

## Appendix

**Appendix Table 1.** Characteristics of included studies examining the association between pregestational diabetes mellitus and congenital heart defects

Citation	Study population, Year	Study design (Population size)	Diabetes exposure	Congenital heart defect subtype	Number exposed with CHD	Crude summary estimate of association (OR or RR) (95% CI)
Agopian et al., 2012 <sup>b,c</sup>	Texas Birth Defects Registry (United States), 2005-2008	Case control (1,538,189)	PGDM diagnosis on medical records	Atrioventricular septal defects	12	8.1 (4.5-14.5)
Bell et al., 2012 <sup>c</sup>	Northern Diabetes in Pregnancy Survey (NorDIP) (North England), 1996-2008	Retrospective cohort (401,149)	PGDM diagnosed at least six months prior to pregnancy	Total congenital heart defect	44	3.6 (2.7-4.9)
				Atrioventricular septal defect	12	6.9 (1.7-28.1)
				Coarctation of the aorta	2	4.7 (1.2-19.1)
				Hypoplastic left heart syndrome	1	3.1 (0.4-21.9)
				Tetralogy of Fallot	4	10.0 (3.7-27.2)
Transposition of the great arteries	3	5.5 (1.8-17.2)				
Chung and Myrianthopoulos, 1975 <sup>d</sup>	Collaborative Perinatal Project (United States), Years not specified	Prospective cohort (47,975)	PGDM diagnosed prior to pregnancy and continuing throughout pregnancy	Total congenital heart defect	14	5.6 (3.3-9.6)
Correa et al., 2012 <sup>c</sup>	National Birth Defects Prevention Study (NBDPS) (United States), 1997-	Case control (11,631)	Maternal report of PGDM diagnosed prior to pregnancy	Total congenital heart defect	215	6.7 (4.5-9.9)
				Atrioventricular septal defect	10	13.3 (6.4-27.9)
				Coarctation of the aorta	12	4.6 (2.3-9.1)
				Hypoplastic left heart syndrome	6	4.2 (1.7-10.2)

	2004			Tetralogy of Fallot	19	6.8 (3.8-12.3)
				Transposition of the great arteries	11	5.5 (2.8-11.2)
Eidem et al., 2010 <sup>c</sup>	Norway Medical Birth Registry, Norwegian type 1 Diabetes Registry (Norway), 1999-2004	Retrospective cohort (350,961)	Type 1 diabetes diagnosed before 15 years of age	Total congenital heart defect	51	3.4 (2.6-4.5)
Erickson, 1991 <sup>d</sup>	Atlanta Birth Defects Case Control Study (United States), 1968-1980	Case control (4,021)	Maternal report of PGDM before conception	Total congenital heart defect	35	3.1 (1.9-5.0)
				Coarctation of the aorta	1	1.3 (0.2-9.8)
				Tetralogy of Fallot	1	1.7 (0.2-13.1)
				Transposition of the great arteries	5	5.4 (2.0-14.6)
Ferencz et al., 1990 <sup>b,e</sup>	Baltimore-Washington Infant Study (United States), 1981-1987	Case control (2,858)	Maternal report of PGDM diagnosed six months before pregnancy	Coarctation of the aorta	2	3.0 (0.7-13.4)
				Hypoplastic left heart syndrome	2	3.7 (0.8-16.6)
				Tetralogy of Fallot	5	6.3 (2.2-17.6)
				Transposition of the great arteries	2	3.1 (0.7-14.0)
Janssen, Rothman, and Schwartz, 1996 <sup>e</sup>	Washington State (United States), 1984-1991	Retrospective cohort (10,437)	Established PGDM noted on birth certificate	Total congenital heart defect	24	5.7 (3.2-9.9)
Knight et al., 2012 <sup>e</sup>	Rochester Strong Memorial Hospital, NY (United States), 2000-2008	Retrospective cohort (426)	Type 2 diabetes diagnosed prior to pregnancy identified by clinic records, birth certificate, or laboratory	Total congenital heart defect	6	1.5 (0.4-5.4)
Loffredo, Wilson, and Ferencz, 2001 <sup>e</sup>	Baltimore-Washington Infant Study	Case control (6,005)	Maternal report of PGDM diagnosed six	Total congenital heart defect	54	3.5 (2.1-5.7)
				Atrioventricular septal defect	5	10.6 (3.9-28.6)

