Role of Conventional Childhood Risk Factors Versus Genetic Risk in the Development of Type 2 Diabetes and Impaired Fasting Glucose in Adulthood: The Cardiovascular Risk in Young Finns Study

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Diabetes Care 2016;39:1393–1399 | DOI: 10.2337/dc16-0167

OBJECTIVE

We examined whether the addition of novel genetic risk variant data to conventional childhood risk factors improves risk assessment of impaired fasting glucose (IFG) and type 2 diabetes in adulthood.

RESEARCH DESIGN AND METHODS

An association of a weighted genetic risk score (wGRS) based on 73 risk variants with IFG and type 2 diabetes was analyzed in 2,298 participants of the Cardiovascular Risk in Young Finns Study who were followed for 24–31 years from childhood to adulthood. In addition, the value of the wGRS in pediatric prediction of type 2 diabetes was examined.

RESULTS

Of the 2,298 participants, 484 (21.8%) and 79 (3.4%) had IFG or type 2 diabetes in adulthood, respectively. Adjusting for age, sex, baseline BMI, parental diabetes, mother's BMI, fasting insulin concentration, systolic blood pressure, and smoking status, wGRS was associated with an increased risk of IFG (odds ratio 1.64 [95% CI 1.33–2.01] per unit increase in the wGRS) and type 2 diabetes (2.22 [1.43–3.44]). Incorporating wGRS into pediatric risk models improved model discrimination and reclassification properties. Area under the receiver operating curve improved for IFG (from 0.678 to 0.691, $P = 0.015$), combined IFG and type 2 diabetes outcome (from 0.678 to 0.692, $P = 0.007$), and type 2 diabetes (from 0.728 to 0.749, $P = 0.158$). The net reclassification improvement and integrated discrimination improvement were significant for all outcomes.

CONCLUSIONS

A multifactorial approach combining genetic and clinical risk factors may be useful in identifying children at high risk for adult IFG and type 2 diabetes.

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Received 27 January 2016 and accepted 6 May 2016.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc16-0167/-/DC1.

Pediatric risk factors for type 2 diabetes include obesity, high systolic blood pressure, high maternal BMI, and family history of type 2 diabetes (1,2). A significant genetic component contributing to type 2 diabetes risk also exists, and genome-wide association studies (GWAS) have identified a number of loci consistently associated with type 2 diabetes and related traits (3–6).

Developing risk prediction models for the early identification of individuals at high risk for type 2 diabetes later in life is important because beneficial lifestyle changes have proven effective in preventing or delaying the onset of type 2 diabetes in individuals at increased risk (7,8). Two previous analyses have addressed the value of genetic risk factors in the pediatric prediction of adult type 2 diabetes: one from the present cohort (1) and the other from the longitudinal Bogalusa Heart Study (9). These reports found no clear support for the hypothesis that novel genetic risk variants would improve the prediction of type 2 diabetes in adulthood above clinical childhood risk factors. However, these studies may have been underpowered to detect a genetic prediction effect due to low numbers of participants with type 2 diabetes and/or an incomplete genetic risk marker panel. Since their publication, an increased number of loci associated with type 2 diabetes has been identified. Additionally, we have identified more patients with type 2 diabetes in the recent follow-up studies of our cohort. In the current study, we aimed to re-examine the value of novel genetic markers in identifying children and adolescents who are at increased risk of adulthood impaired fasting glucose (IFG), an early metabolic abnormality often preceding the onset of type 2 diabetes, and type 2 diabetes by combining phenotype and genotype data in a longitudinal population cohort.

RESEARCH DESIGN AND METHODS

Study Population

The Cardiovascular Risk in Young Finns Study (Young Finns) is a population-based follow-up study of cardiovascular risk factors in Finland. In 1980, 3,596 participants aged 3–18 years were examined. Subsequently, follow-up studies have been conducted regularly. A total of 2,283, 2,204, and 2,060 participants were examined in 2001, 2007, and 2011–2012, respectively. The sample used in the current study (n = 2,298) comprises participants for whom genotype and outcome data as well as risk factor data from baseline and 2001, 2007, and/or 2011–2012 follow-up visits were available. All participants gave written informed consent, and the local ethics committees approved the study.

