Type 2 Diabetes Risk Alleles Are Associated With Reduced Size at Birth

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OBJECTIVE—Low birth weight is associated with an increased risk of type 2 diabetes. The mechanism underlying this association are unknown and may represent heterogeneous programming or two phenotypes of one genotype. The fetal insulin hypothesis proposes that common genetic variants that reduce insulin secretion or action may predispose to type 2 diabetes and also reduce birth weight, since insulin is a key fetal growth factor. We tested whether common genetic variants that predispose to type 2 diabetes also reduce birth weight.

RESEARCH DESIGN AND METHODS—We genotyped single-nucleotide polymorphisms (SNPs) at five recently identified type 2 diabetes loci (CDKAL1, CDKN2A/B, HHEX-IDE, IGF2BP2, and SLC30A8) in 7,986 mothers and 19,200 offspring from four studies of white Europeans. We tested the association between maternal or fetal genotype at each locus and birth weight of the offspring.

RESULTS—We found that type 2 diabetes risk alleles at the CDKAL1 and HHEX-IDE loci were associated with reduced birth weight when inherited by the fetus (21 g [95% CI 11–31], P = 2 × 10−5; and 14 g [4–23], P = 0.004, lower birth weight per risk allele, respectively). The 4% of offspring carrying four risk alleles at these two loci were 80 g (95% CI 39–120) lighter at birth than the 8% carrying none (Ptrend = 5 × 10−7). There were no associations between birth weight and fetal genotypes at the three other loci or maternal genotypes at any locus.

CONCLUSIONS—Our results are in keeping with the fetal insulin hypothesis and provide robust evidence that common disease-associated variants can alter size at birth directly through the fetal genotype. Diabetes 58:1428–1433, 2009

Reduced birth weight is associated with late-onset diseases including type 2 diabetes, hypertension, and heart disease (1). The cause of this association is not known. It is often proposed to reflect fetal programming in utero in response to maternal malnutrition in pregnancy (2). An alternative explanation is that genetic variants that increase disease risk could also reduce fetal growth. In accordance with the fetal insulin hypothesis (3), we proposed that genetic variants that reduce insulin secretion or insulin sensitivity might reduce birth weight as well as predisposing to type 2 diabetes in adulthood, since fetal insulin is a key fetal growth factor.

The fetal insulin hypothesis was initially based on observations of subjects with glucokinase (GCK) mutations, whose birth weight is reduced by 533 g (4) and who have mild hyperglycemia postnatally. Markedly reduced birth weights in patients with monogenic diabetes due to mutations in the INS, INSR, IPF1, KCNJ11, ABCC8, and HNF1B genes (3,5–8) have further established the principle that gene variants can cause both low birth weight and diabetes. However, mutations causing monogenic diabetes are too rare to explain the association between reduced birth weight and type 2 diabetes observed in population studies.

There is epidemiological support for the fetal insulin hypothesis. Offspring of fathers who go on to develop type 2 diabetes later in life have lower birth weights than those born to fathers who do not develop diabetes (9–12). This is consistent with the fetus inheriting, on average, 50% of the father’s genetic predisposition to diabetes and this genetic predisposition reducing fetal growth.

Maternal genotypes may have opposing effects on offspring birth weight compared with fetal genotypes (4). Type 2 diabetes risk alleles, which are present in the mother and which raise maternal glycemia in pregnancy, will increase fetal growth by increasing fetal insulin secretion. Maternal inheritance of common risk alleles in the GCK and TCF7L2 genes, which predispose to hyperglycemia and type 2 diabetes, respectively, were reproducibly associated with higher offspring birth weight (13,14). However, neither of these risk alleles at TCF7L2 and GCK or the type 2 diabetes risk alleles in the PPARG and KCNJ11 genes was associated with birth weight directly through the fetal genotype (13–15).
In this study, we aimed to further test the relationship between known type 2 diabetes variants and size at birth. We selected variants at five loci (CDKAL1, CDKN2A/B, HHEX-IDE, IGF2BP2, and SLC30A8), recently identified through type 2 diabetes genome-wide association studies (16–21), that have not been investigated in relation to fetal growth. Each of these loci has been shown to predispose to diabetes by reducing insulin secretion (22–24). We used data from 19,200 offspring and 7,986 mothers from four studies of white European ancestry, from a singleton pregnancy, with birth weight available, born at a minimum gestational age of 36 weeks, and genotyped for at least one of five SNPs.

