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Glucose tolerance at age 58 and the decline of glucose tolerance in comparison with age 50 in people prenatally exposed to the Dutch famine

Received: 29 August 2005 / Accepted: 10 November 2005 / Published online: 10 February 2006
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Abstract *Aims/hypothesis:* People who were small at birth have an increased risk of type 2 diabetes in later life. People who were in utero during the Dutch famine had decreased glucose tolerance and raised insulin concentrations at age 50. We aimed to evaluate whether prenatal famine exposure leads to more rapid progression of impaired glucose/insulin homeostasis with increasing age. *Methods:* We performed an OGTT in 702 men and women at age 50 and in 699 men and women at age 58, all born as term singletons immediately before, during or after the 1944–1945 Dutch famine. *Results:* People who had been exposed to famine in utero had significantly

higher 120-min glucose concentrations at age 58 compared with people who had not been exposed to famine (difference=0.4 mmol/l, 95% CI 0.1 to 0.7, adjusted for sex and BMI). Glucose tolerance deteriorated between the age of 50 and 58. The unadjusted 120-min glucose concentrations rose by 0.2 mmol/l (95% CI 0.0 to 0.4), while 120-min insulin concentrations had increased by 64 pmol/l (95% CI 48 to 82). There were no differences in the rates of glucose and insulin level increase between the famine-exposed group and the unexposed group ($p=0.28$ for the difference in increase in glucose concentrations and $p=0.09$ for insulin concentrations). *Conclusions/interpretation:* Although we confirmed that undernutrition during gestation is linked to decreased glucose tolerance, the effect does not seem to become more pronounced at age 58 as compared with age 50.

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Keywords Glucose tolerance · Progression ·
Prenatal famine

Abbreviation HPA: hypothalamic-pituitary-adrenal

Introduction

People who were small at birth have an increased risk of type 2 diabetes in later life [1–7]. One interpretation of this association is that an adverse intrauterine environment permanently impairs glucose homeostasis, primarily by inducing insulin resistance [8, 9]. This interpretation is strongly supported by animal studies, which have consistently shown that experimental undernutrition during gestation leads to impaired glucose homeostasis [10]. The Dutch famine was a period of extreme food shortage in the west of the Netherlands that occurred during the last 5–6 months of World War II. The famine offers a unique opportunity to study the effects of prenatal undernutrition on health in later life. In 1998, we found the first direct evidence in humans that exposure to undernutrition during gestation reduced glucose tolerance in later life [11].

The prevalence of type 2 diabetes and IGT increases with age, mainly as a result of the increase in BMI, insulin resistance and a fall in insulin secretion [12–14]. It is not yet known whether the age-related decline in glucose tolerance is increased in people who experienced an adverse intrauterine environment. In animal experiments the effects of prenatal undernutrition on glucose tolerance have been shown to increase with age. Rats that were undernourished during gestation showed a decrease in glucose tolerance between 3 and both 12 and 15 months of age [15, 16]. In humans the prenatal influences on blood pressure have been shown to increase with age [17, 18]. The present study was designed to assess glucose tolerance in the famine cohort at age 58 and to evaluate whether the previously demonstrated effect of prenatal famine exposure on glucose tolerance in the Dutch famine birth cohort progresses with ageing.