Clinical and Biochemical Variables

Height and weight were measured and BMI was calculated as weight in kilograms over height in meters squared. Venous blood samples were drawn after an overnight fast. Mother's weight was obtained by questionnaire at baseline. Participants >12 years of age reported their own smoking status during a study visit without their parents present. Those who had reported smoking daily at some stage before or at age 24 years were categorized as smokers; others were categorized as nonsmokers.

Serum insulin was measured by using a modification of the immunoassay of Herbert et al. (10). Serum triglycerides and HDL cholesterol were measured as previously described (11,12). Serum LDL cholesterol was calculated using the Friedewald equation (13). Plasma glucose concentrations in adulthood were determined by the enzymatic hexokinase method (glucose reagent; Olympus, County Clare, Ireland). Glycated hemoglobin (HbA_{1c}) fraction in whole blood was measured by an ARCHITECT ci8200 analyzer (Abbott Laboratories). The concentration of total hemoglobin was first determined colorimetrically, after which the concentration of HbA_{1c} was measured immunoturbidimetrically with the microparticle agglutination inhibition method (HbA_{1c} reagent; Fisher Diagnostics). These two concentrations were used to calculate the HbA_{1c} percentage.

Blood pressure was measured while seated after a 5-min rest with a standard mercury sphygmomanometer at the baseline visit. An ultrasound device was used to measure blood pressure of 3-year-old participants. Readings to the nearest even number of millimeters of mercury were performed at least three times, and their mean was used in the analyses.

Definition of Diabetes and IFG

Participants were classified as having type 2 diabetes if at any of the follow-up visits (2001, 2007, or 2011–2012) their fasting plasma glucose value was ≥7 mmol/L or if they reported having been given a type 2 diabetes diagnosis by a physician. In addition, individuals whose HbA_{1c} was ≥6.5% (48 mmol/mol) at the 2011 follow-up or who reported taking glucose-lowering medication at the 2007 or 2011 follow-up were classified as having type 2 diabetes. Finally, type 2 diabetes diagnoses were obtained from the National Social Insurance Institution Drug Reimbursement Registry. Information on type 1 diabetes was collected at each follow-up visit. In 2001, type 1 diabetes was defined as having been given a diagnosis at or before age 24 years and/or insulin treatment. During the 2007 and 2011 follow-up visits, participants self-reported a type 1 diabetes diagnosis. Participants with type 1 diabetes were excluded from all analyses (n = 21).

Parental diabetes status was based on questionnaires at baseline. Diabetes type was not specified, and positive parental history of diabetes was defined as one or both parents having diabetes.

IFG was defined as having a fasting plasma glucose ≥5.6 mmol/L by the latest available measurement (14). Additional analyses were performed by using the World Health Organization cutoff (6.1 mmol/L) for IFG. Separate analyses were done for the group of participants with IFG (excluding those categorized as having type 2 diabetes) and for a combined group of participants with either IFG or type 2 diabetes.

Genotyping and Genotype Imputation

Genotyping was performed by using a custom-made Illumina Human 670 K BeadChip. Genotypes were called by using the Illumina clustering algorithm (15), and after quality control, 2,442 samples and 546,677 genotyped single nucleotide polymorphisms (SNPs) were available for further analysis. Genotype imputation was performed using SHAPEIT v1 (16) and IMPUTE2 (17) software and the 1000G Phase I Integrated Release Version 3 as a reference panel (18).

Construction of the Genetic Risk Score

A weighted genetic risk score (wGRS) comprising 73 SNPs found to be associated with type 2 diabetes was calculated as a sum of genotyped risk alleles or imputed allele dosages carried by an

individual, each multiplied by the externally reported effect size (the natural log of the odds ratio [OR]) (6). A list of SNPs and effect sizes used in the wGRS calculation is provided in Supplementary Table 1. Three SNPs for which association results in a population of European ancestry were not reported were omitted from the wGRS. In addition, the SNP rs3132524 at *POU5F1*/*TCF19* was not available among genotyped or imputed SNPs, and a proxy SNP, rs3130501, in high linkage equilibrium was used instead (r^2 = 1.0). We replicated all analyses using another previously published weighted genotype score comprising 46 SNPs found to be associated with type 2 diabetes in populations of European origin (19). In general, the salient results were similar with this score; however, it showed slightly stronger associations with the outcomes and better prediction value possibly because it includes fewer variants with very small effect sizes.

