We also investigated a British patient of Libyan Jewish ancestry who presented with symptoms characteristic of Creutzfeldt-Jakob disease. Results of histological examination of the brain were diagnostic of the disease.

Both patients described were heterozygous for the missense mutation at codon 200 of the prion protein gene. No other pathogenic mutation (insertions or missense mutations at codons 102, 117, 178, 198, and 217) was present. Both patients were homozygous for methionine at codon 129.

## Discussion

We have identified a British family and a further patient of Libyan Jewish ancestry with inherited prion disease (PrP lysine 200). The clinical presentation of those affected and the course of the disease were characteristic of sporadic Creutzfeldt-Jakob disease; the other inherited prion diseases so far described generally present as an illness similar to Gerstmann-Sträussler syndrome with a much longer duration or as atypical dementia.[4 9]

The patient reported on in detail was of British origin with no evidence of either Libyan Jewish or central European ancestry, suggesting a separate, British focus of this disease. Whether these three foci have a common origin or arise from different mutational events is unknown. Interestingly, both patients reported on were homozygous for methionine at codon 129. Homozygosity for either allele of this common polymorphism is associated with earlier onset of inherited disease and predisposes the person to sporadic Creutzfeldt-Jakob disease.[10-12] Some people from both the Libyan Jewish and Slovakian foci of inherited prion disease have been found to carry the mutation at codon 200 and yet remain unaffected at ages similar to or greater than the upper age at onset in most affected relatives.[7 8] Such incomplete penetrance has not been reported in other types of inherited prion disease. These carriers of non-penetrant or late onset genes may be heterozygous at codon 129 since heterozygosity at codon 129 might be expected to delay or protect against the onset of clinical disease. Whether heterozygosity is protective could have an important bearing on genetic counselling in this disease now that presymptomatic detection of this and other mutations in the prion protein gene is possible.[13]

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# Association of low birth weight with β cell function in the adult first degree relatives of non-insulin dependent diabetic subjects

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## Abstract

***Objective*—To examine the relation between birth weight and β cell function in the first degree relatives of non-insulin dependent diabetic subjects.**

***Design*—Cross sectional study of 101 adults of known birth weight from 47 families which had at least one member with non-insulin dependent diabetes.**

***Subjects*—101 white adults aged mean 43 (SD 7) years.**

***Setting*—Oxfordshire, England.**

***Main outcome measures*—Glucose tolerance was measured by continuous infusion glucose tolerance test. β cell function and insulin sensitivity were calculated from the fasting plasma glucose and insulin concentrations with homeostasis model assessment. β cell function was standardised to allow for the confounding effects of age and obesity.**

***Results*—Twenty seven subjects had non-insulin dependent diabetes, 32 had impaired glucose tolerance, and 42 were normoglycaemic. Birth weight correlated with the β cell function of the complete cohort ($r_s$=0·29, p=0·005), the non-insulin dependent diabetic subjects ($r_s$=0·50, p=0·023), and the non-diabetic subjects ($r_s$=0·29, p=0·013). The non-insulin dependent diabetic (n=27) and the non-diabetic (n=74) subjects had similar mean (interquartile range) centile birth weight 50% (19%-91%), and 53% (30%-75%) respectively. Non-insulin dependent diabetic subjects had significantly lower β function than the non-diabetic subjects: 69% (48%-83%) *v* 97% (86%-120%), p < 0·001.**

***Conclusions*—The cause of the association between low birth weight and reduced β cell function in adult life is uncertain. Impaired β cell function in non-insulin dependent diabetic subjects was not accounted for by low birth weight, and genetic or environmental factors are likely to be necessary for development of diabetes.**

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## Introduction

Reduced growth in fetal life and infancy has been linked with an increased risk of developing impaired glucose tolerance in adult life.[1] Increased prevalence of hypertension[2] and death rates from cardiovascular disease[3] have also been reported in subjects with low birth weights. The mechanisms which link low fetal

and infant growth rates with disease in adult life are not defined.

