Fetal and Infant Growth and Glucose Tolerance in the Hertfordshire Cohort Study

A Study of Men and Women Born Between 1931 and 1939

David I.W. Phillips, Peter Goulden, Holly E. Syddall, Avan Aihie Sayer, Elaine M. Dennison, Helen Martin, Cyrus Cooper, and the Hertfordshire Cohort Study Group

The Hertfordshire Cohort Study based in the U.K. was the first to report associations between fetal or infant growth and the prevalence of adult glucose intolerance and diabetes. Many studies have replicated the findings with respect to birth weight, but there have been fewer observations in relationship to infant growth, because this is infrequently recorded in routine datasets. Recently, we carried out glucose tolerance tests in a more recently born group of men and women from the Hertfordshire Cohort Study. The objective was to determine whether the associations with weights at birth and 1 year of age reported in the original study of people born between 1920 and 1930 were observed in people born between 1931 and 1939. Birth weight was inversely related to the overall prevalence of diabetes (comprising newly diagnosed as well as existing cases) in men and women. However, weight at 1 year of age was not associated with diabetes in either sex. Analysis of data from the glucose tolerance tests showed that both sexes had evidence of higher insulin and glucose concentrations in people who were small at birth or during infancy. Finally, direct comparison of 2-h plasma glucose concentrations in the previous and current Hertfordshire study suggested that both surveys showed broad similarity of the trends in glucose tolerance with birth or infant weights; most differences arose at the extremes of the birth weight, possibly because of the small numbers of subjects studied in these groups. *Diabetes* 54 (Suppl. 2):S145–S150, 2005

Studies originating in the Hertfordshire cohort in the U.K. were the first to show that low birth and infant weights are linked with a higher prevalence of impaired glucose tolerance and type 2 diabetes in adult life (1,2). The studies showed strong and continuous associations between early growth and the prevalence of these conditions. For example, the prevalence of men with impaired glucose tolerance fell progressively from 26% among those who had weighed ≤18 lb (≤8.16 kg) at 1 year of age to 13% among those who had weighed ≥27 lb (≥12.25 kg). Corresponding figures for diabetes were 17% and nil. The associations appear to be independent of known adult risk factors for diabetes, including adult BMI. These findings spawned the fetal origins hypothesis, which proposes that the birth and infant weight associations result from fetal undernutrition (3). It is suggested that fetal undernutrition causes long-term changes in body composition and physiology, which in turn predispose to adult glucose intolerance and diabetes. The hypothesis is strongly supported by a large body of data from animal experiments that show that experimental undernutrition during gestation in a variety of species, including rodents, sheep, and guinea pigs, leads to altered glucose tolerance in the offspring (4).

In light of these findings, a number of studies have been carried out in Europe, North America, and developing countries (5). These broadly confirm the Hertfordshire findings, although the strength of the associations with early growth reported varies considerably (6). Most studies have reported the effect of birth weight. Fewer report the effect of infant weight because this information is rarely available in the routine datasets that form the basis for these retrospective studies. In the original Hertfordshire study, the relationship between glucose tolerance and birth weight was far stronger in men (1) than in women (2). However, not many studies have reported results separately for men and women, and at present, there appears to be no consensus as to whether the effect of birth or infant weight differs by sex (6). The original Hertfordshire studies were carried out in men and women born in Hertfordshire between 1920 and 1930. Recently, the Hertfordshire Cohort Study was enlarged to include men and women born between 1931 and 1939; the studies carried out included a full oral glucose tolerance test. In this article, we report the relationship between birth or infant weight and glucose tolerance in this new cohort and how the results compare with the original study.

RESEARCH DESIGN AND METHODS

As previously described (1), in Hertfordshire from 1911 to 1948, each birth was notified by the attending midwife and the birth weight was recorded. Subsequently, health visitors who saw each child during infancy recorded his or her weight at the age of 1 year. We used the National Health Service Central Registry at Southport to trace 1,760 men and 1,447 women born in Hertfordshire between 1931 and 1939 who were singleton births and had both birth and infant weights recorded and were still resident in East Hertfordshire in the late 1990s. Permission to contact 1,397 men and 1,364 women was obtained from the general practitioners. Of these subjects 768 (55%) of the men and 714 (52%) of the women agreed to take part in a home interview in which trained nurses collected information on the medical and social history. The subjects were then invited to a local clinic for several investigations. Anthropometric measurements included height, weight, and waist, hip, mid–upper arm, and mid-thigh circumferences. Skinfold thicknesses were measured in triplicate with the use of Harpenden skinfold calipers (British Indicators, Luton, U.K.) at the triceps, biceps, subscapular, and suprailiac sites on the nondominant side.

