



Multisystem Morbidity and Mortality in Offspring of Women With Type 1 Diabetes (the EPICOM Study): A Register-Based Prospective Cohort Study

Diabetes Care 2015;38:821–826 | DOI: 10.2337/dc14-2907

Sine Knorr,¹ Kirstine Stochholm,²
Zuzana Vlachová,³ Birgitte Bytoft,⁴
Tine D. Clausen,⁵ Rikke Beck Jensen,⁶
Svend Juul,⁷ Per Ovesen,⁸ Peter Damm,⁴
Henning Beck-Nielsen,³ Dorte M. Jensen,³
and Claus Højbjerg Gravholt¹

OBJECTIVE

This study examined the long-term consequences for offspring born to mothers with pregestational type 1 diabetes regarding mortality, hospital admissions, and medication. We also examined the association between HbA_{1c} levels during pregnancy and mortality and incidence of hospital admissions.

RESEARCH DESIGN AND METHODS

We performed a prospective combined clinical and register-based cohort study comparing mortality, hospital admissions, and use of medication in offspring ($n = 1,326$) of women with pregestational type 1 diabetes (index children) with matched control subjects ($n = 131,884$). We also examined the association between HbA_{1c} levels during pregnancy and mortality and the incidence of hospital admissions. Participants were monitored from birth to the age of 13–21 years.

RESULTS

Overall mortality was significantly increased for index children (hazard ratio 2.10, 95% CI 1.33–3.30, $P = 0.001$). The incidence of hospital admissions for index children was significantly increased (incidence rate ratio [IRR] 1.45, 95% CI 1.38–1.53, $P < 0.001$), and this was the case for all age groups until the age of 15 years. The incidence of hospital admissions among index children was positively associated with maternal HbA_{1c} before pregnancy and in the first trimester. In addition, the overall use of medication was increased in index children (IRR 1.13, 95% CI 1.07–1.19, $P < 0.001$).

CONCLUSIONS

Type 1 diabetes during pregnancy has long-term implications on the health of offspring, with increased mortality, incidence of hospital admissions, and use of medication. Among mothers with type 1 diabetes, glycemic regulation is positively associated with incidence of hospital admissions in offspring.

Women with type 1 diabetes have an increased risk of adverse pregnancy outcome, including stillbirth, perinatal mortality, and congenital malformations (1–4). However, studies concerning long-term offspring outcome are sparse and results conflicting. Some studies have demonstrated an increased risk of type 2 diabetes and obesity, whereas others have found no association with BMI, glucose, insulin, or

¹Department of Endocrinology and Internal Medicine and Department of Molecular Medicine, Aarhus University Hospital, and Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

²Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark

³Department of Endocrinology, Odense University Hospital, Odense, Denmark

⁴Center for Pregnant Women with Diabetes, Department of Obstetrics, Rigshospitalet, Institute for Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

⁵Department of Gynaecology and Obstetrics, Nordsjællands Hospital, Hillerød, Denmark

⁶Department of Growth and Reproduction, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

⁷Section for Epidemiology, Department of Public Health, Aarhus University, Aarhus, Denmark

⁸Department of Gynaecology and Obstetrics, Aarhus University Hospital, Skejby, Denmark

Corresponding author: Claus Højbjerg Gravholt, ch.gravholt@dadlnet.dk.

Received 8 December 2014 and accepted 23 January 2015.

This article contains Supplementary Data online at <http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc14-2907/-/DC1>.

© 2015 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered.

blood pressure in the offspring. Many studies include both maternal type 1 diabetes and type 2 diabetes (5–12).

Maternal HbA_{1c} levels in pregnancy have been shown to be positively associated with adverse fetal outcome, but whether maternal HbA_{1c} levels affect long-term offspring outcome remains to be determined (13,14).

The mechanisms behind the adverse pregnancy outcomes in women with pregestational type 1 diabetes are not known. Some have hypothesized that type 2 diabetes and the metabolic syndrome in the offspring is caused by intrauterine hyperglycemia because maternal glucose easily passes the placenta, leading to fetal hyperglycemia and hyperinsulinemia (15,16).

The aim of this study was to assess the long-term consequences of pregnancies complicated by pregestational maternal type 1 diabetes on offspring mortality, hospital admissions, and use of medication. We also examined the association between maternal HbA_{1c} and long-term outcome in offspring.