Controversy exists about the relative importance of pancreatic β cell dysfunction and impaired insulin sensitivity in the genesis of impaired glucose tolerance and non-insulin dependent diabetes.[4] The relation of reduced growth in early life with subsequent β cell function and insulin sensitivity has not been examined. One study has shown that subjects with lower weight at 1 year have higher plasma concentrations of 32-33 split proinsulin in adult life.[1] Intact proinsulin and 32-33 split proinsulin constitute a higher percentage of the total insulin and insulin precursor molecules in the plasma of fasting subjects with non-insulin dependent diabetes[5,6] but this is of uncertain pathophysiological significance.[7]

Non-insulin dependent diabetes has a familial distribution, with an increased prevalence of the disorder in the first degree relatives of affected subjects.[8] Diabetic subjects and their first degree relatives form a suitable population in which to examine the relation between birth weight and the development of impaired glucose tolerance and non-insulin dependent diabetes. We studied 101 family members of 47 non-insulin dependent diabetic subjects to determine the relation of birth weight with β cell function and insulin sensitivity in adult life.

## Subjects and methods

The protocol was approved by the central Oxford research and ethics committee, and informed consent was obtained from all participants.

We studied nuclear families in which at least one member had non-insulin dependent diabetes and in which both parents and their children were available for study. Twenty one families were ascertained through a non-insulin dependent diabetic proband with both parents alive, and 29 families were ascertained through an older proband with non-insulin dependent diabetes and living spouse and children. Siblings of diabetic probands with living parents together with the children of older probands form the subjects in this study. Parents of the subjects had a glucose tolerance test (n=48) or had fasting plasma glucose and glycated haemoglobin concentrations measured (n=52).

The mothers were asked about the birth weight and gestational age of their children. Three mothers did not know the children's birth weights; these mothers had one, two, and four children. These children were excluded from the study, leaving 101 members of 47 families for study. Birth weights had been recorded in pounds (2·2 lb=1 kg) and were converted to the nearest gram. Gestational age was assessed as the last completed week of pregnancy. The obstetric and neonatal charts were available for 29 members of the cohort. The correlation coefficient between the reported birth weights and the birth weights recorded in these charts was $r_s=0{\cdot}83$ ($p<0{\cdot}001$).

The mean age of subjects was 43 (SD 7) years. Twenty six of the 101 subjects were known to have non-insulin dependent diabetes, and non-insulin dependent diabetes was newly diagnosed in one subject by the investigations of this study. Seven of the 26 subjects known to have non-insulin dependent diabetes were receiving insulin, 13 were taking sulphonylureas, and six were taking a specific diet.

Body mass index was calculated as weight (kg)/(height (m)$^2$). Blood pressure was measured with a COPAL UA251 electronic automatic auscultatory blood pressure reading machine (Surgicon Ltd, Brighouse, West Yorkshire). A random zero sphygmomanometer with a large cuff was used for patients with an arm circumference greater than 33 cm. None of the subjects had atrial fibrillation. The readings were taken on the right arm of the seated subject after a minimum of 10 minutes' rest. Three readings were obtained and the mean of the last two was recorded as the blood pressure.

Birth weight was expressed in centiles derived from the standards of Tanner and Thomson.[9] These standards give the distribution of birth weight in a standard population, taking into account the length of gestation, sex, whether the child was firstborn, and maternal height. The distribution was used to determine the appropriate centile group for each subject. For example, subjects in the 50th centile group had a birth weight lying between the 49th and 50th centiles after the above factors had been taken into account. Actual birth weights are also quoted.

