

Long-Term Protective Effect of Lactation on the Development of Type 2 Diabetes in Women With Recent Gestational Diabetes Mellitus

Anette-G. Ziegler,^{1,2} Maike Wallner,¹ Imme Kaiser,² Michaela Rossbauer,¹ Minna H. Harsunen,¹ Lorenz Lachmann,² Jörg Maier,² Christiane Winkler,^{1,2} and Sandra Hummel^{1,2}

Women with gestational diabetes mellitus (GDM) have a high risk of developing postpartum type 2 diabetes. Strategies to prevent postpartum type 2 diabetes are important to reduce the epidemic of diabetes and its societal impact. Breastfeeding was reported to improve early postpartum glucose tolerance and reduce the subsequent risk of type 2 diabetes. To investigate whether breastfeeding influences short- and long-term postpartum diabetes outcomes, women with GDM ($n = 304$) participating in the prospective German GDM study were followed from delivery for up to 19 years postpartum for diabetes development. All participants were recruited between 1989 and 1999. Postpartum diabetes developed in 147 women and was dependent on the treatment received during pregnancy (insulin vs. diet), BMI, and presence/absence of islet autoantibodies. Among islet autoantibody-negative women, breastfeeding was associated with median time to diabetes of 12.3 years compared with 2.3 years in women who did not breastfeed. The lowest postpartum diabetes risk was observed in women who breastfed for >3 months. On the basis of these results, we recommend that breastfeeding should be encouraged among these women because it offers a safe and feasible low-cost intervention to reduce the risk of subsequent diabetes in this high-risk population. *Diabetes* 61:3167–3171, 2012

Gestational diabetes mellitus (GDM) occurs in around 4% of pregnancies and is defined as glucose intolerance with an onset or first diagnosis during pregnancy (1). GDM is known to increase the risk for postpartum type 2 diabetes (2). Of potential relevance for the protection against postpartum diabetes, an analysis of large cohort studies in the U.S. found that the duration of lactation was inversely associated with the incidence of type 2 diabetes (3–5). The risk reductions were particularly marked when breastfeeding was continued for 1 to 2 years or ≥ 2 years. However, women with GDM are less likely to breastfeed and, if they do, breastfeeding usually is continued for a shorter duration than among women without diabetes (6–10). Nevertheless, women with GDM who do breastfeed have

improved lipid and glucose metabolism during the first 3 months after birth (11–13). These findings suggest that breastfeeding may not only have a short-term effect on postpartum glucose tolerance, as previously shown (11–13) but may also delay the long-term development of type 2 diabetes among women with GDM. Nevertheless, few studies have assessed these possibilities (3,12).

The prospective German GDM study has followed patients with GDM from delivery for up to 19 years postpartum to determine the risk of developing diabetes and to identify factors that modify long-term risk for postpartum diabetes. Here, we examined the risk of postpartum diabetes and tested the hypothesis that breastfeeding protects against postpartum type 2 diabetes in women with GDM.

RESEARCH DESIGN AND METHODS

Participants. The prospective German GDM study has followed women with GDM for the development of postpartum diabetes from delivery. As previously described, between 1989 and 1999, 304 patients with GDM were recruited across Germany (14). GDM was diagnosed according to the criteria of the German Diabetes Association. Women were considered to have GDM if two of three capillary blood glucose values exceeded 5 mmol/L (fasting) before an oral glucose tolerance test (OGTT), 10.6 mmol/L at 60 min, and 8.9 mmol/L at 120 min after the OGTT. These diagnostic criteria were consistent during recruitment. All centers participating in the study were asked to follow the therapeutic guidelines for the treatment of GDM recommended by the German Diabetes Association. According to these recommendations, insulin was required if capillary blood glucose values exceeded 5 mmol/L before a meal or 7.8 mmol/L at 60 or 120 min after a meal for at least 1 week despite dietary interventions. Of the participants, 206 women gave birth to their first child, 63 to the second child, 24 to the third, and 11 to the fourth child. All patients gave written informed consent to participate in the study. The study was approved by the ethical committee of Bavaria, Germany (Bayerische Landesärztekammer Nr. 95357).

