SUPPLEMENTARY DATA

**Participants and survey procedures**

**EYHS**

The European Youth Heart Study (EYHS) is a multicentre longitudinal population study in Norway, Denmark, Portugal and Estonia of which the design and data collection has previously been described (1, 2). Children from Estonia (city and county of Tartu) and Denmark (city of Odense) contributed DNA for analysis in this study. The measurement of baseline characteristics occurred between 1997 and 1999 in Denmark and Estonia and a further survey of children aged 9 years old was conducted in 2003 in Denmark only.

Participants were randomly selected to take part in the study and consisted of boys and girls aged 9-11 and 14-16 years old. This choice of age ranges was intentional and chosen to broadly represent pre- and post-pubescent children. At each study location a defined population of children was identified and from this population a two-stage cluster sample of children was randomly selected. Schools were utilised as the primary sampling units with school registers used as secondary units.

Data collection procedures were standardized for use in both countries. The study followed international guidelines on biomedical research and ethical procedures of both Denmark and Estonia. Due to the age of participants, they were not of legal age to give written consent and hence written, informed consent was obtained from the child's parent/legal guardian. The individual giving consent on behalf of the child was given a full written explanation of the study aims, its potential hazards, discomfort and inconvenience. Additionally children had all procedures verbally explained in addition to any possible discomforts they might be exposed to and were given the option to withdraw at any time.

In total 2,194 children agreed to participate and a total of 2,025 children had DNA samples available and complete information on anthropometry, glucose and insulin. In the current study 21 individuals were excluded from analyses based on either non-fasting status (n=17) or due to glucose levels ≥7mmol/L (n=4) leaving a total of 2004 children (927 boys, 1077 girls) contributing data for analysis. For the two separate age ranges of 9-11 and 14-16 years mean age was 9.7 and 15.5 years and mean BMI 17.1 and 20.5 kg/m$^2$ respectively.

**GENDAI**

The Gene-Diet Attica Investigation on childhood obesity (GENDAI) study is a cross-sectional school based study consisting of children from fifth and sixth grade in public schools from the Attica region of Greece with recruitment, study procedures and methods having previously been described (3).

Three interactions occurred with study participants – a) a recruitment session, with an explanation of the study and its methodology b) a one on one session where data collection occurred and c) a telephone interview for a second physical activity and dietary recall. All study personnel were nutrition professionals and paediatricians who were evaluated for technique reliability on all measures. Parents/ guardians and participants received written information on the study and were aware that study participation was voluntary. Parents/guardians signed a written informed consent form with children providing verbal assent.

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From 2492 students initially invited to participate, 920 (491 females, 429 males) took part in the study with the main reasons for excluding participants being lack of interest, refusal, chronic or acute illness, absence from school, relocation or incomplete data. After this initial recruitment phase more children were recruited to the study to give a total sample size of 1200 children and after exclusion of those without data on DNA or fasting glucose or insulin, or those with fasting glucose ≥7mmol/L, a total of 1046 children (491 boys, 556 girls) were provided for analysis in this study with a mean age of 11.2 years and a mean BMI of 20 kg/m$^2$.

**French children**

The study population consisted of lean children from the STANISLAS and FLEURBAIX-LAVENTIE studies and obese children from the Lille ongoing media campaign of which study recruitment has been described previously (4, 5). All children were European Caucasian and born in metropolitan France. The obese children were part of a cohort of 97 Caucasian families collected through a multimedia campaign at the Institut Pasteur de Lille in France and in the Department of Pediatric Endocrinology of Jeanne de Flandres Hospital. Families were included if they had at least two minor probands with a BMI >97$^{th}$ percentile for age and sex before the age of 8 and with two living parents. The families gave written informed consent and were then submitted to detailed personal and medial questionnaires and anthropometrical measurements. In the current analysis a total of 583 children (263 boys, 320 girls) were provided for analysis after exclusion of those without information on ethnicity, phenotypes (fasting glucose, BMI, age and gender) and exclusion of samples without successful genotyping. Children in the study sample had a mean age of 11 years and a mean BMI of 29.6 kg/m$^2$.

Families of lean children were recruited between 1993-1995 at the centre for preventative medicine (CMP) of Vandoeuvre-le` s-Nancy during a periodical health assessment. A total of 1006 families were recruited between 1993-95, with a second visit occurring between 1998-2000 with a participation rate of 75%. A total of 634 children (310 boys, 324 girls) were provided for analysis from the initial sample size after exclusion of those without information on ethnicity, phenotypes (fasting glucose, BMI, age and gender) and exclusion of samples without successful genotyping. The children included in this paper had a mean age of 11.9 years and a mean BMI of 17.6 kg/m$^2$.

