OBJECTIVE — Gestational diabetes mellitus (GDM) is associated with high birth weight in the offspring. This may lead to overweight and insulin resistance during childhood. The aim of the study was to assess the impact of GDM on overweight risk and insulin resistance in offspring.

RESEARCH DESIGN AND METHODS — BMI measurements were collected at age 2, 8, and 11 years from 232 offspring of mothers with GDM (OGDM) and compared with those from 757 offspring of mothers with type 1 diabetes (OT1D) and 431 offspring of nondiabetic mothers (ONDM) born between 1989 and 2000. Insulin resistance (homeostasis model assessment of insulin resistance [HOMA-IR]) was determined at age 8 and 11 years in 751 children (74 OGDM). Overweight was defined as BMI percentile ≥90; insulin resistance was defined by HOMA-IR.

RESULTS — Overweight prevalence was increased in OGDM compared with OT1D and to ONDM throughout childhood (age 11 years 31.1, 15.8, and 15.5%; P = 0.005). Maternal obesity was an important predictor of overweight risk in children (age 11 years odds ratio 7.0 [95% CI 1.8–27.7]; P = 0.006); birth size and maternal smoking during pregnancy were inconsistently associated with and treatment of GDM during pregnancy did not affect overweight risk. HOMA-IR was increased in OGDM compared with offspring of ONDM mothers (P = 0.01, adjusted for sex and age) and was associated with the child’s BMI (P = 0.004).

CONCLUSIONS — Overweight and insulin resistance in children is increased in OGDM compared with OT1D or ONDM. The finding that overweight risk is associated mainly with maternal obesity suggests that familial predisposition contributes to childhood growth in these offspring.
ments and pediatricians and entered into the study before the offspring reached
the age of 3 months. All children were fol-
lowed with similar follow-up visits until
the age of 14 years. In both studies,
>98% of the families were Caucasian. In
families with more than one offspring par-
ticipating in the study, only the oldest one
was included in the analyses.

Data collection
Data on weight and height were collected
at birth and at age 2, 8, and 11 years by
physicians. At birth, length was measured on
a measuring board and weight on a
weighed and categorized as obese (BMI >85 kg/
m²). Data on di-
abetes treatment (categorized as treated
or untreated) and maternal smoking during
pregnancy showed inconsistent associa-
tions with overweight risk in the offspring
(Tables 1 and 2).

Prevalence and predictors of
overweight in OGDM
Prevalence of overweight in OGDM was
17.2% at age 2 years, 20.2% at age 8 years,
and 31.1% at age 11 years. Prevalence of
overweight was increased in OGDM com-
pared with OT1D and ONDM. In OGDM,
overweight up to age 11 years was
strongly associated with maternal obesity
at early pregnancy. Birth size of the child,
maternal smoking during pregnancy, or
treatment modality of GDM were less
consistent predictors of overweight in
children of mothers with GDM. OGDM
also had higher HOMA-IR than ONDM.
Thus, GDM programs a high BMI/insulin
resistance phenotype in children.

This GDM offspring study is a pro-
spective study from birth, in which ques-
nionnaires addressing in pregnancy-
related factors were administered at birth
and children's weight and height were
measured regularly by a pediatrician ac-
cording to standard protocols. Recall bias
and over- or underestimating of growth
that may occur when data are reported by
parents are therefore avoided or limited.
Our results are based on the definition
of overweight as BMI percentile >90,
which has been proposed by the Ger-
man association of obesity during child-
hood and obesity. Findings were
consistent when overweight was de-
fined as BMI >85 or >95 percentile

RESULTS
Prevalence and predictors of
overweight in OGDM
Prevalence of overweight in OGDM was
17.2% at age 2 years, 20.2% at age 8 years,
and 31.1% at age 11 years. Prevalence of
overweight was increased in OGDM com-
pared with OT1D (15.8, 11.0, and 15.8% at
age 2, 8, and 11 years, respectively; P <
0.05, P = 0.03, and P < 0.01, respectively)
and with ONDM (11.4, 10.3, and
15.5%; P = 0.7, P = 0.02, and P = 0.005,
respectively (Fig. 1).

In OGDM, maternal obesity was a
strong predictor of overweight in children
at age 2, 8, and 11 years in the univariate
and multivariate logistic regression model
(Tables 1 and 2). The prevalence of over-
weight in children at 2, 8, and 11 years of
age was 24.6, 36.4, and 45.8% in children
of obese mothers compared with 9.2,
11.3, and 11.9% of children born to
nonobese mothers (P = 0.01, P = 0.02,
and P = 0.003, respectively) (Fig. 2).
Birth size, therapy of GDM during preg-
nancy, and maternal smoking during
pregnancy showed inconsistent associa-
tions with overweight risk in the offspring
(Tables 1 and 2).

