log-rank test.

A Cox proportional hazards model analysis was used to establish an independent association between maternal smoking during pregnancy and future cardiovascular related hospitalization risk while controlling for potential confounders. All analyses were two-sided and a p value of less than 0.05 was considered statistically significant.

## 3. Results

The study population included 242,342 newborns which met inclusion criteria; among them 2861 (1.2%) were born to mothers who smoke during pregnancy. The demographic characteristics and

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