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Baardman, M.E.; Kerstjens-Frederikse, W.S.; Corpeleijn, E.; de Walle, H.E.K.; Hofstra, R.M.W.; Berger, R.M.F.; Bakker, M.K.

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ORIGINAL ARTICLE

Combined adverse effects of maternal smoking and high body mass index on heart development in offspring: evidence for interaction?

Maria E Baardman,[1] Wilhelmina S Kerstjens-Frederikse,[2] Eva Corpeleijn,[3] Hermien E K de Walle,[1] Robert M W Hofstra,[2] Rolf M F Berger,[4] Marian K Bakker[1]

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[1]Eurocat Northern Netherlands, Department of Genetics, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[2]Department of Genetics, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[3]Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[4]Department of Pediatrics, Beatrix Children Hospital, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Correspondence to
Dr Marian K Bakker, Eurocat Northern Netherlands, Department of Medical Genetics, University Medical Centre Groningen, PO Box 30001, 9700 RB Groningen, The Netherlands;
m.k.bakker@umcg.nl

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ABSTRACT

Objective To study the influence of a possible interaction between maternal smoking and high body mass index (BMI) on the occurrence of specific congenital heart anomalies (CHA) in offspring.

Design Case-control study.

Setting Data from a population-based birth defects registry in the Netherlands.

Patients Cases were 797 children and fetuses born between 1997 and 2008 with isolated non-syndromic CHA. They were classified into five cardiac subgroups: septal defects (n=349), right ventricular outflow tract obstructive anomalies (n=126), left ventricular outflow tract obstructive anomalies (n=139), conotruncal defects (n=115) and other CHA (n=68). Controls were 322 children and fetuses with chromosomal anomalies without cardiac anomalies.

Main outcome measures Investigation of whether an interaction between maternal smoking and high BMI influences the occurrence of CHA in offspring by calculation of the synergy factors and 95% CIs.

Results As opposed to smoking or high BMI alone, the risk for CHA in the offspring of women with high BMI ($\geq$25 kg/m^2) who also smoked was significantly increased. The adjusted OR was 2.65 (95% CI 1.20 to 5.87) for all CHA, 2.60 (95% CI 1.05 to 6.47) for septal defects and 3.58 (95% CI 1.46 to 8.79) for outflow tract anomalies. The interaction between maternal high BMI and smoking contributed significantly to the occurrence of all offspring-CHA combined, and to the occurrence of all cardiac subgroup anomalies except right ventricular outflow tract obstructive anomalies.

Conclusions Maternal overweight and smoking may have a synergistic adverse effect on the development of the fetal heart. Overweight women who wish to become pregnant should be strongly encouraged to stop smoking and to lose weight.

INTRODUCTION

Congenital heart anomalies (CHA) are among the most common congenital anomalies with a prevalence of approximately 8 per 1000 births.[1] Little is known about the aetiology of CHA and a plausible cause is found in only 15% of cases[2]; both genetic and exogenous factors may play a role. Exogenous factors that have been associated with an increased risk of CHA include maternal conditions such as phenylketonuria, diabetes, rubella infection and epilepsy. The use of medication in pregnancy such as thalidomide, vitamin A derivatives, antiepileptic drugs, certain selective serotonin reuptake inhibitors and indomethacin is also associated with CHA.[3] Lifestyle factors that have been associated with CHA are smoking and alcohol consumption, whereas the use of folic acid showed a protective effect.[3 4] A high maternal pre-pregnancy weight has also been suggested as a risk factor for CHA in offspring.[5–8]

Smoking rates among Dutch women of fertile age are high with a prevalence of around 25%. More than half of these women continue smoking during pregnancy.[9] The increasing prevalence of overweight and obesity has developed primarily over the last decade. Over 30% of Dutch women aged 25–35 years are now overweight.[10]

Most causes of disease depend on the presence of other factors to assert their effects. This is also known as interaction. Smoking and overweight/obesity are known to interact in the origin of cardiovascular disease, particularly in arteriosclerosis; the combined effect of smoking and obesity augments the risk for stroke, myocardial infarction and sudden death.[11 12] In parallel, we hypothesised that this interaction between maternal high body mass index (BMI) and smoking could also have a substantial influence on the development of the fetal heart.

The interaction between smoking and high maternal BMI on the occurrence of specific CHA in offspring has not been studied to date. CHAs are complex diseases and both genetic factors and exogenous factors play an important role.[13] Important effects may be missed if risk factors are independently examined. If the interaction between risk factors such as maternal smoking and high pre-pregnancy weight is elucidated, this will result in better opportunities for prevention. We therefore investigated whether there is an interaction effect of maternal smoking and high BMI on the risk of CHA using a case-control study design.