RESEARCH DESIGN AND METHODS

From 1992 to 1999, pregnant Danish women with type 1 diabetes were prospectively reported to a registry managed by the Danish Diabetes Association. Information regarding maternal demography, diabetes status, and pregnancy outcome was reported to the registry by local obstetricians at eight hospitals in Denmark who were responsible for antenatal care and delivery for pregnant women with type 1 diabetes. The coverage of cases from the reporting centers spanned from 75 to 93%. This was evaluated by cross-checking with local discharge registries and an insulin-prescription registry, as described by Jensen et al. (17), who also reported deliveries from 1993 to 1999 in a study of perinatal complications.

We identified pregnancies in women with pregestational type 1 diabetes from 1992 until 1999. The inclusion criterion was delivery of a liveborn child after 24 weeks of gestation. Each woman and her offspring were included as index mother ($n = 991$) and index child ($n = 1,326$); siblings and twin pregnancies were accepted in the index and control cohorts.

All index mothers and children were identified in the Danish Civil Registration System and Statistics Denmark

(www.dst.dk), with ~100 control children ($n = 131,884$) identified for each index child. The matching criteria were control mothers and index mothers born the same year and the control mothers giving birth within 90 days of the index mother to a liveborn child (control child) with the same sex as the index child. For twin pregnancies, the control mother gave birth within 5 years of the index mother to liveborn twins with the same sex as the index children (Table 1). Matching was done by the greedy matching technique (18). We retrieved information concerning emigration for index and control children, and individuals who had emigrated during the observation period were excluded from further analyses after the emigration date. Exclusion of an emigrated index child also resulted in exclusion of its matched control children.

Mortality and Hospital Admissions

Information on deaths was retrieved from the Danish Register of Causes of Death (19). Diagnoses before 1994 were classified according to the ICD-8, and from 1994 according to ICD-10. ICD-8 diagnoses were transformed to ICD-10. Diagnoses were categorized into 19 chapters, and analyses of cause-specific mortality were made for each chapter.

Discharge diagnoses describing the primary reason for hospital admission were retrieved from the Danish National Hospital Register. This registry has collected nationwide data from all somatic hospital admissions since 1977 and data from outpatients since 1995 (20,21). From the Danish Psychiatric Central Research Register we retrieved information regarding diagnoses given within the psychiatric system. Because no private psychiatric hospitals exist in Denmark, this nationwide registration can be considered almost complete for severe mental disorders (22). The discharge diagnoses were used as measure of overall and cause-specific morbidity. Both registers used ICD-8 before 1994 and ICD-10 from 1994 and onwards. Diagnoses were categorized as described for mortality. From the Danish Medical Birth Registry we received information regarding gestational age at birth.

The following information was retrieved for 949 index mothers from the Danish Diabetes Association registry: HbA_{1c}, pregestational BMI, and duration of diabetes (Table 1). Details regarding HbA_{1c} calibration are available in the Supplementary Data.

Medication

All prescriptions in Denmark have been registered in the Danish National

Table 1—Baseline characteristics of mothers with pregestational type 1 diabetes (index mothers), their children (index children), and matched control children

	Index children	Control children
Children (n)	1,326	131,884
Male sex	646 (48.7)	64,097 (48.6)
Child's age at end of follow-up (years)	16.8 (13.0–21.0)	16.8 (12.9–21.4)
Singleton pregnancies	1,315 (99.2)	130,696 (99.1)
Children per mother (n)	1.29 (1–5)	1.09 (1–4)
Gestational age at birth (weeks)	36.5 (24–41)	39.5 (24–43)
Mother has a bachelor degree	312 (32)	42,332 (36)
Farther has a bachelor degree	234 (24)	34,077 (30)
	Index mothers	Number with valid information
Index mothers (n)	991	
Maternal age at birth of first child (years)	29.2 (17–46)	991
Pregestational BMI (kg/m^2)	23.9 (17.8–42.3)	904
Duration of diabetes in years	12.4 (0–36)	940
HbA _{1c} (% [mmol/mol])		
Pregestational	7.8 (4.1–15.2) [62 (21–143)]	762
First trimester	7.4 (4.1–13.0) [57 (21–119)]	886
Second trimester	6.7 (4.2–11.6) [50 (22–103)]	903
Third trimester	6.8 (4.1–12.2) [51 (21–110)]	891

Data are presented as mean (range) or as n (%).