Outcome measure. Patients were followed for the development of diabetes postpartum by means of an OGTT at 2 and 9 months; 2, 5, 8, 11, 15, and 19 years after pregnancy; or until the diagnosis of diabetes. OGTTs were performed by the patient physician. An OGTT was conducted at 2 months as part of the recommended routine postpartum testing in women with GDM. All subsequent follow-up OGTTs were performed as part of the study protocol. In addition, if women presented with symptoms of diabetes between follow-up visits, physicians performed blood glucose measurements to test for clinical diabetes. For the study outcome, diabetes onset was defined according to American Diabetes Association criteria, which include unequivocal hyperglycemia with acute metabolic decompensation or the observation on at least two occasions of 1) a 2-h plasma glucose level >200 mg/dL after an oral glucose challenge, or 2) a random blood glucose level >200 mg/dL if accompanied by unequivocal symptoms. Since 1997, a fasting blood glucose level >126 mg/dL on two occasions also has been included as a diabetes diagnosis criteria in the study. Follow-up is ongoing, and this analysis includes follow-up data until November 2011. Of the 304 patients who were recruited, 98 women (32%) left the study during the 15-year follow-up without developing diabetes and were considered dropouts.

Questionnaires and interviews. Age at delivery, diabetes treatment during pregnancy, smoking behavior during pregnancy, and parity status were obtained shortly after delivery. BMI was recorded by the gynecologists at the first obstetric visit and was extracted from the obstetric records at a median

From the ¹Institute of Diabetes Research, Helmholtz Zentrum München, and Forschergruppe Diabetes, Klinikum rechts der Isar, Technische Universität München; and the ²Forschergruppe Diabetes e.V., Neuherberg, Germany. Corresponding author: Anette-G. Ziegler, anette-g.ziegler@helmholtz-muenchen.de.

Received 29 March 2012 and accepted 14 July 2012.

DOI: 10.2337/db12-0393

This article contains Supplementary Data online at <http://diabetes.diabetesjournals.org/lookup/suppl/doi:10.2337/db12-0393/-/DC1>.

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See accompanying commentary, p. 3076.

gestational age of 8 weeks (interquartile range [IQR] 7–10 weeks). Data on lactation (yes/no), the duration of lactation, and full lactation were obtained from questionnaires completed by the child's mother when the child was aged 9 months (7). If the child still was being breastfed at 9 months of age, the same questionnaire was completed again when the child was 2 years of age. Pregnancies after this index pregnancy were not considered in the analysis. Other details of the study protocol and the measurement of islet autoantibodies are described elsewhere (14).

Statistical analysis. The development of diabetes after delivery was used as the outcome measure. Variables analyzed with respect to diabetes risk were diabetes treatment during pregnancy (insulin or diet), BMI (>30 kg/m² or ≤ 30 kg/m² as obese and nonobese, respectively), and duration of breastfeeding (no breastfeeding, breastfeeding ≤ 3 months, breastfeeding >3 months, no full breastfeeding). Time to event methods were used to calculate risks (life-table analysis) and compare outcomes (postpartum diabetes) among patients stratified according to these factors using a Cox proportional hazard model. The outcomes were compared by univariate analysis, and significant risk factors were entered into a multivariate analysis. For all analyses, two-tailed *P* values <0.05 were considered statistically significant. SPSS version 19 (SPSS Inc., Chicago, IL) was used for statistical analysis.

RESULTS

Of the 304 women with GDM participating in the study, 272 (89.5%) were islet autoantibody-negative. Of women without islet autoantibodies, 92 required insulin during pregnancy, and 180 were sufficiently treated with diet (Supplementary Fig. 1). The median age of all participating women was 31 years (IQR 28–34 years).

Postpartum diabetes risk. Postpartum diabetes was diagnosed in 147 women of the 304 women included in the study. The 15-year cumulative risk of postpartum diabetes in all women with GDM was 63.6% (95% CI 55.8–71.4), and the median diabetes-free duration was 7.9 years postpartum (95% CI 5.0–10.8; Supplementary Fig. 2). Diabetes was diagnosed at a median age of 34 years (IQR 30–38 years), and only a few women went through menopause during follow-up.

Stratification of postpartum diabetes risk. Postpartum diabetes risk was extremely high in the 32 islet autoantibody-positive women (Fig. 1). All but one of these patients developed diabetes postpartum, and their median diabetes-free duration postpartum was just 4.5 months (95% CI 2.5–6.5).