Subjects and methods

Participants

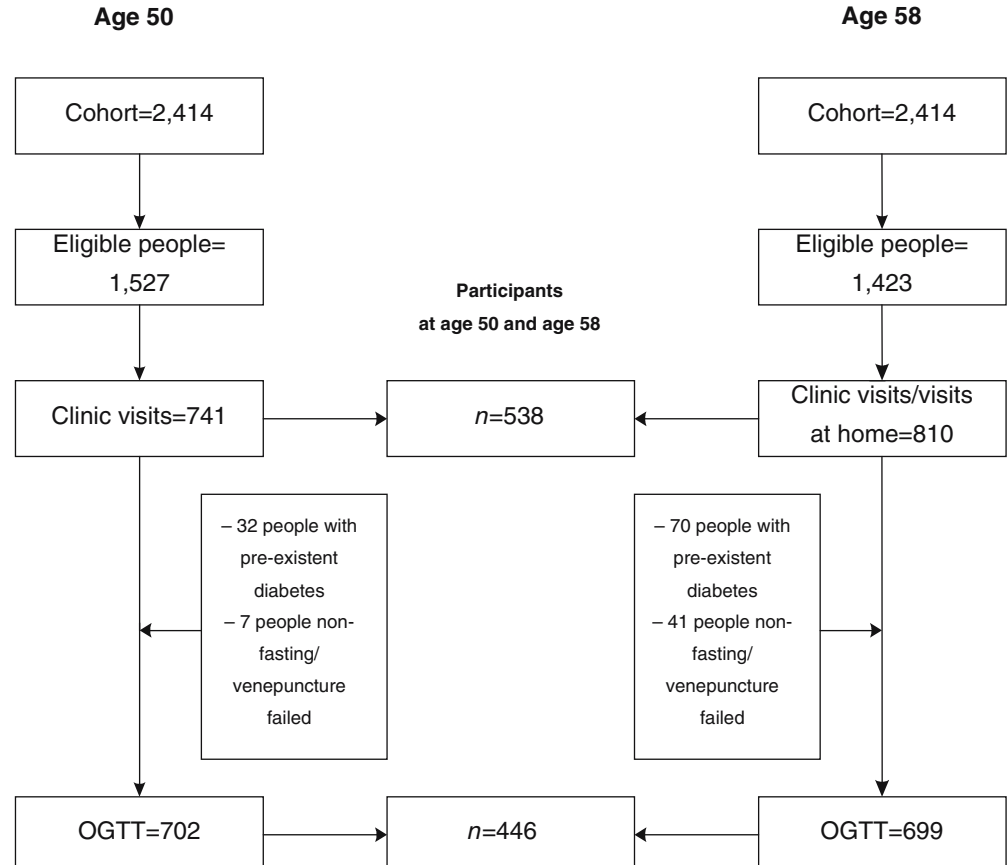
The participants were selected from the Dutch famine birth cohort (see Fig. 1). This cohort consists of 2,414 men and women born as term singletons between 1 November 1943 and 28 February 1947 in the Wilhelmina Gasthuis in Amsterdam. The selection procedures of the cohort have

been described in detail elsewhere [11]. Of the cohort, 1,423 (59%) were still living in the Netherlands and their current address was known. A total of 810 people (57%) agreed to participate and underwent medical examination and a standardised interview. Two-thirds of this group (538 people, 66%) had also participated in the previous study at age 50. People who agreed to participate had mean birthweights similar to those of eligible people who did not participate (3,357 vs. 3,349 g, $p=0.78$). Informed consent was obtained from all participants. The local Medical Ethics Committee had approved the study. The study was carried out in accordance with the Declaration of Helsinki.

Exposure to famine

We defined the famine period based on the official daily rations for the general population older than 21 years. These rations were about 7,560 kJ/day in December 1943 and gradually decreased to about 5,880 kJ in October 1944. On 26 November 1944 the rations fell below 4,200 kJ and after 12 May 1945 they rose above 4,200 kJ again. In June 1945 rations were over 8,400 kJ. The rations during the famine did not apply to children younger than 1 year, who were relatively protected. Their official daily rations were always higher than 4,200 kJ, which is adequate according to The Oxford Nutrition Survey [19]. We considered

Fig. 1 Participants selected from the Dutch famine birth cohort



foetuses to be exposed to famine if the average daily rations of the mother during any 13-week period of gestation were below 4,200 kJ. Babies born between 7 January 1945 and 8 December 1945 were thus exposed. We defined periods of 16 weeks each to differentiate between those who had been exposed in late gestation (born between 7 January and 28 April 1945), in mid-gestation (born between 29 April and 18 August 1945) and in early gestation (born between 19 August and 8 December 1945). Babies born before 7 January 1945 and babies conceived and born after 8 December 1945 were considered as unexposed to famine in utero and acted as a control group.