Statistical Analyses

Group comparisons were performed by using ANOVA or Kruskal-Wallis test for continuous variables and χ^2 or Fisher exact test for categorical variables. Pairwise group comparisons were adjusted for multiple testing by Tukey test for normally distributed variables and Benjamini and Hochberg method for others.

Deviation of genotype distributions from Hardy-Weinberg equilibrium was tested using the exact test. Association of individual SNPs and wGRS with the risk of IFG and type 2 diabetes was analyzed with logistic regression. Statistical models for individual SNPs were adjusted for age and sex, with no correction for multiple comparisons. Multivariable logistic regression models with and without wGRS were constructed for all outcomes, including the following childhood risk factors: BMI, fasting insulin, mother's BMI, parental diabetes, smoking status, and baseline systolic blood pressure. Age- and sex-specific *z* scores were calculated for baseline BMI, fasting insulin, and systolic blood pressure.

The additional value of wGRS in the prediction of adult IFG and type 2 diabetes was examined by using the R packages PredictABEL (20), Hmisc, and pROC (21) to estimate fit, calibration, and the differences in predictive abilities of the models. The discrimination performance of each model was estimated by calculating the receiver operating characteristic area under the curve (AUC) (22). Youden J statistic was used to determine the optimal cutoff value for sensitivity and specificity in each model (23). The improvement of prediction models was assessed by using the continuous net reclassification index (NRI) and integrated discrimination index (IDI), and model calibration was tested using the Hosmer-Lemeshow goodness-of-fit test (24).

RESULTS

Participants were followed for 24–31 years from baseline, and during that time, IFG developed in 484 (21.8%) and type 2 diabetes in 79 (3.4%). The baseline characteristics are shown separately for participants with normal fasting glucose (NFG), IFG, and type 2 diabetes in Table 1.

Most baseline risk factors differed between the groups (Table 1). Those in whom IFG or type 2 diabetes developed were significantly older and had higher wGRS, baseline BMI, maternal BMI, fasting insulin, and systolic blood pressure. The proportion of women was significantly lower in the IFG group than in the NFG and type 2 diabetes groups. The proportion of children with a parental history of diabetes was significantly higher among those in whom type 2 diabetes developed in adulthood, whereas no differences were seen between the NFG and IFG groups. The proportion of smokers was higher in both the IFG and the type 2 diabetes groups than in the NFG group, but no difference was seen between the IFG and type 2 diabetes groups.

Single SNP Analyses

All genotyped SNPs were in Hardy-Weinberg equilibrium except for rs3130501 (P = 0.036), and the information score for imputed SNPs was >0.9 for all except rs7560163 (0.70) and rs11063069 (0.88), indicating high-quality imputations. The results of single SNP associations are shown in Supplementary Table 1. Four SNPs (rs6878122 in the *ZBED3* locus, rs7903146 in the *TCF7L2* locus, rs831571 in the *PSMD6* locus, and rs9470794 in the *ZFAND3* locus) were associated with an increased risk of type 2 diabetes

Table 1—Childhood characteristics of participants according to NGF, IFG, and type 2 diabetes status in adulthood