METHODS

We used data from Eurocat Northern Netherlands (Eurocat NNL), a population-based birth defects registry. The annual number of births covered is approximately 19 000. Live births, stillbirths and terminations of pregnancies for congenital anomalies are included in the database if the mother lived in the registration area at the time of birth and if the child had not reached the age of 16 years at the

time of notification. Notification of children and fetuses with birth defects is voluntary. Registry staff are actively involved in case ascertainment using multiple sources. Written informed consent is obtained from the parents before registration. The participation rate is approximately 80%. Information on characteristics such as age, height, pre-pregnancy weight, chronic illnesses, education and information on lifestyle factors (such as smoking and alcohol consumption) are provided by the parents through a questionnaire. The response rate on the questionnaire is 80%.

Cases were defined as children and fetuses with an isolated non-syndromic CHA, which means that only the heart was affected and the CHA was not accompanied by any other (non-cardiac) congenital anomalies. Cases were born between 1997 and 2008 and included live births, stillbirths, miscarriages and terminations of pregnancy because of congenital anomalies. All children with a CHA in the registration area were seen by a paediatrician or a paediatric cardiologist. Coding and classification of the CHA was based on the diagnostic information in the medical files. Each case was classified into one of the following subgroups according to a system based on current developmental and epidemiological insights[14]: septal defects, conotruncal defects, outflow tract anomalies and other heart defects.

Because Eurocat NNL does not collect information on non-malformed children, controls were defined as children and fetuses with a chromosomal anomaly not accompanied by a CHA. The use of malformed controls from the same geographical area and from the same birth years in case-control studies on risk factors for birth defects is widely accepted.[15] The rationale for choosing chromosomal disorders is that the origin of these disorders is not related to the risk factors being studied. To minimise selection bias, we excluded all children and fetuses with a chromosomal defect and CHA confirmed by a prenatal or postnatal echocardiogram, surgery or autopsy report. We also excluded those without information from an echocardiogram or from an autopsy report to ensure no controls with an undetected structural heart defect were included.

BMI was calculated as pre-pregnancy weight (kg) divided by squared height (m) and classified into the following WHO categories[16]: underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2) and obese (BMI ≥30.0 kg/m^2). The categories overweight and obesity were combined in a group of 'high BMI' (BMI ≥25.0 kg/m^2). We excluded underweight women because the numbers were too small to perform meaningful analysis. Because low BMI is reported as a risk factor for birth defects, we did not include them in the reference group of normal BMI. Smoking was defined as 'smoking before and during the first trimester of pregnancy (periconceptional)', whereas no smoking was defined as 'no smoking during the entire pregnancy period'. Women with missing information on BMI or smoking, women who smoked occasionally or <1 cigarette per day or only during the second and third trimester were excluded from the analyses.

Potential confounders included maternal age, education level, chronic illness (requiring regular medication use), folic acid use, alcohol consumption and gestational diabetes. Three education levels were distinguished: low (primary school, lower general secondary education and lower vocational education), middle (higher general secondary education and intermediate vocational education) and high (university, further tertiary college and higher vocational education). Folic acid use was classified into two groups: correct use (400 or 500 μg per day started 4 weeks before conception and taken until the eighth week of pregnancy) and incorrect use (no use, use in wrong period or wrong dose: <400 μg). Alcohol consumption was defined as any alcohol taken in the first trimester of pregnancy; no alcohol was defined as no consumption in the first trimester. Women who drank alcohol occasionally or only during the second and third trimesters were excluded from the analysis. We excluded mothers with pregestational diabetes because maternal diabetes is related to BMI and smoking and is associated with CHA.

Maternal characteristics were explored using the χ^2 test for categorical variables and the Mann–Whitney U test for maternal age because the distribution of maternal age was skewed in the control group. The risk for CHA was calculated based on four exposure categories: normal weight and non-smoking (reference category); high BMI and non-smoking; normal weight and smoking; and high BMI and smoking. Crude and adjusted ORs were calculated using logistic regression. SPSS for Windows V.16.0 was used for the statistical analyses. A p value of <0.05 and 95% CI excluding 1.0 was considered to be statistically significant.