From the Medical Research Council Epidemiology Resource Centre, University of Southampton, Southampton General Hospital, Southampton, U.K.

Address correspondence and reprint requests to Professor David Phillips, MRC Epidemiology Resource Centre, Southampton General Hospital, Tremona Rd., Southampton, SO16 6YD, U.K. E-mail: diwp@mrc.soton.ac.uk.

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HOMA, homeostasis model assessment.

TABLE 1
Percentages of men and women from the Hertfordshire Cohort Study with impaired glucose tolerance or diabetes according to birth weight

Birth weight [lb (kg)]	*n*	Number (%) with existing diabetes	Number (%) with 2-h glucose (mmol/l) 7.8–11.0	Number (%) with 2-h glucose (mmol/l) ≥11.1	Total number (%) with diabetes
Men					
≤5.5 (2.50)	29	4 (14)	4 (14)	3 (10)	7 (24)
−6.5 (2.95)	122	7 (6)	27 (22)	10 (8)	17 (14)
−7.5 (3.40)	212	12 (6)	39 (18)	15 (7)	27 (13)
−8.5 (3.86)	218	18 (8)	43 (20)	16 (7)	34 (16)
−9.5 (4.31)	101	2 (2)	14 (14)	2 (2)	4 (4)
>9.5 (4.31)	42	2 (5)	9 (21)	5 (12)	7 (17)
Total	724	45 (6)	136 (19)	51 (7)	96 (13)
SD change*			−1.1 (NS)	−13.8 (NS)	−16.1 (NS)
SD change*†			−4.9 (NS)	−18.1 (NS)	−20.6 ($P < 0.05$)
Women					
≤5.5 (2.50)	45	3 (7)	12 (27)	7 (16)	10 (22)
−6.5 (2.95)	123	5 (4)	44 (36)	9 (7)	14 (11)
−7.5 (3.40)	241	6 (2)	79 (33)	21 (9)	27 (11)
−8.5 (3.86)	176	9 (5)	56 (32)	7 (4)	16 (9)
−9.5 (4.31)	61	4 (7)	13 (21)	3 (5)	7 (11)
>9.5 (4.31)	12	0 (0)	3 (25)	0 (0)	0 (0)
Total	658	27 (4)	207 (31)	47 (7)	74 (11)
SD change*			−9.2 (NS)	−34.6 ($P = 0.005$)	−26.1 ($P = 0.02$)
SD change*†			−9.8 (NS)	−35.3 ($P = 0.006$)	−27.7 ($P = 0.01$)

*Percentage change in the prevalence of diabetes or glucose intolerance per SD increase in birth weight. †Trend test adjusted for age, BMI, smoking, alcohol consumption, and current social class. 1 lb = 0.454 kg.

Before and during the study, the procedures for the measurements were standardized. The subjects then went on to have a standard 75-g oral glucose tolerance test. Men and women known to have diabetes were excluded. Measurements on the samples included plasma glucose and insulin concentrations at 0, 30, and 120 min and proinsulin and 32-33 split proinsulin concentrations at 0 min. Impaired glucose tolerance and type 2 diabetes were defined using the previous World Health Organization criteria to facilitate comparison with the previous study (impaired glucose tolerance: 2-h plasma glucose 7.8–11.0 mmol/l; type 2 diabetes: 2-h plasma glucose ≥11.1 mmol/l). Ethical approval for the study was obtained from the Hertfordshire Local Research Ethics Committee, and each person gave written informed consent.

The laboratory methods were the same as in the previous studies. Plasma glucose was measured by an automated hexokinase method, and plasma insulin, proinsulin, and split proinsulin were measured by two-site immunometric assays (7).