Predictors of insulin resistance
during childhood (substudy)
In the substudy on insulin resistance,
OGDM had increased HOMA-IR com-
pared with that of children of ONDM and
of OT1D (P = 0.04 and P = 0.03, ad-
justed for age and sex) (Fig. 3). Within the
OGDM, HOMA-IR was associated with
the child's BMI (P = 0.01, adjusted for
age and sex) (supplementary Fig. 4A,
available in an online appendix at http://
care.diabetesjournals.org/cgi/content/full/ dc10-0139/DC1) but not with maternal
obesity in early pregnancy (supplemen-
tary Fig. 1B).

CONCLUSIONS — This study shows
an increased prevalence of overweight at
2, 8, and 11 years of age in OGDM com-
pared with OT1D and ONDM. In OGDM,
overweight up to age 11 years was
strongly associated with maternal obesity
at early pregnancy. Birth size of the child,
maternal smoking during pregnancy, or
treatment modality of GDM were less
consistent predictors of overweight in
children of mothers with GDM. OGDM
also had higher HOMA-IR than ONDM.
Thus, GDM programs a high BMI/insulin
resistance phenotype in children.

Insulin resistance measurements
substudy
Since 2003, fasting blood samples were
collected for the determination of insulin
resistance in OGDM as well as in offspring
from the BABYDIAB study. Insulin resis-
tance was measured by homeostasis
model assessment of insulin resistance
(HOMA-IR). A total of 751 children (in-
cluding 74 OGDM and 425 OT1D) with
data on HOMA-IR either at age 8 or 11
years were included in this substudy.
Fasting insulin was determined centrally
using an automated immunoassay ana-
lyzer (AIA 360; Tosoh, San Francisco,
CA). The interassay coefficient of varia-
tion of the insulin assay is 8.4% at a
concentration of 22.6 μU/ml and the lower
limit of detection is 0.5 μU/ml.
Although not population based, this is the largest prospective study following Caucasian children of mothers with GDM from birth in defined follow-up intervals, enabling a longitudinal analysis of factors affecting overweight risk. Nevertheless, the numbers of children of mothers with GDM remains relatively low at ages 8 and 11 years. As a consequence, CIs for some of the risk estimates are wide, and some associations may change with a larger number of subjects.

A small number of studies have examined the impact of maternal diabetes on overweight risk in offspring, differentiating between OGDM and offspring of mothers with preexisting type 1 diabetes (10,11). Clausen et al. (11) reported an increased prevalence of overweight in adults who were from GDM pregnancies (40%) or type 1 diabetes pregnancies (41%) compared with control subjects (24%). Lawlor et al. (10) found only a minor increase in the prevalence of overweight in OGDM children (30%) compared with control children (23%) and OT1D (23%). The findings of Lawlor et al. support our previous report that OT1D are not at higher risk for overweight compared with ONDM (6). However, in the current study, we saw a pronounced difference between OGDM and OT1D, whereas differences are not significant in the study of Lawlor et al. To reconcile this discrepancy, it is noted that our study in Germany reported a lower background prevalence of overweight in children compared with the U.S. and that the numbers of OT1D and OGDM are larger in our study. Our findings are unlikely to be biased with respect to the comparisons between OGDM and OT1D children because both cohorts were recruited over the same period and from the same region and ethnic background. They are also supported by expected associations of maternal BMI with overweight risk in the OGDM. However, data for potential confounders such as socioeconomic status, dietary habits during childhood, and physical activity were not collected, and we cannot exclude the possibility that the associations observed could, in some cases, be due to one or more of these confounding variables.

The finding that overweight risk is significantly higher in OGDM compared with OT1D indicates that exposure to hyperglycemia during pregnancy per se can only partly explain the increased prevalence of overweight in these children. Ma-

