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Increased Risk of Type 2 Diabetes in Elderly Twins

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OBJECTIVE—Genetic susceptibility, low birth weight (LBW), and aging are key etiological factors in the development of type 2 diabetes. LBW is common among twins. It is unknown whether twin status per se is associated with risk of type 2 diabetes, and valid concordance rates of type 2 diabetes in twins on a lifetime perspective are lacking.

RESEARCH DESIGN AND METHODS—A clinical study was done on a population-based cohort of same-sex elderly monozygotic (MZ) and dizygotic (DZ) twins (n = 297) and singleton control subjects (C) (n = 71) including measures of anthropometry and glucose tolerance. In addition, type 2 diabetes incidence cases in twins (n = 626) and singletons (n = 553) were identified through the National Diabetes Register.

RESULTS—Twins were more abdominally obese, insulin resistant, and glucose intolerant, as evidenced by a higher A1C (%) (means ± SD) (MZ: 6.0 ± 1.0, DZ: 5.8 ± 0.7, C: 5.6 ± 0.3, P = 0.004) and 120-min post–oral glucose tolerance test plasma glucose levels (in mmol/l) (MZ: 8.6 ± 4.6, DZ: 8.4 ± 3.9, C: 6.8 ± 2.4, P = 0.003) compared with singletons. Importantly, twins had a higher prevalence of type 2 diabetes (MZ: 17.5% [95% CI 14.4–20.6], DZ: 15.7% [13.1–18.3], C: 5.6% [3.0–8.2], P = 0.03) together with a 60% higher incidence rate of type 2 diabetes compared with singletons. Cumulative concordance rates of type 2 diabetes to the age of 84 years were similar among elderly MZ (0.76 [0.68–0.84]) and DZ (0.71 [0.63–0.78]) twins.

CONCLUSIONS—Twin status per se is associated with abdominal obesity, insulin resistance, and increased prevalence of type 2 diabetes in elderly twins. The data support a quantitatively significant impact of the fetal environment as opposed to genetics on risk of type 2 diabetes. ***Diabetes*** **58:1350–1355, 2009**

Type 2 diabetes is a complex disease with a multifactorial etiology. The finding of higher concordance rates among monozygotic (MZ) compared with dizygotic (DZ) twins in some (1–3) but not all (4) twin studies has been considered as strong evidence of a significant genetic component in type 2 diabetes. Further support has been provided by the recent identification of a number of type 2 diabetes–associated genes in the genome-wide association studies (5,6). However, the combined effect of these type 2 diabetes susceptibility genes accounts for <10% of the population risk of the disease, and even for the most significant type 2 diabetes susceptibility genes, such as the *TCF7L2* gene, the predominant proportion of the carriers of risk alleles will not develop type 2 diabetes on a lifetime perspective (5).

Low birth weight is another known risk factor for type 2 diabetes and is more common in twins compared with singletons (7). In accordance with the "fetal origin hypothesis" (8–10), we have demonstrated elevated plasma glucose and insulin profiles during an oral glucose challenge in MZ compared with DZ twins (11). A more recent study of nondiabetic elderly twins (12) provided some mechanistic explanation in such that monozygosity was associated with reduced peripheral insulin sensitivity. Furthermore, twin status per se was related to increased hepatic glucose production (i.e., hepatic insulin resistance) compared with elderly age-matched singleton control subjects (12). Whether these metabolic differences within and between twins and singletons have any clinical importance, as reflected in an increased risk of developing overt type 2 diabetes, is currently unknown.

Age is an important etiological factor in type 2 diabetes and has been shown to play a key role in unmasking the unfavorable metabolic effects associated with adverse fetal environment (13,14). In addition, age may be equally important in modulating the genetic influence on type 2 diabetes; however, valid concordance rates of type 2 diabetes among the oldest twins are lacking. We hypothesized that age may change the relative genetic effect on type 2 diabetes as well as the effect of twin and zygosity status on type 2 diabetes. Therefore, we performed a 10-year follow-up study of a population-based cohort of elderly twins examined in 1995 (4,11) together with an age-matched cohort of singleton control subjects.

RESEARCH DESIGN AND METHODS

This study represents a 10-year follow-up study of a population-based cohort of elderly MZ and same-sex DZ twins (n = 626) previously investigated in 1995 (4,11). Among these twins, 122 subjects (MZ, n = 43 [16.6%]; DZ, n = 79 [21.5%]), P = 0.17) were deceased in 2005 when the follow-up study was performed. Of the remaining 504 twins, 207 twins (MZ, n = 91; DZ, n = 116) either did not wish to or were refrained from participation by the investigator because of severe current or chronic illness, including cancer or severe dysfunction of major organ systems. Although the clinical examination was performed in close proximity to the homes of the participants, and transportation was provided, some subjects were not able to participate solely due to reduced mobility. A total of 297 twins (MZ, n = 125, of which 49 were full pairs; DZ, n = 172, of which 55 were full pairs) equivalent to 57.9 and 59.7% of eligible MZ and DZ twins, respectively, participated in a subsequent clinical examination. One additional MZ twin (cotwin to a twin participating in the baseline 1994–1995 study) was included in the follow-up study. The final sample of twins undergoing the clinical examination was 298 twins. The singleton control subjects (n = 71) were recruited among spouses to the participating twins.