For both cohorts of French children only unrelated individuals were included in the analysis with one sibling ascertained per family.

**Raine**

The Western Australian pregnancy cohort (Raine) Study consisted of 2,900 women who were enrolled in a controlled trial to examine ultrasound imagining at or before the 18th week of gestation from the antenatal booking clinics at a tertiary level obstetric hospital in Perth, Western Australia between 1989 and 1991 (6). Approximately 100 mothers were enrolled per month over a total of 30 months commencing in May 1989 and finishing in November 1991 with the last children of these women born in April 1992. 2868 children were born to 2804 mothers who remained within the study and the Western Australian Pregnancy (Raine) cohort was formed.

All mothers were assessed at 18 and 34 weeks of pregnancy with data collected on both parents during this time (including information related to diet, exercise, work and health). In addition, mothers in the intensive arm of the trial were also assessed at 24, 28 and 38 weeks of pregnancy. After birth children were assessed at one year, two years, three years and five years of age. Information on height, weight,

eating, walking, talking, eating, behaviour, and health issues was collected. Further follow up at eight, ten, fourteen and seventeen years of age was also carried out with data from the Child and Parent collected at all time points. 1,198 singleton births without congenital abnormalities of Caucasian ethnicity had GWAS data available and the current study utilised 1,051 of these who had the relevant phenotype data at the year 13 follow up. The study sample was composed of children with a mean age of 14.1 years and a mean BMI of 21.5 kg/m$^2$.

**ALSPAC**

The Avon longitudinal study of parents and children (ALSPAC) is a UK population based birth cohort study which initially recruited >13,000 pregnant women with estimated dates of delivery between April 1991 and December 1992 (7). The women, the children arising from the index pregnancy and partners of the women have been extensively followed from the 8$^{th}$ gestational week onwards using a combination of postal self-reported questionnaires, clinical assessment, abstraction from medical records and use of linkage to routine information. From a total sample size of 14,062 live births, 13,988 were alive at 1 year and after attrition we have included data on 1, 736 children after exclusion of those without information on DNA or fasting glucose/insulin. The sample of children used in this study had a mean age of 15.4 years and a mean BMI of 21.3 kg/m$^2$. Ethical approval was obtained from the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees. All parents also provided written informed consent.

**Measurements**

**EYHS**

Measurements techniques were as described in our previous study (8). Each child had a blood sample taken and underwent a physical examination including anthropometric and blood pressure measurements using the same equipment in both countries. Blood samples were collected after an overnight fast and analysed by a Clinical Pathology Accreditation (CPA) accredited laboratory in Bristol and Cambridge, England. Glucose concentrations were measured by standard methods using Olympus AU600 random-access analysers. Plasma-specific insulin was determined by two-site immunometric assays with either 125I or alkaline phosphatase labels. Between-laboratories correlations were 0.94–0.98 for 30 randomly selected samples analyzed in both Bristol and Cambridge. The homeostasis model assessment was used to estimate insulin resistance (HOMA-IR=(fasting glucose (mmol/L) x insulin (μU/ml))/ 22.5) and β-cell function (HOMA-B=(insulin (μU/ml) x 20)/ (glucose (mmol/L)-3.5) (9), both of which have been validated as surrogate markers in healthy children (10).

Weight was measured in light clothing to the nearest 0.1 kg using a calibrated beam balance scale. Height was measured without shoes to the nearest 0.5 cm using a transportable Harpenden stadiometer. Four skinfold measurements (triceps, biceps, subscapula, and suprailiac) were taken on the left side of the body according to the criteria described by Lohman et al. All measurements were taken twice and in rotation. If the difference between the two measurements differed by more than 2 mm, a third measurement was taken and the two closest were averaged. Body mass index (BMI) was calculated (kg/m$^2$). Pubertal status was assessed by trained personnel according to Tanner's five-level classification of biological maturity, using breast development in girls and public hair in boys. Children were later classified as being pre-pubertal (Tanner stage 1), at early (Tanner stages 2-3) or at later (Tanner stages 4-5) stages of puberty."

SUPPLEMENTARY DATA

**GENDAI**

Each child had a blood sample taken and underwent a physical examination including blood pressure and anthropometric measurements. In addition children were also given a dietary and physical activity assessment. Venous blood samples were collected after an overnight fast (>10 h) and analysed at the Laboratory of Nutrition and clinical dietetics, Harokopio University, Athens. Serum glucose was determined in duplicate by use of commercially available enzyme colorimetric assays (Sigma diagnostics, St. Louis, MO, USA) on an automated ACE analyzer (Schiapparelli Biosystems, Inc., Fairfield, NJ, USA). Serum insulin was measured via immunofluorescence on an automatic AIA 600II analyser (Tosoh Corp., Tokyo, Japan) using a commercially available kit (ST AIA-PACK IRI, Tosoh Corp.) Intra- and Inter-assay coefficients of variability did not exceed 5% for glucose and 10% for insulin.