Interaction was assessed using the synergy factors (SF) by the method of Cortina-Borja.[17] This model is based on departure from multiplicativity. The SF is defined as the ratio of the observed OR for two dichotomous determinants (x and y) combined to the predicted OR assuming independent effects of each other: $SF = OR_{xy}/(OR_x \times OR_y)$.[18] For more information on synergy factor analysis we recommend the open access supplementary files in the paper by Cortina-Borja[17] on the website http://www.biomedcentral.com/1756-0500/2/105. We assumed that smoking and BMI were neither sufficient nor necessary for the development of CHA, but interact on a more general physiological pathway that affects the development of CHA.

In addition to these analyses, we explored the association between smoking and BMI separately with the main cardiac subgroups and with specific CHA to check the validity of our data. Specific heart anomalies with <5 affected cases (smoking or BMI subgroups) were not analysed separately but only included in the main cardiac subgroup. Logistic regression was used to determine the adjusted ORs (OR_{adj}) and 95% CI.

RESULTS

On 1 October 2009 there were 6399 children and fetuses with a congenital anomaly registered in the Eurocat database, including 1462 with a malformation of the circulation system (22.8%). In 1014 cases (69.4%) there was an isolated non-syndromic CHA, of which 212 (20.9%) had a complex CHA and 802 (79.1%) had a single CHA. We identified 411 controls with a non-cardiac chromosomal disorder. The majority of the controls had a numeric chromosomal anomaly (trisomy 21 in 44%, trisomy 18 in 8%, Turner syndrome in 6%, triploidy in 4%, trisomy 13 in 2%). The remaining 36% of the controls had deletions of the autosomes, unbalanced translocations or other chromosomal abnormalities and Mendelian-inherited disorders. After excluding mothers with pregestational diabetes (7 cases, 3 controls), those who were underweight (28 cases, 9 controls) and those with no information on smoking and BMI (182 cases, 77 controls), we identified 797 cases with a CHA and 322 controls with a non-cardiac chromosomal disorder. Table 1 shows the characteristics of these subjects.

As expected there was a difference in maternal age between the cases and controls, since the prevalence of chromosomal anomalies increases with higher maternal age. More miscarriages, stillbirths and terminations of pregnancies occurred among the controls. There were no statistically significant differences between cases and control with respect to first

Table 1 Characteristics of the cases and non-cardiac chromosomal controls

	Cases (n=797) n (%)	Controls (n=322) n (%)	p Value*
Year of birth			
1997–1998	141 (17.7)	68 (21.1)	0.33
1999–2000	147 (18.4)	66 (20.5)	
2001–2002	152 (19.1)	74 (23.0)	
2003–2004	147 (18.4)	45 (14.0)	
2005–2006	137 (17.2)	41 (12.7)	
2007–2008	73 (9.2)	28 (8.7)	
Type of birth/death			
Livebirth	699 (87.7)	232 (72.0)	0.00
Died after birth	80 (10.0)	20 (6.2)	
Miscarriage	2 (0.3)	15 (4.7)	
Termination of pregnancy	9 (1.1)	35 (10.9)	
Stillbirth	7 (0.9)	20 (6.2)	
Sex			
Boys	421 (52.8)	174 (54.0)	0.71
Girls	376 (47.2)	148 (46.0)	
Education level			
Low	154 (19.4)	62 (19.4)	0.57
Middle	393 (49.6)	149 (46.6)	
High	245 (31.0)	109 (34.0)	
Unknown	5	2	
Maternal age at delivery (years)			
Median (25th–75th percentile)	30 (27–34)	33 (29–36)	0.00
First pregnancy			
No	515 (64.6)	224 (69.6)	0.11
Yes	282 (35.4)	98 (30.4)	
Correct use of folic acid supplements			
No use or wrong period	306 (49.7)	123 (46.9)	0.46
Yes	310 (50.3)	139 (53.1)	
Unknown	181	60	
Periconceptional alcohol consumption			
No	599 (79.0)	239 (76.4)	0.17
Yes	159 (21.0)	74 (23.6)	
Unknown or only after the first trimester	39	9	
Maternal chronic illness			
No	658 (85.5)	278 (87.7)	0.33
Yes	112 (14.5)	39 (12.3)	
Unknown	27	5	
Gestational diabetes			
Yes	8 (1.0)	3 (0.9)	0.91
No	789 (99.0)	319 (99.1)	

*χ^2 test.

pregnancy, chronic illness, education level, folic acid use, alcohol consumption or gestational diabetes.