All spouses (n = 553) of the 626 twins included in the baseline study were identified through the Civil Registration System. Both twins and spouses were followed for death through the Civil Registration System and occurrence of type 2 diabetes through the Danish National Diabetes Register (NDR) (15).

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TABLE 1
Baseline clinical characteristics of 626 MZ and DZ elderly twins stratified according to whether they were deceased or alive and eligible for the follow-up study conducted in 2005

	MZ				DZ			
	Deceased	No follow-up	Follow-up		Deceased	No follow-up	Follow-up	
n (M/F)	43 (23/20)	91 (37/54)	125 (71/54)	P_{MZ}	79 (50/29)	116 (51/65)	172 (75/97)	P_{DZ}
Age at baseline (years)	69.1 ± 3.7	68.1 ± 3.8	65.5 ± 4.9		68.3 ± 3.5	66.9 ± 5.1	64.7 ± 5.3	
Anthropometry								
Height (cm)	162.8 ± 8.5	164.5 ± 9.7	167.9 ± 9.7	0.004	167.2 ± 10.4	164.8 ± 9.1	167.2 ± 8.4	0.02
Weight (kg)	67.9 ± 14.0	70.0 ± 13.9	74.3 ± 13.6	0.12	71.6 ± 15.2	71.2 ± 13.3	72.4 ± 12.9	0.27
BMI (kg/m^2)	25.5 ± 4.2	25.8 ± 4.6	26.3 ± 4.3	0.55	25.6 ± 4.8	26.2 ± 4.7	25.8 ± 3.9	0.28
Waist (cm)	90.1 ± 14.1	88.9 ± 12.6	91.1 ± 11.5	0.84	92.2 ± 13.8	89.7 ± 12.3	87.7 ± 12.4	0.13
Hip (cm)	100.3 ± 8.7	102.5 ± 9.0	102.7 ± 7.8	0.45	101.6 ± 8.9	102.8 ± 9.5	103.0 ± 8.1	0.52
WHR	0.90 ± 0.10	0.87 ± 0.08	0.89 ± 0.08	0.31	0.91 ± 0.08	0.87 ± 0.09	0.85 ± 0.10	0.01
OGTT: glucose (mmol/l)								
0 min	6.3 ± 1.4	6.1 ± 1.5	6.1 ± 1.9	0.78	6.3 ± 1.9	6.2 ± 1.8	5.9 ± 1.4	0.10
30 min	10.4 ± 2.3	9.8 ± 2.3	9.8 ± 2.5	0.36	10.6 ± 3.3	9.8 ± 2.7	9.0 ± 2.3	0.001
120 min	9.0 ± 4.3	8.5 ± 4.6	7.4 ± 4.1	0.06	8.7 ± 4.7	8.3 ± 4.6	7.0 ± 3.6	0.004
OGTT: insulin (pmol/l)								
0 min	52.9 ± 31.9	45.3 ± 26.3	45.9 ± 24.2	0.43	44.8 ± 25.3	48.9 ± 37.6	41.7 ± 22.5	0.05
30 min	309.4 ± 197.3	324.2 ± 353.7	324.5 ± 196.1	0.36	304.0 ± 273.1	320.8 ± 285.4	259.5 ± 167.9	0.08
120 min	418.6 ± 389.4	371.1 ± 513.1	253.7 ± 194.3	0.05	301.8 ± 306.0	345.7 ± 338.8	245.7 ± 223.3	0.01
Glucose tolerance status								
Type 2 diabetes/IGT/NGT (%)	23.3/27.9/48.8	17.6/23.1/59.3	8.1/16.0/75.9	0.008	21.5/30.4/48.1	13.8/25.9/60.3	5.8/16.9/77.3	<0.001

Data are means ± SD unless otherwise stated. *P* value expresses the level of statistical significance for the comparison between the three groups (deceased, no follow-up, and follow-up) (ANOVA) within MZ (P_{MZ}) and DZ (P_{DZ}) twins, respectively. The analyses have been adjusted for sex.

The register-based diagnosis of type 2 diabetes is based on hospital diagnosis (in- or outpatient) and/or consecutive plasma glucose measures performed in the primary health care sector (15).

The study was approved by the regional ethical committees and was conducted according to the principles of the Helsinki Declaration.