Study parameters

Birth measurements and information about the health and status of the mother were taken from the medical birth records [11]. Trained nurses carried out the medical examinations and the interview. Methods for OGTT and anthropometry at age 50 have been described in detail elsewhere [11]. At age 58, a standard 75-g OGTT was performed after an overnight fast. People with pre-existent diabetes, defined as taking oral or injected glucose-lowering medication, were excluded from the test. Plasma glucose concentrations were measured by a standardised enzymatic photometric assay on a Modular P Analyzer (Roche, Basel, Switzerland) and plasma insulin concentrations by an immunoluminometric assay on an Immulite 2000 Analyzer (Diagnostic Product Corporation, Los Angeles, CA, USA). We measured height with a fixed or portable stadiometer, weight with SECA and portable Tefal scales and waist and hip circumferences with a flexible tape measure. We interviewed all participants and asked them about their socio-economic status, their medical history, lifestyle and use of medication, using standardised questions. Current socio-economic status was coded according to ISEI-92, which is based on the person's, or their partner's occupation, whichever status was highest.

Statistical methods

In order to make the results comparable with those of our previous study, we defined IGT as a 120-min glucose concentration of 7.8–11.0 mmol/l and type 2 diabetes as a 120-min glucose concentration of >11.0 mmol/l. Logarithmic transformations were applied to glucose, insulin and BMI values, because they had skewed distributions. We used linear regression analysis to determine the effect of prenatal exposure to famine at different stages of gestation on glucose tolerance at age 58. To detect a possible age-related deterioration in glucose tolerance, we only included data of subjects participating at age 50 as well as at age 58, using repeated-measures analysis. We first calculated differences between the exposed and unexposed groups.

Then differences were calculated between unexposed subjects and subjects prenatally exposed to famine in late, mid- or early gestation. We adjusted for maternal and birth characteristics, sex, BMI, smoking and socio-economic status. For the last three variables, measurements at age 50 and age 58 were both included in the repeated-measures analysis.

Results

Study group characteristics

We were able to perform a standard OGTT on 699 of the 810 people (86%) asked to participate in the study at age 58. Seventy of the 810 people had to be excluded from the OGTT, because they had pre-existing diabetes (see Table 1 for distribution over study groups). The test was not performed on another 41 people because they had not adhered to fasting instructions ($n=7$) or because of difficulties in venepuncture ($n=34$). For 446 of these 699 people, data on 120-min glucose and insulin values at age 50 were available. Of the 699 participants, 291 (42%) had been exposed to famine in utero. The response rates were similar in the famine-exposed and control groups. Table 1 shows that mothers exposed in late and mid-gestation weighed significantly less at the last prenatal visit than mothers who were unexposed to famine. Mothers exposed during late gestation gained almost no weight in the last trimester of pregnancy. Babies exposed to famine in late and mid-gestation were lighter and shorter than unexposed babies. They also had smaller heads and placentas.

Famine exposure and plasma glucose and insulin concentrations at age 58

People who had been exposed to famine in utero had significantly higher plasma glucose concentrations 120 min after administration of the standard oral glucose load than unexposed people (Table 2). After adjusting for sex and BMI, 120-min glucose concentrations were 0.4 mmol/l (95% CI 0.1 to 0.7) higher among the exposed people than among unexposed people. For people exposed during late gestation the difference compared with unexposed people was 0.3 mmol/l (95% CI -0.1 to 0.8), for people exposed during mid-gestation 0.4 mmol/l (95% CI 0.0 to 0.9) and for people exposed during early gestation 0.4 mmol/l (95% CI -0.1 to 1.0). After adjustment for sex and BMI, 120-min insulin concentrations were 27 pmol/l (95% CI 0 to 58) higher among exposed than among unexposed people. The difference for people exposed during late gestation compared with unexposed people was 25 pmol/l (95% CI -12 to 68). The difference for people exposed during mid-gestation was 22 pmol/l (95% CI -18 to 68) and for people exposed during early gestation 37 pmol/l (95% CI -12 to 97).