Height and weight were measured in light clothing without shoes. BMI was calculated as weight (kg) divided by height ($m^2$) and used to classify individuals as normal weight, overweight or obese, according to cut off points defined by the International Obesity Taskforce (IOTF). Sexual maturity status was ascertained by self-diagnosis of the subject in the presence of a trained paediatrician according to Tanner's criteria for breast, pubic hair and genital development.

**French children**

Each child had a blood sample taken and underwent a physical examination including blood pressure and anthropometric measurements. For both French lean and obese children fasting plasma glucose samples were collected in the morning after an overnight fast using the Glucose oxidase colorimetric assay (Merck, Darnsstadt, Germany automated on au5021 (Olympus, Rungis, France)) and insulin was measured using a double antibody radioimmunoassay. BMI was calculated as weight (kg) divided by height ($m^2$). For the obese sample obesity was defined as a BMI >97th percentile for age and sex in the tables of a French reference population provided by the European Childhood Obesity Group.

**Raine**

Each child had a blood sample taken and underwent a physical examination including anthropometric measurements. Fasting plasma glucose samples were collected after a fast of at least 8-12 hours and analysed by the hexokinase method using an automated Technicon Axon analyzer (Bayer Diagnostics, Sydney, Australia). Insulin was measured by automated radioimmunoassay (Tosoh, Tokyo, Japan).

BMI was calculated as weight (kg) divided by height ($m^2$). Children who had height and weight taken during a school visit had weight taken on scales accurate to 0.5kg and height measured by a steady stadiometer accurate to 0.5 cm. Children who were assessed at the assessment clinic had weight measured using a sit down scale (Wedderburn) accurate to 0.01 kg, and height measured to an accuracy of 0.1 cm (Holtan Limited).

**ALSPAC**

Each child had a blood sample taken and underwent a physical examination including anthropometric measurements. Fasting plasma glucose samples were collected after an overnight fast and were analysed by the hexokinase method. Insulin was determined using a commercially available ELISA with <0.01% cross-reactivity with pro-insulin (Mercodia AB, Uppsala, Sweden), with a coefficient of variation <4%.

BMI was calculated as weight (kg) divided by height ($m^2$).

SUPPLEMENTARY DATA

## Genotyping

Studies were asked to provide information on the following lead SNPs which have previously been shown to be associated with fasting glucose levels in adults at genome wide significance levels: *MTNR1B* (*rs10830963*), *G6PC2* (*rs560887*), *GCK* (*rs4607517*) *DGKB (rs2191349), GCKR (rs780094), ADCY5 (rs11708067), MADD (rs7944584), ADRA2A (rs10885122), CRY2 (rs11605924), FADS1 (rs174550), PROX1 (rs340874), SLC2A2 (rs11920090), GLIS3 (rs7034200), FAM148B (rs11071657), SLC30A8 (rs13266634),* and *TCF7L2 (rs7903146)*. In addition studies were also requested to provide information on a single SNP near *IGF1* (*rs35767*) which has previously been shown to be significantly associated with fasting insulin at genome wide significance in adults.

Details of genotyping, sample QC and imputation are provided in supplementary table ST1 and details of the method of genotyping (de novo/in silico) in addition to information on any proxies used are provided below for each study sample.

### EYHS

All genotyping was de novo and no proxies were used.

### GENDAI

All genotyping was de novo and no proxies were used.

### French children

Data provided was in silico with a mixture of typed and imputed SNPs. *G6PC2* (*rs560887*), *GCK* (*rs4607517*) *DGKB (rs10244051), GCKR (rs780094), CRY2 (rs11605924), MADD (rs7944584), FADS1 (rs174537), PROX1 (rs340874)* and *TCF7L2* (*rs12255372*) were all genotyped, whereas *MTNR1B* (*rs10830963*), *ADRA2A (rs10885122), ADCY5 (rs11708067), IGF1 (rs35767), GLIS3 (rs7034200), SLC2A2 (rs11920090)* and *FAM148B (rs11071657)* were all imputed.