The subjects had a continuous infusion glucose tolerance test.[10] Glucose was continuously infused at a rate of 5 mg/kg ideal weight/min for 60 minutes. Ideal weight was determined from the Metropolitan Life Insurance tables for a medium frame. Achieved plasma glucose and insulin concentrations were determined as the mean of the 50, 55, and 60 minute samples. Six subjects did not consent to a glucose tolerance test and tolerance was determined from fasting plasma glucose and insulin concentrations. Non-insulin dependent diabetes was defined according to the World Health Organisation fasting criteria.[11] Impaired glucose tolerance was defined as a fasting or achieved plasma glucose concentration more than 2 SD above the mean concentration of a non-diabetic population matched for age and weight. The reproducibility, sensitivity, and specificity of the continuous infusion glucose tolerance test have been reported.[12]

We measured plasma glucose concentration with a hexokinase method using a centrifugal analyser. Plasma insulin concentration was measured in duplicate by radioimmunoassay with a charcoal absorption step to separate bound from free insulin; Novo Human MC Insulin was used as the standard (Novo Research Laboratories, Bagsvaerd, Denmark) and Wellcome RD 10 guinea pig antiporcine insulin antiserum (Wellcome Research Laboratories, Beckenham, Kent) and insulin labelled with iodine-125 (Amersham International, Amersham, Buckinghamshire) as tracer. Between assay coefficient of variation for duplicates was 12·9% at 8 mU/l (n=89) and 9·9% at 28 mU/l (n=16). Intra-assay coefficient of variation was $<10\%$ in the range encountered in this study.

### STATISTICAL ANALYSES

The fasting plasma glucose and insulin concentrations were interpreted by homeostasis model assessment to assess β cell function and insulin sensitivity.[13] This method uses a mathematical model of the body's glucose and insulin interactions as a frame of reference. The major feedback loops are stimulation of insulin secretion by glucose and reduction of hepatic glucose output and increase in uptake of glucose into muscles by insulin. Different degrees of insulin resistance and impaired β cell function can be introduced into the model, and for each combination the homeostatic fasting plasma glucose and insulin results achieved by the feedback loops are calculated. Each patient's fasting plasma glucose and insulin measurements can be interpreted by the model to predict the β cell function and insulin sensitivity that are likely to have given those measurements. The seven diabetic subjects receiving insulin were excluded from the correlation analyses with these variables. β cell function and insulin sensitivity are expressed as centile groups defined relative to a non-diabetic population aged below 35 years and weighing less than 115% of ideal weight. β cell function and insulin sensitivity measured by homeostatic model assessment have been shown to

correlate with measures obtained by hyperglycaemic clamp and euglycaemic clamp.[13,14]

To allow for the confounding effects of age and obesity on β cell function[14] we calculated the standardised residual β cell function with respect to the regression of β cell function with age and obesity in a population of 104 non-diabetic people (age 21-76 years, percentage of ideal weight 86%-158%). This is termed standardised β cell function.

Variables are expressed as mean (SD) or as median and interquartile range. Groups were compared with the Mann-Whitney U test. Correlations between variables were examined with Spearman's rank correlation coefficients.

## Results

Of the 101 subjects, 27 had non-insulin dependent diabetes, 32 had impaired glucose tolerance, and 42 were normoglycaemic (table). No significant differences were found in birth weight between the non-insulin dependent diabetic subjects, those with impaired glucose tolerance, and the normoglycaemic subjects. There was no significant difference between the birth weight of diabetic subjects not receiving insulin (3·39±(0·58) kg, n=20) and the birth weight of those with impaired glucose tolerance and with normoglycaemia. The diabetic subjects not receiving insulin had significantly lower β cell function (median 69%) than the subjects with impaired glucose tolerance (median 96%, $p<0·001$) and the subjects with normoglycaemia (median 98%, $p<0·001$).