Prescription Registry since 1995 and from 1996 also for children (23). We retrieved information regarding the medication prescribed to index and control children. The type of medication is registered according to the Anatomical Therapeutic Chemical (ATC) Classification System along with the dispense date.

Education

The educational status of parents of index and control children was retrieved from Statistics Denmark, which keeps information on education achieved since 1981. Parents were classified as having or not having completed an education at bachelor level. No information was available on either parent for 3,819 children, and their parental education was classified as missing.

Statistics

For the analysis of mortality we estimated hazard ratios (HRs) using stratified Cox regression with each index child and the matched control children as a stratum. Because siblings for index and control children were included, robust variance estimates of HRs were used. When stratified Cox regression was performed, the date of entry was the date of birth, and individuals were censored at the date of emigration or 31 December 2012, the last date of registration. Data concerning date of death were updated until 31 December 2012, but the Register of Causes of Death was only updated until 31 December 2011.

Hospital admissions and medications were analyzed by mixed-effects negative binomial regression yielding incidence rate ratios (IRR) as the measure of association. These data are clustered at two levels. First, the data for each child on hospital admissions and medications constitute a cluster, and we allowed for this clustering by using a random-effects model.

Second, each index child and his or her matched control child constitute a cluster, and we allowed for this clustering by using robust variance estimates. We used negative binomial regression rather than Poisson regression to allow for overdispersion. The method is computationally demanding, and we therefore restricted the number of control children per index child to 10, selected at random, with negligible loss of precision.

We calculated HRs and IRRs with and without adjustment for parental

educational level. The incidence of hospital admissions and use of medications, omitting siblings from the computations, did not change the overall results for mortality (data not shown).

Two supplementary analyses were made for hospital admissions. The risk of ever being admitted was analyzed using conditional logistic regression, and the incidence of admissions among children who were ever admitted was analyzed with mixed-effects negative binomial regression.

The associations between maternal HbA_{1c} and mortality and hospital admissions were analyzed among index children after excluding younger siblings and twin pregnancies. HbA_{1c}, maternal age at birth, and year of childbirth were included as continuous variables. The calculated HRs and IRRs for HbA_{1c} corresponded to a 1-percentage point increase (e.g., an HbA_{1c} increase from 6% [42 mmol/mol] to 7% [53 mmol/mol]).

Stata 13.1 software was used for statistical analyses. *P* values of less than 0.05 were considered significant. We did not adjust for multiple testing but included this issue in the discussion. The study was approved by the Danish Data Protection Agency.

RESULTS

Mortality

Mortality was significantly increased for index children (HR 2.10, 95% CI 1.33–3.30, *P* = 0.001). A total of 977

individuals died during the observation period (20 index children and 957 control children; Fig. 1 and Supplementary Table 1). Fifteen index children and 641 control children died before the age of 1 year, and mortality in this age period was significantly increased for index children (HR 2.37, 95% CI 1.40–4.03, *P* = 0.001). After the age of 1 year, the HR was insignificantly elevated.

The specific cause of death was known for 946 individuals, and the HR could be estimated for 7 of 19 ICD-10 chapters. HRs were significantly increased due to circulatory diseases, genitourinary diseases, and perinatal disorders.

Information about HbA_{1c} was available for approximately two-thirds of the index pregnancies, including 11 index children who died. We analyzed possible relations between HbA_{1c} and mortality, and no significant association was found (Supplementary Table 2).

Hospital Admissions

The overall incidence of hospital admissions was significantly increased in the index children (IRR 1.45, 95% CI 1.38–1.53, *P* < 0.001; Table 2). The incidence of hospital admissions was significantly increased in all age groups until the age of 15 years. After the age of 15 years, the incidence was insignificantly increased. The incidence of admissions was elevated for several diagnostic groups, especially infections, endocrine diseases, perinatal disorders,