				P value			
	NFG	IFG	Type 2 diabetes	Overall	NFG vs. IFG	NFG vs. type 2 diabetes	IFG vs. type 2 diabetes
n	1,735	484	79				
Female	59.9	34.5	53.2	4.6×10^{-22}*	2.0×10^{-22}	0.283	0.003
Age (years)	10.2 ± 5.0	11.8 ± 4.8	13.1 ± 4.6	4.9×10^{-13}†	3.3×10^{-9}	1.5×10^{-6}	0.074
BMI (kg/m^2)	17.7 ± 3.0	18.4 ± 3.1	19.7 ± 3.4	1.8×10^{-11}†	6.3×10^{-6}	4.6×10^{-8}	0.002
Fasting insulin (pmol/L)	56.3 ± 35.5	61.7 ± 35.4	77.0 ± 41.0	1.4×10^{-7}‡	0.0009	6.0×10^{-6}	0.002
Systolic blood pressure (mmHg)§	112 ± 11.9	115 ± 12.1	117 ± 11.6	7.6×10^{-9}†	2.9×10^{-7}	0.001	0.535
Mother's BMI (kg/m^2)	23.8 ± 3.7	24.3 ± 4.0	26.1 ± 4.5	3.4×10^{-8}†	0.009	2.7×10^{-7}	0.0004
Parental diabetes	2.0	2.9	8.9	0.003‖	0.325	0.005	0.028
Daily smoking¶	25.1	30.6	36.7	0.006*	0.043	0.043	0.338
wGRS (range 4.99–8.35)	6.61 ± 0.51	6.72 ± 0.53	6.84 ± 0.55	2.2×10^{-7}†	6.0×10^{-5}	0.0002	0.128

Data are % or mean ± SE. IFG cutoff is 5.6 mmol/L. *χ^2 test. †ANOVA. ‡Kruskal-Wallis test. §*n* = 2,298. ‖Fisher exact test. ¶At any stage in early life before or at the age of 24 years.

($P < 0.05$). In addition, rs7955901 in the *TSPAN8* locus was significantly associated with lower risk of type 2 diabetes (OR 0.68, $P = 0.033$). Altogether, nine SNPs were associated with IFG, all with effect in the expected direction (ORs 1.17–1.34, $P = 0.0003$–0.047).

Association of wGRS With IFG and Type 2 Diabetes

The wGRS ranged from 4.99 to 8.35 (mean 6.64, SD 0.52) and was significantly associated with IFG (OR 1.64 per unit increase in the wGRS, $P = 2.5 \times 10^{-6}$), type 2 diabetes (2.22, $P = 0.0004$), and the combined IFG and type 2 diabetes outcome (1.73, $P = 3.0 \times 10^{-8}$) in multivariable logistic regression models adjusted for childhood risk factors (Table 2). Associations remained significant when the cutoff of 6.1 mmol/L was used to define IFG. To examine whether the effect of the wGRS was similar across all age-groups, the age–wGRS interaction term was included in the multivariable models for all outcomes, but statistically significant interactions were not seen.

Model Discrimination and Reclassification

Adding wGRS to the childhood risk factor model improved the AUC for isolated IFG and the combined outcome (Table 3). For IFG, the AUC increased from 0.678 to 0.691 ($P = 0.015$) and for the combined IFG and type 2 diabetes outcome, from 0.678 to 0.692 ($P = 0.002$). For the combined outcome, the result remained statistically significant when the cutoff value of 6.1 mmol/L was used for IFG. Compared with the model without the wGRS, the model with genetic information showed a reduction in the number of false-positive type 2 diabetes cases from 673 to 617 and in the number of false-negative cases from 26 to 24 when using the threshold corresponding to the best sum of sensitivity and specificity. Similarly, the number of false positives was reduced from 611 to 593 and false negatives from 172 to 170 for IFG.

The net percentage of individuals with IFG correctly classified upward (event NRI) was 7.4% and of those without IFG correctly classified downward (nonevent NRI), 9.3%, resulting in an overall statistically significant continuous NRI of 0.167 ($P = 0.001$). Furthermore, the IDI was 0.011 ($P = 1.3 \times 10^{-5}$), indicating that the difference in average predicted risks between individuals with and without the outcome increased significantly when the wGRS was included in the prediction model (Table 4).

