Maternal Diabetes, Birth weight, and Infant Risk of Congenital Heart Defects in Norway, 1994-2009

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Précis

A threefold increased risk of congenital heart defects in offspring of women with pregestational diabetes has remained unchanged since the 1990s.

Abstract

Objective: To investigate the association between pregestational or gestational diabetes and infant risk of congenital heart defects, and the association between large for gestational age birthweight and risk of cardiac defects in offspring of diabetic women..

Methods: Information on pregestational diabetes, gestational diabetes, cardiac defects, and birth weight among all births in Norway 1994-2009 was ascertained from the Medical Birth Registry of Norway, national health registries, and the Cardiovascular Disease in Norway project. The relative risk (aRR) compared offspring risk of cardiac defects for maternal diabetes with offspring risk in non-diabetic mothers, adjusted for year of birth, maternal age, and parity.

Results: Among 914,427 births (live births, stillbirths, terminated pregnancies), 5,618 (0.61%) were complicated by maternal pregestational diabetes and 9,726 (1.06%) by gestational diabetes. Congenital heart defects were identified in 10,575 offspring. The prevalence of cardiac defects differed between groups: 344/10,000 births to women with pregestational diabetes,172/10,000 to women with gestational diabetes and 114/10,000 in women without diabetes (aRRs 2.92 (95% confidence interval (CI) 2.54-3.36) and 1.47 (95% CI 1.26-1.71)). During the study period, the aRRs for congenital heart defects did not change. The risk of cardiac defects in infants very large for gestational age (birth weight >3 SD above mean) was compared to infants with birth weight appropriate for gestational age: For pregestational diabetes the prevalences of cardiac defects were 561 versus 248 per 10,000 births (aRR 2.23; 95% CI 1.39-3.59), and for gestational diabetes 388 versus 132 per 10,000 (aRR 2.73; 95% CI 1.53-4.85).

Conclusions: The increased risk of having a child with congenital heart defect has not changed for diabetic women in Norway since 1994. Among women with pregestational or gestational diabetes,large for gestational age birthweight was associated with 2-3 fold increased risk of cardiac defects compared to infants with normal birth weight.

Introduction

Affecting 5-13 per 1000 births worldwide(1, 2), congenital heart defects (CHD) are the most common birth defect(3, 4). The etiology seems multifactorial, with both genetic and environmental factors(5, 6). Increased risk for CHD is reported in offspring of women with pregestational diabetes(7-9), and gestational diabetes may also increase the risk of CHD, although to a lesser extent(10). The CHD risk has been shown to correlate with maternal glucose levels in early pregnancy, with higher risk in births after pregnancies with poor early glycemic control(11). Whether modern perinatal care for women with diabetes has changed the risk of congenital defects in their children is unclear.

Birth weight large for gestational age is more prevalent in offspring of diabetic women with poor glycemic control(12, 13). Assuming hyperglycemia is important in the etiology of CHD in offspring of diabetic women, we hypothesized that infants large for gestational age would have higher CHD risk as compared to normal-weight infants of diabetic mothers.

National registries and databases have facilitated population-based studies of CHD in Norway(2). Our aims were to study time trends for CHD risk in offspring of mothers with diabetes compared to the CHD risk in non-diabetic mothers, to describe whether pregestational and gestational diabetes affect the risk of all types of cardiac defects, and to investigate the association of excessive fetal growth and CHD risk in offspring of diabetic mothers.

Materials and Methods

The Norwegian Population Register contains demographic data and vital statistics on all residents and assigns a unique personal identification number to every resident in Norway enabling linkage of data between national registries and other data sources.

The Medical Birth Registry of Norway has recorded information on all births since 1967 (live births and stillbirths from 16th week of gestation; from 1999 including all pregnancies terminated because of fetal anomalies from the 12th week of gestation.)(14, 15). Information on the mother´s health, the course of the pregnancy, and the health of the child is entered by midwives and physicians attending the mother and child at delivery and the following days. The diabetes diagnoses in the Medical Birth Registry have previously been validated by comparing the variables with information in the Norwegian Diabetes Registry(7) and medical records(16) with high sensitivity (pregestational diabetes 97% before 1999, 94% in 2000-2004) and a high positive predictive value (80% for pregestational diabetes, 89% for gestational diabetes in year 1998). Information in the Medical Birth Registry was compared

with the Norwegian Mother and Child Study(17) with very good agreement in the two sources for birth weight, parity, and prematurity. Using the Mother and Child study as gold standard, the sensitivity for CHD in the Medical Birth Registry was 69%. In our study, 15.2% of CHD diagnoses were retrieved from the Medical Birth Registry, the majority of these were pregnancies terminated because of a fetal abnormality.

Oslo University Hospital's clinical database for children with heart disease contains recordings of all children with a heart defect treated or examined at the hospital since 1992(18), serving as an equivalent to the medical records. Senior pediatric cardiologists have entered and updated the codes for cardiac defects and procedures in this database at each hospital stay or outpatient consultation. The database is therefore considered the gold standard in our data set. The diagnoses of this database were coded in the detailed van Mierop system, which increased the specificity of the diagnoses. Oslo University Hospital cared for 80% of the child heart surgeries in Norway until 2004, and essentially all thereafter. In the present study, 47% of all CHD diagnoses and 75% of severe CHD diagnoses were collected from Oslo University Hospital's clinical database for children with heart disease.

The multipurpose research project Cardiovascular Disease in Norway established in collaboration between the University of Bergen and the Norwegian Knowledge Centre for the Health Services provides information on CHD retrieved from the electronic Patient Administrative Systems of all hospitals in Norway, 1994-2009(19). Information about discharge diagnoses, surgical procedures, and date of discharge was included in the database. Among infants with CHD registered in several sources the cardiac phenotypes retrieved from the Patient Administrative Systems were compared with the phenotypes retrieved from Oslo University Hospital's clinical database with 78% agreement, and with phenotypes from the Medical Birth Registry with 86% agreement. We used the information from this database in 36.1% of our cases.