	(United States), 1981-1989		months before pregnancy			
Nielsen et al., 2005 <sup>c</sup>	Hungarian Congenital Abnormality Registry and Hungarian National Birth Registry (Hungary), 1980- 1996	Case control (42,630)	Maternal report of diabetes and insulin use prior to pregnancy or in medical log- book	Total congenital heart defect	20	3.4 (2.0-5.7)
Peticca et al., 2009 <sup>f</sup>	Niday Perinatal Database, Ontario (Canada), 2005- 2006	Retrospective cohort (51,805)	Medical record of PGDM	Total congenital heart defect	6	1.3 (0.6-3.0)
Sharpe et al., 2005 <sup>d</sup>	South Australian Birth Defects Register; South Australian Department of Health's Pregnancy Outcome Statistics Unit (Australia), 1986- 2000	Retrospective cohort (275,525)	Medical record of PGDM	Total congenital heart defect	23	2.9 (1.9-4.3)
Sheffield et al., 2002 <sup>d</sup>	Parkland Hospital, Dallas TX (United States), 1991- 2000	Prospective cohort (142,919)	Diagnosis of PGDM from medical record when entering hospital to deliver	Total congenital heart defect	5	8.4 (3.5-20.4)

CI, confidence interval; PGDM, pregestational diabetes mellitus

<sup>a</sup> Inclusion criteria: comparison between pregnancies of women with PGDM and a comparison group of women without a diagnosis of PGDM, contained one or multiple CHD(s) as an outcome, was a case-control or cohort study, was retrospective or prospective, and was conducted in human subjects

<sup>b</sup> Only included in the meta-analyses of specific CHD subtypes

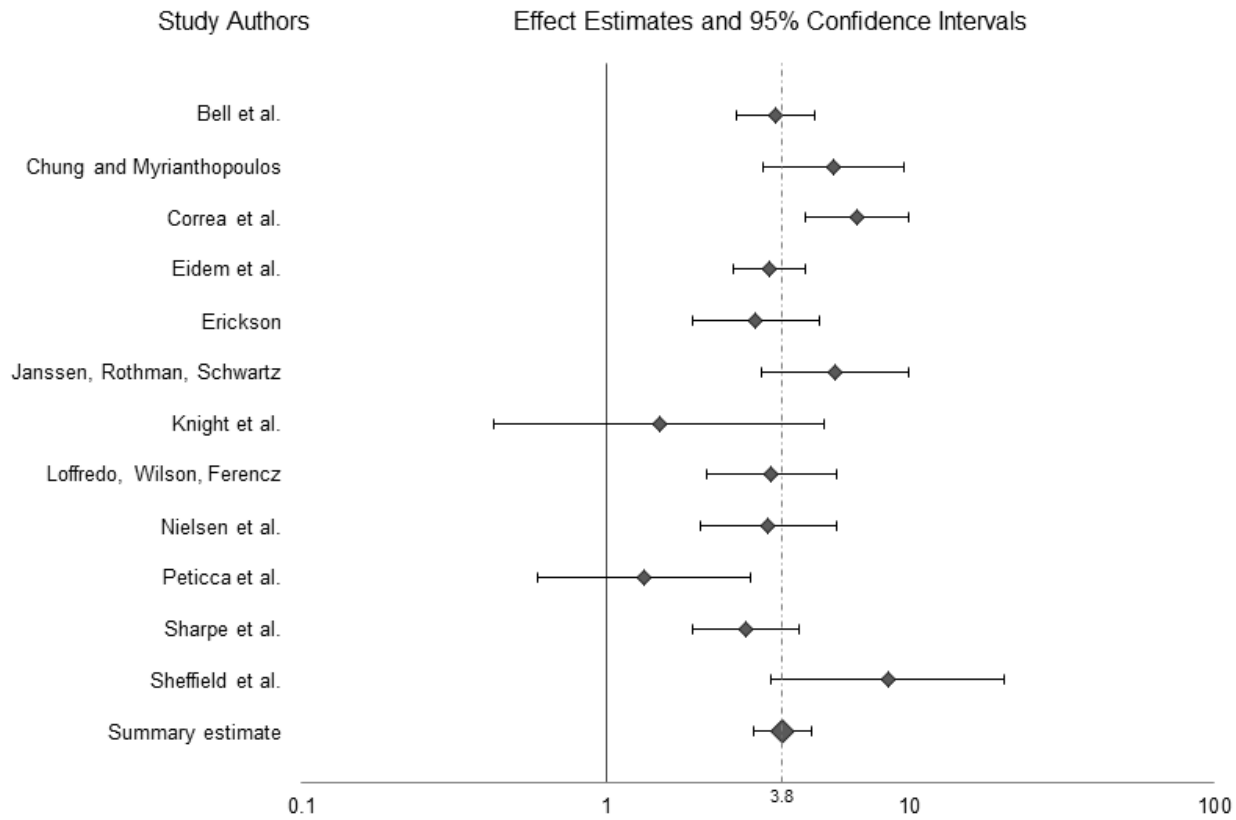
<sup>c</sup> Liveborn infants, stillborn infants, and terminated pregnancies