Similarly, the improvement in the reclassification properties of the type 2 diabetes prediction model was statistically significant, with the continuous nonevent NRI 16.4% and the overall continuous NRI 0.278 ($P = 0.015$) and IDI 0.010 ($P = 0.013$), whereas the event NRI was nonsignificant. For the combined IFG and type 2 diabetes outcome, all measures of reclassification properties except event NRI improved significantly when the wGRS was added to the model (Table 4). The Hosmer-Lemeshow goodness-of-fit test *P* values were nonsignificant for all models except the IFG model with cutoff value 6.1 mmol/L ($P = 0.037$), indicating that there was no evidence of poor fit for most models.

CONCLUSIONS

Whether recently discovered genetic variants are useful in predicting cardiometabolic risk in young individuals is a clinically relevant question that can be addressed by cohort data spanning the life course from childhood to adulthood. In this study, we provide novel data from the longitudinal Young Finns data by demonstrating that a wGRS associates with IFG and type 2 diabetes in young adults and that the performance of pediatric risk prediction for these outcomes is improved when wGRS is included in the model together with other well-established childhood risk factors.

Genetic risk factors differ from conventional risk factors in that their measurement is unambiguous, they remain unchanged during the life course, and they are not affected by disease outcomes. As the costs of genotyping decline and genomic profiling becomes more common, genetic variants may become increasingly useful in identifying individuals at increased risk for complex diseases, such as type 2 diabetes (25). Although genetic variants are strongly associated with incident type 2 diabetes, only limited added clinical value has been reported in the short-term prediction of type 2 diabetes in adulthood (9,26–28). However, a recent large U.K.-based consortium of prospective studies concluded that the addition of genetic risk score to the type 2 diabetes risk score derived from the Framingham Offspring Study leads to a potentially clinically important improvement in discrimination of incident type 2 diabetes over a median of 10 years of follow-up (29). Furthermore, genetic variants may be better predictors in younger individuals and even over longer follow-up periods (27,30). We have similarly shown for other cardiometabolic outcomes, such as adult hypertension (31,32) and dyslipidemia (33), that genetic information provides incremental predictive information in addition to nongenetic childhood risk factors. Genetic information could conceivably help to identify individuals with a high risk for type 2 diabetes in early life when other risk factors have not yet developed. The current results are in line with this hypothesis, demonstrating that genetic variants provide incremental information over clinical risk factors in identifying children and adolescents who are at risk for IFG or type 2 diabetes in adulthood.

Lifestyle interventions have proven effective in preventing or delaying the onset of type 2 diabetes in individuals at increased risk (7,8). Furthermore,

Table 2—Association of wGRS with IFG, type 2 diabetes, and combined IFG and type 2 diabetes outcome in pediatric multivariable logistic regression models

Outcome	OR (95% CI)	*P* value	*n*
IFG (cutoff 5.6 mmol/L)	1.64 (1.33–2.01)	2.53×10^{-6}	2,219
IFG (cutoff 6.1 mmol/L)	1.68 (1.19–2.38)	0.003	2,219
Type 2 diabetes	2.22 (1.43–3.44)	0.0004	2,298
Type 2 diabetes + IFG (cutoff 5.6 mmol/L)	1.73 (1.43–2.10)	3.01×10^{-8}	2,298
Type 2 diabetes + IFG (cutoff 6.1 mmol/L)	1.89 (1.43–2.50)	9.48×10^{-6}	2,298

OR is per unit increase in wGRS. Adjusted for age, sex, baseline BMI *z* score, baseline fasting insulin *z* score, mother's baseline BMI, parental history of diabetes, baseline systolic blood pressure *z* score, and smoking status.

Table 3—Discriminating properties of the pediatric multivariable IFG and type 2 diabetes prediction models

Outcome	AUC (95% CI) Without wGRS	With wGRS	*P* value*
IFG (cutoff 5.6 mmol/L)	0.678 (0.652–0.705)	0.691 (0.665–0.717)	0.015
IFG (cutoff 6.1 mmol/L)	0.701 (0.658–0.744)	0.716 (0.673–0.758)	0.114
Type 2 diabetes	0.728 (0.672–0.784)	0.749 (0.695–0.802)	0.158
Type 2 diabetes + IFG (cutoff 5.6 mmol/L)	0.678 (0.653–0.703)	0.692 (0.668–0.717)	0.007
Type 2 diabetes + IFG (cutoff 6.1 mmol/L)	0.699 (0.663–0.735)	0.716 (0.681–0.752)	0.041