The Cause of Death Registry contains information about the causes of death recorded on the death certificate. Only 0.7% of our diagnoses were retrieved from the Cause of Death Registry. Statistics Norway provided demographic data for all residents(21). The study was approved by the Regional Scientific Ethics Committee (036.09).

CHD diagnoses among all live births, stillbirths and pregnancies terminated due to fetal anomalies in Norway, 1994-2009, were ascertained from four national health registries and clinical databases as described in our previous article(2), and classified into cardiac phenotypes according to Botto et al.(1) and Øyen et al(22) as showed in Table 1. Atrial

septum defects (ASD), patent ductus arteriosus (PDA), and pulmonary stenosis were recorded at postnatal age > 6 weeks or with surgical correction. Severe CHD was defined as heterotaxia, conotruncal defects, atrioventricular septal defect, anomalous pulmonary venous return, left ventricle outflow tract obstruction, right ventricle outflow tract obstruction (except valvular pulmonary stenosis), or other complex defects.

The diagnostic criteria for diabetes were revised by WHO in 1998, lowering the cut-off level for fasting plasma glucose from ≥7.8 mmol/l (140 mg/dl) to ≥7.0 mmol/l (126 mg/dl)(23), while the cut-off levels for random glucose and glucose load test (both 11.1 mmol/l (200 mg/dl)) were unchanged. The criteria for gestational diabetes were extended to include impaired glucose tolerance with plasma glucose ≥7.8 mmol/l after a glucose load test, or fasting glucose level ≥7.0 mmol/l.

Diagnoses of maternal pregestational diabetes and gestational diabetes were ascertained from the Medical Birth Registry, and from the Cardiovascular Disease in Norway database. Until 1998, diabetes mellitus was registered in the Medical Birth Registry's standard notification form by two check boxes, for pregestational diabetes or gestational diabetes. In 1999, the notification form was revised, with three check boxes; for pregestational type 1 diabetes, pregestational type 2 diabetes, and gestational diabetes. In addition, maternal diabetes has been notified in the maternal health text field using the International Classification of Diseases (ICD) codes for type 1 diabetes [ICD-10 codes E10.0-E10.9, O24.0; ICD-9 code 250.1], type 2 diabetes [ICD-10: E11.0-E11.9, O24.1; ICD-9: 250.2], gestational diabetes [ICD-10: O24.4, O24.9; ICD-9: 648.8], and unspecified diabetes [ICD-10: E13.0-E13.9, E14.0-E14.9, O24.3; ICD-9: 250.0, 250.3-250.9]. Any antidiabetic medication during pregnancy was registered by a yes–no variable.

We also used information on maternal diabetes from the Cardiovascular Disease in Norway database, to refine the information on time of onset (before pregnancy or during pregnancy) and type of diabetes. If unspecified diabetes had been registered before estimated time of gestation (date of birth minus gestational age) we assigned the condition as pregestational diabetes. Diabetes registered for the first time during pregnancy was classified as gestational diabetes. Women with diagnoses of both type 1 diabetes and type 2 diabetes were classified as having unspecified pregestational diabetes. The Cardiovascular Disease in Norway database identified additional 171 births with maternal pregestational diabetes and 1772 with gestational diabetes.

We excluded women with antidiabetic medication during pregnancy without a registered diabetes diagnosis as this could represent use in women with polycystic ovary syndrome.

We used offspring birth weight adjusted for gestational age as a proxy for maternal hyperglycemia during pregnancy(12, 13), since information on glycemic control during pregnancy by glycosylated hemoglobin or fasting glucose measurements was not available in the current study. Birth weight and gestational age of infants, 20 to 44 weeks of gestational age, registered in the Medical Birth Registry were compared to a Norwegian standard of birth weight by gestational age(24). Gestational age was estimated by information of the last menstrual period, or by ultrasound measurements if available. Infants with birth weight < -1.28 standard deviations (SD) from the standard mean (< 10^{th} percentile) were considered small for gestational age (SGA); infants with birth weight -1.28 SD to +1.28 SD were classified as appropriate for gestational age (AGA); and infants with birth weight > +1.28 SD (> 90^{th} percentile) large for gestational age (LGA). LGA was further classified into LGA1 (birth weight +1.28 to +2.0 SD), LGA2 (birth weight +2.0 to +3.0 SD), and LGA3 (birth weight >+3.0 SD).

All births registered in The Medical Birth Registry from 1994 through 2009 (954,413 individuals) were followed until 31st December 2009 for information on CHD registered in any of our 4 data sources. We excluded 36,378 births (3.8% of data set) due to fetal chromosomal aberrations and relevant genetic disorders (n=3,103), and multiple births (n=33,380). Chromosomal aberrations or genetic disorders associated with CHD were defined by ICD codes [8^{th} revision 759.3-759.5, 9^{th} revision 758.0-759.9, 10^{th} revision D82.1, Q87.1, Q87.2, Q90.0-Q99.9], and van Mierop codes [8000-8004, 8009-8025, 8072]. After excluding 325 infants of mothers using antidiabetic medication without a registered diabetes diagnosis and 3,283 births with missing information of maternal health, 914,427 births were left for analysis.

For birth weight analysis we excluded 34,862 infants with missing information on birth weight, gestational age or both, 1,578 with gestational age <20 weeks, 328 with recorded gestational age >44 weeks, and 844 registered with birth weight z-score >+5.0 SD

above the standard mean, leaving 876,815 individuals for analysis. Birth weight was missing for all terminated pregnancies.