Among the 272 islet autoantibody-negative women, postpartum diabetes risk and the rate of diabetes development were stratified according to therapy received during pregnancy and BMI (Fig. 1). The highest risk was observed in 92 women without islet autoantibodies who required insulin during pregnancy (15 year risk 92.3% [95% CI 84.7–99.9]) compared with diet-treated women (39.7 [28.8–50.6]). The median diabetes-free duration was 2.1 and 16.3 years, respectively ($P = 10^{-22}$). Stratification for BMI (≤ 30 vs. >30 kg/m²) did not affect the risk or rate of developing diabetes among women with GDM who were treated with insulin (median diabetes-free duration, 2.1 vs. 2.1 years; $P = 0.4$). In contrast, islet autoantibody-negative women who were treated with diet with a BMI >30 kg/m² had a significantly increased postpartum risk for diabetes (15 year risk, 69.1% [95% CI 50.0–88.2] vs. 28.6 [16.5–40.7]; $P = 0.002$) and faster progression (median diabetes-free duration, 10.2 years) relative to women with BMI ≤ 30 kg/m² (median diabetes-free duration, 18.2 years). None of the islet autoantibody-negative women with GDM developed islet autoantibodies during the follow-up.

Lactation and diabetes outcome. Breastfeeding data were available for 264 women. Of these, 201 (76%) breastfed their child and 109 continued breastfeeding for >3 months (Supplementary Fig. 1). Full breastfeeding was

practiced by 62% of the women and the duration of full breastfeeding was strongly correlated with any breastfeeding duration ($r^2=0.71$; $P < 0.0001$). These values are notably less than frequencies reported for women in Germany (8,9). The median duration of breastfeeding in the women with GDM was 9 weeks (IQR 1–25 weeks), and the median duration of full breastfeeding was 4 weeks (0–16 weeks). Duration of breast-feeding was shorter in women who required insulin (median of 5 weeks vs. 12 weeks in those treated with diet; $P = 0.003$) and in women who were overweight (median 5 weeks vs. 12 weeks in women with BMI <30 kg/m²; $P = 0.003$), but it was not associated with islet autoantibody positivity (positives breastfed for a median of 6 weeks vs. negatives, who breastfed for a median of 9 weeks; $P = 0.47$). No differences in breastfeeding were observed with respect to dropout status (median of 11 weeks in women who dropped out vs. 9 weeks in those who stayed in the study; $P = 0.97$). Women who entered the study during the second half of the recruitment period were more likely to breastfeed their child than women entering the study during the first half of the recruitment period (82 vs. 72%; $P = 0.04$), and this was most obvious for full breastfeeding (72 vs. 53%; $P = 0.003$).

Lactation did not affect diabetes development among islet autoantibody-positive women (data not shown). Among islet autoantibody-negative women, lactation was associated with a marked delay in diabetes development compared with women who did not breastfeed (median diabetes-free duration, 12.2 years [95% CI 7.7–16.8] vs. 2.2 [0.0–6.1]; $P = 0.012$). Notably, the duration of lactation was inversely associated with postpartum diabetes risk ($P = 0.002$), and women who breastfed for >3 months had the lowest postpartum diabetes risk (15-year risk: 42% [95% CI 28.9–55.1] vs. no or ≤ 3 months of breastfeeding, 72% [60.5–84.7]; $P = 0.0002$) and a longer diabetes-free duration (18.2 years [95% CI 10.4–25.9]; Fig. 2). Postpartum diabetes risk also was inversely associated with full breastfeeding duration ($P = 0.001$), with a lower 15-year risk in women who practiced full breastfeeding for at least 3 months (34.8% [95% CI 18.3–41.3] vs. 71.7 [60.3–83.1]; $P = 0.001$).

Multivariate analysis showed that insulin therapy (hazard ratio 5.5 [95% CI 3.7–8.2]; $P = 10^{-16}$), BMI >30 kg/m² (1.7 [1.1–2.5]; $P = 0.009$), and any breastfeeding >3 months (0.55 [0.35–0.85]; $P = 0.009$) were significantly and independently associated with the risk of postpartum diabetes in islet autoantibody-negative women with GDM, whereas age at delivery, parity status, year of study enrollment, and smoking during pregnancy were not (Table 1). Stratification of women into diet versus insulin-treated cases or BMI <30 versus BMI >30 suggested that breastfeeding may be more effective in reducing postpartum diabetes risk in women treated with diet than in women treated with insulin, but numbers after stratification were small in some groups (Supplementary Table).