Statistical methods. Birth and infant weights had been measured in pounds and ounces and were often rounded to the nearest quarter pound (1 lb = 0.454 kg). Because of this and to facilitate comparison with the original study, we retained the original units in the analysis. To characterize the effects of birth weight and infant weight gain, SD scores were calculated for birth weight and weight at 1 year conditional on birth weight (equivalent to infant weight gain conditional on birth weight). The conditional SD score for weight at 1 year (wt1) was calculated on a sex-specific basis as follows: [(SD score for wt1) − ($r \times$ SD score for bwt)]/$\sqrt{}$ [1 − ($r \times r$)], where r is the correlation coefficient between birth weight (bwt) and weight at 1 year. This score is independent of birth weight and, because it ranks an individual's infant weight gain relative to the gain expected in an average individual of the same birth weight, is free of the effects of regression to the mean. This conditional measure of weight at 1 year enables the effects of birth weight and infant weight gain on outcome to be clearly partitioned; this would not be possible if the crude difference between weight at birth and 1 year was used as a marker of infant growth.

Plasma concentrations of glucose and insulin had skewed distributions and were therefore transformed to normality before analysis, and the means and SDs presented are therefore geometric. Assessment of insulin secretion and insulin resistance was by homeostasis model assessment (HOMA) (8). The averages of the triplicate skinfold measurements at each site were taken, and the percentage of body fat was derived according to the method of Durnin and Wormsley (9). The data were analyzed with linear and logistic regression; P values refer to analyses using the full range of continuously distributed variables.

RESULTS

A total of 737 men (aged 59–70 years, mean 64.3) attended the clinic. Of these, 50 reported that they were being treated for diabetes. Five men were diagnosed before the age of 40 years, treated with insulin, and therefore assumed to have type 1 diabetes and were excluded from further analysis, leaving a total of 45 (6.1%) with type 2 diabetes (6 diet treated, 31 on oral hypoglycemic agents, and 8 on insulin). Likewise, 675 women (aged 60–71 years, mean 65.7) attended the clinic. After exclusion of 4 individuals who reported the onset of diabetes before the age of 40 years, 27 (4.0%) had previous type 2 diabetes (7 diet treated, 16 on oral hypoglycemic agents, and 4 on insulin). Eight of the men and 13 of the women did not complete their glucose tolerance tests.

The mean birth weight and weight at 1 year of the men was 7.8 ± 1.2 and 22.6 ± 2.4 lb (means ± SD), respectively, and for the women, 7.4 ± 1.1 and 21.3 ± 2.3 lb, respectively. Mean BMI was 27.0 ± 3.7 kg/m^2 in the men and 27.5 ± 4.9 kg/m^2 in the women. The BMI correlated with both birth weight ($r = 0.12$, $P = 0.002$) and weight at 1 year ($r = 0.09$, $P = 0.02$) in men but not in women. The mean percent body fat was 28.8 ± 5.4% in the men and 40.3 ± 4.6% in the women. Percent body fat was unrelated to birth weight or weight at 1 year of age.

Table 1 shows the relationships between birth weight and the prevalence of glucose intolerance and diabetes in the men and women. In men, there was an inverse relationship between birth weight and the prevalence of diabetes (newly diagnosed and previous cases) in an adjusted model allowing for age, BMI, smoking, alcohol consumption, and social class ($P < 0.05$). Similarly, in women, the overall prevalence of diabetes fell with increasing birth weight ($P = 0.02$ in an unadjusted model

TABLE 2
Percentages of men and women from the Hertfordshire Cohort Study with impaired glucose tolerance or diabetes according to weight at 1 year

Weight at 1 year [lb (kg)]	*n*	Number (%) with existing diabetes	Number (%) with 2-h glucose (mmol/l)		Total number (%) with diabetes
			7.8–11.0	≥11.1	
Men					
≤18.5 (8.16)	33	1 (3)	8 (24)	5 (15)	6 (18)
−20 (9.07)	117	9 (8)	24 (21)	5 (4)	14 (12)
−22 (9.98)	222	12 (5)	42 (19)	19 (9)	31 (14)
−24 (10.89)	227	15 (7)	46 (20)	15 (7)	30 (13)
−26 (11.79)	84	4 (5)	10 (12)	4 (5)	8 (10)
>26 (11.79)	41	4 (10)	6 (15)	3 (7)	7 (17)
Total	724	45 (6)	136 (19)	51 (7)	96 (13)
SD change			−13.1 (NS)	−10.1 (NS)	−2.8 (NS)
SD change*			−14.4 (NS)	−12.8 (NS)	−5.0 (NS)
Women					
≤18.5 (8.16)	66	3 (5)	23 (35)	7 (11)	10 (15)
−20 (9.07)	187	7 (4)	44 (24)	12 (6)	19 (10)
−22 (9.98)	228	10 (4)	72 (32)	20 (9)	30 (13)
−24 (10.89)	129	5 (4)	28 (22)	6 (5)	11 (9)
−26 (11.79)	35	1 (3)	5 (14)	2 (6)	3 (9)
>26 (11.79)	13	1 (8)	3 (2)	0 (0)	1 (8)
Total	658	27 (4)	207 (31)	47 (7)	74 (11)
SD change†			−23.0 (P = 0.003)	−6.1 (NS)	1.0 (NS)
SD change*†			−25.6 (P = 0.001)	−15.0 (NS)	−4.9 (NS)