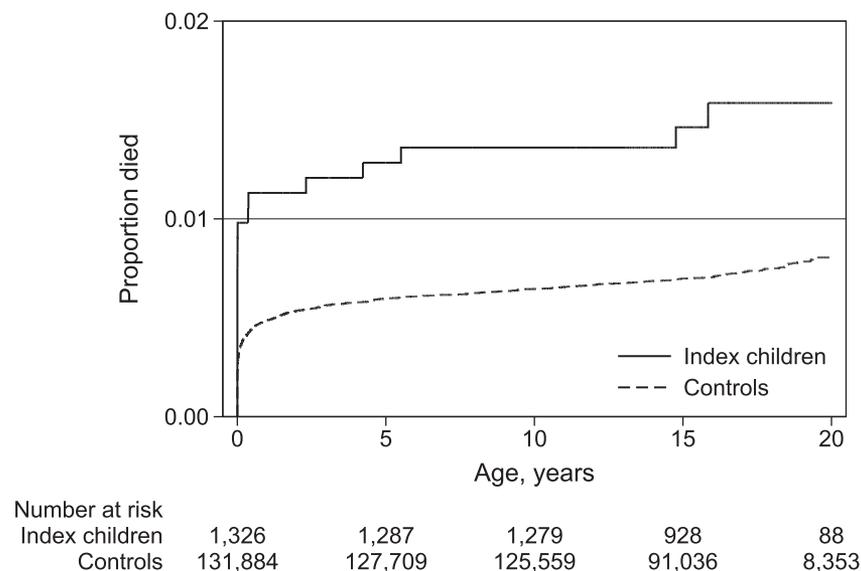


Figure 1—Kaplan-Meier plot displays overall mortality among children born to mothers with pregestational type 1 diabetes (index children) and matched control children.

Table 2—IRRs for hospital admissions, by age

Child's age	IRR (95% CI)	
	Not adjusted	Adjusted for parental education
All	1.45 (1.38–1.53)*	1.40 (1.33–1.47)*
<1 month	7.09 (6.71–7.49)*	7.04 (6.65–7.44)*
1–11 months	1.60 (1.42–1.81)*	1.60 (1.42–1.81)*
1–4 years	1.14 (1.05–1.23)*	1.13 (1.04–1.22)*
5–9 years	1.15 (1.05–1.26)*	1.15 (1.05–1.25)*
10–14 years	1.14 (1.03–1.25)*	1.14 (1.03–1.25)*
>15 years	1.07 (0.95–1.22)	1.06 (0.93–1.20)

Children of mothers with pregestational type 1 diabetes (index children) compared with matched control children. *IRRs significant at the 5% level.

congenital malformations, and unspecified diseases (Table 3), and the elevation was consistent over age groups (Supplementary Table 3). Most of the increased IRRs can be explained by an increased proportion of index children ever admitted rather than by a higher number of admissions among those ever admitted (Table 3 and Supplementary Table 3). The prevalence of ever being admitted with a congenital malformation was elevated among index children compared with control children (odds ratio 1.65, 95% CI 1.40–1.96, $P < 0.001$).

Among index children, we analyzed the association between maternal HbA_{1c} and hospital admissions. The overall incidence of hospital admissions was significantly associated with pregestational and first trimester HbA_{1c}. The association was consistent over all age groups, except for the first month of life and from 5 to 9 years of age (Supplementary Table 4). The associations for second and third trimester HbA_{1c} were weak and insignificant. Supplementary Table 5 reports details about the association between HbA_{1c} measurements and specific diagnoses. Among the index

children, we did not find an association between maternal HbA_{1c} and the incidence of congenital malformations. A total of 145 index children were diagnosed with a diagnosis from ICD-10 chapter 17 (congenital malformations). Of these children, we had knowledge of HbA_{1c} from pregestational, 99; first trimester, 125; second trimester, 126; and third trimester, 131.

Medications

The overall use of medications was increased for index children compared with control children (IRR 1.13, 95% CI 1.07–1.19, $P < 0.001$). The use of medications from 8 of 14 ATC groups was significantly increased, including the following groups: alimentary and metabolism, systemic hormones, anti-infectives, musculoskeletal system, nervous system, respiratory system, sensory organs, and drugs without ATC classification. The use of medications from the ATC group, antineoplastic and immunomodulating, was significantly reduced (Supplementary Table 6).

Education

As reported in Table 1, fewer parents of index children than of control children had a bachelor degree. When adjusted for parental educational status, the estimates regarding mortality, hospital admissions, and medications were slightly attenuated but essentially unchanged (Table 2 and Supplementary Tables 7–9).