Relative risks (RR) were calculated as the risk of CHD in the exposed group (offspring of mothers with pregestational diabetes or gestational diabetes) divided by the CHD risk in the non-exposed group (offspring of women without diabetes). RR estimates with 95% confidence intervals (CI) were adjusted for year of birth, maternal age (<20, 20-24, 25-29, 30-34 and >34 years), and parity (0, 1 or ≥2 previous pregnancies) by binomial log-linear regression. In initial analyses maternal education, marital status, and family income were considered as possible confounders; however, these variables did not change the measures of association between maternal diabetes and offspring CHD, and were not included in the final model.

RRs of CHD for maternal diabetes type 1 vs. type 2 were compared using the suest (seemingly unrelated estimation) command. In the Medical Birth Registry, pregestational diabetes was mostly registered as unspecified before 1999, and analyses of type 1 and type 2 diabetes were therefore restricted to 1999-2009. Time trends for CHD risk by maternal diabetes and year of birth were analyzed by Mantel-Haenszel homogeneity test. All analyses were performed using Stata version 14 (STATA Corp., Texas, USA). The population attributable fraction was calculated by the formula $P_{pop}x(RR-1) / (P_{pop}x(RR-1)+1)$, where P_{pop} is the proportion of exposed (offspring of mothers with pregestational diabetes or gestational diabetes) in the birth cohort.

Results

Among 914,427 singleton births (live births, stillbirths, termination of pregnancy for fetal anomaly) without chromosomal aberrations or genetic disorders, 10,575 received a diagnosis of CHD (prevalence 116 per 10,000 births). Pregestational diabetes (type 1, type 2, unspecified) was diagnosed in 5,618 births (61 per 10,000), and gestational diabetes in 9,726 births (106 per 10,000). Diabetes was more frequent in mothers of older age and with previous births (Table 2). While the prevalence of diabetes type 1 increased slightly from 42.2 per 10,000 in 1999 to 47.3 per 10,000 in 2009, type 2 diabetes more than doubled in the same period from 10.6 to 27.1 per 10,000, and gestational diabetes increased from 72.2 per 10,000 in 1994, to 84.9 per 10,000 in 1999, and 165.5 per 10,000 in 2009 (Figure 1).

Compared to offspring of women without diabetes, infants of women with pregestational diabetes had almost three times the risk of any CHD and more than tripled risk

for severe CHD (Table 3); the prevalences of CHD were 344 per 10,000 births and of severe CHD 78 per 10,000 births compared to 114 and 24 per 10,000 births of non-diabetic mothers. There was no significant difference in RR for any CHD between type 1 and type 2 diabetes (aRR 2.95 (95% CI 2.44, 3.56) and aRR 2.53 (95% CI 1.86, 3.43), p=0.40), or for severe CHD (aRR 3.00 (95% CI 1.96, 4.61) and aRR 4.62 (95% CI 2.74, 7.80), p=0.21). Infants whose mothers had gestational diabetes had a 47% risk increase for any CHD (prevalence 172 per 10,000) as compared to offspring of non-diabetic mothers. The aRRs for CHD phenotypes ranged from 2.17-6.60 in pregnancies with pregestational diabetes and 1.10-2.34 in pregnancies with gestational maternal diabetes (not reporting aRR for anomalous pulmonary venous return with 1 exposed case).

In Figure 2, aRRs for CHD are shown by year of birth for maternal pregestational diabetes and gestational diabetes. In the study period, there was no significant change in aRR for CHD in infants whose mothers had pregestational diabetes (p=0.36) or gestational diabetes (p=0.29) as compared to infant risk of CHD for non-diabetic mothers. The proportion of CHD in the population attributable to pregestational diabetes was 1.1% (0.9% in 1994-1998, 1.2% in 1999-2003, and 1.2% in 2004-2009), and for severe CHD 1.4% (1.3%, 1.8%, and 1.7% in the three time periods).

Among births with maternal pregestational diabetes or gestational diabetes, we investigated the association between birth weight for gestational age and CHD risk in offspring, using birth weight appropriate for gestational age (AGA) as the reference in each group (Table 4). For increasing birth weight for gestational age, the risks of CHD increased for pregestational diabetes (p trend 0.001) and for gestational diabetes (p trend <0.001). Among offspring of women with pregestational diabetes, the CHD prevalence for the very large infants (birth weight >+3 SD more than the Norwegian mean) was 561 per 10,000 births, compared to the prevalence for AGA infants of 248 per 10,000 births; the adjusted RR was 2.23 (95% CI 1.39, 3.59). For gestational diabetes the prevalences of CHD were 388 and 132 per 10,000 for infants very large and AGA, respectively; aRR.2.73 (95% CI 1.53, 4.85). There was no association between low birth weight for gestational age and risk of CHD, as compared to AGA infants in the pregestational diabetes group (aRR 1.27(95% CI 0.64, 2.50)) or the group with gestational diabetes (aRR 1.24 (95% CI 0.61, 2.55)).

Among infants of non-diabetic women, LGA >+3 SD was also associated with increased risk for CHD as compared to AGA children, with prevalences of CHD 166 and 96 per 10,000 births; aRR 1.75 (95% CI 1.38, 2.22). We therefore compared CHD risk in offspring of diabetic women with CHD risk in offspring of non-diabetic women within

categories of birth weight. The risk for CHD in offspring of women with pregestational diabetes compared to non-diabetic pregnancies was similar in children AGA and in children LGA >+3SD, with aRR 2.46 and aRR 3.01, respectively (p=0.28), while the aRRs of CHD in offspring of women with gestational diabetes compared to non-diabetic pregnancies were 1.35 in children AGA and aRR 2.27 in children LGA >+3SD (p=0.09).