*Percentage change in the prevalence of glucose intolerance or diabetes per standard deviation increase in weight at 1 year of age (conditional on birth weight). †Trend test adjusted for age, BMI, smoking, alcohol consumption, and current social class. 1 lb = 0.454 kg.

and P = 0.01 in an adjusted model). Table 2 shows the effect of weight at 1 year on the same parameters in men and women. There were no significant trends in men, whereas women showed relationships between weight at 1 year and impaired glucose tolerance (P = 0.003 unadjusted and P = 0.001 adjusted) but not diabetes. The results were similar if the data were adjusted for other available measures of obesity, for example, waist-to-hip ratio or percent body fat.

Table 3 shows the trends in glucose, insulin, and proin-

TABLE 3
Mean plasma glucose, insulin, and proinsulin concentrations during the glucose tolerance tests in the 679 men and 631 women according to birth weight

	Birth weight [lb (kg)]								
	≤5.5 (2.50)	−6.5 (2.95)	−7.5 (3.40)	−8.5 (3.86)	−9.5 (4.31)	>9.5 (4.31)	All	Trend	Trend*
Men									
Fasting samples									
n	25	115	200	200	99	40	679		
Glucose (mmol/l)	6.25	5.9	6.0	5.9	5.6	6.14	5.9	NS	NS
Insulin (pmol/l)	65	68	70	72	62	72	69	NS	NS
Proinsulin (pmol/l)	3.5	3.1	3.0	2.8	2.6	2.9	2.9	NS	NS
Split proinsulin (pmol/l)	10.9	8.8	8.52	8.27	7.76	9.5	8.5	NS	NS
Glucose tolerance									
30-min glucose (mmol/l)	9.4	9.25	9.5	9.2	9.0	9.3	9.3	NS	0.03
120-min glucose (mmol/l)	6.8	6.7	6.5	6.6	5.7	6.9	6.5	NS	0.02
30-min insulin (pmol/l)	454	470	511	489	454	423	481	NS	NS
120-min insulin (pmol/l)	356	337	298	309	240	232	295	0.009	0.001
Women									
Fasting samples									
n	42	118	235	167	57	12	631		
Glucose (mmol/l)	6.0	5.8	5.8	5.7	5.7	5.8	5.8	0.01	0.002
Insulin (pmol/l)	96	91	85	76	77	66	83	0.003	<0.001
Proinsulin (pmol/l)	3.3	3.0	2.8	2.6	2.6	2.4	2.8	0.005	<0.001
Split proinsulin (pmol/l)	10.0	9.0	8.4	8.0	8.1	5.8	8.4	0.02	<0.001
Glucose tolerance									
30-min glucose (mmol/l)	9.7	9.8	9.4	9.2	9.1	9.4	9.4	0.005	0.001
120-min glucose (mmol/l)	7.9	7.7	7.5	7.1	6.7	6.2	7.4	<0.001	<0.001
30-min insulin (pmol/l)	729	694	618	650	644	412	644	0.04	0.04
120-min insulin (pmol/l)	545	619	520	504	401	302	516	<0.001	<0.001

*Trend test adjusted for age, BMI, smoking, alcohol consumption, and current social class.

TABLE 4
Mean plasma glucose, insulin, and proinsulin concentrations during the glucose tolerance tests in 679 men and 631 women according to weight at 1 year