Adjusted for age, sex, baseline BMI *z* score, baseline fasting insulin *z* score, mother's baseline BMI, parental history of diabetes, wGRS, baseline systolic blood pressure *z* score, and smoking status. *Model with wGRS vs. model without wGRS.

lifestyle changes may attenuate the adverse effects of genetic risk variants (34,35). Early identification of individuals with increased genetic risk of type 2 diabetes might enable the introduction of lifestyle and therapeutic disease prevention. Furthermore, as dietary and physical activity habits are established in early life, implementation of lifestyle changes may be more efficient at younger ages (36,37). We have shown that obese children who become nonobese adults have a normalized type 2 diabetes risk in adulthood (38), which further emphasizes the importance of targeted lifestyle interventions aimed at children at increased risk of type 2 diabetes.

Parental history of diabetes partly reflects genetic predisposition and partly shared environmental and lifestyle factors. Because adding wGRS to a risk model already including parental history of diabetes improved discrimination and reclassification properties of the model, the present results suggest that parental history does not capture all genetic influences.

The mechanisms underlying the relationship between most of the risk SNPs and type 2 diabetes are currently unknown. In individual SNP analyses, partly different variants were associated with the two outcomes type 2 diabetes and IFG. A larger number of SNPs were significantly associated with IFG, which may be explained by higher statistical power as a result of a larger number of cases. On the other hand, differences might also exist in the genetic architecture of type 2 diabetes and IFG. Whereas most genetic variants associated with type 2 diabetes in GWAS are known to influence insulin secretion, IFG mainly reflects hepatic insulin resistance (39). Insights into the potential mechanisms could be gained by following individuals with high genetic risk of type 2 diabetes at an early stage by using multiomics approaches (e.g., by using nested designs with appropriate controls) to prospectively follow the manifestation of disease biology at a very early stage through to disease onset.

We used three statistical measures (AUC, NRI, and IDI) to assess the performance of the present risk prediction models. The AUC describes the overall performance of the model in discriminating individuals with and without the outcome, but it is relatively insensitive to change if risk factors with strong associations with the outcome are already included in the initial model. In the current study, the increase in AUCs was 1.3% for IFG and 1.4% for the combined outcome, both statistically significant (38), and 2.1% for type 2 diabetes (P = 0.158). For type 2 diabetes, the genetic model identified 56 fewer false-positive cases compared with the model without genetic data. For IFG, the reduction of false-positive cases was 18.

The observed improvement in the overall NRI was mostly driven by the nonevent NRI, indicating that the wGRS correctly decreased the risk estimates for nonevents. Alternatively, this may be a result of a low number of events. The IDI was statistically significant for all models, indicating that the difference in average predicted risks between the individuals with and without the outcome increased significantly when the wGRS was included in the models.

The major strength of this study is the use of a large prospective cohort followed from childhood to adulthood. Most genetic prediction studies have examined the value of genetic risk factors in type 2 diabetes prediction in adult populations. The novelty of this study is that the participants were

Table 4—Improvement of reclassification properties of the pediatric type 2 diabetes and IFG prediction models, including wGRS compared with models without wGRS

Outcome	Nonevent NRI (95% CI)	Event NRI (95% CI)	Overall NRI (95% CI)	IDI (95% CI)
IFG (cutoff 5.6 mmol/L)	0.093 (0.046 to 0.140)	0.074 (−0.015 to 0.163)	0.167 (0.067 to 0.268)	0.011 (0.006 to 0.016)
P value	0.0001	0.101	0.001	1.3×10^{-5}
IFG (cutoff 6.1 mmol/L)	0.101 (0.058 to 0.143)	0.158 (−0.009 to 0.326)	0.259 (0.085 to 0.432)	0.005 (0.001 to 0.010)
P value	3.8×10^{-6}	0.065	0.003	0.014
Type 2 diabetes	0.164 (0.123 to 0.205)	0.114 (−0.105 to 0.333)	0.278 (0.055 to 0.500)	0.010 (0.002 to 0.017)
P value	5.7×10^{-15}	0.308	0.015	0.013
Type 2 diabetes + IFG (cutoff 5.6 mmol/L)	0.106 (0.059 to 0.152)	0.058 (−0.031 to 0.147)	0.163 (0.063 to 0.264)	0.012 (0.007 to 0.018)
P value	1.0×10^{-5}	0.202	0.001	1.8×10^{-5}
Type 2 diabetes + IFG (cutoff 6.1 mmol/L)	0.127 (0.084 to 0.169)	0.179 (0.047 to 0.312)	0.306 (0.167 to 0.445)	0.011 (0.005 to 0.017)
P value	5.6×10^{-9}	0.008	1.6×10^{-5}	0.0004