<sup>d</sup> Liveborn and stillborn infants

<sup>e</sup> Liveborn infants

<sup>f</sup> Liveborn, stillborn, termination not specified

**Appendix Figure 1.** Forest plot, effect estimates for random effects meta-analysis of association between pregestational diabetes and congenital heart defects.



## **Appendix. Systematic review search strategy**

### **MEDLINE**

#### **I. Diabetes**

**exp \*diabetes mellitus/ or (diabet\* or IDDM or NIDDM or MODY).tw**

#### **II. Congenital Heart Defects**

**exp congenital abnormalities/ or congenital or ((birth or cardiovascular or ventric\* or heart or valv\* or aort\* or septal or conotruncal or atrial or atrioventricular or pulmonary) adj5**

**(abnormalit\* or defect\* or deform\* or anomal\* or malform\* or coarctation or hypoplastic or Ebstein\*)) or ((pulmonary or tricuspid) adj3 (atresia\*)) or ((aqueduct\* or valv\* or aort\* or pulmonary) adj3 (stenos\*)) or ventriculomegal\* or arteriosus or Heterotaxia or "Tetralogy of**

**Fallot" or (transposition adj5 arteries) or "Double-outlet right ventricle" or "Double outlet right ventricle" or "left ventricular outflow tract" or "left ventricular outflow track" or "right atrioventricular connection"**

**Heart Defects, congenital/ is a subheading of exp congenital abnormalities/**

#### **III. Pregnancy**

**exp pregnancy/ or exp mother/ or exp maternal exposure/ or exp maternal-fetal relations/**

**or exp maternal-fetal exchange/ or exp maternal behavior/ or exp mother-child relations/**

**or exp fetus/ or (pregnan\* or gestat\* or mother\* or maternal\* or fetus\* or periconception\* or "in utero" or conception or preconception).tw**

**not**

cats or cattle or chick embryo or dogs or goats or guinea pigs or toad or hamsters or horses or mice or mouse or rabbits or rabbit or rat or rats or sheep or swine or primate\* or monkey\* or plant or plants or animal\*