### RESEARCH DESIGN AND METHODS

Subjects included in our analyses were selected from four studies (Table 1). The Avon Longitudinal Study of Parents and Children (ALSPAC) (25) is a prospective study that recruited pregnant women from Bristol, U.K., with expected delivery dates between April 1991 and December 1992. The Exeter Family Study of Childhood Health (EFSOCH) (26) is a prospective study of children born between 2000 and 2004 and their parents from a geographically defined region of Exeter, U.K. The Northern Finland Birth Cohort of 1966 (NFBC1966) (27) is a study of individuals born in the two northern-most provinces of Finland to women with expected dates of delivery in 1966. The 1958 British Birth Cohort (1958BC) (28) is a national cohort of subjects from the U.K. born during the same week in March 1958. Fetal DNA was available from all studies, and maternal DNA was available in the ALSPAC and EFSOCH studies. In all studies, birth weight and gestational age were obtained from hospital records. Important covariates were recorded, including maternal prepregnancy BMI, parity, and maternal smoking. Subjects included in the analyses were of white European ancestry, were singletons, and were born at gestational age ≥36 weeks. All subjects (or for children, their parents) gave informed consent, and ethics approval was obtained from the local review committee for each study.

**Genotyping.** Single nucleotide polymorphism (SNP) was chosen to represent the type 2 diabetes association signal at each of the five loci (rs10946838 [CDKAL1], rs19811601 [CDKN2A/B], rs1111875 [HHEX-IDE], rs440260 [IGF2BP2], and rs13266634 [SLC30A8]). Genotyping was performed using standard methods with robust quality-control criteria, details of which are presented in the online appendix (available at http://diabetes.diabetesjournals.org/cgi/content/full/db161738/DC1).

**Statistical analysis.**

**Analysis of fetal genotype and birth weight.** Within each of the four studies, we examined the association between birth weight and fetal genotype for each SNP using linear regression, with genotype coded as zero, one, or two risk alleles and sex and gestational age as covariates. Consistent with previous studies confirming associations of five SNPs with type 2 diabetes (16–20), we used an additive genetic model, assuming a constant change in birth weight per additional risk allele. The distribution of birth weight was approximately normal, so it was not transformed for analysis. Subjects with extreme birth weight values (>3 SD from the sex mean) were removed before analysis (see the online appendix). We repeated the analysis, with maternal prepregnancy BMI; smoking; parity; and, in the EFSOCH study, maternal fasting glucose included as additional covariates.

**Analysis of maternal genotype and offspring birth weight.** Within each of the two studies with maternal genotype available (ALSPAC and EFSOCH), we examined the association between birth weight and maternal genotype for each SNP using linear regression under the same model as was used for fetal genotype, with sex and gestational age as covariates. We combined data from the two studies using inverse-variance meta-analysis. Since we tested the associations with birth weight of J fetal and 2 maternal genotypes for all five SNPs, we used α = 0.05/10 to make study-wide adjustments of P values.

**Adjustment of maternal and fetal genotype effects for one another.** Maternal and fetal genotypes are not independent (r = −0.5) and may have opposing effects on birth weight (4). To examine the effects of maternal and fetal genotypes that were independent of one another, we used the mother-offspring pairs from the ALSPAC and EFSOCH cohorts with both maternal and fetal genotype available (n = 5,342–5,507). Within each study, we performed a linear regression analysis of birth weight against maternal genotype, fetal genotype, sex, and gestation. We performed two meta-analyses for each SNP, combining regression coefficients from the two studies for fetal and maternal genotype.