	Weight at 1 year [lb (kg)]								
	≤18.5 (8.16)	−20 (9.07)	−22 (9.98)	−24 (10.89)	−26 (11.79)	>26 (11.79)	All	Trend	Trend*
Men									
Fasting samples									
n	32	108	210	212	80	37	679		
Glucose (mmol/l)	6.5	5.8	6.0	5.9	5.8	5.6	5.9	0.004	0.002
Insulin (pmol/l)	63	64	72	73	67	58	69	NS	NS
Proinsulin (pmol/l)	3.5	3.1	3.0	2.8	2.9	2.5	2.9	NS	0.03
Split proinsulin (pmol/l)	10.6	8.5	8.9	8.2	8.5	6.7	8.5	NS	0.02
Glucose tolerance									
30-min glucose (mmol/l)	10.4	9.4	9.4	9.3	8.9	8.4	9.3	<0.001	<0.001
120-min glucose (mmol/l)	7.7	6.3	6.7	6.6	5.9	5.6	6.5	0.005	0.007
30-min insulin (pmol/l)	468	468	509	468	508	407	481	NS	NS
120-min insulin (pmol/l)	358	292	320	306	251	190	295	0.07	0.06
Women									
Fasting samples									
n	63	180	218	124	34	12	631		
Glucose (mmol/l)	5.8	5.9	5.8	5.7	5.6	5.5	5.8	NS	NS
Insulin (pmol/l)	80	82	89	75	85	84	83	NS	NS
Proinsulin (pmol/l)	2.9	23.9	2.9	2.5	2.9	2.8	2.8	NS	0.08
Split proinsulin (pmol/l)	8.0	8.4	9.0	7.6	8.7	7.6	8.4	NS	NS
Glucose tolerance									
30-min glucose (mmol/l)	9.5	9.5	9.6	9.1	9.0	8.6	9.4	0.06	0.06
120-min glucose (mmol/l)	7.7	7.7	7.5	6.8	6.6	7.0	7.4	0.07	0.03
30-min insulin (pmol/l)	631	603	693	620	646	736	644	NS	NS
120-min insulin (pmol/l)	543	553	548	433	425	515	516	NS	0.08

* Trend test adjusted for age, body mass index, smoking, alcohol consumption, and current social class.

sulin concentrations with birth weight in men and women. In men, only the 120-min insulin concentration was significantly and inversely related to birth weight. However, in the fully adjusted model allowing for age, BMI, smoking, alcohol consumption, and social class, both 30- and 120-min glucose concentrations as well as the 120-min insulin concentrations correlated inversely with birth weight. The trends in the women were much stronger. Both the fasting and postprandial measurements of insulin and glucose were strongly and significantly associated with birth weight both before and after adjustment. Table 4 shows the relationships between the concentrations of glucose, insulin, and proinsulin with weight at 1 year of age. In men, fasting, 30-min, and 120-min glucose concentrations fell with increasing infant weight, a trend that was significant both before and after adjustment. In contrast, associations between the weight at 1 year and insulin concentrations were weaker and only observed after adjustment of the data. In women, the trends were much weaker. Only the 120-min glucose concentrations were inversely related to weight at 1 year. Formal statistical tests for sex interactions, however, did not reach statistical significance.

Table 5 shows the relationships between birth weight or weight at 1 year of age and measurements of insulin resistance and secretion derived from the oral glucose tolerance test. In men, HOMA insulin resistance fell with increasing birth weight but only in the adjusted model. Among women, resistance fell with increasing birth weight, which was accompanied by a fall in insulin secretion. Neither secretion nor resistance was related to weight at 1 year.

Figure 1 compares the 2-h glucose concentrations in the present study with the original Hertfordshire study in relationship to birth weight, whereas Fig. 2 shows the same analysis for weight at 1 year. The trends with both birth weight and weight at 1 year were similar except at the extremes of birth and infant weight categories, where the numbers of subjects are much smaller.

TABLE 5
Relationship between early growth and estimates of insulin secretion and insulin resistance in the men and women in the Hertfordshire study

	Birth weight		Weight at 1 year	
	Unadjusted	Adjusted*	Unadjusted	Adjusted*
Men				
HOMA resistance	−2.2 (NS)	−5.6 (P = 0.02)	−3.4 (NS)	−4.3 (NS)
HOMA secretion	−0.1 (NS)	−2.9 (NS)	1.0 (NS)	1.0 (NS)
Women				
HOMA resistance	−8.3 (P = 0.001)	−9.4 (P = <0.001)	1.0 (NS)	−1.1 (NS)
HOMA secretion	−4.0 (P = 0.05)	−4.5 (P = 0.02)	1.0 (NS)	1.0 (NS)

The table shows the percentage change in insulin secretion or insulin resistance per SD increase in birth weight or weight at 1 year of age conditional on birth weight. *Adjusted for age, BMI, smoking, alcohol consumption, and current social class.