Table 1 Maternal, birth and adult characteristics according to timing of prenatal exposure to the Dutch famine

	Exposure to famine					All (\pm SD)	n
	Born before	In late gestation	In mid-gestation	In early gestation	Conceived after		
General							
Number	215	122	104	65	193	699	–
Proportion of men	0.48	0.43	0.39	0.40	0.51	0.46	699
Maternal characteristics							
Age at delivery (years)	29	31 ^b	29	27	29	29 (\pm 6)	699
Proportion of primiparous women	0.37	0.21 ^b	0.32	0.43	0.35	0.33	699
Proportion doing manual labour	0.82	0.71	0.71	0.61 ^b	0.70	0.73	566
Weight gain 3rd trimester (kg)	2.8	0.1 ^b	4.4 ^b	5.0 ^b	3.5	2.9 (\pm 2.9)	486
Weight at last antenatal visit (kg)	66.4	62.8 ^b	63.6 ^b	69.2	69.2	66.4 (\pm 8.7)	613
Birth outcomes							
Gestational age (days)	284	283	286	288	286	285 (\pm 11)	598
Birth weight (g)	3387	3206 ^b	3181 ^b	3470	3497	3363 (\pm 474)	699
Birth length (cm)	50.5	49.6 ^b	49.6 ^b	50.8	50.8	50.3 (\pm 2.1)	691
Head circumference (cm)	32.8	32.5 ^b	32.2 ^b	32.9	33.3	32.8 (\pm 1.6)	690
Ponderal index (kg/m ³)	26.2	26.1	26.0	26.4	26.7	26.3 (\pm 2.4)	691
Placental area (cm ²)	297	269 ^b	269	276	275	280 (\pm 68)	594
Adult characteristics							
BMI (kg/m ²) ^a	27.6	27.8	27.5	27.3	28.5	27.9 (\pm 1.2)	698
Current smoker (%)	22	25	26	32	24	25	696
Current SES (ISEI-92)	46	50 ^b	50 ^b	45	47	47 (\pm 1)	689
Proportion of diabetic patients excluded from OGTT	0.10	0.09	0.10	0.08	0.07	0.09	810

^aGeometric means and SD^b $p < 0.05$ for difference from people who were not prenatally exposed to famine

SES Socio-economic status

Effects of mother's weight and birthweight

The weight of the mother at the last prenatal visit, birthweight, birth length and head circumference were all inversely related to 120-min glucose and insulin concentrations. Adjusted for sex and BMI the 120-min glucose concentrations increased by 0.8% (95% CI 0.5 to 1.1) per

kilogram decrease in mother's last weight, 13.2% (95% CI 7.4 to 19.2) with each kilogram decrease in birthweight, 2.6% (95% CI 1.4 to 3.9) with each centimetre decrease in birth length and 1.9% (95% CI 0.3 to 3.7) with each centimetre decrease in head circumference, all adjusted for sex and adult BMI. The 120-min insulin concentrations increased by 17 pmol/l (95% CI 10 to 23) per kilogram

Table 2 Means of plasma glucose and insulin concentrations and prevalences of IGT and type 2 diabetes according to timing of prenatal exposure to the Dutch famine

	Exposure to famine					All (\pm SD)	n	P
	Born before	In late gestation	In mid-gestation	In early gestation	Conceived after			
Fasting								
Glucose (mmol/l) ^a	5.6	5.5	5.5	5.6	5.6	5.6 (\pm 1.1)	697	0.99
Insulin (pmol/l) ^a	57	59	55	58	57	57 (\pm 1.8)	692	0.21
HbA _{1c} (%) ^a	5.5	5.5	5.6	5.6	5.6	5.6 (\pm 1.1)	692	0.81
120-min								
Glucose (mmol/l) ^a	5.8	6.2	6.2	6.2	5.9	6.0 (\pm 1.4)	678	0.02
Insulin (pmol/l) ^a	242	263	254	269	240	249 (\pm 2.1)	672	0.06
Prevalence of diabetes based on OGTT (%)	5	5	5	6	4	5	678	0.43
Prevalence of IGT based on OGTT (%)	16	16	15	14	14	15	678	0.76

^aGeometric means and SD p values are for differences between exposed and non-exposed groups adjusted for sex and BMI

decrease in the mother's last weight. Additional adjusting for birthweight showed that the effect of prenatal exposure to famine on 120-min glucose concentrations was larger than could be explained by the famine-related differences in birthweight. After adjustment for sex, BMI and birthweight, 120-min glucose concentrations were 0.2 mmol/l (95% CI -0.1 to 0.6) higher among the exposed than among unexposed people. Adjusting for other possible confounding variables including maternal age at delivery, current smoking status, current socio-economic status or alcohol consumption had little effect on the association between famine exposure and 120-min glucose concentrations. The prevalence of IGT and type 2 diabetes based on the OGTT did not differ significantly between the exposed and the unexposed people.