Table 3—IRRs and odds ratios for hospital admissions, by primary diagnosis, in children of mothers with pregestational type 1 diabetes (index children) compared with matched control children

Main diagnosis	IRR (95% CI) [†]	Odds ratio (95% CI) [‡]	IRR (95% CI) [§]
All diagnoses	1.45 (1.38–1.53)*	24.30 (9.08–65.01)*	1.30 (1.23–1.36)*
Infections	1.41 (1.18–1.68)*	1.37 (1.17–1.61)*	1.09 (0.95–1.25)
Neoplasms	2.05 (1.07–3.91)*	1.61 (1.16–2.25)*	0.76 (0.50–1.15)
Blood/immune system	1.09 (0.49–2.41)	1.30 (0.79–2.13)	0.64 (0.46–0.88)*
Endocrinology	7.84 (5.41–11.80)*	3.62 (2.96–4.42)*	0.84 (0.67–1.05)
Psychiatric	1.25 (0.89–1.76)	1.24 (0.95–1.63)	1.03 (0.83–1.28)
Central nervous system	1.93 (1.11–3.34)*	1.30 (1.00–1.70)	1.30 (0.92–1.84)
Eye	1.99 (1.39–2.85)*	1.62 (1.28–2.04)*	1.11 (0.90–1.36)
Ear	1.39 (1.02–1.89)*	1.26 (1.03–1.56)*	1.04 (0.85–1.26)
Circulation	2.25 (1.10–4.59)*	1.72 (1.15–2.56)*	1.16 (0.71–1.91)
Respiratory system	1.14 (0.98–1.33)	1.09 (0.96–1.24)	1.06 (0.95–1.17)
Gastrointestinal	1.19 (0.98–1.45)	1.20 (1.02–1.41)*	1.01 (0.89–1.14)
Skin	0.77 (0.56–1.07)	0.79 (0.61–1.01)	1.05 (0.83–1.35)
Musculoskeletal system	1.27 (1.03–1.57)*	1.17 (0.99–1.37)	1.10 (0.95–1.27)
Genitourinary system	1.58 (1.12–2.22)*	1.12 (0.91–1.38)	1.37 (1.07–1.74)*
Pregnancy	0.95 (0.43–2.10)	0.89 (0.46–1.72)	1.06 (0.64–1.75)
Perinatal	9.83 (9.02–10.71)*	59.52 (48.95–72.38)*	0.93 (0.89–0.98)*
Congenital malformations	2.34 (1.75–3.13)*	1.65 (1.40–1.96)*	1.16 (0.98–1.38)
Unspecified	1.48 (1.38–1.58)*	1.92 (1.68–2.20)*	1.14 (1.08–1.21)*
External influences	0.95 (0.88–1.01)	1.01 (0.88–1.15)	0.95 (0.89–1.00)

[†]IRR of hospital admissions. [‡]Odds ratio of ever being admitted (conditional logistic regression). [§]IRR of admissions among children ever admitted. *Estimates significant at the 5% level.

CONCLUSIONS

The dominant result of this study was a different health profile in offspring of women with type 1 diabetes compared with their matched control offspring. We found increased mortality, increased use of medications, and increased incidence of hospital admissions, the latter extending into the childhood years.

Our study confirmed an increased mortality in the first year of life in offspring of mothers with type 1 diabetes. Most of the excess mortality was due to perinatal disorders. We found no significant association between maternal HbA_{1c} during pregnancy and offspring mortality, possibly due to the small number of deaths with information on HbA_{1c}.

The overall morbidity as expressed by hospital admissions was increased, and this pattern was present up to the age of 15 years. The increased incidence of admissions before the age of 1 month is

explained to some extent by routine admissions of children born to mothers with type 1 diabetes during the period when the registry was established.

The increased incidence of perinatal and endocrine diseases and congenital malformations supports existing literature (1–6,8,9), and an increase in infections and in neurological and developmental disorders was previously shown by Aberg and Westbom (24). The increased incidence of circulatory disorders might be due to cardiac malformations as well as to the increased risk of cardiac hypertrophy in offspring of mothers with type 1 diabetes, a condition that has been reported to normalize in early life (25,26).

The reason offspring of women with type 1 diabetes have an increased risk of developing infections is not easily explained. One explanation could be the higher number of caesarean sections in women with type 1 diabetes compared with the background population (17). Focus on the effect of mode of delivery on intestinal microbiota and development of the immune system has recently increased (27). Thus, because women with diabetes more often give birth by caesarean section, their offspring may be more prone to infections later in life. Also, perinatal disease (e.g., respiratory distress syndrome) and congenital malformations could contribute to a later increased risk of infections.