Proxies (rs number; $r^2$ with lead SNP) were used for the following variants: *DGKB (rs10244051;* 1), *FADS1 (rs174537;* 1), *TCF7L2 (rs12255372;* 0.72*),*

### Raine

Data provided was in silico with a mixture of typed and imputed SNPs. *G6PC2* (*rs560887*), *GCK* (*rs4607517*)*, GCKR (rs780094), PROX1 (rs340874)* and *TCF7L2* (*rs7903146*) were all genotyped, whereas and *ADCY5 (rs11708067)*, *DGKB (rs2191349)*, *CRY2 (rs11605924)*, *MADD (rs7944584)*, *FADS1 (rs174550)*, *MTNR1B* (*rs10830963*), *ADRA2A (rs10885122)*, *IGF1 (rs35767)*, *GLIS3 (rs7034200), SLC2A2 (rs11920090)*, *FAM148B (rs11071657)* were all imputed.

### ALSPAC

All SNPs were imputed with no proxies used.

## References

1. Lawlor DA, Riddoch CJ, Page AS, Anderssen SA, Froberg K, Harro M, Stansbie D, Smith GD: The association of birthweight and contemporary size with insulin resistance among children from Estonia and Denmark: findings from the European Youth Heart Study. *Diabet Med* 22:921-930, 2005

2. Riddoch CJ, Bo Andersen L, Wedderkopp N, Harro M, Klasson-Heggebo L, Sardinha LB, Cooper AR, Ekelund U: Physical activity levels and patterns of 9- and 15-yr-old European children. *Med Sci Sports Exerc* 36:86-92, 2004

3. Papoutsakis C, Vidra NV, Hatzopoulou I, Tzirkalli M, Farmaki AE, Evagelidaki E, Kapravelou G, Kontele IG, Skenderi KP, Yannakoulia M, Dedoussis GV: The Gene-Diet Attica investigation on childhood obesity (GENDAI): overview of the study design. *Clin Chem Lab Med* 45:309-315, 2007

4. Visvikis-Siest S, Siest G: The STANISLAS Cohort: a 10-year follow-up of supposed healthy families. Gene-environment interactions, reference values and evaluation of biomarkers in prevention of cardiovascular diseases. *Clin Chem Lab Med* 46:733-747, 2008

5. Meyre D, Lecoeur C, Delplanque J, Francke S, Vatin V, Durand E, Weill J, Dina C, Froguel P: A genome-wide scan for childhood obesity-associated traits in French families shows significant linkage on chromosome 6q22.31-q23.2. *Diabetes* 53:803-811, 2004

6. Newnham JP, Evans SF, Michael CA, Stanley FJ, Landau LI: Effects of frequent ultrasound during pregnancy: a randomised controlled trial. *Lancet* 342:887-891, 1993

7. Golding J: Children of the nineties. A longitudinal study of pregnancy and childhood based on the population of Avon (ALSPAC). *West Engl Med J* 105:80-82, 1990

8. Kelliny C, Ekelund U, Andersen LB, Brage S, Loos RJ, Wareham NJ, Langenberg C: Common genetic determinants of glucose homeostasis in healthy children: the European Youth Heart Study. *Diabetes* 58:2939-2945, 2009

9. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412-419, 1985

10. Gungor N, Saad R, Janosky J, Arslanian S: Validation of surrogate estimates of insulin sensitivity and insulin secretion in children and adolescents. *J Pediatr* 144:47-55, 2004

SUPPLEMENTARY DATA

**Supplementary Table 1. Genotyping and phenotyping methods and quality control (QC) metrics in each study.**

| | | | | | | |
|---|---|---|---|---|---|---|
| | **ALSPAC** | **French obese** | **French controls** | **GENDAI** | **Raine** | **EYHS** |
| | | | | | | |
| **EXCLUSIONS**<br>**(FG=fasting glucose)** | Diabetes, FG>=7 mmol/L | Diabetes, FG>=7 mmol/L | Diabetes, FG>=7 mmol/L | Diabetes, FG>=7 mmol/L | Diabetes, FG>=7 mmol/L, non-fasting | Diabetes, FG>=7 mmol/L |
| **GENOTYPING** | | | | | | |
| In silico/ de novo | In silico | In silico | In silico | de novo | In silico | de novo |
| Genotyping platform & SNP panel | Illumina HumanHap 317K and 610 SNP chip | Illumina Human CNV370-Duo Array | Illumina Human CNV370-Duo Array | Applied Biosystems Taqman® | Quad 660W Illumina chip | Applied Biosystems Taqman® |
| Genotyping centre | Sanger and CNG Paris | Lille, France | Lille, France | Oxford | Centre for Applied Genomics, Toronto | MRC Epidemiology Unit, Cambridge |
| Genotyping calling algorithm | Illumina Beadsation Genotyping Solution | Illumina Beadsation Genotyping Solution | Illumina Beadsation Genotyping Solution | - | Illumina Beadsation Genotyping Solution | ABI PRISM 7900HT Sequence Detection System |
| **SAMPLE QC** | | | | | | |
| Call rate<br>[filter detail / N excluded] | ≥97% | ≥ 95% / 13 | ≥ 95% / 50 | >95% | >95% (15 individuals) | - |
| Heterozygosity<br>[filter detail / N excluded] | >0.36 or <0.34 | - | - | - | - | - |
| Ethnic outliers excluded | No - corrected using Eigenstrat | - | - | - | Adjust for principle components (no | - |