Discussion

In this nationwide study of 914,427 births and 10,575 children with CHD, maternal pregestational diabetes was diagnosed in 61 per 10,000 births, and gestational diabetes in 106 per 10,000 births. While the prevalence of maternal diabetes type 1 was relatively stable over time, the prevalence of type 2 diabetes and gestational diabetes doubled from 1999 to 2009. Compared to offspring of non-diabetic women, there was a 3-fold higher risk of CHD in offspring of women with pregestational diabetes, and a 47% risk increase if the mother had gestational diabetes, which did not change during the study period. In offspring of women with diabetes, large for gestational age was associated with additional increased risk for CHD.

Similar to previous studies(25-28) we found an increasing prevalence of pregestational diabetes, especially type 2 diabetes, over time. The association of pregestational diabetes with a threefold increased infant risk of cardiac defects is similar to findings in a cohort study from England, Wales and Northern Ireland 2002-2003(9), a population-based Canadian study of children born 2002-2010(29), an American multicenter case-control study with children born 1997-2003(26), and a recent population-based Danish cohort-study 1978-2011(28). The two latter studies also reported a 30-60% increased risk for CHD in pregnancies with gestational diabetes, which is comparable to a 47% increase of CHD in the present study.

The increase in relative risk of CHD with increasing birth weight by gestational age in offspring of mothers with either pregestational or gestational diabetes found in the current study suggests a role for maternal glucose in the etiology of fetal cardiac anomalies. First-trimester glycemic control measured by glycosolated hemoglobin in women with pregestational diabetes correlates with birth weight of the child(12). Although birth weight may be influenced by hyperglycemia in third trimester of the pregnancy and most heart defects develop during early first trimester, high relative birth weight could be an indicator of hyperglycemia in early pregnancy leading to fetal hyperinsulinemia and high glucose flux from the mother to the fetus through the placenta later in pregnancy(30). Surprisingly, the relative risk of CHD was also increased in LGA births of women without a diagnosis of diabetes. This could be caused by unrecognized maternal diabetes or by impaired maternal

glucose tolerance not meeting the criteria for diabetes, or by high sugar intake resulting in hyperglycemic spikes during a vulnerable period of fetal cardiac development. Impaired glucose tolerance before pregnancy could also explain the increased CHD risk in offspring of women developing gestational diabetes. A periconceptional sugar rich diet has been associated with an increased risk for several birth defects in offspring of non-diabetic women in recent studies(31). We did not have information on maternal weight or diet during pregnancy, however, maternal overweight is probably a weak confounder, since infant risk of CHD is only increased by 17-30%(32).

The major strength of this study was the cohort design with linkage of data from comprehensive national registries, and minimal loss to follow-up. Detailed cardiac diagnoses ascertained from 4 administrative and clinical registries enabled a virtually complete registration of CHD, including cardiac defects in terminated pregnancies(2). A possible weakness may be related to the exposure and outcome variables, as medical records were not accessible to us. Maternal diabetes increases the risk of preterm birth and perinatal morbidity(33), leading to more frequent use of cardiac echo in the newborn. This could have introduced an overestimation of CHD risk in children of diabetic women. However, the relative risks of septal defects and severe CHD for maternal diabetes were similar, so detection bias was less likely. In addition, we did not include untreated ASD and PDA reported during the first 6 weeks postpartum as CHD. The diagnostic changes of diabetes as defined by WHO from 1998 had no clear influence on the time trend of maternal diabetes. Improved diabetes screening in women could have contributed to the increasing prevalences of pregestational diabetes and gestational diabetes. Models for estimation of relative risk of rare cardiac subtypes could be overfitted, although adjustment did not change the RRs much.

We did not find any significant change in the increased risk for CHD in children of women with pregestational diabetes and gestational diabetes during the period 1994-2009. Very high birth weight for gestational age represents a risk marker for CHD in infants of diabetic women, with 2-3 times increased risk compared to AGA children, supporting an association between maternal hyperglycemia and offspring CHD risk. The opportunities to reduce CHD risk could be improved glucose control in diabetic women when planning a pregnancy and during early pregnancy, and weight control in fertile women in order to prevent development of type 2 diabetes and gestational diabetes.