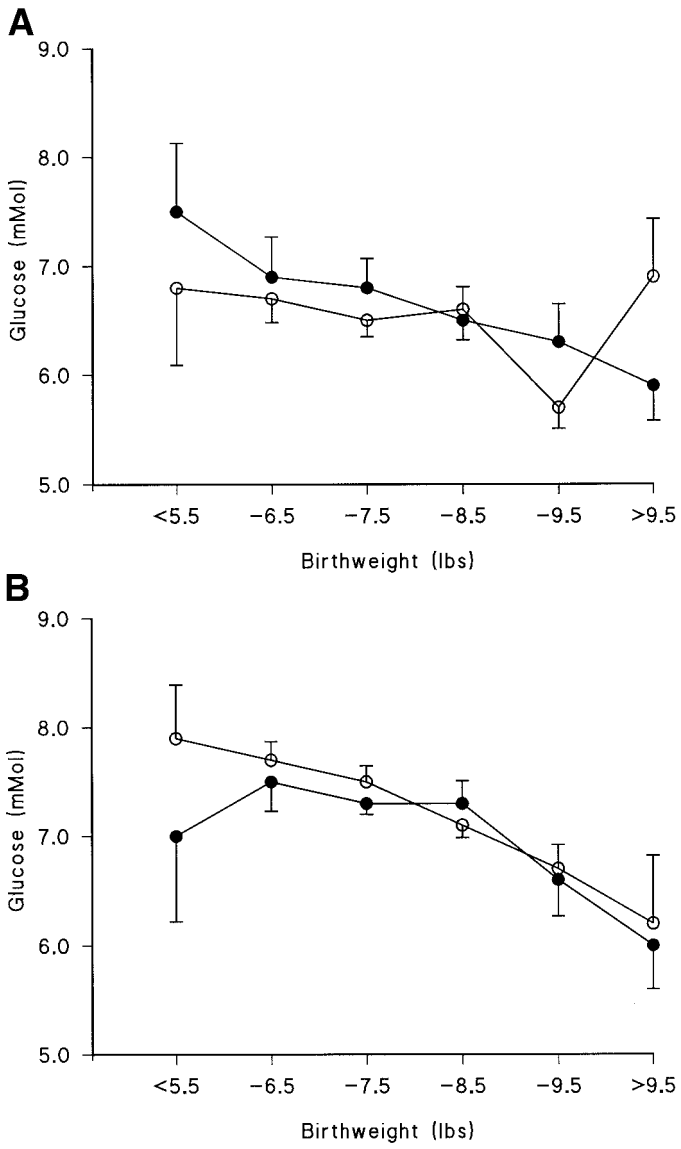

FIG. 1. Comparison of the relationship between birth weight and the 2-h plasma glucose concentrations in the previous Hertfordshire study (●) with the current data (○) in men (*A*) and women (*B*). Data are means ± SE.