In total, 281 case mothers (35.3%) and 94 control mothers (29.2%) had a high BMI. Periconceptional smoking was recorded for 199 case mothers (25.0%) and 61 control mothers (18.9%). Table 2 shows the distribution of BMI and periconceptional smoking among case and control mothers. It should be noted that both smoking and obesity were recorded for 19 case mothers in the periconceptional period, whereas none of the obese mothers in the control group smoked in this period.

In table 3 the numbers, crude and adjusted ORs and 95% CI of the four exposure groups are shown. We found no significantly increased ORs for all CHA and for the cardiac subgroups in the exposure categories high BMI/no smoking and normal BMI/smoking. In the combined exposure group high BMI/smoking a significantly increased OR was found for all CHA and for the specific cardiac subgroups. The adjusted ORs were lower but still

Table 2 Distribution of combined maternal pre-pregnancy weight and periconceptional smoking among informative cases and non-cardiac chromosomal controls in the Eurocat database (1997–2008)

	Cases (n=797)		Controls (n=322)	
	Smoking		Smoking	
	No	Yes	No	Yes
Normal BMI	390 (49%)	126 (16%)	175 (54%)	53 (17%)
High BMI	208 (26%)	73 (9%)	86 (27%)	8 (2%)
Overweight	146 (18%)	54 (7%)	69 (21%)	8 (2%)
Obese	62 (8%)	19 (2%)	17 (5%)	0 (0%)

Normal body mass index (BMI) 18.5–24.9 kg/m^2; high BMI ≥25.0 kg/m^2; overweight 25.0–29.9 kg/m^2; obese ≥30 kg/m^2.

statistically significant for all cardiac subgroups except for conotruncal defects. The highest adjusted OR was found for right ventricular outflow tract obstructive anomalies (RVOTO).

In table 4 the SF and 95% CI are shown for the combined exposure group high BMI/smoking. Except for RVOTO defects, the SF was statistically significant for all the subgroups.

With respect to the main effects of smoking and high BMI (specified as overweight and obese) on the subgroups and specific types of CHA, we found that RVOTO defects were significantly associated with high BMI. When taking the BMI categories overweight and obesity into account, we found a significant association between RVOTO and overweight. Obesity was significantly associated with all CHA, septal defects, ventricular septal defects (VSD) perimembraneous and VSD combined/not otherwise specified. Smoking was significantly associated with atrial septal defects, secundum type (ASDII) and pulmonary valve stenosis/atresia with ASDII and/or VSD (see appendix in online supplement).

DISCUSSION

Our study has shown that smoking and high BMI strongly interact in the risk of CHA in offspring. We found that the combination of maternal smoking and high BMI increased the risk for CHA in offspring more than would be expected from the product of the individual effects of these two exposures.

Although the combined adjusted OR was the highest for RVOTO defects (table 3), the interaction was not statistically significant for this cardiac subgroup (table 4). Lack of power could be an explanation, since RVOTO is one of the smallest subgroups in our study. The use of a multiplicative model to calculate interaction could be another explanation. Other studies have argued that a multiplicative model is often 'too strong' to pick up signals of small joint effects of two biological risk factors and therefore 'biological interaction' needs to be calculated on an additive scale.[17 19–21] Interaction effects with a more additive character might not show an interaction on a multiplicative scale when the combined OR is similar to the predicted OR (SF = ORxy/(ORx × ORy) eg, 15/(3 × 5)=1). However, there is still a lot of discussion on how additive interaction should be calculated for case-control studies. Furthermore, it is unclear how to interpret outcome measures of interaction calculated on an additive scale. We therefore used a multiplicative model to measure interaction.

The results of our study need to be interpreted in the light of the complexity of the disease. Because the association between environmental factors and CHA is probably strongest in children with an isolated non-syndromic CHA, we carefully defined the inclusion criteria for the case group in order to create a homogeneous group without other (complicating) anomalies. In addition, we defined a range of cardiac subgroups to study

Table 3 Crude and adjusted ORs (95% CI) for maternal smoking, high BMI and both factors combined for different cardiac subgroups relative to non-cardiac chromosomal controls in the Eurocat database (1997–2008)