We studied whether the increased incidence of hospital admissions was due to a higher risk of ever being admitted among the index children or an increased number of admissions among those ever admitted. For most diagnoses, we found an increased proportion of index children ever being admitted compared with the control children.

Among index children, we found an association between the mother's pregestational and first trimester HbA_{1c} and the admission rate. We are, to our knowledge, the first to show an association between maternal HbA_{1c} and overall morbidity after the perinatal period. Also, we found an association between maternal HbA_{1c} and hospital admissions for infections and unspecified diseases (Supplementary Table 4). In a previous clinical follow-up study, we found an association between maternal hyperglycemia and prediabetes and type 2 diabetes in adult offspring (5). In the present epidemiological

study, we did not find an association between HbA_{1c} and endocrine diseases on an ICD-10 chapter level. In the original work describing adverse pregnancy outcome in the deliveries between 1993 and 1999, Jensen et al. (13) described an increased risk of congenital malformations with maternal periconceptional HbA_{1c} ≥ 10.4 compared with the background population. In the current study, we found no significant association between HbA_{1c} and congenital malformations among the index children. However, the two studies are not in disagreement: both show an increased risk of malformations among children of mothers with type 1 diabetes compared with other children but no significant association between HbA_{1c} level and malformation risk among children of mothers with type 1 diabetes. Nevertheless, our findings in relation to long-term offspring outcome support that pregnancy counseling of women with type 1 diabetes is relevant.

Our findings on morbidity, as expressed by hospital contacts, correspond well with findings related to medication. The overall use of medication was increased for offspring of mothers with type 1 diabetes, and the use of medication from 8 of 14 ATC groups was significantly increased. The increased number of prescriptions related to alimentary tract and metabolism, infections, sensory organs, and the nervous system is consistent with our results concerning hospital contacts due to endocrine diseases, infections, diseases of the eyes and ears, and psychiatric diseases.

Socioeconomic status and childhood health are known to be linked (28,29), and in a supplementary analysis, we adjusted for parental education as a marker of socioeconomic status. This only resulted in subtle changes of our findings (Table 2 and Supplementary Tables 7–9). Thus, our findings cannot be explained by the fact that fewer children in the index group had parents with a bachelor level education. We find that the study lends strong support to the hypothesis that a hyperglycemic intrauterine environment affects the child's health.

The index children were born an average of 3 weeks earlier than the control children. Maternal diabetes is a strong predictor of preterm birth and, consequently, of adverse offspring

outcome. Gestational age and birth weight are probably important intermediate variables in the pathway between maternal diabetes and offspring outcome, and therefore, we did not adjust for it in our main analysis because doing so would conceal the effect of maternal diabetes by the introduction of a special form of bias, described as collider bias and extensively discussed by Wilcox et al. (30). In a supplementary analysis, we adjusted mortality before the age of 1 year and incidence of hospital admissions before the age of 1 month for gestational age (Supplementary Table 10). As expected, the adjustment reduced the contrast between index children and control children considerably, but we do not interpret this as the main results being biased by gestational age at birth.

The strength of this study is that it was performed in a large group of prospectively studied offspring of mothers with type 1 diabetes. Our index mothers were well characterized, and no mothers with type 2 diabetes or gestational diabetes were included in the cohort. The coverage level was high, and the cross-checks with local discharge registries and an insulin-prescription registry ensured that the register was not contaminated with false-positive cases. The opportunities to conduct association studies between type 1 diabetes and morbidity and mortality in this well-defined group are unique.

A possible bias of this study is that the women with the poorest glycemic control may not be monitored regularly during pregnancy and are therefore underrepresented in the register. If this were the case, it would lead to an underestimation of the effects of maternal diabetes on the offspring. The validity of discharge diagnoses from the Danish National Hospital Register ranges between 73% and 90%, which could affect the results (21). However, because this study only used discharge diagnoses at the ICD chapter level, we regard this as a minor problem. Furthermore, we have no reason to believe that the validity of diagnoses given to index children differs from diagnoses given to control children, and such undifferentiated misclassification would lead to an underestimation of the effects of maternal diabetes on the offspring. It is, however, possible that the threshold to seek medical help is lower for women with a

serious diagnosis as type 1 diabetes and that may affect the incidence of contacts and medications among index children.