**Analysis of the combined effects of CDKAL1 and HHEX-IDE on birth weight.** To assess the combined effect of the fetal risk alleles at CDKAL1 and HHEX-IDE on birth weight, we generated a risk allele score (from 0 to 4) for individuals genotyped at both loci. We then performed a linear regression analysis, within each of the four studies, of birth weight against the fetal risk allele score (additive model), sex, and gestation. We combined the per-risk allele effect sizes and SEs using inverse-variance meta-analysis (n = 18,438).

To gain estimates of the differences in birth weights between individuals with no risk alleles and individuals with either one, two, three, or four risk alleles, we repeated the within-study analysis including the fetal risk allele score as indicator variables and then meta-analyzed the effect size estimates for each comparison.

### RESULTS

The fetal risk alleles of SNPs rs1094638 (CDKAL1) and rs1111875 (HHEX-IDE) were associated with reduced birth weight in the meta-analysis (21 g [95% CI 11–31], P = 2 × 10⁻⁵, and 14 g [4–23], P = 0.004, lower birth weight per risk allele, respectively) (Table 2 and Fig. 1) (see Table 3 for individual study results). Fetal genotypes at the other three loci were not associated with birth weight (all P > 0.01). The variability of effect size estimates among studies was consistent with random statistical fluctuations, suggesting no underlying heterogeneity (all P > 0.1). Adjust-
ment for additional covariates of birth weight made little
difference to the results (data not shown).

In the two studies with maternal DNA available, mater-
nal genotypes at five loci were not associated with off-
spring birth weight (all \( P > 0.05 \); except HHEX-IDE, \( P = 0.045 \)) (online appendix Table 1). Using the mother-
offspring pairs with both genotypes available (\( n = 5,342–
5,507 \)), we assessed the association of fetal genotype with
birth weight that was independent of maternal genotype
(online appendix Table 2). For CDKAL1, the per–risk
allele effect size estimate of the association between fetal
genotype and birth weight was \(-25 \text{ g (95% CI } -43 \text{ to } -7)\)
\((P = 0.005)\) before adjustment for maternal genotype and
\(-36 \text{ g (}-56 \text{ to } -16)\) \((P = 0.0005)\) after adjustment. In
accordance with this, the maternal risk allele at CDKAL1
showed a nominal association with increased birth weight
after adjustment for fetal genotype \((P = 0.04)\). For HHEX-
IDE, the per–risk allele effect size estimate of the associ-
ation between fetal genotype and birth weight was \(-25 \text{ g (}-
43 \text{ to } -9)\) \((P = 0.003)\) before adjustment for maternal
genotype and \(-29 \text{ g (}-48 \text{ to } -10)\) \((P = 0.003)\) after
adjustment. The maternal risk allele at HHEX-IDE showed
no association with birth weight after adjustment for fetal
genotype \((P = 0.5)\).

Using 18,438 individuals from all four studies, we com-
bined information from the CDKAL1 and HHEX-IDE loci
into a fetal risk allele score and tested the association with
birth weight. We observed a 17-g (95% CI 10–24) reduction
in birth weight per additional risk allele \((P = 5 \times 10^{-7})\).
The 4% of offspring who carried four type 2 diabetes risk
alleles were 80 g (39–120) lighter at birth than the 8%
carrying none (Fig. 2).

**DISCUSSION**

Using a total of 19,200 offspring and 7,986 mothers from
four studies of white Europeans, we have shown that fetal
inheritance of the type 2 diabetes risk alleles at CDKAL1
and HHEX-IDE is associated with reduced birth weight.
This is consistent with the fetal insulin hypothesis (3)
and provides the first robust evidence that common disease-
associated genetic variants can directly influence size at
birth. While the individual effect sizes were small, our
combined analysis showed a difference in birth weight of
80 g (95% CI 39–120) between offspring carrying four risk
alleles and those carrying none. This is similar to the effect
on birth weight of a mother smoking three cigarettes per
day in the third trimester of pregnancy (31).