SUPPLEMENTARY DATA

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | 'extreme' outliers) | |
| Other exclusions | Sex Discrepancy; Cryptic relatedness | - | - | - | IBS>0.8, duplicates | - |
| **SNP QC (prior to imputation)** | | | | | | |
| MAF<br>[filter detail / N SNPs excluded] | ≥ 0.5% | 0.01 (0) | 0.01 (0) | - | >0.1 | - |
| HWE<br>[filter detail / N SNPs excluded] | $p<5.00 \times 10^{-7}$ | $p<1x10^{-4}$ (354) | $p<1x10^{-4}$ (354) | - | $p<5.7 \times 10^{-7}$ | p>0.07 |
| Call rate<br>[filter detail / N SNPs excluded] | ≥97% | 95% (1556) | 95% (1556) | - | >95% | >98.9% |
| Other | - | - | - | - | | |
| **IMPUTATION STATS** | | | | | | |
| Imputation software | MACH using CEU hapmap_270_r22_b36 | IMPUTE (v0.3.2, genotyped SNPs used where available) | IMPUTE (v0.3.2, genotyped SNPs used where available) | - | MACH | - |
| Imputation quality metrics | None during imputation bar "autoflip" to match hapmap strands | proper_info>0.4 | proper_info>0.4 | - | | - |
| Other SNP QC filters applied? | No | - | - | - | - | - |
| **GLUCOSE MEASUREMENTS** | | | | | | |
| Sample | Fasting venous plasma | Fasting venous plasma | Fasting venous plasma | Fasting venous plasma | Fasting venous plasma | Fasting venous |

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| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | plasma |
| Collection method | - | Morning after overnight fast | Morning after overnight fast | Overnight fast/snapfrozen samples | Overnight fast | Overnight fast |
| Assay | plasma glucose was measured by automated enzymatic assay (Hexokinase) | Glucose Oxidase | Glucose Oxidase | Colorimetric assay | Hexokinase method on an Architect c1600 Analyser using Glucose Reagent (Abbott Diagnostics, Abbott Laboratories, Abbott Park, IL 60064, USA) | Olympus AU600 random-access analysers |
| Assay sensitivity | - | - | - | - | At 4.8mmol/L CV=0.8% At 15.9mmol/L CV= 0.7% | 1.8% at 3.4 mmol/L |
| **INSULIN MEASUREMENTS** | | | | | | |
| Sample | Fasting | Fasting | Not Available | Fasting venous serum | Fasting | Fasting venous plasma |
| Collection method | Overnight fast | Overnight fast | Not Available | Fasting venous serum | Overnight fast | Overnight fast |
| Assay | ELISA | Double antibody radioimmuno-assay | Not Available | Immunofluorescent assay | Solid phase, two site chemiluminescent immunometric assay using an Immunite 2000 Analyser (Siemens Medical Solutions Diagnostic, 5210 Pacific Concourse Drive, Los Angeles, CA 90045-6900-USA) | Two-site immunometric assays |
| Assay sensitivity | COV <4% | Not Available | Not Available | Intra and inter-assay variability <5% | CV=4.8% at 8.48 & 13.03mIU/L<br>CV=5.9% at 22.67mIU/L | 12.5% at 15.8 mU/L |

SUPPLEMENTARY DATA

**Supplementary Table 2. Associations of fasting glucose loci with fasting glucose levels in each study and the overall meta-analysis.**