Effects of age

Table 3 shows the effects of age on progression of 120-min glucose and insulin concentrations in people who participated at age 50 as well as at age 58. Mean glucose concentrations after 120 min had increased by 0.2 mmol/l (95% CI 0.0 to 0.4). Mean insulin concentrations after 120 min had increased by 64 pmol/l (95% CI 48 to 82). A large part of the increase in 120-min glucose and insulin concentrations could be attributed to an increase in BMI. Mean BMI had increased by 1.1 units (95% CI 0.9 to 1.3). Adjusted for sex and BMI at both ages, the 120-min glucose concentrations between age 50 and 58 had increased non-significantly by 0.1 mmol/l (95% CI -0.1 to 0.2), while the adjusted 120-min insulin concentrations had increased by 51 pmol/l (95% CI 38 to 64). Exposure to famine in utero was not associated with an excess in age-related glucose tolerance deterioration (0.0 vs. 0.1 mmol/l for exposed vs. unexposed, $p=0.28$), nor with an excess of age-related rise in insulin (39 vs. 58 pmol/l for exposed vs. unexposed, $p=0.09$), nor an excess of age-related rise in BMI (1.0 vs. 1.2 unit for exposed vs. unexposed, $p=0.48$)

(all adjusted for sex and BMI). Table 3 shows that the relatively largest increases in plasma glucose and insulin concentrations occurred among people who were born before the famine compared with people conceived after the famine. The mean plasma glucose was 0.4 mmol/l higher ($p=0.04$) and the mean plasma insulin was 24 pmol/l higher ($p=0.08$). There was a small effect of birthweight on the increase in 120-min glucose concentrations between the age of 50 and 58. For each kilogram decrease in birthweight, there was a 6% (95% CI 0 to 12) larger increase in 120-min glucose concentrations, adjusted for sex and BMI at both ages. Birthweight did not affect the increase in 120-min insulin concentrations.

Discussion

In this unique cohort study of subjects born before, during and after the Dutch famine, we found that undernutrition during gestation was associated with reduced glucose tolerance and raised insulin concentrations at age 58. This confirms our previous findings at age 50 [11]. We found that both 120-min glucose and insulin concentrations were higher in people exposed to famine at any stage of foetal development than in unexposed people. Importantly, this effect was larger than could be explained by the lower birthweight of babies born during the famine and by the low weight gain of their mothers. As with our previous study, this association was independent of people's current BMI [11].

This is a population-based study of men and women recruited from the original famine cohort and still living in the Netherlands. At this age a significant number of individuals have overt type 2 diabetes and related diseases, especially cardiovascular disease. Selective participation of the more healthy subjects in our cohort could have influenced our results. Although we maximised response rates by visiting and studying subjects in their homes if necessary, people with type 2 diabetes, cardiovascular

Table 3 Progression of 120-min glucose and insulin levels and BMI between age 50 and age 58, according to timing of prenatal exposure to the Dutch famine

	Exposure to famine					All (CI) ^c	n	p
	Born before (CI) ^c	In late gestation (CI) ^c	In mid-gestation (CI) ^c	In early gestation (CI) ^c	Conceived after (CI) ^c			
n	135	80	67	43	121	446	-	-
Proportion of men (%)	52	47	42	43	49	48	446	-
120-min glucose (mmol/l) ^a	0.3 (0.0 to 0.6)	-0.1 (-0.6 to 0.2)	-0.1 (-0.5 to 0.3)	0.2 (-0.4 to 0.8)	-0.1 (-0.4 to 0.3)	0.1 (-0.1 to 0.2)	446	0.28
120-min insulin (pmol/l) ^a	71 (48 to 92)	35 (-1 to 66)	33 (-9 to 7)	54 (-2 to 98)	47 (21 to 70)	51 (38 to 64)	446	0.09
BMI (kg/m ²) ^b	1.1 (0.5 to 1.6)	0.8 (-3.0 to 4.1)	1.3 (-0.3 to 2.8)	0.9 (-0.5 to 2.6)	1.3 (0.7 to 1.9)	1.1 (0.9 to 1.3)	446	0.48