We did not observe an association between maternal
genotype and offspring birth weight. However, maternal
and fetal genotypes are 50% correlated and may confound
each other. When we assessed the effects of maternal and
fetal genotype that were independent of one another using
mother–offspring pairs, the effect size of the association
between fetal genotype and birth weight at CDKAL1
changed from \(-25 \text{ g (95% CI } -43 \text{ to } -7)\) to \(-36 \text{ g (}-56 \text{ to } -16)\).
This suggests that maternal and fetal genotypes at this
locus may have opposing effects on birth weight, as
has been observed in mother–offspring pairs with heterozy-
gous mutations in the GCK gene (4). However, this result
requires confirmation in further large studies of mothers
and offspring.

We acknowledge some limitations to our study. First,
although we have studied the largest cohorts available for
genetic studies of birth weight, our power to detect effects

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**FIG. 1.** A: Meta-analysis plot showing the association of fetal CDKAL1
genotype with birth weight across all four studies (overall \( P = 2 \times
d0^{-5}\); total \( n = 18,679 \); heterogeneity statistics: \( I^2 = 19.9\%, P = 0.29 \)).
B: Meta-analysis plot showing association of fetal HHEX-IDE genotype
with birth weight across all four studies (overall \( P = 0.004 \); total \( n =
18,958 \); heterogeneity statistics: \( I^2 = 49.7\%, P = 0.11 \)). Analyses are
adjusted for sex and gestational age.
### Analysis of fetal genotype and birth weight within four studies