| Locus | Effect Allele (freq.) | n | Beta (95% CI) | p-value | $I^2$ (%) | | Locus | Effect Allele (freq.) | n | Beta (95% CI) | p-value | $I^2$ (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | |
| **GCK (rs4607517)** | A | | | | | | **G6PC2 (rs560887)** | C | | | | |
| GENDAI | 0.18 | 970 | 0.090 (0.035, 0.145) | | | | GENDAI | 0.71 | 947 | 0.096 (0.049, 0.143) | | |
| FRENCH controls | 0.18 | 631 | 0.078 (0.025, 0.131) | | | | FRENCH controls | 0.70 | 634 | 0.030 (-0.015, 0.075) | | |
| EYHS | 0.14 | 1926 | 0.028 (-0.006, 0.060) | | | | EYHS | 0.70 | 1934 | 0.084 (0.059, 0.109) | | |
| FRENCH cases | 0.17 | 582 | 0.034 (-0.108, 0.040) | | | | FRENCH cases | 0.70 | 581 | 0.081 (0.018, 0.144) | | |
| Raine | 0.17 | 1046 | 0.057 (0.016, 0.098) | | | | Raine | 0.70 | 1045 | 0.074 (0.039, 0.109) | | |
| ALSPAC | 0.18 | 1736 | 0.077 (0.046, 0.108) | | | | ALSPAC | 0.70 | 1736 | 0.068 (0.043, 0.093) | | |
| **Meta-analysis** | **0.17** | **6891** | **0.060 (0.038, 0.081)** | **$3.67\times10^{-8}$** | 30.3 | | **Meta-analysis** | **0.70** | **6877** | **0.073 (0.058, 0.088)** | **$1.95\times10^{-22}$** | 6.4 |
| | | | | | | | | | | | | |
| **PROX 1 (rs340874)** | **C** | | | | | | **GCKR (rs780094)** | **C** | | | | |
| GENDAI | 0.51 | 937 | 0.032 (-0.011, 0.075) | | | | GENDAI | 0.52 | 920 | -0.014 (-0.057, 0.029) | | |
| FRENCH controls | 0.56 | 634 | 0.030 (-0.011, 0.071) | | | | FRENCH controls | 0.55 | 630 | 0.019 (-0.022, 0.060) | | |
| EYHS | 0.51 | 1929 | 0.010 (-0.014, 0.034) | | | | EYHS | 0.63 | 1914 | 0.001 (-0.023, 0.026) | | |
| FRENCH cases | 0.55 | 583 | -0.002 (-0.059, 0.054) | | | | FRENCH cases | 0.56 | 581 | 0.026 (-0.031, 0.083) | | |
| Raine | 0.56 | 1046 | 0.017 (-0.016, 0.050) | | | | Raine | 0.60 | 1044 | 0.044 (0.013, 0.075) | | |
| ALSPAC | 0.57 | 1736 | 0.007 (-0.017, 0.031) | | | | ALSPAC | 0.60 | 1736 | 0.004 (-0.019, 0.028) | | |
| **Meta-analysis** | **0.54** | **6865** | **0.013 (0.0005, 0.026)** | **0.042** | 0.0 | | **Meta-analysis** | **0.59** | **6825** | **0.012 (-0.004, 0.028)** | **0.14** | 26.9 |

SUPPLEMENTARY DATA

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **SLC2A2 (rs11920090)** | **T** | | | | | | **ADRA2A (rs10885122)** | **G** | | | | |
| GENDAI | 0.83 | 936 | 0.037 (-0.022, 0.096) | | | | GENDAI | 0.88 | 947 | 0.003 (-0.064, 0.070) | | |
| FRENCH controls | 0.86 | 632 | 0.013 (-0.046, 0.072) | | | | FRENCH controls | 0.90 | 634 | 0.012 (-0.055, 0.079) | | |
| EYHS | 0.87 | 1899 | 0.049 (0.013, 0.084) | | | | EYHS | 0.87 | 1934 | 0.033 (-0.002, 0.067) | | |
| FRENCH cases | 0.85 | 579 | 0.036 (-0.042, 0.114) | | | | FRENCH cases | 0.90 | 581 | -0.036 (-0.126, 0.054) | | |
| Raine | 0.87 | 1044 | 0.042 (-0.007, 0.091) | | | | Raine | 0.92 | 1045 | 0.026 (-0.037, 0.089) | | |
| ALSPAC | 0.88 | 1736 | 0.032 (-0.003, 0.067) | | | | ALSPAC | 0.89 | 1736 | -0.027 (-0.070, 0.016) | | |
| **Meta-analysis** | **0.86** | **6826** | **0.037 (0.018, 0.056)** | **$1.30 \times 10^{-4}$** | 0.0 | | **Meta-analysis** | **0.89** | **6710** | **0.008 (-0.016, 0.031)** | **0.54** | 16.0 |
| | | | | | | | | | | | | |
| **CRY2 (rs11605924)** | **A** | | | | | | **MTNR1B (rs10830963)** | **G** | | | | |
| GENDAI | 0.55 | 945 | 0.027 (-0.016, 0.070) | | | | GENDAI | 0.29 | 856 | 0.010 (-0.141, 0.061) | | |
| FRENCH controls | 0.46 | 623 | -0.002 (-0.043, 0.039) | | | | FRENCH controls | 0.33 | 452 | 0.051 (0.006, 0.096) | | |
| EYHS | 0.54 | 1887 | 0.015 (-0.009, 0038) | | | | EYHS | 0.29 | 1936 | 0.069 (0.040, 0.090) | | |
| FRENCH cases | 0.47 | 574 | 0.004 (-0.051, 0.058) | | | | FRENCH cases | 0.30 | 428 | 0.081 (0.008, 0.0154) | | |
| Raine | 0.47 | 1037 | 0.028 (-0.005, 0.061) | | | | Raine | 0.31 | 673 | 0.140 (0.101, 0.179) | | |
| ALSPAC | 0.48 | 1736 | 0.012 (-0.012, 0.036) | | | | ALSPAC | 0.30 | 1736 | 0.074 (0.045, 0.103) | | |
| **Meta-analysis** | **0.50** | **6802** | **0.015 (0.002, 0.028)** | **0.025** | 0.0 | | **Meta-analysis** | **0.30** | **6081** | **0.072 (0.042, 0.102)** | **$2.22 \times 10^{-6}$** | 72.5 |
| | | | | | | | | | | | | |
| **DGKB (rs2191349)** | **T** | | | | | | **ADCY5 (rs11708067)** | **A** | | | | |
| GENDAI | 0.55 | 883 | 0.013 (-0.032, 0.058) | | | | GENDAI | 0.84 | 850 | 0.035 (-0.026, 0.096) | | |
| FRENCH controls | 0.42 | 633 | 0.003 (-0.036, 0.042) | | | | FRENCH controls | 0.82 | 590 | 0.011 (-0.042, 0.064) | | |