This report presents numerous statistical tests and CIs, and the risk of false-positive results due to multiple testing is obvious. We did not attempt any formal adjustment for multiple testing because it leads to a high risk of concealing actual associations, but the findings must be interpreted with caution. However, when Supplementary Table 3 presents 135 IRR estimates, and 55 of them are significant in the same direction at the 5% level, it can hardly be dismissed as a chance finding.

In conclusion, we found evidence of adversely affected health in the offspring of women with type 1 diabetes. The overall incidence of hospital admissions was positively associated with maternal HbA_{1c} before and during early pregnancy. Type 1 diabetes during pregnancy had pervasive short-term and long-term implications on the offspring, exemplified by increases in mortality, hospital admissions, and use of medication.

Acknowledgments. The Danish Diabetes Association is acknowledged for originally assisting in the creation of a registry of pregnant women with type 1 diabetes. Data collection in the original registry was performed by Lars Mølsted-Pedersen, Joachim Klebe, Niels Hahnemann, Margrethe Møller, Jes G. Westergaard, Hans Gjessing, Jens Kragh Mostrup, K.H. Frandsen, Edna Stage, Anders Thomsen, Thea Lousen, Kresten Rubeck Petersen, Bjarne Øvlisen, Jan Kvetny, and Hedvig Poulsen (The Danish Diabetes Working Group for Type 1 Diabetes Pregnancy). Apart from P.D. and H.B.-N., the original registry working group included Anders Frøland, Lars Mølsted-Pedersen, Joachim Klebe, and Carl Erik Mogensen.

Funding. This study was supported by grants from the European Foundation for the Study of Diabetes; Danish Ministry of Science, Innovation and Higher Education; Lundbeck Foundation; Aarhus University; Danish Diabetes Academy; Beckett Foundation; Danielsen Foundation; and Central Denmark Region. The study sponsors had no involvement in the design, the conduct, or the interpretation of the study.

Duality of Interest. R.B.J., P.O., P.D., H.B.-N., and C.H.G. have given talks for Novo Nordisk. P.O. is participating in a multinational study in collaboration with Novo Nordisk. H.B.-N. receives research support from Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. P.D. and H.B.-N. contributed to the establishment of the original registry. P.O., P.D., and D.M.J. contributed to data collection. S.K., Z.V., B.B., T.D.C., R.B.J., P.O., P.D., H.B.-N., D.M.J., and C.H.G. contributed substantially to conception and design of the study. S.K., K.S., S.J., and C.H.G. analyzed

and interpreted the data. S.K. drafted the manuscript and designed the tables. All authors critically revised the manuscript and approved the final version for publishing. C.H.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Preliminary results from this study were presented in abstract form at the 74th Scientific Sessions of the American Diabetes Association, San Francisco, CA, 13–17 June 2014; and in abstract form at the Annual Meeting of the Diabetic Pregnancy Study Group of the European Association for the Study of Diabetes, Budapest, Hungary, 2–5 October 2014.

References

- Casson IF, Clarke CA, Howard CV, et al. Outcomes of pregnancy in insulin dependent diabetic women: results of a five year population cohort study. *BMJ* 1997;315:275–278
- Boulot P, Chabbert-Buffet N, d'Ercole C, et al.; Diabetes and Pregnancy Group, France. French multicentric survey of outcome of pregnancy in women with pregestational diabetes. *Diabetes Care* 2003;26:2990–2993
- Evers IM, de Valk HW, Visser GH. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. *BMJ* 2004;328:915
- Macintosh MC, Fleming KM, Bailey JA, 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;333:177
- Clausen TD, Mathiesen ER, Hansen T, et al. High prevalence of type 2 diabetes and pre-diabetes in adult offspring of women with gestational diabetes mellitus or type 1 diabetes: the role of intrauterine hyperglycemia. *Diabetes Care* 2008;31:340–346
- Clausen TD, Mathiesen ER, Hansen T, et al. Overweight and the metabolic syndrome in adult offspring of women with diet-treated gestational diabetes mellitus or type 1 diabetes. *J Clin Endocrinol Metab* 2009;94:2464–2470
- Weiss PA, Scholz HS, Haas J, Tamussino KF, Seissler J, Borkenstein MH. Long-term follow-up of infants of mothers with type 1 diabetes: evidence for hereditary and nonhereditary transmission of diabetes and precursors. *Diabetes Care* 2000;23:905–911
- Lawlor DA, Lichtenstein P, Långström N. Association of maternal diabetes mellitus in pregnancy with offspring adiposity into early adulthood: sibling study in a prospective cohort of 280,866 men from 248,293 families. *Circulation* 2011;123:258–265
- Silverman BL, Rizzo TA, Cho NH, Metzger BE; The Northwestern University Diabetes in Pregnancy Center. Long-term effects of the intrauterine environment. *Diabetes Care* 1998;21(Suppl. 2):B142–B149
- Rijpert M, Evers IM, de Vroede MA, de Valk HW, Heijnen CJ, Visser GH. Risk factors for childhood overweight in offspring of type 1 diabetic women with adequate glycemic control during pregnancy: nationwide follow-up study in the Netherlands. *Diabetes Care* 2009;32:2099–2104
- Manderson JG, Mullan B, Patterson CC, Hadden DR, Traub AI, McCance DR. Cardiovascular