The clinical examination included a standardized 75-g oral glucose tolerance test (OGTT) performed after an overnight fast. Blood samples were taken before and 30, 60, and 120 min after glucose ingestion. Plasma glucose and insulin concentrations were analyzed as previously described (4,11). The fasting blood samples were furthermore analyzed for serum triglycerides and HDL cholesterol using commercial kits from Boerhinger Mannheim (Mannheim, Germany).

Weight and height were measured with the subject in lightweight clothes without shoes, and BMI was calculated. Waist circumference was measured using a soft tape on standing subjects midway between the lowest rib and the iliac crest. Hip circumference was measured over the widest part of the gluteal region, and the waist-to-hip ratio (WHR) was calculated accordingly.

The same type 2 diabetes diagnostic criteria were used in both the baseline and follow-up study: *1*) known type 2 diabetes, that is, diagnosis of diabetes after the age of 40 years and current treatment with antidiabetic agents or diet, and/or *2*) a fasting plasma glucose concentration ≥7.8 mmol/l and/or 2-h post-OGTT plasma glucose concentration ≥11.1 mmol/l. Impaired glucose tolerance (IGT) was defined as fasting plasma glucose concentration <7.8 mmol/l and 2-h post-OGTT plasma glucose concentrations between 7.8 and 11.1 mmol/l.

Areas under the curve (AUC) for plasma glucose, insulin, and C-peptide were calculated for the initial 30-min period and for the entire 120-min period using the trapezoidal method. Insulin resistance was assessed using the homeostasis model assessment (HOMA) (16) and whole-body insulin sensitivity indexes (17). As measurements for insulin secretion, we calculated the HOMA β-cell function and insulinogenic indexes, i.e., the ratio between the 30-min increment in insulin and glucose concentration after oral glucose loading.

Statistical methods. The distributions of zygosity and sex among nonparticipating and participating twin pairs as well as the prevalence of type 2 diabetes and IGT were compared by χ^2 tests. The comparisons of continuous variables between participating and nonparticipating MZ and DZ twins and singletons were performed with a mixed model (proc mixed in SAS, version 9.1, SAS Institute). We adjusted for the intra–twin-pair relationship in the analyses by including a random-effect term for twin-pair membership with zygosity-specific variance and a fixed-effect term for zygosity in the model. Raw data are presented as means ± SD.

Cumulative proband-wise concordance rates of type 2 diabetes from age 45 to 84 years were estimated for MZ and DZ twins and compared with a χ^2 test (18,19). Proband-wise concordance rate expresses the risk of disease among co-twins of affected twins and is comparable to the recurrence risk in other groups of relatives and in the general population.

The incidence rates of diabetes from the NDR (15) were tabulated by zygosity (MZ, DZ, spouse), sex and age, and calendar time in 1-year classes using the SAS-macro %Lexis for splitting follow-up time, and modeled using a Poisson regression model with smooth effects of age and calendar time, and effects of sex and zygosity in three classes (MZ, DZ, spouse). Prevalence of type 2 diabetes from the Danish National Diabetes Register as of 31 December 2005 was tabulated by sex, zygosity, and age.

RESULTS

Clinical characteristics of MZ and DZ twins at baseline according to participation in the follow-up study. Both MZ and DZ twins participating in the follow-up study were younger, taller, and had lower post-OGTT plasma glucose and insulin levels at baseline than those not participating. Moreover, the participating DZ had lower WHR than nonparticipating DZ twins (Table 1). Finally, the distribution of type 2 diabetes, IGT, and NGT baseline was different in the twins participating in the follow-up study among both MZ ($P = 0.008$) and DZ ($P < 0.001$) twins (Table 1). There was no difference in participation according to glucose tolerance status between MZ and DZ ($P = 0.76$).

Follow-up study glucose profiles. During the 10-year follow-up period, fasting plasma glucose levels (means ± SD, mmol/l) were unchanged within both MZ (MZ_{1995}: 6.1 ± 1.9 vs. MZ_{2005}: 6.1 ± 1.8, $P = 0.87$), and DZ (DZ_{1995}: 5.9 ± 1.4 vs. DZ_{2005}: 5.8 ± 1.0, $P = 0.78$) twins. In MZ twins, the 30-min plasma glucose level was unchanged (MZ_{1995}: 9.8 ± 2.5 vs. MZ_{2005}: 9.6 ± 2.6, $P = 0.39$), whereas there was a significant increase over time within DZ twins (DZ_{1995}: 9.0 ± 2.3 vs. DZ_{2005}: 9.6 ± 2.1, $P < 0.0001$). Accordingly, the increment in 30-min plasma glucose