## **EMBASE**

### **I. Diabetes**

exp \*diabetes mellitus/ or (diabet\* or IDDM or NIDDM or MODY).tw

### **II. Congenital Heart Defects**

exp congenital disorder/ or congenital or ((birth or cardiovascular or ventric\* or heart or valv\* or aort\* or septal or conotruncal or atrial or atrioventricular or pulmonary) adj5 (abnormalit\* or defect\* or deform\* or anomal\* or malform\* or coarctation or hypoplastic or Ebstein\*)) or ((pulmonary or tricuspid) adj3 (atresia\*)) or ((aqueduct\* or valv\* or aort\* or pulmonary) adj3 (stenos\*)) or ventriculomegal\* or arteriosus or Heterotaxia or "Tetralogy of Fallot" or (transposition adj5 arteries) or "Double-outlet right ventricle" or "Double outlet right ventricle" or "left ventricular outflow tract" or "left ventricular outflow track" or "right atrioventricular connection"

### **III. Pregnancy**

exp pregnancy/ or exp mother/ or exp maternal exposure/ or exp expectant mother/ or exp mother fetus relationship/ or exp mother child relation/ or exp mother/ or exp maternal behavior/ or exp fetus/ or (pregnan\* or gestat\* or mother\* or maternal\* or fetus\* or periconception\* or "in utero" or conception or preconception).tw

**not**

cats or cattle or chick embryo or dogs or goats or guinea pigs or toad or hamsters or horses or mice or mouse or rabbits or rabbit or rat or rats or sheep or swine or primate\* or monkey\* or plant or plants or animal\*

## **CINAHL**

### **I. Diabetes**

(MM "Diabetes Mellitus+") or (diabet\* or IDDM or NIDDM or MODY)

### **II. Congenital Heart Defects**

(MH "Abnormalities+") or congenital or ((birth or cardiovascular or ventric\* or heart or valv\* or aort\* or septal or conotruncal or atrial or atrioventricular or pulmonary) N5 (abnormalit\* or defect\* or deform\* or anomal\* or malform\* or coarctation or hypoplastic or Ebstein\*)) or ((pulmonary or tricuspid) N3 (atresia\*)) or ((aqueduct\* or valv\* or aort\* or pulmonary) N3 (stenos\*)) or ventriculomegal\* or arteriosus or Heterotaxia or "Tetralogy of Fallot" or (transposition N5 arteries) or "Double-outlet right ventricle" or "Double outlet right ventricle" or "left ventricular outflow tract" or "left ventricular outflow track" or "right atrioventricular connection"

### **III. Pregnancy**

(MH "Pregnancy+") OR (MH "Pregnancy Outcomes") OR (MH "Pregnancy Complications") OR (MH "Expectant Mothers") OR (MH "Periconceptual Period") OR (MH "Mothers+") OR (MH "Mother-Child Relations") OR (MH "Mother-Infant Relations") OR (MH "Maternal Exposure") OR (MH "Maternal Behavior") OR (MH "Maternal-Fetal Exchange") OR (MH



"Fetus+") or (pregnan\* or gestat\* or mother\* or maternal\* or fetus\* or periconception\* or "in utero" or conception or preconception)

## **POPLINE**

### **I. Diabetes**

TITLE:(diabet\* / IDDM / NIDDM / MODY)

### **II. Congenital Heart Defects**

TITLE AND KEYWORDS:(congenital / cardiovascular / ventric\* / heart / valv\* / aort\* / septal / conotruncal / atrial / atrioventricular / pulmonary / abnormalit\* / defect\* / deform\* / anomal\* / malform\* / coarctation / hypoplastic / Ebstein\* / tricuspid / atresia\* / aqueduct\* / stenosis\* / ventriculomegal\* / arteriosus / Heterotaxia / Fallot / arteries)

## Appendix. Statistical Methods

A Bayesian approach was used to summarize the gathered information on the association between pregestational diabetes mellitus (PGDM) and the risk of having a child with a congenital heart defect (CHD). In doing so, it was assumed that the expected value for the observed natural log of the odds ratio relating diabetes and CHD reported in study  $i$  could be modeled as the sum of the unknown true underlying log odds ratio relating these attributes, referred to as  $\mu$ , and a random study-specific effect,  $\lambda_i$ , reflecting the heterogeneity due to inter-study variability. Under this assumption, the observed log odds ratio in study,  $\log(OR_i)$ , is considered to be a random sample from a normal distribution with mean given by  $\mu + \lambda_i$  and variance

$$\frac{1}{c_i(d)} + \frac{1}{n_i(d) - c_i(d)} + \frac{1}{c_i(nd)} + \frac{1}{n_i(nd) - c_i(nd)} . \quad [1]$$