| Genotype (number of type 2 diabetes risk alleles) | Mean birth weight (g) | n  | Mean birth weight (g) | n  | Mean birth weight (g) | n  | Total n | Per-risk allele effect size (g)* | P*  |
|--------------------------------------------------|-----------------------|----|-----------------------|----|-----------------------|----|---------|---------------------------------|-----|
| rs10946398 (CDKAL1)                              |                       |    |                       |    |                       |    |         |                                 |     |
| ALSPAC                                          | 3,496 (3,481–3,510)   | 3,494| 3,471 (3,456–3,486)   | 3,210| 3,462 (3,431–3,494)   | 758| 7,462   | −20 ± 8                           | 0.010|
| EFSoCH                                          | 3,512 (3,466–3,557)   | 350| 3,504 (3,457–3,551)   | 329| 3,520 (3,420–3,620)   | 72 | 751     | −1 ± 24                           | 0.983|
| NFBC1966                                        | 3,568 (3,546–3,589)   | 1,795| 3,516 (3,497–3,534)   | 2,295| 3,506 (3,474–3,539)   | 742| 4,832   | −35 ± 10                          | 0.0002|
| 1958BC                                          | 3,380 (3,362–3,397)   | 2,675| 3,367 (3,348–3,386)   | 2,354| 3,354 (3,319–3,390)   | 605| 5,634   | −13 ± 9                           | 0.162|
| rs10811661 (CDKN2A/B)                           |                       |    |                       |    |                       |    |         |                                 |     |
| ALSPAC                                          | 3,451 (3,396–3,507)   | 236| 3,482 (3,463–3,500)   | 2,105| 3,483 (3,471–3,495)   | 5,176| 7,517   | 7 ± 9                             | 0.465|
| EFSoCH                                          | 3,396 (3,196–3,597)   | 18 | 3,506 (3,443–3,569)   | 182| 3,509 (3,473–3,545)   | 554| 754     | 20 ± 31                           | 0.515|
| NFBC1966                                        | 3,543 (3,463–3,624)   | 125| 3,523 (3,498–3,549)   | 1,249| 3,537 (3,522–3,552)   | 3,448| 4,822   | 8 ± 13                            | 0.539|
| 1958BC                                          | 3,349 (3,282–3,414)   | 162| 3,358 (3,335–3,380)   | 1,618| 3,380 (3,365–3,394)   | 3,878| 5,658   | 20 ± 11                           | 0.084|
| rs1111875 (HHEX/IDE)                            |                       |    |                       |    |                       |    |         |                                 |     |
| ALSPAC                                          | 3,529 (3,505–3,553)   | 1,289| 3,475 (3,461–3,489)   | 3,652| 3,471 (3,454–3,488)   | 2,573| 7,514   | −25 ± 7                           | 0.0007|
| EFSoCH                                          | 3,495 (3,421–3,569)   | 132| 3,509 (3,464–3,555)   | 350| 3,505 (3,453–3,556)   | 275| 757     | 3 ± 22                            | 0.804|
| NFBC1966                                        | 3,547 (3,520–3,574)   | 1,100| 3,536 (3,518–3,554)   | 2,466| 3,516 (3,490–3,541)   | 1,266| 4,832   | −16 ± 9                           | 0.095|
| 1958BC                                          | 3,373 (3,345–3,400)   | 1,020| 3,372 (3,352–3,389)   | 2,836| 3,375 (3,355–3,396)   | 1,999| 5,855   | 1 ± 9                             | 0.872|
| rs4402960 (IGF2BP2)                             |                       |    |                       |    |                       |    |         |                                 |     |
| ALSPAC                                          | 3,480 (3,465–3,494)   | 3,718| 3,481 (3,466–3,497)   | 3,123| 3,500 (3,468–3,533)   | 692| 7,538   | 7 ± 8                             | 0.385|
| EFSoCH                                          | 3,469 (3,422–3,514)   | 345| 3,554 (3,508–3,559)   | 346| 3,443 (3,336–3,550)   | 63 | 754     | 29 ± 25                           | 0.247|
| NFBC1966                                        | 3,536 (3,518–3,555)   | 2,386| 3,528 (3,500–3,555)   | 1,972| 3,540 (3,498–3,583)   | 446| 4,804   | −2 ± 10                           | 0.829|
| 1958BC                                          | 3,375 (3,356–3,393)   | 2,413| 3,366 (3,348–3,385)   | 2,172| 3,391 (3,351–3,430)   | 506| 5,091   | 2 ± 10                            | 0.851|
| rs13266634 (SLC30A8)                            |                       |    |                       |    |                       |    |         |                                 |     |
| ALSPAC                                          | 3,471 (3,438–3,504)   | 666| 3,480 (3,465–3,497)   | 3,178| 3,485 (3,471–3,499)   | 3,619| 7,463   | 6 ± 8                             | 0.422|
| EFSoCH                                          | 3,421 (3,315–3,528)   | 63 | 3,548 (3,501–3,596)   | 315| 3,479 (3,435–3,523)   | 368| 746     | −13 ± 25                          | 0.613|
| NFBC1966                                        | 3,504 (3,490–3,540)   | 631| 3,536 (3,517–3,555)   | 2,274| 3,512 (3,521–3,562)   | 1,933| 4,838   | 15 ± 10                           | 0.124|
| 1958BC                                          | 3,321 (3,284–3,358)   | 558| 3,372 (3,353–3,390)   | 2,383| 3,377 (3,350–3,394)   | 2,714| 5,655   | 19 ± 9                            | 0.037|

Data are means (95% CI) or means ± SE, unless otherwise indicated. *Linear regression of birth weight against fetal genotype (coded zero, one, or two risk alleles), with sex and gestation as covariates. Mean birth weights (95% CI) are adjusted for sex and gestational age.
of maternal genotype was limited due to its availability in only two of four studies (maximum \( n = 7,821 \)). While this gave us 80% power to detect changes in birth weight of 30 g for the most common minor allele (frequency 40%; \( \alpha = 0.005 \)), we estimate that we would have needed a maternal sample size ranging from \( n = 10,200 \) to 19,250 to detect effects of 20 g per risk allele, given the allele frequency variation of the SNPs tested. The second limitation is that we have only studied individuals of European origin. Further studies are needed in large cohorts of other ethnic groups. Third, our statistical evidence for association of \( CDKAL1 (P = 2 \times 10^{-5}) \) and \( HHEX-IDE (P = 0.004) \) with birth weight does not meet the generally accepted criterion for genome-wide adjustment. However, the robust prior evidence for association of all five loci can alter size at birth directly through the fetal genotype. Risk alleles at \( CDKAL1 \) and \( HHEX-IDE \) are both associated with reduced birth weight. This is consistent with the fetal insulin hypothesis, which proposed that predisposition to both type 2 diabetes and low birth weight are two phenotypes of a single genotype and explains, at least in part, the association of low birth weight with type 2 diabetes.