SUPPLEMENTARY DATA

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EYHS | 0.54 | 1897 | 0.003 (-0.020, 0.027) | | | | EYHS | 0.80 | 1888 | 0.038 (0.008, 0.067) | | |
| FRENCH cases | 0.45 | 583 | -0.049 (-0.104, 0.006) | | | | FRENCH cases | 0.80 | 533 | 0.073 (0.002, 0.144) | | |
| Raine | 0.56 | 1046 | 0.029 (-0.004, 0.062) | | | | Raine | 0.78 | 1013 | -0.004 (-0.045, 0.037) | | |
| ALSPAC | 0.54 | 1736 | 0.023 (-0.001, 0.047) | | | | ALSPAC | 0.75 | 1736 | 0.029 (0.002, 0.056) | | |
| **Meta-analysis** | **0.53** | **6778** | **0.010 (-0.007, 0.026)** | **0.25** | 31.7 | | **Meta-analysis** | **0.79** | **6610** | **0.028 (0.012, 0.044)** | **0.001** | 0.0 |
| | | | | | | | | | | | | |
| **MADD (rs7944584)** | **A** | | | | | | **FADS1 (rs174550)** | **T** | | | | |
| GENDAI | 0.70 | 826 | 0.027 (-0.024, 0.078) | | | | GENDAI | 0.71 | 930 | 0.013 (-0.034, 0.060) | | |
| FRENCH controls | 0.69 | 631 | -0.028 (-0.073, 0.017) | | | | FRENCH controls | 0.68 | 632 | 0.00014 (-0.043, 0.043) | | |
| EYHS | 0.74 | 1904 | 0.043 (0.015, 0.070) | | | | EYHS | 0.67 | 1908 | 0.005 (-0.020, 0.029) | | |
| FRENCH cases | 0.70 | 583 | -0.0003 (-0.061, 0.060) | | | | FRENCH cases | 0.68 | 582 | 0.017 (-0.044, 0.078) | | |
| Raine | 0.74 | 1044 | -0.0005 (-0.038, 0.037) | | | | Raine | 0.64 | 1043 | 0.026 (-0.009, 0.061) | | |
| ALSPAC | 0.72 | 1736 | 0.027 (-0.0004, 0.054) | | | | ALSPAC | 0.67 | 1736 | 0.010 (-0.015, 0.035) | | |
| **Meta-analysis** | **0.72** | **6724** | **0.016 (-0.005, 0.037)** | **0.14** | 44.2 | | **Meta-analysis** | **0.67** | **6831** | **0.010 (-0.004, 0.024)** | **0.14** | 0.0 |
| | | | | | | | | | | | | |
| **GLIS3 (rs7034200)** | **A** | | | | | | **C2CD4B (rs11071657)** | **A** | | | | |
| GENDAI | 0.52 | 912 | 0.024 (-0.019, 0.067) | | | | GENDAI | 0.66 | 869 | -0.029 (-0.077, 0.019) | | |
| FRENCH controls | 0.50 | 633 | 0.033 (-0.008, 0.074) | | | | FRENCH controls | 0.65 | 632 | -0.001 (-0.042, 0.041) | | |
| EYHS | 0.48 | 1853 | 0.007 (-0.017, 0.030) | | | | EYHS | 0.64 | 1904 | 0.013 (-0.012, 0.037) | | |
| FRENCH cases | 0.50 | 576 | 0.019 (-0.037, 0.074) | | | | FRENCH cases | 0.62 | 580 | 0.025 (-0.034, 0.084) | | |
| Raine | 0.48 | 1037 | 0.030 (-0.003, 0.063) | | | | Raine | 0.64 | 939 | 0.003 (-0.032, 0.038) | | |