References

1.Botto LD, Lin AE, Riehle-Colarusso T, Malik S, Correa A. Seeking causes: Classifying and evaluating congenital heart defects in etiologic studies. Birth Defects Res A Clin Mol Teratol 2007 Oct;79(10):714-27.
2.Leirgul E, Fomina T, Brodwall K, Greve G, Holmstrom H, Vollset SE, et al. Birth prevalence of congenital heart defects in Norway 1994-2009-A nationwide study. Am Heart J 2014 Dec;168(6):956-64.
3.van der Linde D, Konings EE, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJ, et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol 2011 Nov 15;58(21):2241-7.
4.EUROCAT Access Prevalence Tables. 2008-2012 [cited 2016; Available from: http://www.eurocat-network.eu/AccessPrevalenceData/PrevalenceTables
5.Gelb BD, Chung WK. Complex genetics and the etiology of human congenital heart disease. Cold Spring Harb Perspect Med 2014 Jul;4(7):a013953.
6.Jenkins KJ, Correa A, Feinstein JA, Botto L, Britt AE, Daniels SR, et al. Noninherited risk factors and congenital cardiovascular defects: current knowledge: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young: endorsed by the American Academy of Pediatrics. Circulation 2007 Jun 12;115(23):2995-3014.
7.Eidem I, Stene LC, Henriksen T, Hanssen KF, Vangen S, Vollset SE, et al. Congenital anomalies in newborns of women with type 1 diabetes: nationwide population-based study in Norway, 1999-2004. Acta Obstet Gynecol Scand 2010 Nov;89(11):1403-11.
8.Liu S, Joseph KS, Lisonkova S, Rouleau J, Van den Hof M, Sauve R, et al. Association between maternal chronic conditions and congenital heart defects: a population-based cohort study. Circulation 2013 Aug 6;128(6):583-9.
9.Macintosh MC, Fleming KM, Bailey JA, Doyle P, Modder J, Acolet D, et al. Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study. BMJ 2006 Jul 22;333(7560):177.
10.Balsells M, Garcia-Patterson A, Gich I, Corcoy R. Major congenital malformations in women with gestational diabetes mellitus: a systematic review and meta-analysis. Diabetes Metab Res Rev 2012 Mar;28(3):252-7.
11.Starikov R, Bohrer J, Goh W, Kuwahara M, Chien EK, Lopes V, et al. Hemoglobin A1c in pregestational diabetic gravidas and the risk of congenital heart disease in the fetus. Pediatr Cardiol 2013 Oct;34(7):1716-22.
12.Riskin-Mashiah S, Younes G, Damti A, Auslender R. First-trimester fasting hyperglycemia and adverse pregnancy outcomes. Diabetes Care 2009 Sep;32(9):1639-43.
13.Leipold H, Worda C, Gruber CJ, Kautzky-Willer A, Husslein PW, Bancher-Todesca D. Large-for-gestational-age newborns in women with insulin-treated gestational diabetes under strict metabolic control. Wien Klin Wochenschr 2005 Aug;117(15-16):521-5.
14.Folkehelseinstituttet. Annual Report 2001-2002, Medical Birth Registry of Norway. [cited 2004; Available from: http://www.fhi.no/dav/f1065301e2.pdf
15.Irgens LM. The Medical Birth Registry of Norway. Epidemiological research and surveillance throughout 30 years. Acta Obstet Gynecol Scand 2000 Jun;79(6):435-9.
16.Aamodt G, Stene LC, Njolstad PR, Sovik O, Joner G, Norwegian Childhood Diabetes Study G. Spatiotemporal trends and age-period-cohort modeling of the incidence of type 1 diabetes among children aged <15 years in Norway 1973-1982 and 1989-2003. Diabetes Care 2007 Apr;30(4):884-9.
17.Folkehelseinstituttet. Does the information in The Norwegian Morther and Child study and The Medical Birth Registry correlate for variables that are mapped in both data sources? 2009.
18.Hagemo PS. BERTE--a database for children with congenital heart defects. Stud Health Technol Inform 1994;14:98-101.

19.Sulo G IJ, Vollset SE, Nygård O, Øyen N, Tell GS. Cardiovascular disease and diabetes mellitus in Norway during 1994-2009 CVDNOR – a nationwide research project. Norwegian journal of epidemiology 2013;23(1):101-7.
21.Statistics Norway. [cited; Available from: http://www.ssb.no/en/forside
22.Øyen N, Poulsen G, Boyd HA, Wohlfahrt J, Jensen PK, Melbye M. National time trends in congenital heart defects, Denmark, 1977-2005. Am Heart J 2009 Mar;157(3):467-73 e1.
23.Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998 Jul;15(7):539-53.
24.Skjaerven R, Gjessing HK, Bakketeig LS. Birthweight by gestational age in Norway. Acta Obstet Gynecol Scand 2000 Jun;79(6):440-9.
25.Bell R, Bailey K, Cresswell T, Hawthorne G, Critchley J, Lewis-Barned N. Trends in prevalence and outcomes of pregnancy in women with pre-existing type I and type II diabetes. BJOG 2008 Mar;115(4):445-52.
26.Correa A, Gilboa SM, Besser LM, Botto LD, Moore CA, Hobbs CA, et al. Diabetes mellitus and birth defects. Am J Obstet Gynecol 2008 Sep;199(3):237 e1-9.
27.Feig DS, Hwee J, Shah BR, Booth GL, Bierman AS, Lipscombe LL. Trends in incidence of diabetes in pregnancy and serious perinatal outcomes: a large, population-based study in Ontario, Canada, 1996-2010. Diabetes Care 2014 Jun;37(6):1590-6.
28.Oyen N, Diaz LJ, Leirgul E, Boyd HA, Priest J, Mathiesen ER, et al. Prepregnancy Diabetes and Offspring Risk of Congenital Heart Disease: A Nationwide Cohort Study. Circulation 2016 Jun 7;133(23):2243-53.
29.Moazzen H, Lu X, Liu M, Feng Q. Pregestational Diabetes Induces Fetal Coronary Artery Malformation via Reactive Oxygen Species Signaling. Diabetes 2014 Nov 24.
30.Desoye G, Nolan CJ. The fetal glucose steal: an underappreciated phenomenon in diabetic pregnancy. Diabetologia 2016 Jun;59(6):1089-94.
31.Parker SE, Werler MM, Shaw GM, Anderka M, Yazdy MM, National Birth Defects Prevention S. Dietary glycemic index and the risk of birth defects. Am J Epidemiol 2012 Dec 15;176(12):1110-20.
32.Stothard KJ, Tennant PW, Bell R, Rankin J. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. JAMA 2009 Feb 11;301(6):636-50.
33.Gabbe SG, Graves CR. Management of diabetes mellitus complicating pregnancy. Obstet Gynecol 2003 Oct;102(4):857-68.