Lactation and BMI postpartum. Postpartum BMI was obtained in 289 of the women at a median of 4.85 years postpartum (IQR 2.0–7.4 years). Duration of lactation continued to be associated with postpartum BMI ($P = 0.0006$). However, lactation did not influence BMI trends postpartum, as proven by the lack of correlation between the duration of lactation and the delta postpregnancy BMI ($r^2=0.01$; $P = 0.12$; Supplementary Fig. 3). The mean delta postpregnancy BMI among women who breastfed for at least 3 months was 0.36 (SD 2.0) compared with 0.12 (2.6) in women who breastfed <3 months ($P = 0.44$).

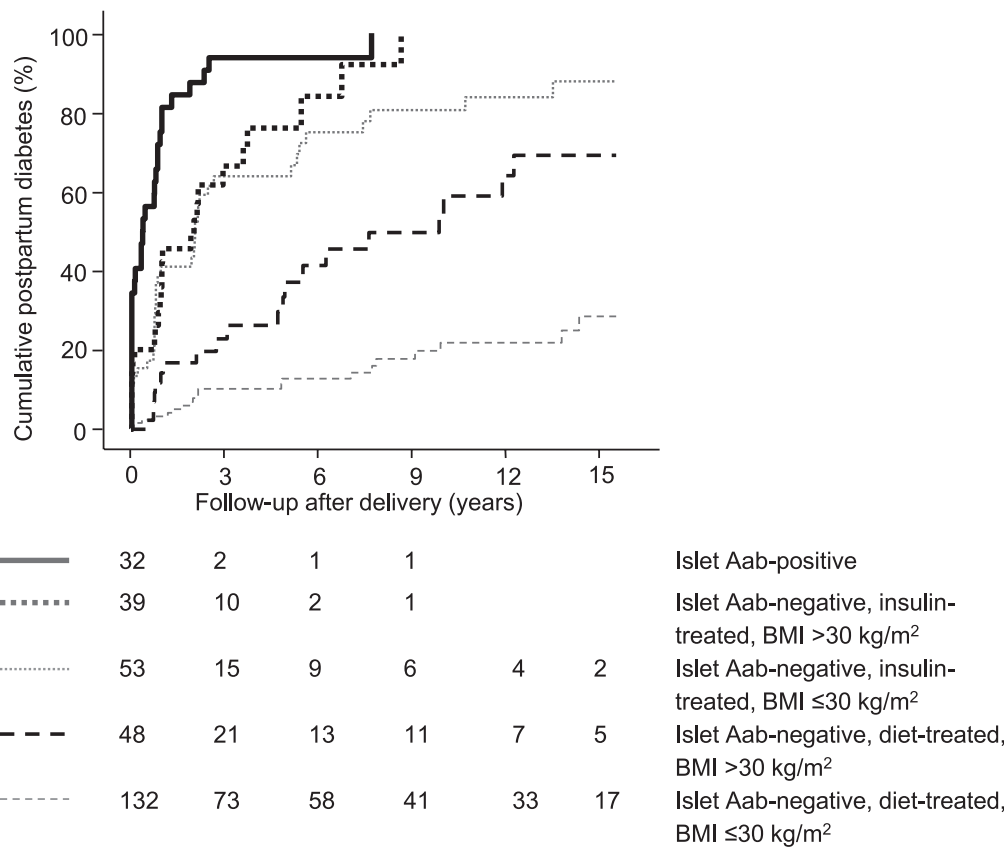


FIG. 1. Cumulative life-table risk of postpartum diabetes in 304 women with GDM who were followed prospectively from delivery. Risk is shown for women who were islet autoantibody-positive (solid black line; $n = 32$); were islet autoantibody-negative, received insulin therapy during pregnancy, and had a BMI >30 kg/m² (thick black dotted line; $n = 39$); were islet autoantibody-negative, received insulin therapy during therapy, and had a BMI <30 kg/m² (thin gray dotted line; $n = 53$); were islet autoantibody-negative, did not receive insulin therapy during therapy, and had a BMI >30 kg/m² (black dashed line; $n = 48$); and were islet autoantibody-negative, did not receive insulin therapy during therapy, and had a BMI <30 kg/m² (thin gray dashed line; $n = 132$). Numbers below the graph indicate the number of subjects at each follow-up.

DISCUSSION

Breastfeeding by women who had GDM was associated with a $>40\%$ long-term reduction of the risk of developing postpartum diabetes. Risk reduction was most pronounced when lactation was continued for at least 3 months, and the beneficial effects of lactation on diabetes risk were sustained over time. Postpartum diabetes risk also was influenced by islet autoantibody status, insulin treatment during pregnancy, and obesity.