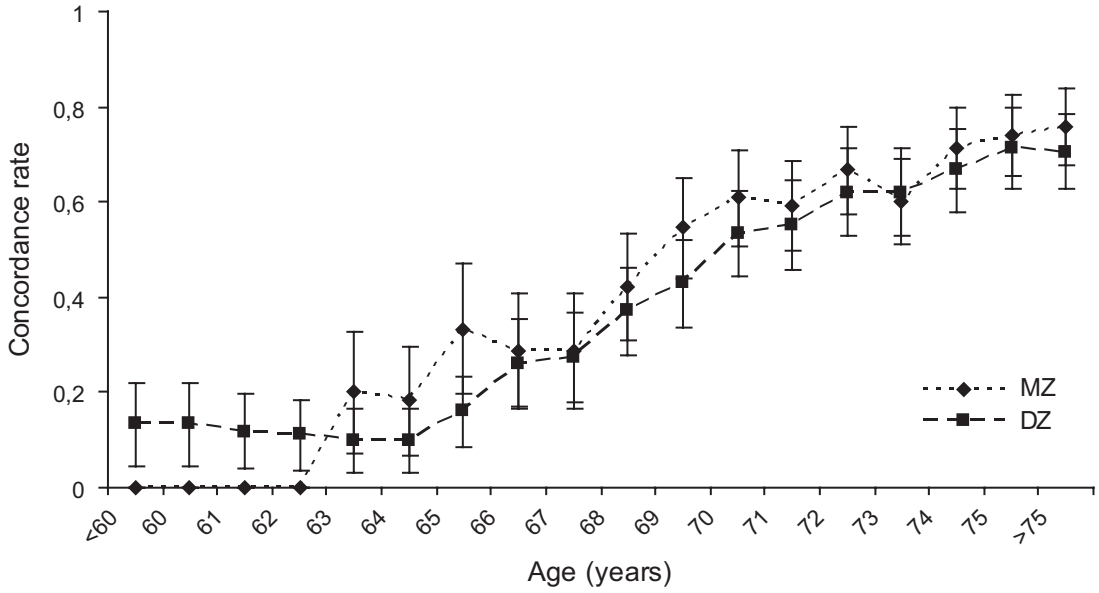

FIG. 1. Age-related cumulative concordance rates (SE) for type 2 diabetes in MZ and DZ elderly twins.

levels over the 10-year follow-up period was significantly higher in DZ twins (MZ: −0.18 ± 2.2; DZ: 0.6 ± 1.8, P = 0.006). There was a significant deterioration in glucose tolerance with age with an increase in 120-min plasma glucose levels in both MZ (MZ_{1995}: 7.4 ± 4.1 vs. MZ_{2005}: 8.5 ± 4.7, $P < 0.0001$) and DZ twins (DZ_{1995}: 7.0 ± 3.6 vs. DZ_{2005}: 8.4 ± 3.9, $P < 0.0001$). The increment in 120-min plasma glucose levels was of similar magnitude in MZ (1.1 ± 2.7) and DZ (1.6 ± 2.4) twins (P = 0.22).

Cumulative concordance rates. The age-adjusted cumulative proband-wise risk at age 84 years, which approximates the lifetime risk of type 2 diabetes, was similar in MZ (0.76 [0.68–0.84]) and DZ (0.71 [0.63–0.78]) twin pairs (Fig. 1).

Influence of zygosity and twin status on glucose metabolism. A total of 71 singletons were included as control subjects in the 2005 follow-up study. The singleton control subjects were slightly younger than the twins (P = 0.004), and the distribution of sex differed significantly between the groups of singletons and twins (P = 0.006). Therefore, adjustments were performed for sex and age in the subsequent analyses. Adult height, weight, and BMI were similar in twins and singletons, whereas twins were significantly more abdominally obese with a higher WHR than singletons (P = 0.02) (Table 2). Plasma glucose levels during the OGTT were similar in MZ and DZ twins, whereas post-OGTT plasma glucose levels at time points 30 (P = 0.05), 60 (P = 0.04), and 120 (P = 0.004) min were significantly higher in twins than in singletons (Fig. 2*A*), as were the incremental $AUC_{glucose}$ levels during the initial 30 min and the total 120 min of the OGTT. Accordingly, A1C concentration was higher (P = 0.004) in twins than singletons, and most importantly, the prevalence of type 2 diabetes was higher in twins than in singletons (MZ: 17.5%; DZ: 15.7%; singletons: 5.6%, P = 0.03), whereas the prevalence of IGT was similar (MZ: 27.8%; DZ: 25.0%; singletons: 22.5%).