In this variance formula,  $c_i(d)$  is the number of CHD cases in study  $i$  for which the mother had PGDM,  $n_i(d)$  is the total number of women in that study with PGDM,  $c_i(nd)$  is the number of CHD cases in study  $i$  with no diabetes and  $n_i(nd)$  is the total number of non-diabetic women in study  $i$ . To apply the Bayesian approach, assumed prior distributions for  $\mu$  and  $\lambda_i$  reflecting the uncertainty concerning possible values for these parameters prior to evaluating information observed in the collection of studies were specified. These prior distributional assumptions are updated based on the observed information to derive final, or posterior, estimates for the parameters. The focus was on development of posterior estimates for  $\mu$ , the true log odds ratio relating diabetes and CHD, that is a key component in estimating the attributable fraction.

A vague prior distribution was assumed for  $\mu$  in which uncertainty concerning the parameter was modeled using a Normal distribution with mean zero and a large prior standard deviation of 2.7. This assumption corresponds to a vague prior belief that the true odds ratio relating PGDM and CHD has a median value of one with a 95% probability of being between 0.005 and 200 as defined by the 2.5<sup>th</sup> and 97.5<sup>th</sup> percentiles of prior distribution. In addition, the study random effects,  $\lambda_i$ , were assumed to be sampled from a normal prior distribution with mean zero and standard deviation,  $\sigma_\lambda$ . Note that the parameter  $\sigma_\lambda$  reflects the level of inter-study heterogeneity. The prior distribution for  $\ln(\sigma_\lambda^2)$  was assumed to be normal with a mean of -2 and a standard deviation of 1.6. This assumption on the prior for the log of the variance of the random study-level effects was chosen based on previous findings that substantial bias can be introduced into meta-analysis by assuming a value for the prior variance of the inter-study heterogeneity parameters that is too large, especially when the analysis is based on a small number of studies.<sup>1</sup> In summary, the models used in the meta-analyses were based on the assumption that

$$\log(OR_i) \sim N(\mu + \lambda_i, \sigma_i^2),$$

where  $\sigma_i^2$  is treated as known and is defined in equation [1]. The prior distributions for the model parameters were assumed to be

$$\mu \sim N(0, 7.3),$$

$$\lambda_i \sim N(0, \sigma_\lambda^2),$$

and

$$\log(\sigma_\lambda^2) \sim N(-2, 2.6).$$

Sensitivity assessments were conducted to evaluate the impact of differing assumptions on the priors of both the log of the true odds ratio and the study-level random effects on posterior

estimates. Identical assumptions on the prior distributions for the unknown parameters were used both in the analysis of all CHDs and in developing summary estimates for specific CHD subtypes.

Prior assumptions on the values of the unknown parameters were updated using the information retrieved from the selected studies using an iterative Markov Chain Monte Carlo (MCMC)<sup>2</sup> algorithm in which new parameter estimates are developed based on the current estimated values of all other parameters at each stage of the updating process. The MCMC process is begun by selecting a random value from the prior distribution for each parameter and using that value as the initial estimate in a chain that is updated at each step. This process is continued until the sampled values for the parameters are judged to arrive at a posterior distribution on which final estimates are based. To increase the likelihood of convergence to this posterior, the chains for each parameter of interest were run for 100,000 iterations with the first 50,000 values discarded. In addition, to reduce the level of autocorrelation in the final estimates, only every 5<sup>th</sup> value of the remaining 50,000 samples were retained for estimating the posterior distribution. As a result, estimates of the true odds ratios relating CHD and maternal diabetes were based on 10,000 samples from the posterior distribution. These posterior estimates for the odds ratio, that is  $\exp(\mu)$ , are summarized using the median of the 10,000 posterior samples and the 95% credible interval defined as the range separating the 2.5<sup>th</sup> and 97.5<sup>th</sup> percentiles of the sampled values.