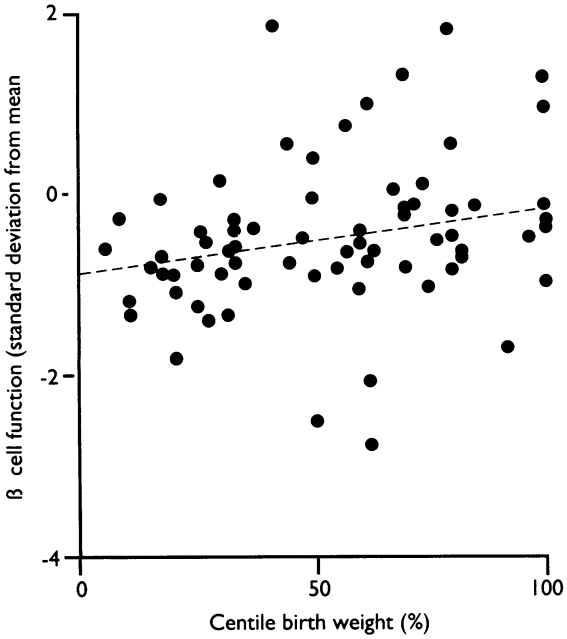


FIG 1—*β cell function standardised for age and obesity according to centile group for birth weight*

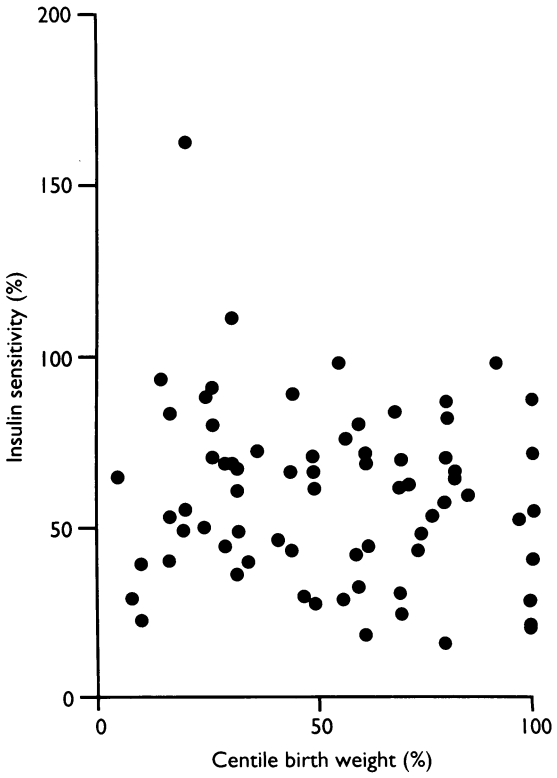


FIG 2—*Insulin sensitivity according to centile group for birth weight*

Centile group for birth weight was correlated with the standardised β cell function of the complete cohort ($r_s=0·29$, $p=0·005$) (fig 1). The correlation was significant in both non-insulin dependent diabetic subjects ($r_s=0·50$, $p=0·023$) and the non-diabetic subjects ($r_s=0·29$, $p=0·013$) when these groups were considered separately. The correlation was significant in the 29 subjects whose birth weights were validated from the obstetric and neonatal charts ($r_s=0·43$, $p=0·019$). Analysis of birth weight in kilograms rather than by centiles did not affect these correlations, the absolute value for the whole cohort correlating with the standardised β cell function ($r_s=0·28$ ($p=0·007$).

No significant correlation was found between centile group for birth weight and insulin sensitivity (fig 2), body mass index, fasting plasma glucose concentration, or blood pressure. These findings were unchanged when the non-insulin dependent diabetic subjects were excluded from the analyses.