Plasma insulin levels were similar in twins and singletons before and during the OGTT, except at time point 120 min, where twins had significantly higher levels compared with singletons (P = 0.01) (Fig. 2*B*). Plasma C-peptide levels were significantly increased in twins compared with singletons at all time points, as were the incremental $AUC_{C\text{-}peptide}$ levels (all $P < 0.001$) (Fig. 2*C*). Twins tended to be more insulin resistant than singletons, expressed as the HOMA (P = 0.12) and whole-body insulin sensitivity indexes (P = 0.04). Finally, systolic and diastolic blood pressure as well as serum lipids (i.e., triglycerides, total cholesterol, LDL cholesterol, and HDL cholesterol) were similar in twins and singletons (data not shown).

Incidence rate of diabetes by zygosity and twin status. The singleton control subjects exhibited a significantly lower prevalence of type 2 diabetes subsequent to oral glucose testing compared with twins. To determine whether this was a true finding or merely due to selection, we investigated incidence rates of type 2 diabetes, as recorded in the NDR during the 10-year follow-up period. The rate ratio of type 2 diabetes adjusted for sex and age between the groups was 1.51 (0.93–2.44, P = 0.09) for MZ versus singletons, 1.69 (1.10–2.59, P = 0.02) for DZ versus singletons, and 1.12 (0.71–1.77, P = 0.63) for MZ versus DZ. The rate ratio between all twins and singletons was 1.62 (1.10–2.38, P = 0.02). The register-based diabetes prevalence by the end of 2005 was 4.0% in singletons and 9.1% (MZ: 8.2%; DZ: 9.8%) in twins (all participants in the baseline examination, P = 0.004).

DISCUSSION

We have demonstrated that elderly twins exhibit a higher degree of abdominal obesity, glucose intolerance, and insulin resistance, and most importantly, a higher prevalence and incidence rate of type 2 diabetes than singletons. This is in accordance with the idea of pre- and early postnatal programming as an underlying key player in the development of the dysmetabolic syndrome later in life.

Singletons were included in the follow-up study because of our previous observation that elderly nondiabetic twins exhibited higher rates of hepatic glucose production (12) compared with age-matched singletons and therefore may be at increased risk of developing overt type 2 diabetes. In this study, we found a higher prevalence of type 2 diabetes in twins than singletons. Unfortunately, the methodology does not allow mechanistic explanations of this phenom-

TABLE 2
Clinical characteristics in elderly MZ and DZ twins and singletons included in the follow-up study in 2005

	MZ	DZ	Singleton	*P*
n (M/F)	126 (71/55)	172 (74/97)	71 (24/47)	0.006
Age at follow-up	74.4 ± 9.5	73.7 ± 0.5	71.4 ± 0.7	0.004
Birth anthropometry				
Weight (g)	2,656 ± 478	2,672 ± 459	3,513 ± 529	<0.0001
Length (cm)	46.9 ± 3.5	48.1 ± 2.1	51.4 ± 2.1	<0.0001
Ponderal index (g/cm^3)	24.7 ± 6.2	23.7 ± 3.9	26.2 ± 3.2	0.001
Adult anthropometry				
Weight (kg)	73.2 ± 13.6	72.2 ± 12.7	71.3 ± 12.8	0.91
Height (cm)	166.8 ± 9.8	166.3 ± 8.6	165.4 ± 8.9	0.71
BMI (kg/m^2)	26.3 ± 4.7	26.1 ± 3.9	26.1 ± 4.1	0.97
WHR	0.92 ± 0.09	0.89 ± 0.10	0.86 ± 0.09	0.02
A1C	6.0 ± 1.0	5.8 ± 0.7	5.6 ± 0.3	0.004
OGTT: glucose				
$iAUC_{0–30\ min}$	54.1 ± 22.1	56.3 ± 23.8	47.2 ± 21.1	0.05
$iAUC_{0–120\ min}$	361.9 ± 232.7	376.1 ± 229.5	264.7 ± 185.4	0.03
OGTT: insulin				
$iAUC_{0–30\ min}$	4,410 ± 2,871	4,004 ± 2,830	4,331 ± 2,827	0.32
$iAUC_{0–120\ min}$	33,531 ± 18,978	32,425 ± 22,589	31,010 ± 19,985	0.40
OGTT: C-peptide				
$iAUC_{0–30\ min}$	22,251 ± 10,397	20,748 ± 10,024	17,304 ± 10,356	<0.0001
$iAUC_{0–120\ min}$	222,194 ± 80,846	214,865 ± 81,998	162,184 ± 90,572	<0.0001
HOMA-IR	2.2 ± 2.4	1.8 ± 1.1	1.5 ± 0.9	0.12
Insulin sensitivity index	15.7 ± 8.7	16.5 ± 7.9	19.4 ± 8.8	0.04
HOMA-IS	64.7 ± 43.3	63.2 ± 35.2	56.1 ± 25.5	0.29
Insulinogenic index	103.1 ± 129.4	79.2 ± 74.4	90.5 ± 175.5	0.07

Data are means ± SD. *P* value expresses the level of statistical significance for the comparison between the three groups (MZ, DZ, and singletons) (ANOVA). The analyses have been adjusted for sex and age. iAUC, incremental area under curve.

enon, although the indirect OGTT measures of insulin resistance and secretion indicates reduced insulin sensitivity in twins relative to singletons. Notably, despite the somewhat subtle influence of twin status on OGTT plasma insulin levels, plasma C-peptide concentrations at all time points were increased in twins compared with singletons, consistent with a state of compensatory increased pancreatic insulin secretion in the presence of a higher hepatic insulin extraction in twins compared with singletons. Indeed, studies have suggested an elevated hepatic extraction rate in diabetic subjects (20,21).