Sensitivity of the meta-analysis results was evaluated by comparing the final estimates derived under the prior assumptions stated above to those resulting from using alternative assumptions on the prior distributions of  $\mu$  and  $\lambda_i$ . The alternative priors considered for the true log odds

ratio were vague uniform distributions on both the log odds ratio and the odds ratio itself.<sup>2</sup> In addition, we evaluated both alternative priors on the odds ratio in combination with a vague uniform prior, bounded by zero and ten, on the standard deviation of the study-level random effects,  $\sigma_{\lambda}$ .<sup>3</sup> In all cases, the alternative prior assumptions had negligible impact on the values of the posterior estimates except for the fact that, as expected, use of the vague prior for the variance of the inter-study heterogeneity resulted in wider posterior uncertainty intervals.<sup>1</sup> Additional sensitivity analyses were conducted to assess the potential impact of study design on the meta-analysis results. In this assessment, a term was added to the model for the log OR in each study indicating if that study was conducted under either a case-control or cohort design. For all assumptions on the prior distributions for  $\mu$  and  $\lambda_i$ , the posterior estimates indicated no impact due to study design. In addition, the sensitivity of the meta-analysis results were assessed by limiting the assessment to only those study populations that included a mix of subjects with type 1 and type 2 diabetes and by limiting the analysis to studies published between 2000 and 2012. In both cases, there were no meaningful differences in the estimated posterior OR as compared to the primary results presented here.

As an illustration of meta-analysis results, Appendix Figure 2 shows the estimated posterior distribution for the OR relating PGDM and CHD which is summarized using the median value of 3.8 with a 95% Credible Interval (CrI) of [3.0, 4.9]. In addition, for all CHDs, the standard deviation of the study-level random effects had a posterior median of 0.28 with a 95% CrI of [0.09, 0.62] indicating high likelihood of meaningful heterogeneity among the selected studies.

## **Population Attributable fraction and estimated preventable number of congenital heart defects with complete blood glucose control prior to pregnancy**

A Monte Carlo simulation approach to incorporate the various sources of uncertainty in the inputs to the models used to predict the population attributable fraction (PAF) and preventable number of outcomes was used. This incorporated uncertainty included the sampling variability in the estimates of diabetes prevalence and the number of live births affected with each CHD outcome and the uncertainty associated with the posterior estimates of the summary odds ratios. For the PGDM prevalence and the estimated number of live births with each CHD outcome, uncertainty concerning the true values of these parameters was modeled using a Normal distribution with means and standard deviations set to reported values.<sup>4,5</sup> Uncertainty concerning the true value of the odds ratio relating diabetes and CHD risk was modeled based on the 10,000 samples from the posterior distribution developed in the meta-analysis. Ten thousand iterations in the Monte Carlo simulation process in which random samples for the possible values for diabetes prevalence and the number of live births with each CHD outcome were matched with one of the posterior samples for the odds ratio were used. This approach produced 10,000 possible values for the PAF and the preventable number of CHD cases. These estimates were summarized using the median of the 10,000 Monte Carlo samples and a 95% uncertainty interval (UI) defined as the 2.5<sup>th</sup> and 97.5<sup>th</sup> percentile of the distribution of the 10,000 possible values. Note that uncertainty in the modeled PAF and prevented number of cases is summarized using uncertainty intervals as opposed to credible intervals as were used in summarizing the meta-analysis results. This differentiation reflects the use of the Monte Carlo sampling in developing the PAF and prevented cases estimates as opposed to a fully Bayesian estimation. All estimates of preventable number of CHD live births were rounded to the nearest multiple of 5 to avoid

over-stating the precision of these estimates. The Monte Carlo simulations were implemented using SAS 9.3 (SAS Institute, Cary, NC).

## **References**

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**Appendix Figure 2.** Posterior distribution for the odds ratio relating pregestational diabetes and total congenital heart defects