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REFERENCES

1. Barker DJ, Hales CN, Fall CH, et al. Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. Diabetologia 1995;38:62–67
2. Godfrey KM, Barker DJ. Fetal nutrition and adult disease. Am J Clin Nutr 2000;71:1344S–1352S
3. Hattersley AT, Tocke JE. The fetal insulin hypothesis: an alternative explanation of the association of low birthweight with diabetes and vascular disease. Lancet 1999;353:1789–1792
4. Hattersley AT, Beards F, Ballantyne E, et al. Mutations in the glucokinase gene of the fetus result in reduced birth weight. Nat Genet 1998;19:268–270
5. Hattersley AT. The fetal insulin hypothesis: an alternative explanation of the association of low birth weight and diabetes in adult life. J Clin Endocrinol Metab 2000;85:3963–3968
6. Zeggini E, Weedon MN, Lindgren CM, et al. Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. Science 2007;316:1336–1341
7. Steinthorsdottir V, Thorleifsson G, Reynisdottir I, et al. A variant in CDRKL1 influences insulin response and risk of type 2 diabetes. Nat Genet 2007;39:770–775
8. Scott LJ, Mohlke KL, Bonnycastle LL, et al. A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. Science 2007;316:1341–1345
9. Saxena R, Voight BF, Lyssenko V, et al. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. Science 2007;316:1331–1336
10. Sladek R, Rocheleau G, Rung J, et al. A genome-wide association study identifies novel risk loci for type 2 diabetes. Nature 2007;445:881–885
11. Wellcome Trust Case Control Consortium: Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007;447:661–678
12. Pascoe I, Tura A, Patel SK, et al. Common variants of the novel type 2 diabetes genes CDRKL1 and HHEX/IDE are associated with decreased pancreatic β-cell function. Diabetes 2007;56:3101–3104
13. Grarup N, Rose CS, Andersson EA, et al. Studies of association of variants near the HHEX, CDKN2A/B, and IGF2BP2 genes with type 2 diabetes and impaired insulin release in 10,705 Danish subjects: validation and extension of genome-wide association studies. Diabetes 2007;56:3105–3111
14. Palmer ND, Goodarzi MO, Langefeld CD, et al. Quantitative trait analysis of type 2 diabetes susceptibility loci identified from whole genome association studies in the Insulin Resistance Atherosclerosis Family Study. Diabetes 2008;57:1093–1100
15. Golding J, Pembrey M, Jones R. ALSPAC: the Avon Longitudinal Study of Parents and Children. I. Study methodology. Paediatr Perinat Epidemiol 2001;15:74–87
16. Knight B, Shields BM, Hattersley AT. The Exeter Family Study of Childhood Health (EPSOCH): study protocol and methodology. Paediatr Perinat Epidemiol 2006;20:172–179
17. Rantakallio P. The longitudinal study of the northern Finland birth cohort of 1966. Paediatr Perinat Epidemiol 1988;2:59–88
18. Power C, Elliott J. Cohort profile: 1958 British birth cohort (National Child Development Study). Int J Epidemiol 2006;35:34–41
19. Harris R, Bradbum M, Deeks J, et al.: METAN: Stata module for fixed and random effects meta-analysis. Statistical Software Components S456798, Boston College Department of Economics, revised 19 Feb 2007. Available at http://ideas.repec.org/c/boc/bocode/s456798.html. Accessed 2 July 2008
20. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–560
21. Wellcome Trust Case Control Consortium: Genome-wide association studies in the Insulin Resistance Atherosclerosis Family Study. Nature 2007;447:661–678
22. Steinthorsdottir V, Thorleifsson G, Reynisdottir I, et al. A variant in CDRKL1 influences insulin response and risk of type 2 diabetes. Nat Genet 2007;39:770–775
23. Scott LJ, Mohlke KL, Bonnycastle LL, et al. A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. Science 2007;316:1341–1345