The possible influence of maternal hyperglycaemia was assessed by analysing separately the 55 subjects who had a normoglycaemic mother and the 46 subjects who had a mother with non-insulin dependent diabetes

*Clinical details of 101 subjects from 47 families which had at least one member with non-insulin dependent diabetes. Values are mean (SD) unless stated otherwise*

| | Normoglycaemic subjects | p Value for difference between subjects with normoglycaemia and impaired glucose tolerance | Subjects with impaired glucose tolerance | p Values for difference between subjects with impaired glucose tolerance and non-insulin dependent diabetes | Non-insulin dependent diabetic subjects |
|---|---|---|---|---|---|
| No | 42 | | 32 | | 27 |
| Sex (M/F) | 19/23 | | 17/15 | | 19/8 |
| Age (years) | 42 (6) | NS | 43 (7) | NS | 45 (7) |
| Fasting plasma glucose (mmol/l) | 5·0 (0·4) | <0·001 | 5·6 (0·5) | <0·001 | 8·4 (2·7)* |
| Achieved plasma glucose (mmol/l) | 8·7 (0·7) | <0·001 | 9·9 (1·0) | <0·001 | 12·7 (2·8)* |
| Body mass index (kg/m²) | 26·9 (4·4) | NS | 28·3 (7·4) | 0·028 | 30·7 (5·9) |
| Birth weight (kg) | 3·47 (0·48) | NS | 3·46 (0·53) | NS | 3·46 (0·63) |
| Median (interquartile range) centile group for birth weight | 50 (30-77) | NS | 56 (32-73) | NS | 50 (19-91) |
| Median (interquartile range) centile group for β cell function | 98 (86-116) | NS | 96 (85-121) | <0·001 | 69 (48-83)† |
| Median (interquartile range) centile group for insulin sensitivity | 66 (45-80) | 0·009 | 49 (29-65) | <0·001 | 28 (20-34)† |

*Non-insulin dependent diabetic subjects receiving treatment. †Seven subjects receiving insulin were excluded.

or impaired glucose tolerance. The correlation coefficient between centile group for birth weight and standardised β cell function for the offspring of the normoglycaemic mothers was $r_s=42$ ($p=0{\cdot}015$). The correlation did not reach significance in the offspring of the hyperglycaemic mothers. When the offspring of the normoglycaemic mothers were considered separately, there was no significant difference in birth weight between the 22 offspring who were normoglycaemic, the 11 who had impaired glucose tolerance, and the 22 who developed diabetes (3·44 (0·40), 3·39 (0·47), and 3·39 (0·63) kg, respectively). When the offspring of the hyperglycaemic mothers were considered separately, there was no significant difference in birth weight between the 20 offspring who were normoglycaemic, the 21 who had impaired glucose tolerance, and the five who developed diabetes (3·59 (0·49), 3·47 (0·40), 3·74 (0·54) kg respectively).

## Discussion

We found that birth weight in first degree relatives of non-insulin dependent diabetic subjects correlated with the β cell function at mean age 43 years. This is compatible with the hypothesis that prenatal nutrition affects subsequent pancreatic function.

Gestational age, birth order, sex, and maternal height all affect birth weight. The birthweight standards of Tanner and Thomson[9] describe weight for gestation. Boys and girls are considered separately, as are firstborn and later children. Adjustment scales are available for maternal height. Birthweight data are expressed according to centile groups from these standards. We gave centile group for birthweight data to avoid confounding from gestational age, birth order, sex, and maternal height. When birth weights are standardised for these variables the social class gradient disappears.[15] Analysis of absolute birth weight in kilograms did not affect the reported relations.

We asked mothers the birth weights of their children and validated the reports of a subset from the obstetric and neonatal charts. The close correlation between the data obtained from these two sources suggests that recall error is unlikely to be a confounding factor. This conclusion is supported by the significant correlation observed between birth weight and β cell function in the subjects with validated birthweight data. Although interobserver error and the different weighing devices used to weigh infants might have caused variability in the data, the association between birth weight and adult β cell function was significant at the 1% level. The association therefore seems to be robust.