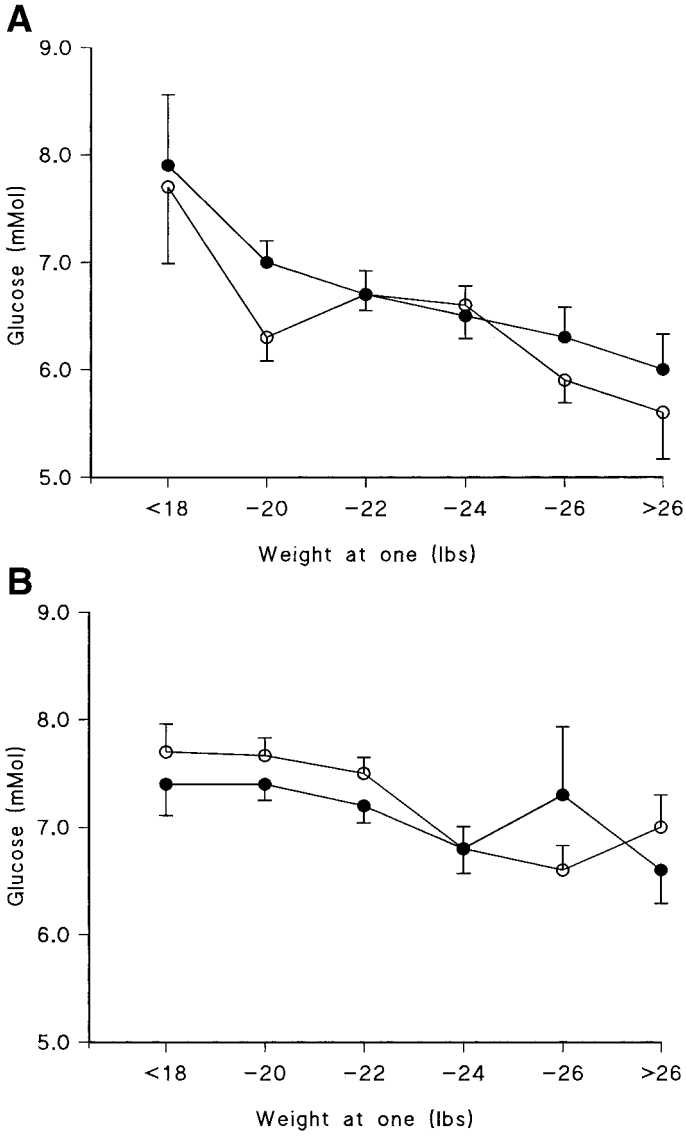

FIG. 2. Comparison of the relationship between weight at 1 year and the 2-h plasma glucose concentrations in the previous Hertfordshire study (●) with the current data (○) in men (*A*) and women (*B*). Data are means ± SE.

DISCUSSION

In this study, we evaluated the prevalence of impaired glucose tolerance and diabetes in a large retrospective birth cohort of men and women born between 1931 and 1939. The prevalences of glucose intolerance (19% in men and 31% in women) and diabetes (13% in men and 11% in women) are consistent with survey data from populations of a comparable age and Caucasian ethnicity (10). Our data broadly confirm previous studies showing that low birth or infant weights are associated with increased glucose and insulin concentrations, insulin resistance, and a higher prevalence of type 2 diabetes.

Our study comprised men and women who had complete health visitor records, who were traced and still living in East Hertfordshire, and who were willing to take part in the study. No differences occurred between mean birth weight or weight at 1 year between the subjects traced and not traced or between those who agreed to take part and those who did not. Because our analysis is based on internal comparisons, the selection of the sample would only introduce bias if the relationship between early growth and the glucose and insulin measurements differed between those studied and not studied. This is unlikely.

In both sexes, most of the associations with insulin and glucose measurements from the glucose tolerance test (Tables 3 and 4) are observed in unadjusted data and remain statistically significant after adjustment for potential confounding factors including obesity, age, smoking or alcohol habit, and social class. In comparison with the previous Hertfordshire study, we had available more elaborate measurements of obesity including an assessment of total body percentage fat derived from skinfold measurements. The effect of early growth on glucose tolerance was independent of the various measures of adiposity available in this study. As with the previous Hertfordshire study, we found that the effect of low birth or infant weight was independent of but added to that of obesity (measured as the BMI) in predicting insulin or glucose concentrations

during the glucose tolerance test. Some studies have reported interactions between early growth and obesity and the prediction of outcomes (11). However, in specific tests for interactions with obesity, we found none to be statistically significant.

As in the previous Hertfordshire study, sex differences were observed in the data. For example, in men, the measurements of insulin and glucose during the glucose tolerance tests correlated more strongly with weight at 1 year of age than birth weight, whereas among women, the associations between birth weight and glucose and insulin measurements were more robust than the associations with weight at 1 year (Tables 3 and 4). Insulin resistance as assessed by HOMA was significantly and inversely related to birth weight in women more strongly than in men (Table 5). However, formal statistical testing of these sex differences did not achieve statistical significance, suggesting that they should be interpreted with caution. Very large sample sizes will be needed to confirm or refute the presence of sex differences.

Figure 1 compares the results of this study with the previous Hertfordshire studies in men and women, which were published in 1991 and 1995, respectively (1,2). The ages of the populations are almost identical and the mean birth weights are very similar (7.9 lb previously vs. 7.8 lb currently in men and 7.6 vs. 7.4 lb in women). The levels of obesity were also comparable (26.9 vs. 27.0 kg/m^2 in men and 27.0 vs. 27.5 kg/m^2 in women). The measurements of 2-h plasma glucose concentrations in relationship to birth weight and weight at 1 year of age are remarkably similar. Most differences occur at the extremes of birth weight where the numbers of subjects studied are much smaller and the mean glucose concentrations are therefore subject to greater variability. These findings therefore suggest that the factors that result in low birth or infant weights and altered glucose tolerance in adult life are little changed and are still operational in this cohort of adults born a decade later compared with the men and women who participated in the original Hertfordshire study.

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