	Normal BMI No smoking (n)	High BMI (≥25 kg/m^2) No smoking (n)	Normal BMI Smoking (n)	High BMI (≥25 kg/m^2) Smoking (n)
Chromosomal controls (n=322)	175	86	53	8
All CHA (n=797)				
N	390	208	126	73
OR (95% CI)	ref	1.09 (0.80 to 1.48)	1.07 (0.64 to 1.54)	**4.10 (1.93 to 8.68)**
OR_{adj} (95% CI)*	ref	1.05 (0.72 to 1.54)	0.96 (0.61 to 1.05)	**2.65 (1.20 to 5.87)**
Septal defects (n=349)				
N	177	86	59	27
OR (95% CI)	ref	0.99 (0.69 to 1.42)	1.10 (0.72 to 1.69)	**3.34 (1.48 to 7.55)**
OR_{adj} (95% CI)*	ref	0.95 (0.60 to 1.50)	1.00 (0.58 to 1.70)	**2.60 (1.05 to 6.47)**
Conotruncal defects (n=115)				
N	60	31	15	9
OR (95% CI)	ref	1.05 (0.63 to 1.74)	0.83 (0.43 to 1.57)	**3.28 (1.21 to 8.89)**
OR_{adj} (95% CI)*	ref	1.00 (0.55 to 1.83)	0.67 (0.30 to 1.49)	2.86 (0.93 to 8.84)
Outflow tract anomalies (n=265)				
N	121	75	39	30
OR (95% CI)	ref	1.26 (0.86 to 1.86)	1.06 (0.66 to 1.71)	**5.42 (2.40 to 12.24)**
OR_{adj} (95% CI)*	ref	1.35 (0.85 to 2.17)	0.90 (0.49 to 1.64)	**3.58 (1.46 to 8.79)**
Left ventricular outflow tract obstructive anomalies (n=139)				
N	66	38	20	15
OR (95% CI)	ref	1.17 (0.73 to 1.89)	1.00 (0.56 to 1.80)	**4.79 (2.01 to 12.27)**
OR_{adj} (95% CI)*	ref	1.18 (0.67 to 2.10)	0.78 (0.37 to 1.67)	**3.32 (1.12 to 9.80)**
Right ventricular outflow tract obstructive anomalies (n=126)				
N	55	37	19	15
OR (95% CI)	ref	1.37 (0.84 2.24)	1.14 (0.63 to 2.09)	**5.97 (2.40 to 14.82)**
OR_{adj} (95% CI)*	ref	1.57 (0.86 to 2.87)	1.02 (0.47 to 2.21)	**4.63 (1.68 to 12.75)**

*OR adjusted for maternal age, education level, folic acid use and periconceptional alcohol consumption.
BMI, body mass index; CHA, congenital heart anomalies.

specific associations. Because Eurocat NNL registers children up to 16 years of age, CHA cases that were discovered later in childhood were also included in the study whereas other studies normally include only children diagnosed up to 1 year of age. Our registry also contains information on genetic defects associated with heart defects discovered later in childhood. We are therefore able to identify isolated non-syndromic cardiac malformations and to exclude heart defects with a known genetic cause. However, it is possible that, with improved techniques, a genetic cause will be found in the future in some cases with an isolated non-syndromic CHA.

In the absence of non-malformed controls and because smoking and BMI have been associated with different congenital malformations, we included only children and fetuses with non-cardiac chromosomal anomalies in the control group. Although associations between maternal smoking and early fetal loss have been described,[22] causality between the risk factors being studied and chromosomal anomalies has not been proven. Because we cannot rule out the possibility that lifestyle factors and other determinants differ between mothers of children with a chromosomal disorder and mothers of non-malformed children, the translation of the results to the general population of pregnant women should be regarded with caution. We encourage other researchers to verify our results in their datasets using non-malformed controls.

Table 4 Interaction (adjusted synergy factors and 95% CIs) for maternal smoking and high BMI combined for different cardiac subgroups relative to non-cardiac chromosomal controls

Cardiac subgroups	Interaction (SF) (95% CI)*	p Value
All CHA (n=797)	2.62 (1.12 to 6.17)	0.027
Septal defects (n=349)	2.75 (1.07 to 7.08)	0.036
Conotruncal defects (n=115)	4.28 (1.26 to 14.51)	0.020
Outflow tract anomalies (n=265)	2.94 (1.12 to 7.71)	0.028
Left ventricular outflow tract obstructive anomalies (n=139)	3.59 (1.19 to 10.87)	0.024
Right ventricular outflow tract obstructive anomalies (n=126)	2.87 (0.94 to 8.79)	0.065

*Adjusted for maternal age, education level, folic acid use and periconceptional alcohol consumption.
BMI, body mass index; CHA, congenital heart anomalies; SF, synergy factors.