We have previously demonstrated significantly elevated 30-min concentrations and AUCs of plasma glucose and insulin in MZ compared with DZ twins (11). We were able to replicate these differences in plasma glucose profiles at baseline in the subpopulation of MZ and DZ twins participating in both studies. However, the 10-year follow-up study revealed similar OGTT plasma glucose profiles in MZ and DZ twins. The convergence of these metabolic profiles during the 10-year follow-up period was primarily due to a somewhat "delayed" increase in 30-min plasma glucose levels in the DZ twins. MZ and DZ twins had similar 2-h plasma glucose levels at baseline and follow-up and had similar increments with advancing age. These findings suggest that the deterioration in plasma glucose profiles after a glucose challenge associated with advancing age (22) may be more accelerated in MZ twins, whereas DZ twins preserve a conspicuous degree of insulin sensitivity to a higher age, resulting in lower postprandial glucose profiles.

The twins participating in the follow-up study were younger and more glucose tolerant at baseline than the twins that were either deceased or nonparticipants. Nevertheless, we demonstrated an approximately twofold higher prevalence of type 2 diabetes in these surviving and healthy twins compared with singleton control subjects. Although the NDR may not be complete, there is no reason to suspect any dissimilar or skewed recordings between twins and singletons. The NDR incidence rates of a 60% higher type 2 diabetes risk in twins compared with singletons, including all twins and spouses irrespective of participation in follow-up study or death, indeed confirmed the data obtained from the clinical (OGTT) examinations.

The effect of aging on the relative genetic influence on the development of type 2 diabetes was assessed by means of cumulative concordance rates. Interestingly, the lifetime risk of type 2 diabetes (to age 84 years) among healthy co-twins to diabetic twins was similar in MZ and DZ twins, suggesting that the relatively modest influence of genetic variation on the development of type 2 diabetes per se does not change significantly within the range of 60–80 years of age. Most interestingly, the cumulative concordance rate (and hence recurrence risk of) type 2 diabetes of ~70% in DZ twins is considerably higher than the lifetime risk of ~35% (23) for first-degree relatives (i.e., siblings) who share the same amount of genes with their diabetic or nondiabetic proband as DZ twins. Furthermore, the cumulative concordance rate for type 2 diabetes to age 84 years exceeds 0.50, which represents the rate that should be expected in DZ twins for a dominant inherited monogenic disease. These results indeed support that twin status per se represents a risk factor for the development of type 2 diabetes. Although the birth weights differed markedly between twins and singletons (Table 2), we did not find any statistically significant association between birth weight in the subset of twins ($n = 188$) or singletons ($n = 59$) with known birth weights. This may to some extent be due to lack of statistical power