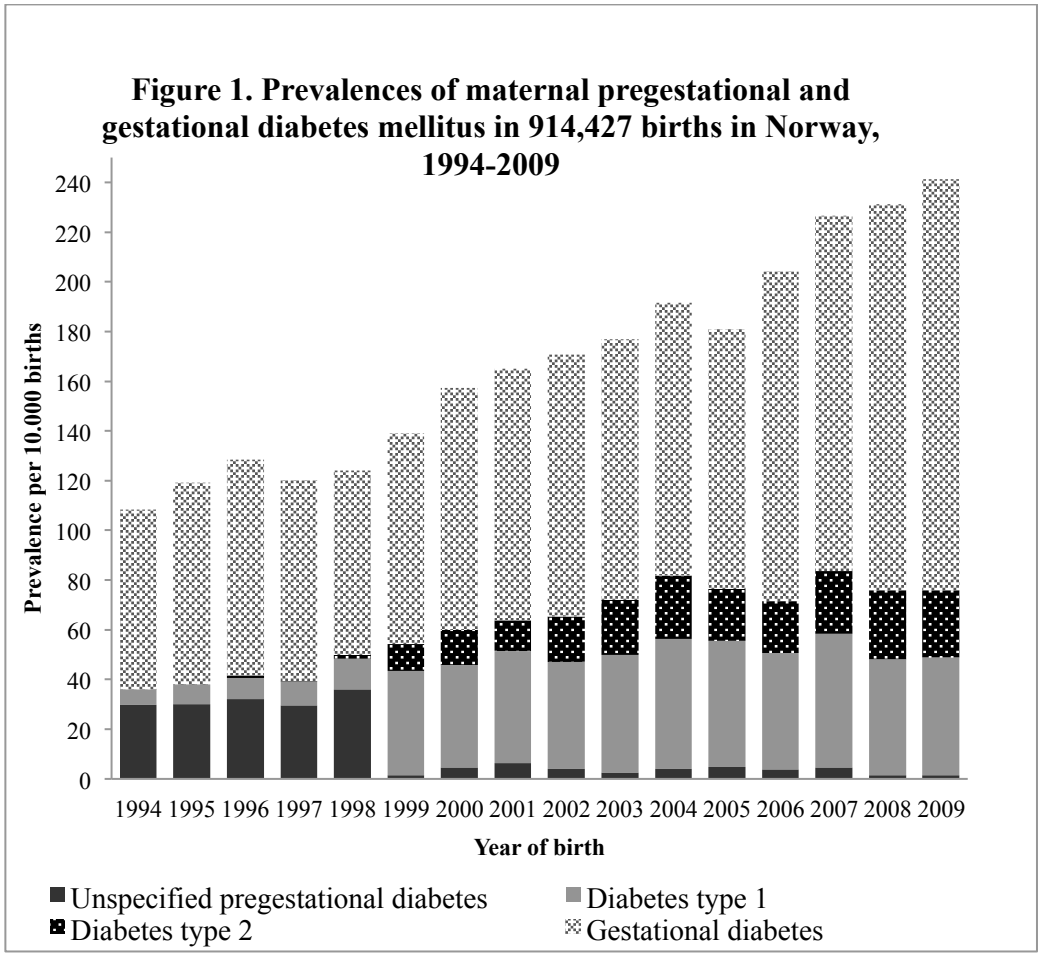

Figure 1. Prevalence of maternal diabetes mellitus by year of birth in 914,427 live births, stillbirths, and terminated pregnancies registered in the Medical Birth Registry of Norway, 1994-2009, excluding multiple births and births with chromosomal aberrations or genetic disorders. Diabetes type 1 and type 2 were registered as unspecific before 1999.

Figure 2. Relative risk for CHD by maternal pregestational and gestational diabetes mellitus in 914,427 births in Norway, 1994-2009