^aEstimated marginal means (adjusted for sex and BMI) for differences

^bEstimated marginal means (adjusted for sex) for differences

^c95% CIs of estimated marginal means for differences

p values are for differences between exposed and unexposed groups adjusted for sex and BMI

disease, high cholesterol levels and high blood pressure were less likely to attend the survey clinic (data not shown). However, there was no evidence of a difference in response rates between those who were famine-exposed or non-exposed. Consequently, we do not think that selective participation has affected the relative differences in glucose and insulin levels among the exposed and the unexposed groups. It could, however, have affected our power to detect effects of famine on type 2 diabetes.

Glucose tolerance deteriorated between the age of 50 and 58. A large part of this decline could be attributed to an increase in BMI. The decline in glucose tolerance was not more marked in the famine-exposed groups than in the control groups (Table 3). People who were born before the famine had the relatively largest increase in 120-min glucose and insulin concentrations. A possible explanation is that these people experienced the famine during their first year of life, which may have affected their postnatal growth pattern. Reduced early growth has been shown to be associated with later IGT and type 2 diabetes [20, 21]. Although infants were relatively protected during the famine, their official daily rations always being higher than 4,200 kJ, we do not know whether the famine affected their growth [19]. Early mortality rates were highest for people born before the famine and the deaths were mainly related to undernutrition or infections, indicating that growth was probably also affected [22].

We found that people with low birthweight had a greater age-related progression of glucose intolerance. A larger age-related progression of raised blood pressure has already been demonstrated for people with low birthweight, but to the best of our knowledge this is the first direct evidence of an age-related amplification of the effect of reduced foetal growth on glucose tolerance in humans [17, 18].

The effect of prenatal exposure to famine on glucose tolerance could be mediated through a number of mechanisms. Animal experiments indicate that undernutrition during gestation affects the development of the pancreas, which leads to an impaired function of the beta cell and consequently insulin deficiency [23]. In contrast, most human evidence points to the importance of insulin resistance. People who were thin at birth or had low birthweights were shown to be more insulin resistant than adults [24, 25]. The raised insulin concentrations that we found in famine-exposed individuals (Table 2) are consistent with insulin resistance acting as a mediator of the effect of famine exposure on glucose tolerance. Increasing evidence suggests that skeletal muscle is a key site for programming of insulin resistance. Muscle is a major site of glucose uptake and associations between a low ponderal index and altered metabolism of adult skeletal muscle have been found [26, 27]. Recently, an association between low birthweight and specific changes in muscle insulin-signalling protein expression was found [28]. Another mechanism that could explain the association between prenatal exposure to famine and later glucose intolerance involves the hypothalamic-pituitary-adrenal

(HPA) axis. Maternal sheep and guinea pigs that were undernourished in late gestation gave birth to offspring in which HPA function was altered in adult life [29, 30]. In humans, low birthweight is associated with elevated basal plasma cortisol concentrations and increased adrenocortical responsiveness to adrenocorticotrophin at adult age [31, 32]. It has been hypothesised that undernutrition during gestation alters the setpoint of the HPA axis resulting in an increased activity and consequently an increased secretion of glucocorticoids, which is associated with glucose intolerance and insulin resistance [33, 34].

In summary, although we confirmed that poor nutrition in utero is related to decreased glucose tolerance in later life, the effect of prenatal exposure to the Dutch famine does not seem to become more pronounced at age 58 as compared with age 50. Progression of glucose intolerance was found to be related to famine exposure during the first year of life and to low birthweight. This suggests that prenatal famine exposure, famine exposure during the first year of life and low birthweight may contribute to glucose intolerance by different mediating mechanisms.

Acknowledgements This study was funded by the Netherlands Heart Foundation (Grant Number 2001B087), the Academic Medical Centre (Amsterdam, the Netherlands) and the Medical Research Council (UK). We thank the participants for their willing cooperation.

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