24. Saxena R, Voight BF, Lyssenko V, et al. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. Science 2007;316:1331–1336
25. Sladek R, Rocheleau G, Rung J, et al. A genome-wide association study identifies novel risk loci for type 2 diabetes. Nature 2007;445:881–885
26. Wellcome Trust Case Control Consortium: Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007;447:661–678
27. Pascoe I, Tura A, Patel SK, et al. Common variants of the novel type 2 diabetes genes CDRKL1 and HHEX/IDE are associated with decreased pancreatic β-cell function. Diabetes 2007;56:3101–3104
28. Grarup N, Rose CS, Andersson EA, et al. Studies of association of variants near the HHEX, CDKN2A/B, and IGF2BP2 genes with type 2 diabetes and impaired insulin release in 10,705 Danish subjects: validation and extension of genome-wide association studies. Diabetes 2007;56:3105–3111
29. Palmer ND, Goodarzi MO, Langefeld CD, et al. Quantitative trait analysis of type 2 diabetes susceptibility loci identified from whole genome association studies in the Insulin Resistance Atherosclerosis Family Study. Diabetes 2008;57:1093–1100
30. Golding J, Pembrey M, Jones R. ALSPAC: the Avon Longitudinal Study of Parents and Children. I. Study methodology. Paediatr Perinat Epidemiol 2001;15:74–87
31. Knight B, Shields BM, Hattersley AT. The Exeter Family Study of Childhood Health (EPSOCH): study protocol and methodology. Paediatr Perinat Epidemiol 2006;20:172–179
32. Rantakallio P. The longitudinal study of the northern Finland birth cohort of 1966. Paediatr Perinat Epidemiol 1988;2:59–88
33. Power C, Elliott J. Cohort profile: 1958 British birth cohort (National Child Development Study). Int J Epidemiol 2006;35:34–41
34. Harris R, Bradbum M, Deeks J, et al.: METAN: Stata module for fixed and random effects meta-analysis. Statistical Software Components S456798, Boston College Department of Economics, revised 19 Feb 2007. Available at http://ideas.repec.org/c/boc/bocode/s456798.html. Accessed 2 July 2008
35. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–560
36. Bernstein IM, Mongeon JA, Badger GJ, et al. Maternal smoking and its association with birth weight and diabetes. Diabetes 2000;49:445–449
37. Lindsay RS, Dabelea D, Roumain J, et al. Type 2 diabetes and low birth weight. Nat Genet 1998;19:268–270
38. Berg H, Brolin C, Ekelund U, et al. Association between paternal diabetes in late adulthood and maternal smoking during pregnancy. Int J Epidemiol 2006;35:34–41
39. Harris R, Bradbum M, Deeks J, et al.: METAN: Stata module for fixed and random effects meta-analysis. Statistical Software Components S456798, Boston College Department of Economics, revised 19 Feb 2007. Available at http://ideas.repec.org/c/boc/bocode/s456798.html. Accessed 2 July 2008
40. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–560
41. Bernstein IM, Mongeon JA, Badger GJ, et al. Maternal smoking and its association with birth weight and diabetes. Diabetes 2000;49:445–449
42. Weedon MN, Clark VJ, Qian Y, et al. A common haplotype of the glucokinase gene alters fasting glucose and birth weight: association in six studies and population-genetics analyses. Am J Hum Genet 2006;79:991–1001
43. Freathy RM, Weedon MN, Bennett A, et al. Type 2 diabetes TCF7L2 risk genotypes alter birth weight: a study of 24,053 individuals. Am J Hum Genet 2007;80:1150–1161
44. Bennett AJ, Sovio U, Ruokonen A, et al. No evidence that established type 2 diabetes susceptibility variants in the PPARG and KCNJ11 genes have pleiotropic effects on early growth. Diabetologia 2008;51:82–85
45. Zeggini E, Weedon MN, Lindgren CM, et al. Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. Science 2007;316:1336–1341