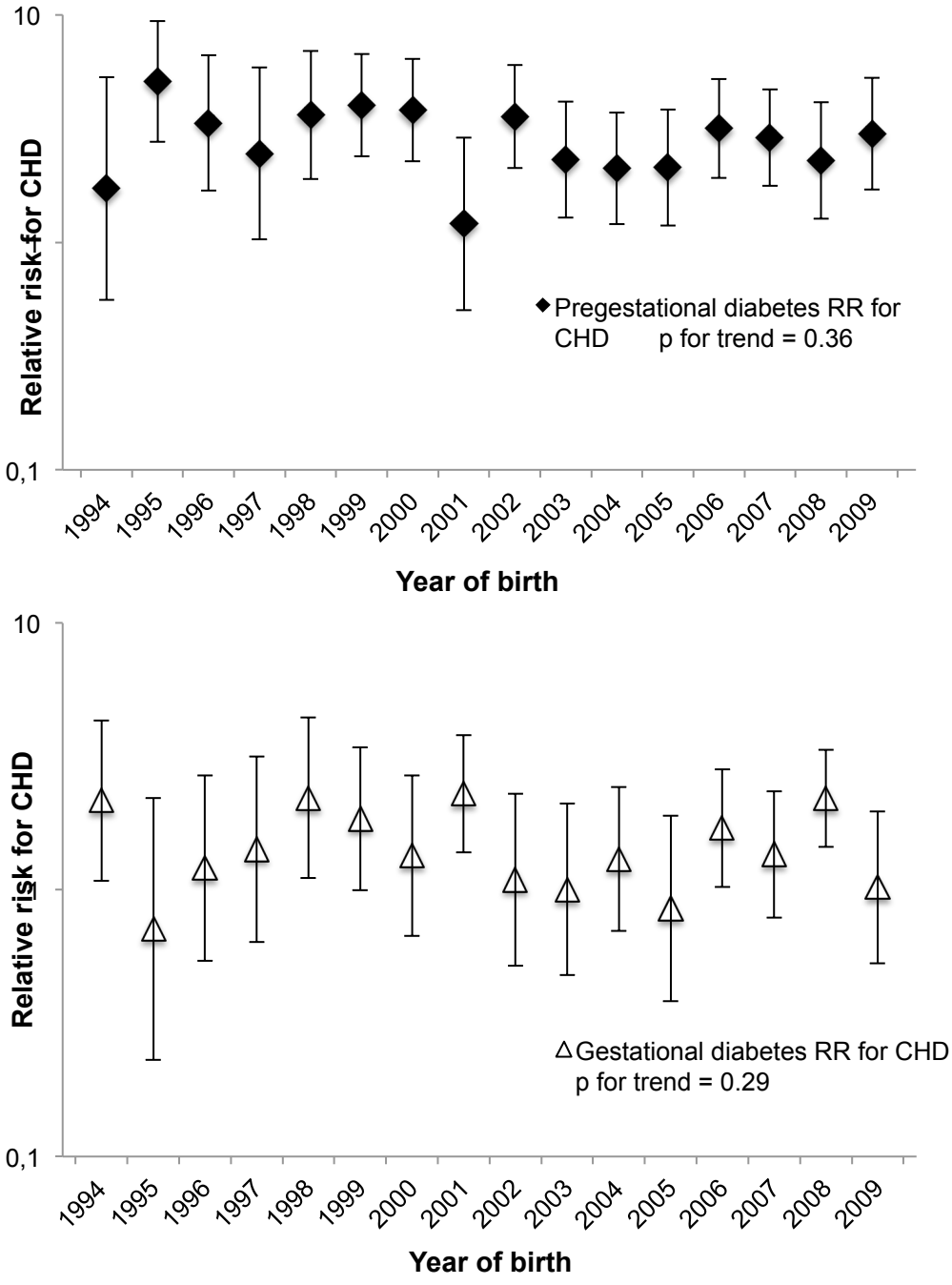

Figure 2. Adjusted relative risks of CHD (not included preterm PDA) with 95% confidence interval by maternal pregestational diabetes, (squares) and gestational diabetes (triangles,) and by year of birth, in 914,427 live births, stillbirths, and terminated pregnancies registered in the Medical Birth Registry of Norway, 1994-2009, excluding multiple births and births with chromosomal aberrations or genetic disorders. Relative risks are shown with logarithmic scale

Table 1. The CHD classification system	
Main groups	**Detailed cardiac phenotypes**
Heterotaxia	Situs inversus Isomerism Dextrocardia or levocardia with other CHD
Conotruncal defects	Truncus arteriosus Transposition of the great arteries (TGA) Tetralogy of Fallot (ToF) Pulmonary atresia with ventricular septal defect (ToF type) Double outlet right ventricle (DORV) Conoventricular septal defect Interrupted aortic arch type B or C Supravalvular aortic stenosis Aortopulmonary window
Atrioventricular septal defects	Atrioventricular septal defects
Anomalous pulmonary venous return (APVR)	Total anomalous pulmonary venous return Partial anomalous pulmonary venous return
Left Ventricular Outflow Tract Obstructions (LVOTO)	Hypoplastic left heart syndrome (HLHS) Mitral valve stenosis Coarctation of the aorta (CoA) Interrupted aortic arch type A Valvular aortic stenosis
Right Ventricular Outflow Tract Obstructions (RVOTO)	Tricuspid atresia / stenosis Hypoplastic right heart syndrome (HRHS) Ebstein anomaly Valvular pulmonary atresia (not ToF anatomy) Arterial pulmonary atresia Valvular pulmonary stenosis
Septal defects	Atrial septal defects (ASD) Ventricular septal defects (VSD) ASD + VSD Otherwise specified or not specified septal defects
Other complex cardiac defects	Congenitally corrected transposition of the great arteries (ccTGA) Single ventricle (non-HLHS, non-HRHS) Double inlet left ventricle (DOLV) Absent pulmonary valve
Other cardiac defects	Infundibular pulmonary stenosis Pulmonary insufficiency Subaortic stenosis Aortic insufficiency Mitral insufficiency Pulmonary arterial stenosis Cor triatriatum Coronary malformations Other specified malformation of the heart Unspecified malformations of the heart, great arteries, great veins
Isolated Patent ductus arteriosus (PDA)	Isolated patent ductus arteriosus (PDA)
Severe CHD: Heterotaxia, conotruncal defects, atrioventricular septal defect, APVR, LVOTO, RVOTO (except valvular pulmonary stenosis), and other complex defects.	

Table 2. Birth characteristics according to maternal diabetes in 914,427 births in Norway 1994-2009*

	Non-diabetes 899,083	Pregestational diabetes 5,618 (61 per 10,000 births)		Gestational diabetes mellitus 9,726 (106 per 10,000 births)	
Characteristics	No.	No.	prevalence†	No.	prevalence†
Year of birth					
1994	57919	211	36	423	72
1995	57943	223	38	476	81
1996	58490	246	42	515	87
1997	57246	228	39	469	81
1998	55911	283	50	419	74
1999	56807	312	54	489	85
2000	56652	345	60	560	97
2001	54204	352	64	558	101
2002	53012	353	65	567	105
2003	54051	397	72	577	105
2004	54442	454	82	610	110
2005	54378	423	76	579	105
2006	55942	409	72	757	133
2007	55666	477	84	813	143
2008	57632	448	76	917	155
2009	58788	457	76	997	165
Maternal age, years					
<20	23504	99	42	111	47
20-24	146873	704	47	1029	69
25-29	308981	1837	59	2664	85
30-34	283447	1807	63	3309	115
>34	117032	951	79	2080	173
Parity					
0	367904	2190	59	3442	92
1	320986	2026	62	3352	103
≥2	210193	1402	65	2932	137
Birth weight by gestational age					
SGA	73199	282	38	498	67
AGA	694484	3085	44	6372	91
LGA1 (+1.28- +2.0 SD)	65918	876	129	1306	192
LGA2(+2.0 - +3.0 SD)	24060	762	297	856	333
LGA3(+3.0- +5.0 SD)	4032	374	789	335	707
Missing data	36654	222	60	334	90

SGA small for gestational age (< -1.28 SD), AGA adequate for gestational age (-1.28 - +1.28 SD), LGA large for gestational age LGA1 (+1.28 - +2.0 SD), LGA2 (+2.0 - +3.0 SD), LGA3 (> +3.0 SD)

*Live births, stillbirths and terminated pregnancies, excluding multiple births and children with chromosomal or genetic disorders.