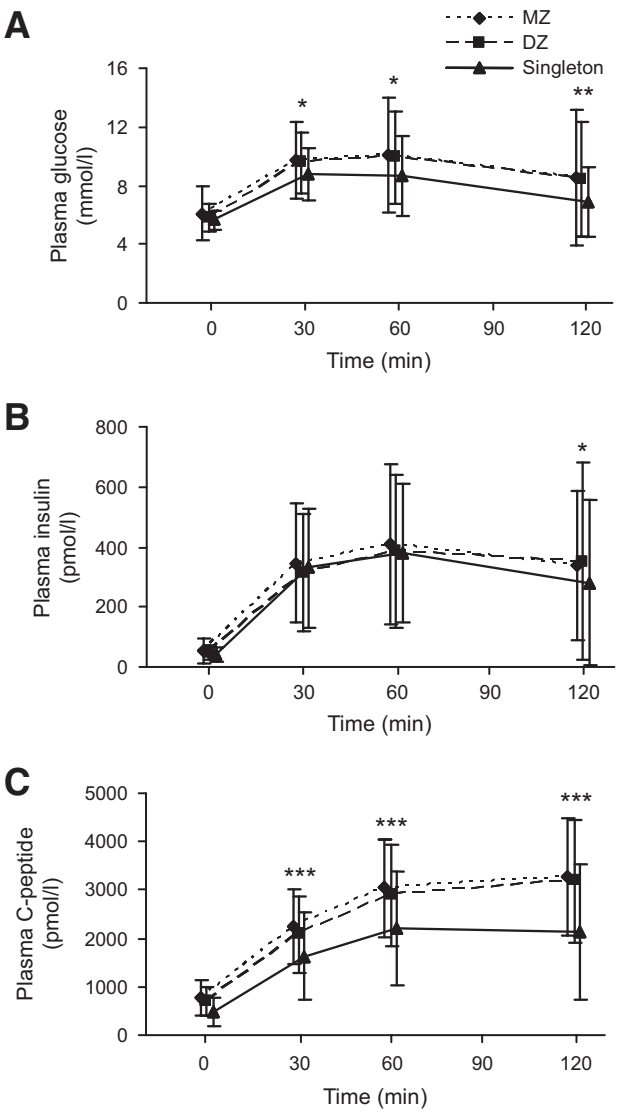

FIG. 2. Plasma glucose (*A*), insulin (*B*), and C-peptide (*C*) concentrations during an OGTT in elderly MZ and DZ twins and singletons included in the follow-up study. Data are presented as means ± SD. **P* < 0.05, ***P* < 0.01, ****P* < 0.001 twins vs. singleton.

in each of the subgroups. Furthermore, it supports our previous conclusion of the impact of fetal programming by twin and zygosity status going beyond the impact of birth weight per se in twins (12).

Although the BMI was similar in twins and singletons at the clinical follow-up examination, both MZ and DZ twins had an elevated WHR, and thereby increased abdominal obesity, compared with the singleton control subjects. Indeed, we and others have previously shown that low birth weight and an adverse intrauterine environment is associated with abdominal obesity (24,25). Abdominal obesity is a hallmark of insulin resistance, type 2 diabetes, and the metabolic syndrome, contributing to some unknown extent to the documented insulin resistance and glucose intolerance in the twins compared with singletons in this study. The possibility remains that an accelerated postnatal catch-up growth in the twins rather than their documented lower birth weights per se may explain the increased abdominal obesity in the twins. Furthermore, other effects of twinning not directly related to fetal growth rate including periconceptional nutrition might theoretically explain the finding of increased abdominal obesity and risk of type 2 diabetes in twins compared with singletons (26).

In conclusion, twin status is evidently associated with an increased risk of type 2 diabetes, with elderly twins exhibiting a higher degree of abdominal obesity, glucose intolerance, and insulin resistance and most importantly a higher prevalence of type 2 diabetes compared with singletons. These findings together with the indication of a predominant role of nongenetic factors in the etiology of type 2 diabetes support the notion of pre- and early postnatal programming as a key player in the development of type 2 diabetes and various components of the metabolic syndrome in adult life.