These are novel findings in women with GDM; no previous study has shown a sustained effect of lactation on diabetes risk reduction for up to 15 years postpartum. Strengths of the study include the long prospective follow-up (up to 19 years after delivery) and regular screening for diabetes using an OGTT. Unlike other studies, the recall period was short, with lactation duration data obtained at 9 months and 2 years postpartum. A proportion of participants had developed diabetes by the time lactation status was assessed, and some recall bias cannot be excluded. This is likely to be small because the potential benefit of lactation on diabetes risk was not known when mothers were interviewed. Consistent with other countries (15,16), there was a slight increase in the percentage of lactating mothers over time in this cohort. However, lactation was strongly associated with decreased risk for postpartum diabetes after adjustment for the recruitment period, and it is unlikely that the findings reflect changing breastfeeding practices over time.

Potential limitations of the study are limited access to information regarding diet and activity postpartum, which may have contributed to lactation-associated risk reduction. It also was not possible to determine whether breastfeeding reduced postpartum diabetes risk in a subgroup of women with GDM. This would be helpful in understanding the mechanism behind the protective effect of lactation and identifying risk groups for counseling. Data suggested that women with lower a priori risk may benefit most (e.g., women treated with diet), but numbers after stratification were small and the results inconclusive.

Our findings are supported by a number of cohort studies of apparently healthy middle-aged/elderly women (3–5), which found that an increased duration of lactation was associated with a reduced risk of type 2 diabetes and cardiovascular disease. In comparison with our study, these studies had larger sample sizes but a long recall window for duration of lactation and other pregnancy-related parameters (up to 40 years), and they did not focus on patients with GDM. In these previous studies, longer duration of breastfeeding remained a significant protective factor after adjustment for lifestyle factors such as BMI, diet, exercise, multivitamin use, and smoking status. In our study, increased BMI was associated with lower duration of breastfeeding, but breastfeeding remained protective for diabetes after adjustment for BMI. We also had the opportunity to examine postpartum BMI. Breastfeeding duration continued to be associated with postpartum BMI. However,

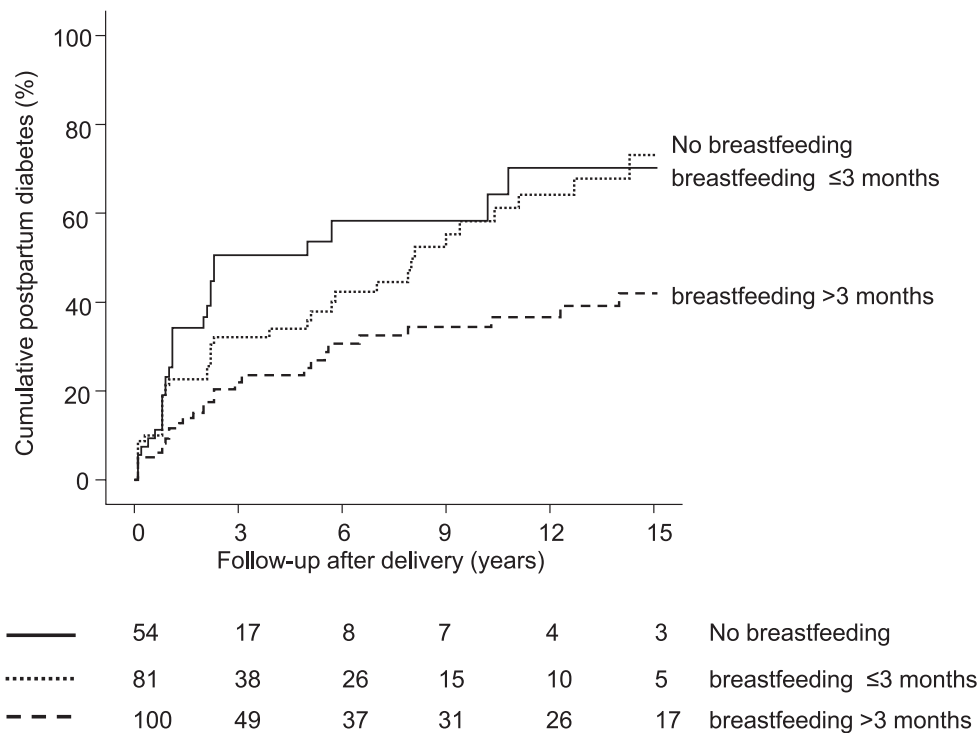


FIG. 2. Cumulative life-table risk of postpartum diabetes in islet autoantibody-negative women with GDM who breastfed for >3 months (dashed line) compared with those who breastfed for ≤3 months (solid line; $P = 0.029$) or did not breastfeed (dotted line; $P = 0.002$). No significant difference was observed between women who breastfed >2 months compared with women who breast-fed ≤3 months ($P = 0.2$). Numbers below the graph indicate the number of subjects at each follow-up.

breastfeeding did not influence BMI trends postpartum, as proven by the lack of correlation between the duration of breastfeeding and the delta postpregnancy BMI.