†Prevalence of diabetes mellitus per 10,000 births

Table 3. Relative risk (RR) of congenital heart defects by cardiac phenotype and maternal diabetes, pregestational and gestational diabetes mellitus, in 914,427 births in Norway, 1994-2009*

Heart defect phenotype	Births	Pregestational diabetes mellitus					Gestational diabetes mellitus				
	No.	No.	RR†	aRR‡	95% CI	p	No	RR†	aRR‡	95% CI	p
Any CHD	10575	193	3.02	2.92	(2.54-3.36)	<0.001	167	1.51	1.47	(1.26-1.71)	<0.001
CHD excl. preterm PDA	9732	170	2.90	2.81	(2.42-3.26)	<0.001	153	1.50	1.47	(1.25-1.72)	<0.001
Severe CHD	2210	44	3.36	3.34	(2.48-4.49)	<0.001	32	1.39	1.40	(0.98-1.98)	0.06
Heterotaxia	127	5	6.88	6.60	(2.69-16.17)	<0.001	3	2.34	2.25	(0.71-7.09)	0.17
Conotruncal defect	895	19	3.61	3.54	(2.25-5.57)	<0.001	15	1.62	1.59	(0.95-2.65)	0.08
AVSD	215	8	6.42	6.38	(3.15-12.94)	<0.001	3	1.37	1.41	(0.45-4.40)	0.56
APVR	97	1	1.71	1.73	(0.24-12.44)	0.58	0	1.00	1.00		
LVOTO	691	9	2.19	2.21	(1.14-4.26)	0.02	8	1.10	1.13	(0.56-2.27)	0.74
RVOTO	466	6	2.17	2.16	(0.97-4.83)	0.06	7	1.44	1.43	(0.68-3.02)	0.35
Septal defect, isolated	5276	88	2.79	2.65	(2.15-3.27)	<0.001	73	1.32	1.27	(1.01-1.60)	0.04
Isolated PDA	1787	41	3.90	3.72	(2.73-5.06)	<0.001	35	1.90	1.83	(1.31-2.55)	<0.001
At term gestation	944	18	3.25	3.19	(2.00-5.09)	<0.001	21	2.16	2.16	(1.40-3.33)	<0.001
Preterm gestation§	843	23	4.66	4.29	(2.83-6.49)	<0.001	14	1.61	1.48	(0.87-2.52)	0.14
Other CHD	1021	16	2.66	2.68	(1.63-4.38)	<0.001	23	2.18	2.15	(1.42-3.26)	<0.001

CHD congenital heart defect, AVSD atrioventricular septal defect, APVR anomalous pulmonary venous return, LVOTO left ventricular outflow tract obstructions, RVOTO right ventricular outflow tract obstructions, PDA patent ductus arteriosus,

* Live births, stillbirths, and terminated pregnancies registered in the Medical Birth Registry, after excluding multiple births and children with chromosomal or genetic disorders.

†Crude relative risk of CHD compared to children of non-diabetic women.

‡Relative risk adjusted for year of birth, mother´s age, parity.

§ Preterm gestation <37 weeks

Table 4. Congenital heart defects according to birth weight and maternal diabetes in 876,815 births in Norway, 1994-2009*

	Non-diabetes					Pregestational diabetes mellitus					Gestational diabetes mellitus				
	No.	CHD†	prev‡	aRR§	95 % CI	No.	CHD†	prev‡	aRR§	95 % CI	No.	CHD†	prev‡	aRR§	95 % CI
Overall	862065	8796	102			5382	157	292			9368	148	158		
SGA	73313	1169	159	1.68	(1.58-1.79)	282	9	319	1.27	(0.64-2.51)	498	8	161	1.24	(0.61-2.55)
AGA	694720	6656	96	1		3088	75	248	1		6373	84	132	1	
LGA1	65931	605	92	0.96	(0.88-1.04)	876	26	297	1.22	(0.78-1.89)	1306	22	168	1.23	(0.77-1.96)
LGA2	24065	299	124	1.30	(1.16-1.46)	762	26	341	1.42	(0.91-2.20)	856	21	245	1.72	(1.07-2.77)
LGA3	4036	67	166	1.75	(1.38-2.22)	374	21	561	2.23	(1.39-3.59)	335	13	388	2.73	(1.53-4.85)

SGA small for gestational age (< -1.28 SD), AGA adequate for gestational age (-1.28 - +1.28 SD), LGA large for gestational age LGA1 (+1.28 - +2.0 SD), LGA2 (+2.0 - +3.0 SD), LGA3 (> +3.0 SD)

SD standard deviation

* Live births and stillbirths with gestational week 20-44 registered in the Medical Birth Registry, after excluding multiple births, children with chromosomal disorders, and individuals with missing information on gestational age or birth weight

†CHD congenital heart defect excluding preterm PDA

‡Prevalence of CHD per 10,000

§Relative risk of CHD compared to AGA children, adjusted for mother´s age, parity, and year of birth