### EXPLAINING THE ASSOCIATION

The mechanisms which link low birth weight with reduced β cell function in later life are unknown. Much of the development of the islets of Langerhans occurs in utero[16] and β cell mass increases more than 130-fold between the 12th intrauterine week and the fifth postnatal month. Infants who are small for dates have fewer β cells,[17] and non-insulin dependent diabetes is associated with a moderate reduction of β cells.[18] Two hypotheses need to be considered. The first is that of Hales *et al*,[1] who suggested that nutritional factors determining fetal and infant growth influence the size of vascularity of the adult pancreatic β cells. Impaired glucose tolerance could then develop in adult life, especially when accompanied by the development of impaired insulin sensitivity from obesity, physical inactivity, or aging.

An alternative hypothesis is that lower birth weight results from the phenotypic expression of a genetic β cell defect associated with reduced fetal insulin secretion and reduced anabolic activity in utero. Mutations in the glucokinase gene in subjects with maturity onset diabetes of the young are associated with impaired β cell function but affected members of one pedigree who had a missense mutation in the glucokinase gene had normal birth weights (R C L Page *et al*, unpublished data).[19,20] Thus no evidence to support this alternative hypothesis is available. The association between birth weight and β cell function was not significant in the offspring of mothers with hyperglycaemia, possibly because of the confounding effect of maternal hyperglycaemia during pregnancy. The possibility that non-insulin dependent diabetes in the mother impairs fetal growth thus seems unlikely to account for the association between low birth weight and reduced β cell function.

The non-insulin dependent diabetic subjects had similar birth weight to subjects with normoglycaemia or impaired glucose tolerance. No significant differences were seen between these three groups when the offspring of hyperglycaemic and normoglycaemic mothers were considered separately. The non-insulin dependent diabetic offspring had a considerably reduced β cell function, even though 13 of these subjects were taking sulphonylureas, which increase β cell function about twofold.[21] No information was available on placental size or other indicators of in utero nutrition, and subnormal prenatal nutrition of those who subsequently became diabetic cannot be excluded. Our results pertain to a sample of 101 subjects, in many of whom the birth weight was obtained by maternal recall. Nevertheless, the lack of association between reduced birth weight and the subsequent development of diabetes suggests that defects of β cell function, in addition to that which may be induced by malnutrition in utero, are probably required for the development of non-insulin dependent diabetes.

In contrast to a previous report,[2] we found no significant inverse relations between birth weight and blood pressure. The absence of this association might be due to the smaller number of subjects in our study. Retarded intrauterine growth has been proposed as the link between hypertension and diabetes,[1] but our data provide no evidence to support this hypothesis.

In conclusion, low birth weight in first degree relatives of non-insulin dependent diabetic subjects was associated with reduced β cell function at mean age 43 years. Impaired nutrition in utero may play a part in reducing adult β cell function. However, additional genetic or environmental factors leading to more severely impaired β cell function are likely to be necessary for the development of non-insulin dependent diabetes.

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# Effect of using safer blood products on prevalence of HIV infection in haemophilic Canadians

Canadian Hemophilia Clinic Directors Group

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Concentrates of clotting factors VIII and IX transmitted HIV to many haemophilic patients during the early 1980s.[1] In Canada all blood products are distributed by the Canadian Red Cross Blood Transfusion Service. Products that had been heat treated to inactivate HIV were introduced in July 1985 and all untreated products were recalled.[2] This study was carried out to determine the number of haemophilic patients seropositive for HIV antibodies and the mortality from HIV infection and to confirm that young children were not being exposed to the virus.

## Methods and results

The data were obtained from the Canadian Hemophilia Registry.[3] This was updated to include data collected up to December 1991 and the results of testing patients for HIV antibodies. Deaths due to HIV infection have been recorded prospectively since 1988. Deaths occurring before 1988 were collected retrospectively and were validated by reports from the Federal Centre for AIDS. Haemophilia was graded as severe if the patient's concentration of coagulation factor was $<0{\cdot}01$ of the normal value, moderate if it was 0·01-0·05, or mild if it was $>0{\cdot}05$.