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

REFERENCES

1. Diabetes mellitus in twins: a cooperative study in Japan. Committee on Diabetic Twins, Japan Diabetes Society. Diabetes Res Clin Pract 1988;5:271–280
2. Kaprio J, Tuomilehto J, Koskenvuo M, Romanov K, Reunanen A, Eriksson J, Stengård J, Kesäniemi YA. Concordance for type 1 (insulin-dependent) and type 2 (non-insulin- dependent) diabetes mellitus in a population-based cohort of twins in Finland. Diabetologia 1992;35:1060–1067
3. Newman B, Selby JV, King MC, Slemenda C, Fabsitz R, Friedman GD. Concordance for type 2 (non-insulin-dependent) diabetes mellitus in male twins. Diabetologia 1987;30:763–768
4. Poulsen P, Kyvik KO, Vaag A, Beck-Nielsen H. Heritability of type II (non-insulin- dependent) diabetes mellitus and abnormal glucose tolerance: a population-based twin study. Diabetologia 1999;42:139–145
5. Frayling TM. Genome-wide association studies provide new insights into type 2 diabetes aetiology. Nat Rev Genet 2007;8:657–662
6. Zeggini E, Scott LJ, Saxena R, Voight BF, Marchini JL, Hu T, de Bakker PI, Abecasis GR, Almgren P, Andersen G, Ardlie K, Bostrom KB, Bergman RN, Bonnycastle LL, Borch-Johnsen K, Burtt NP, Chen H, Chines PS, Daly MJ, Deodhar P, Ding CJ, Doney AS, Duren WL, Elliott KS, Erdos MR, Frayling TM, Freathy RM, Gianniny L, Grallert H, Grarup N, Groves CJ, Guiducci C, Hansen T, Herder C, Hitman GA, Hughes TE, Isomaa B, Jackson AU, Jorgensen T, Kong A, Kubalanza K, Kuruvilla FG, Kuusisto J, Langenberg C, Lango H, Lauritzen T, Li Y, Lindgren CM, Lyssenko V, Marvelle AF, Meisinger C, Midthjell K, Mohlke KL, Morken MA, Morris AD, Narisu N, Nilsson P, Owen KR, Palmer CN, Payne F, Perry JR, Pettersen E, Platou C, Prokopenko I, Qi L, Qin L, Rayner NW, Rees M, Roix JJ, Sandbaek A, Shields B, Sjogren M, Steinthorsdottir V, Stringham HM, Swift AJ, Thorleifsson G, Thorsteinsdottir U, Timpson NJ, Tuomi T, Tuomilehto J, Walker M, Watanabe RM, Weedon MN, Willer CJ, Illig T, Hveem K, Hu FB, Laakso M, Stefansson K, Pedersen O, Wareham NJ, Barroso I, Hattersley AT, Collins FS, Groop L, McCarthy MI, Boehnke M, Altshuler D. Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. Nat Genet 2008;40:638–645
7. Hall JG. Twinning. Lancet 2003;362:735–743
8. Hales CN, Barker DJ, Clark PM, Cox LJ, Fall C, Osmond C, Winter PD. Fetal and infant growth and impaired glucose tolerance at age 64. BMJ 1991;303:1019–1022
9. Ravelli AC, van der Meulen JH, Michels RP, Osmond C, Barker DJ, Hales CN, Bleker OP. Glucose tolerance in adults after prenatal exposure to famine. Lancet 1998;351:173–177
10. Ravelli GP, Stein ZA, Susser MW. Obesity in young men after famine exposure in utero and early infancy. N Engl J Med 1976;295:349–353
11. Poulsen P, Vaag A, Beck-Nielsen H. Does zygosity influence the metabolic profile of twins? A population based cross sectional study. BMJ 1999;319:151–154
12. Poulsen P, Vaag A. The intrauterine environment as reflected by birth size and twin and zygosity status influences insulin action and intracellular glucose metabolism in an age- or time-dependent manner. Diabetes 2006;55:1819–1825
13. Ozanne SE, Wang CL, Coleman N, Smith GD. Altered muscle insulin sensitivity in the male offspring of protein-malnourished rats. Am J Physiol 1996;271:E1128–E1134

14. Poulsen P, Levin K, Beck-Nielsen H, Vaag A. Age-dependent impact of zygosity and birth weight on insulin secretion and insulin action in twins. Diabetologia 2002;45:1649–1657
15. Carstensen B, Kristensen J, Ottosen P, Borch-Johnsen K, on behalf of the steering group of the National Diabetes Register. The Danish National Diabetes Register: trends in incidence, prevalence and mortality. Diabetologia 2008;51:2187–2196
16. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–419
17. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 1999;22:1462–1470
18. McGue M. When assessing twin concordance, use the probandwise not the pairwise rate. Schizophr Bull 1992;18:171–176
19. Smith C. Concordance in twins: methods and interpretation. Am J Hum Genet 1974;26:454–466
20. Cobelli C, Toffolo GM, Dalla Man C, Campioni M, Denti P, Caumo A, Butler P, Rizza R. Assessment of beta-cell function in humans, simultaneously with insulin sensitivity and hepatic extraction, from intravenous and oral glucose tests. Am J Physiol Endocrinol Metab 2007;293:E1–E15
21. Tura A, Ludvik B, Nolan JJ, Pacini G, Thomaseth K. Insulin and C-peptide secretion and kinetics in humans: direct and model-based measurements during OGTT. Am J Physiol Endocrinol Metab 2001;281: E966–E974
22. Harris MI, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, Little RR, Wiedmeyer HM, Byrd-Holt DD. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults: the Third National Health and Nutrition Examination Survey, 1988–1994. Diabetes Care 1998;21:518–524
23. Kobberling J, Tillil H. Empirical risk figures for first degree relatives of non-insulin dependent diabetes. *Seronto Symposium No 47: The Genetics of Diabetes Mellitus*. Academic Press, 1982
24. Rasmussen EL, Malis C, Jensen CB, Jensen JE, Storgaard H, Poulsen P, Pilgaard K, Schou JH, Madsbad S, Astrup A, Vaag A. Altered fat tissue distribution in young adult men who had low birth weight. Diabetes Care 2005;28:151–153
25. Vielwerth SE, Jensen RB, Larsen T, Holst KK, Mølgaard C, Greisen G, Vaag A. The effect of birthweight upon insulin resistance and associated cardiovascular risk factors in adolescence is not explained by fetal growth velocity in the third trimester as measured by repeated ultrasound fetometry. Diabetologia 2008;51:1483–1492
26. Rumball CW, Harding JE, Oliver MH, Bloomfield FH. Effects of twin pregnancy and periconceptional undernutrition on maternal metabolism, fetal growth and glucose-insulin axis function in ovine pregnancy. J Physiol 2008;586:1399–1411