SUPPLEMENTARY DATA

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ALSPAC | 0.47 | 1736 | 0.008 (-0.016, 0.032) | | | | ALSPAC | 0.62 | 1736 | -0.008 (-0.041, 0.025) | | |
| **Meta-analysis** | **0.49** | **6747** | **0.016 (0.003, 0.029)** | **0.018** | 0.0 | | **Meta-analysis** | **0.64** | **6660** | **0.003 (-0.012, 0.017)** | **0.71** | 0.0 |
| **SLC30A8 (rs13266634)** | **C** | | | | | | **TCF7L2 (rs7903146)** | **T** | | | | |
| GENDAI | n/a | n/a | n/a | | | | GENDAI | 0.36 | 850 | -0.046 (-0.092, 0.000) | | |
| FRENCH controls | 0.71 | 667 | 0.033 (-0.012, 0.078) | | | | FRENCH controls | 0.32 | 633 | -0.024 (-0.068, 0.019) | | |
| EYHS | 0.67 | 1944 | 0.033 (0.001, 0.058) | | | | EYHS | 0.26 | 1967 | -0.017 (-0.044, 0.010) | | |
| FRENCH cases | 0.71 | 681 | 0.049 (-0.016, 0.114) | | | | FRENCH cases | 0.29 | 583 | 0.043 (-0.019, 0.105) | | |
| Raine | 0.69 | 1044 | 0.001 (-0.033, 0.035) | | | | Raine | 0.29 | 1040 | -0.016 (-0.053, 0.021) | | |
| ALSPAC | 0.7 | 1736 | 0.027 (0.0015, 0.052) | | | | ALSPAC | 0.3 | 1736 | 0.015 (-0.010, 0.040) | | |
| **Meta-analysis** | **0.69** | **6072** | **0.026 (0.011, 0.041)** | **0.0005** | 0.0 | | **Meta-analysis** | **0.30** | **6809** | **-0.009 (-0.030, 0.012)** | **0.41** | 41.7 |

SUPPLEMENTARY DATA

**Supplementary Table 3. $I^2$ and p-value for heterogeneity for comparison of effect sizes of fasting glucose loci in adults and children**

| Gene | $I^2$ (%) | P | Difference between adult and children effect size (95% CI) |
|---|---|---|---|
| | | | |
| G6PC2 | 0 | 0.81 | 0.002 (-0.014, 0.018) |
| MTNR1B | 0 | 0.75 | -0.005 (-0.036, 0.026) |
| GCK | 0 | 0.86 | 0.002 (-0.020, 0.024) |
| DGKB | 80 | 0.026 | 0.02 (0.0029, 0.037) |
| GCKR | 74 | 0.051 | 0.017 ($-8.8 \times 10^{-5}$, 0.034) |
| ADCY5 | 0 | 0.91 | -0.001 (-0.018, 0.016) |
| SLC30A8 | 0 | 0.91 | 0.001 (-0.016, 0.018) |
| TCF7L2 | 87 | 0.005 | 0.032 (0.0095, 0.054) |
| ADRA2A | 18 | 0.27 | 0.014 (-0.010, 0.038) |
| MADD | 0 | 0.65 | 0.005 (-0.017, 0.027) |
| SLC2A2 | 62 | 0.11 | -0.017 (-0.038, 0.0036) |
| GLIS3 | 0 | 0.78 | 0.002 (-0.012, 0.016) |
| FADS1 | 0 | 0.37 | 0.007 (-0.0082, 0.022) |
| CRY2 | 0 | 1.0 | 0 (-0.014, 0.014) |
| PROX1 | 0 | 1.0 | 0 (-0.014, 0.014) |
| C2CD4B | 0 | 0.53 | 0.005 (-0.010, 0.020) |