At the end of the survey the number of registered haemophilic patients was 1818, and 1584 were tested for HIV antibodies. Untested patients were either inaccessible or unwilling to be tested but all were alive. Altogether 617 (97%) of the 634 patients with severe haemophilia, 330 (95%) of the 349 with moderate haemophilia, and 637 (76%) of the 835 with mild haemophilia were tested. A total of 484 (31%) were positive for HIV antibodies. The prevalence increased with the severity of haemophilia and was higher in patients with factor VIII deficiency. Among those with factor VIII deficiency the proportions with HIV antibodies were 323/534 (60%), 74/208 (36%), and 57/539 (11%) for those with severe, moderate, and mild haemophilia respectively. Among those with factor IX deficiency the proportions with HIV antibodies were 19/83 (23%), 10/122 (8%), and 1/98 (1%) respectively. The highest prevalence (82%) was in those with severe factor VIII deficiency who were over 10 years old.

The table shows the prevalence of HIV antibodies according to age. No children aged 0-4 were seropositive; this zero prevalence was significantly lower than the prevalence of 4·8% in the next age group ($p=0{\cdot}029$, Fisher's exact test, one tailed). None of the 120 children aged under 6 who were tested were seropositive but the true prevalence could be as high as 2·5% (the upper limit of the 95% confidence interval).

The number of haemophilic patients dying due to infection with HIV for each year from 1980 to 1991 was 1, 0, 0, 1, 0, 1, 4, 8, 14, 20, 24, and 35. The total number of people infected with HIV has therefore been 592 (108 dead and 484 alive).

*Prevalence of seropositivity for HIV antibodies among haemophilic patients according to age*

| Age (years) | No tested | No positive for HIV antibodies | Prevalence (95% confidence interval) of seropositivity (%) |
|---|---|---|---|
| 0-4 (n=111) | 89 | | 0 (0 to 4·1) |
| 5-9 (n=210) | 188 | 9* | 4·8 (2·2 to 8·9) |
| 10-14 (n=214) | 188 | 37 | 19·7 (14·3 to 26·1) |
| 15-24 (n=382) | 355 | 140 | 39·4 (34·3 to 44·7) |
| 25-34 (n=379) | 337 | 163 | 48·4 (42·9 to 53·9) |
| 35-44 (n=264) | 229 | 92 | 40·2 (33·8 to 46·8) |
| 45-54 (n=128) | 111 | 31 | 27·9 (19·8 to 37·2) |
| 55-64 (n=64) | 52 | 10 | 19·2 (9·6 to 32·5) |
| 65-74 (n=32) | 24 | 1 | 4·2 (0·1 to 21·1) |
| 75-84 (n=10) | 8 | 1 | 12·5 (0·3 to 52·7) |
| ≥85 (n=5) | 2 | | 0 (0 to 84·2) |
| Unknown (n=19) | 1 | | 0 (0 to 97·5) |
| Total (n=1818) | 1584 | 484 | 30·6 (28·3 to 32·9) |

*One was aged 6, one aged 7, four aged 8, and three aged 9.

## Comment

The very low prevalence of seropositivity for HIV antibodies in children aged under 6 is encouraging since these children will have received only blood products that had been treated to inactivate HIV. A previous survey, similar in methodology to ours, used data collected in the United Kingdom up to August 1985, before virally inactivated concentrates were introduced.[4] Fifteen percent of those aged under 5, 22% of those aged 5-9, and 41% of those aged 10 and over were seropositive compared with 0%, 5%, and 37% in this study. The relative risk of being seropositive in the British study compared with age peers in our study is infinite for 0-4 year olds, 4·6 for 5-9 year olds, and only 1·1 for subjects aged 10 or over. These relative risks are significantly different ($p<0{\cdot}0001$, Mantel-Haenszel test of homogeneity) among the three age groups, indicating that the protective effect of viral inactivation is greater in the younger age groups.

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