Data on maternal BMI and periconceptional smoking were obtained retrospectively for both cases and controls through a questionnaire filled in by the mother. The use of malformed controls minimises the possibility of differential recall between the cases and controls. It is likely that we have underestimated the proportion of overweight and obese mothers because women tend to report a lower weight than in reality. However, any recall bias in this direction would most likely be non-differential and result in an underestimation of the effect.

In our analyses we adjusted for potential confounding factors such as educational level and alcohol consumption, which are known to interfere with determinants and outcome variables in other studies. We did not adjust for gestational diabetes (GDM) for different reasons. First, GDM develops throughout the second trimester of pregnancy when most of the heart structures have already developed. Second, blood glucose levels were analysed in all the women in the first trimester of pregnancy. In addition, the results in table 3 were comparable when excluding mothers with GDM.

Previous case-control studies on maternal smoking and high BMI in relation to CHA risk in human offspring have found

both positive and negative associations.[3] However, these studies did not determine whether there was interaction between smoking and BMI but merely adjusted for these factors. By confirming associations identified previously between smoking and BMI for different specific cardiac subgroups, we show the validity of our data. We confirmed previously described associations with high BMI and increased risk for RVOTO defects,[6] as well as previously described associations between periconceptional smoking and atrial septal defects and pulmonary valve stenosis.[23 24]

The interaction found between high BMI and smoking for specific cardiac subgroups strengthens the hypothesis that heart defects are complex in origin and that a pathogenic mechanism could be shared by both risk factors. In a recent study Hobbs *et al* suggest that genetic polymorphisms in genes encoding enzymes in folate-dependent pathways could act as such a shared mechanism.[25] Studies on the role of different genetic polymorphisms that hypothetically interact with maternal lifestyle factors are still inconclusive, but they do suggest that these polymorphisms play only a minor role.[26]

Proposed mechanisms on maternal overweight and the increased risk for CHA in offspring are hyperglycaemia-induced oxidative stress because of insulin resistance[27 28] and fetal hypoxia.[29] The latter is also mentioned in literature as the underlying mechanism that causes CHA associated with intrauterine tobacco smoke exposure.[30] Although several suggestions have been made, the exact mechanisms underlying the teratogenicity associated with maternal overweight and/or tobacco smoke remain unclear. Interestingly, obesity and smoking affect plasma cholesterol levels, often resulting in dyslipidaemia with increased low density lipoprotein levels and decreased high density lipoprotein levels.[11 12] Cholesterol is essential for fetal cardiac development regulated by the sonic hedgehog transcription pathway.[31] In the first trimester of pregnancy, maternally-derived cholesterol is an important source of cholesterol for the fetus, as animal studies have indicated.[32] The heart defects in our study that were associated with these lifestyle factors (eg, RVOTO, septal defects) have been previously described in relation to errors in the cholesterol metabolism and downstream pathways.[33–35] We therefore hypothesise maternal dyslipidaemia as a possible shared mechanism to explain the interaction between maternal smoking and overweight.

In conclusion, our study is the first to suggest that there is strong interaction between maternal smoking and high BMI in the risk for CHA in offspring. The results indicate that maternal smoking and overweight may both be involved in the same pathway that causes congenital heart defects. It is important to replicate our findings in larger datasets with non-malformed controls and enough statistical power to analyse the interaction in smaller CHA subgroups and more BMI subgroups. We furthermore suggest that future case-control studies should include interaction calculations when exploring risk factors for congenital (heart) anomalies.

Our results add to the strong existing evidence that both smoking and overweight are related to adverse pregnancy outcomes such as intrauterine fetal death, small for gestational age and preterm birth. We recommend that smoking cessation should be strongly emphasised in preconception care, especially in overweight women. Further research into the effect of maternal cholesterol disturbances and maternal-fetal cholesterol transport defects in the aetiology of congenital heart defects is particularly important, since women of childbearing age are increasingly suffering from cholesterol-related diseases and conditions such as obesity and diabetes.

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Competing interests None.

Ethics approval Ethical approval for this study was not necessary. Parents have consented to the data being registered and used in studies on risk factors for congenital anomalies.

Contributors MEB, WSK-F, RMWH, RMFB and MKB designed the study. MEB, WSK-F and RMFB classified the cases. MKB, HEKdW and MEB compiled the study database. MEB, EC and MKB conducted the statistical analysis and interpreted the results. MEB, WSK-F and MKB drafted the paper. MEB constructed the tables. All authors corrected all versions of the paper. MKB is guarantor.

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Maria E Baardman, Wilhelmina S Kerstjens-Frederikse, Eva Corpeleijn, et al.

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