A mechanism for the prolonged protection against diabetes offered by 3 or more months of lactation is not forthcoming. As mentioned, although we cannot exclude other postpartum lifestyle confounder effects, we speculate that lactation provides some form of direct protection. Lactation for 1 to 3 months after delivery improves glucose and lipid metabolism (13), and estrogen levels are lower in lactating than in nonlactating women without differences in visceral fat and subcutaneous fat distribution and mass (17–19). Furthermore, a recent retrospective analysis of premenopausal women demonstrated that mothers who had breastfed exhibited lower amounts of metabolically

active visceral fat than mothers who did not breastfeed (20). Our data, in which duration of lactation was associated with BMI pre- and postpartum but not with a change in BMI postpartum, suggest that differences in body fat distribution may not be a consequence of breastfeeding but secondary to prepartum differences. Duration of lactation also has been shown to be directly related to ghrelin and peptide YY levels 3 years postpartum (21). Little is known, however, about the long-term changes that could provide protection, and such studies that control established diabetes risk factors such as BMI and lifestyle are warranted.

Our study also showed that women with GDM who required insulin treatment during pregnancy had a markedly increased risk of postpartum diabetes independent of their body weight. More than 90% of these women were predicted to develop diabetes by 15 years postpartum, and their median diabetes-free survival was less than 2.5 years. We speculate that the reason for this high diabetes risk is a more severe gestational diabetes phenotype, more insulin deficiency, or both, and both would be reflected by insulin requirement during pregnancy. Further studies are needed to support this finding.

We conclude that breastfeeding decreases long-term postpartum risk of type 2 diabetes in women with GDM. Breastfeeding represents a low-cost intervention for women at an increased risk of developing type 2 diabetes. Training, education, and support should be provided to instruct and encourage breastfeeding, especially among women with GDM.

ACKNOWLEDGMENTS

This study was supported in part by a grant from the German Federal Ministry of Education and Research (BMBF) to the German Center for Diabetes Research

TABLE 1
Multivariate analysis in islet autoantibody-negative women with GDM

	Adjusted hazard ratio for postpartum type 2 diabetes (95% CI)*	<i>P</i>
Insulin treatment during pregnancy	5.5 (3.7–8.2)	10^{-16}
BMI >30 at early pregnancy	1.5 (1.1–2.1)	0.014
Breastfeeding >3 months	0.54 (0.34–0.85)	0.008
Maternal age	0.99 (0.95–1.03)	0.58
Smoking during pregnancy	1.1 (0.5–2.1)	0.85
Parity status	1.03 (0.92–1.17)	0.58
Recruitment year	0.96 (0.85–1.08)	0.48

*Model adjusted for all variables shown in the table.

(DZD e.V.) and by grants from the German Federal Ministry for Education and Research (BMBF 01KD9601), the German Diabetes Association, the foundation "Children With Type 1 Diabetes" (Stiftung Das Zuckerkrankte Kind), and the German Competence Net for Diabetes Mellitus (01GI0805). This study forms part of the dissertation of Imme Kaiser (Forschergruppe Diabetes e.V., Neuherberg, Germany).

No potential conflicts of interest relevant to this article were reported.

A.-G.Z. designed the study, provided major input to the analysis and interpretation of data, contributed to writing, and critically revised the manuscript. M.W. contributed to acquisition, analysis, and interpretation of data and drafted the manuscript. I.K., M.R., M.H.H., L.L., and J.M. contributed to acquisition of the data. C.W. and S.H. provided input to the analysis and the interpretation of data. A.-G.Z. 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.

The authors thank Annette Knopff and Stephanie Krause, Institute of Diabetes Research, Helmholtz Zentrum München, Forschergruppe Diabetes, Klinikum rechts der Isar, Technische Universität München, Forschergruppe Diabetes e.V, Germany, for technical assistance; and Ezio Bonifacio, Center for Regenerative Therapies, Dresden University of Technology, Dresden, Germany, for his critical reading of the manuscript.

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