and metabolic abnormalities in the offspring of diabetic pregnancy. *Diabetologia* 2002;45:991–996

- Sobngwi E, Boudou P, Mauvais-Jarvis F, et al. Effect of a diabetic environment in utero on predisposition to type 2 diabetes. *Lancet* 2003;361:1861–1865
- Jensen DM, Korsholm L, Ovesen P, et al. Periconceptual A1C and risk of serious adverse pregnancy outcome in 933 women with type 1 diabetes. *Diabetes Care* 2009;32:1046–1048
- Suhonen L, Hiilesmaa V, Teramo K. Glycaemic control during early pregnancy and fetal malformations in women with type I diabetes mellitus. *Diabetologia* 2000;43:79–82
- Plagemann A. Maternal diabetes and perinatal programming. *Early Hum Dev* 2011;87:743–747
- Pedersen J. Weight and length at birth of infants of diabetic mothers. *Acta Endocrinol (Copenh)* 1954;16:330–342
- Jensen DM, Damm P, Moelsted-Pedersen L, et al. Outcomes in type 1 diabetic pregnancies: a nationwide, population-based study. *Diabetes Care* 2004;27:2819–2823
- Parsons L. Ovation Research Group. *Reducing Bias in a Propensity Score Matched-Pair Sample Using Greedy Matching Techniques* [article online]. Available from <http://www2.sas.com/proceedings/sugi26/p214-26.pdf>. Accessed 10 January 2014
- Helweg-Larsen K. The Danish Register of Causes of Death. *Scand J Public Health* 2011;39(Suppl.):26–29
- Andersen TF, Madsen M, Jørgensen J, Møller-Jensen L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999;46:263–268
- Nickelsen TN. Data validity and coverage in the Danish National Health Registry. A literature review. *Ugeskr Laeger* 2001;164:33–37 [in Danish]
- Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. *Scand J Public Health* 2011;39(Suppl.):54–57
- Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011;39(Suppl.):38–41
- Aberg A, Westbom L. Association between maternal pre-existing or gestational diabetes and health problems in children. *Acta Paediatr* 2001;90:746–750
- Aman J, Hansson U, Ostlund I, Wall K, Persson B. Increased fat mass and cardiac septal hypertrophy in newborn infants of mothers with well-controlled diabetes during pregnancy. *Neonatology* 2011;100:147–154
- Gutgesell HP, Speer ME, Rosenberg HS. Characterization of the cardiomyopathy in infants of diabetic mothers. *Circulation* 1980;61:441–450
- Penders J, Thijs C, Vink C, et al. Factors influencing the composition of the intestinal microbiota in early infancy. *Pediatrics* 2006;118:511–521
- Bradley RH, Corwyn RF. Socioeconomic status and child development. *Annu Rev Psychol* 2002;53:371–399
- Biering-Sørensen S, Søndergaard G, Vitting Andersen K, Andersen AM, Mortensen LH. Time trends in socio-economic factors and risk of hospitalisation with infectious diseases in pre-school children 1985–2004: a Danish register-based study. *Paediatr Perinat Epidemiol* 2012;26:226–235
- Wilcox AJ, Weinberg CR, Basso O. On the pitfalls of adjusting for gestational age at birth. *Am J Epidemiol* 2011;174:1062–1068