Table 1—Associations of maternal BMI in early pregnancy, birth size, therapy modality, and smoking behavior during pregnancy on overweight-risk (BMI ≥ 90th percentile) in OGDM at 2, 8, and 11 years of age: univariate analysis

| Maternal BMI in early pregnancy | 2 years of age | 8 years of age | 11 years of age |
|--------------------------------|----------------|----------------|----------------|
| n OR (95% CI) P value          | n OR (95% CI) P value | n OR (95% CI) P value |
| Maternal BMI in early pregnancy | 71 Reference | 29 Reference | 24 Reference |
| Normal weight (BMI <25.0 kg/m²) | 48 1.3 (0.4–4.4) 0.7 | 22 16.0 (1.8–140.9) 0.01 | 24 9.3 (1.8–48.7) 0.008 |
| Overweight (BMI 25.0–29.9 kg/m²) | 57 3.5 (1.3–9.9) 0.02 | 24 7.4 (0.8–68.2) 0.08 | 24 3.1 (0.96–9.8) 0.06 |
| Obesity (BMI ≥30 kg/m²) | 57 3.5 (1.3–9.9) 0.02 | 24 7.4 (0.8–68.2) 0.08 | 24 3.1 (0.96–9.8) 0.06 |
| Birth size | AGA 115 Reference | 48 Reference | 39 Reference |
| AGA | 10 1.1 (0.1–9.1) 1.0 | 2 | 1 |
| SGA | 59 5.2 (2.3–11.8) <0.0001 | 21 3.1 (0.96–9.8) 0.06 | 21 2.6 (0.9–8.1) 0.09 |
| LGA | 138 Reference | 55 Reference | 43 Reference |
| Therapy modality in pregnancy | Diet | 31 0.6 (0.2–1.9) 0.4 | 28 1.0 (0.4–2.7) 1.0 |
| Insulin | 72 2.4 (1.2–4.9) 0.02 | 31 0.6 (0.2–1.9) 0.4 | 28 1.0 (0.4–2.7) 1.0 |
| Maternal smoking during pregnancy | No | 111 Reference | 61 Reference | 48 Reference |
| ≥1 cigarette/day | 18 1.8 (0.5–6.3) 0.3 | 7 0.7 (0.08–6.2) 0.7 | 5 0.2 (0.02–1.6) 0.1 |
| Breast-feeding | Fully breast-fed <3 months | 94 1.0 | 43 1.0 | 45 1.0 |
| Fully breast-fed ≥3 months | 51 0.7 (0.2–1.9) 0.5 | 23 0.9 (0.2–3.6) 0.9 | 18 0.2 (0.02–1.6) 0.1 |

AGA, appropriate for gestational age; LGA, large for gestational age; SGA, small for gestational age.
ternal obesity in early pregnancy was the strongest predictor of overweight risk at 2, 8, and 11 years in OGDM. Others have shown that maternal pregravid BMI is the strongest predictor of childhood obesity independent of maternal glucose status or birth weight (7). It has also been shown that childhood BMI correlates more closely with maternal BMI than does paternal BMI, indicating that in addition to genetic influences an obese intrauterine environment per se may contribute to the higher overweight risk in children of obese mothers (12,13). This finding is strengthened by results from animal studies showing that feeding-induced obesity at conception increases the prevalence of obesity in offspring. Programming of obesity in animals was independent of changes in birth weight and was associated with significant changes in metabolic and endocrine parameters and adipose tissue cellularity independent of postnatal caloric intake (13). Finally, the possibility that the influence of maternal obesity on childhood overweight could also be due to similar adverse dietary and physical activity behaviors in obese mothers and their offspring should be considered. Similarly, the observation that maternal smoking during pregnancy is associated with overweight in the child could further indicate an influence via an “unhealthy” postnatal environment. The relationship between childhood obesity and both maternal obesity and smoking during pregnancy became more pronounced with age, further giving support to this hypothesis.

Not unexpectedly given the increased risk for overweight in OGDM, our sub-study found higher HOMA-IR in OGDM than in ONDM and also in OT1D. HOMA-IR was associated with the child’s BMI in OGDM. This is consistent with the finding of Krishnaveni et al. (14) who also reported a relationship between offspring BMI and insulin resistance in a small group of 23 female OGDM. A recently published study found that in offspring of mothers with pregravid obesity fetal insulin resistance strongly correlated with fetal adiposity (15). We could not find a significant association between insulin resistance in the offspring and maternal obesity in early pregnancy, but numbers were relatively small.

In summary, our results show that prevalence of overweight and, as a consequence, HOMA-IR during childhood is higher in OGDM than in OT1D, indicating that maternal diabetes type affects overweight risk. The finding that overweight risk was associated with maternal obesity and to a lesser extent with birth size suggests that a combination of genetic
predisposition, fetal overnutrition and lifestyle factors are likely to contribute to childhood growth in OGDM.

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H.B. researched data, contributed to discussion, and wrote the manuscript. M.P. and L.H. researched data and contributed to discussion. A.-G.Z. and S.H. researched data, contributed to discussion, wrote the manuscript, and reviewed/edited the manuscript.

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Figure 3—HOMA-IR (mean ± 1 SE) at age 11 years in OGDM compared with OT1D and ONDM.