Adjusted for age, sex, baseline BMI *z* score, baseline fasting insulin *z* score, baseline mother's BMI, parental history of diabetes, wGRS, baseline systolic blood pressure *z* score, and smoking status.

followed from childhood to adulthood, with comprehensive collection of data on childhood risk factors for type 2 diabetes. The study population of Finnish individuals is racially homogeneous, and the results may not be directly generalizable to populations with different ethnic backgrounds. Although we used age- and sex-specific *z* scores of baseline BMI, fasting insulin concentration, and systolic blood pressure to account for age differences in risk factor levels and did not find any evidence for age–wGRS interaction in the statistical models, one limitation of the study is the wide age range of the children at baseline. In addition, the participants are still relatively young, and some classified as unaffected in this study will have disease onset in the future. Similarly, information on parental diabetes status was collected at baseline when the children's parents were still relatively young and may have not yet experienced the onset of type 2 diabetes.

At present, in clinical practice, type 2 diabetes risk in children and adolescents is estimated through traditional risk factors such as age, BMI, family history, and fasting insulin levels. The current results suggest that when genetic information is added, the improvement in discrimination and reclassification properties of the models increases statistically significantly. Nevertheless, replication of this finding in other longitudinal cohorts would be important to verify its clinical utility so that the knowledge can be incorporated into guidelines for pediatric risk prediction.

One major limitation of genetics studies of type 2 diabetes, both risk variant discovery and risk prediction, is an imprecise definition of diabetes type. Particularly, latent autoimmune diabetes in adults (LADA) often is misdiagnosed as type 2 diabetes and is estimated to account for ~7% of all diabetes cases (40). We were not able to exclude LADA cases, and this may have resulted in an underestimated association between wGRS and IFG/type 2 diabetes because the genetic architecture of LADA and type 2 diabetes differs significantly (40). Similarly, type 1 diabetes and type 2 diabetes do not have a shared genetic background (40), and we were not able to separate parental status by diabetes type. Most of the variants included in our risk score were identified in GWAS performed in cross-sectional adult populations. In addition, the true causal variant is not necessarily identified by a GWAS approach because many of the variants included in the wGRS may be proxy variants that are in close linkage disequilibrium with the causal variant, which may weaken the effect of the wGRS.

In summary, the present data demonstrate that a multifactorial approach that takes genetic risk factors into account could improve the identification of children at high risk for adult IFG and type 2 diabetes.

Funding. Young Finns has been financially supported by the Academy of Finland (grants 286284 [to T.L.]; 134309 [Eye]; 126925, 121584, 124282, and 129378 [Salve]; 117787 [Gendi]; and 41071 [Skidi]); the Social Insurance Institution of Finland; Kuopio, Tampere, and Turku University Hospital Medical Funds (grant X51001 to T.L.); Juho Vainio Foundation; Paavo Nurmi Foundation; Finnish Foundation of Cardiovascular Research; Finnish Cultural Foundation; Sigrid Juselius Foundation; Tampere Tuberculosis Foundation; Emil Aaltonen Foundation; and Yrjö Jahnsson Foundation.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. N.P. contributed to the study design, statistical analyses, data interpretation, and drafting of the manuscript. M.J. and T.R. contributed to the data collection and critical revision of the manuscript for important intellectual content. M.A.S. and N.H.-K. contributed to the critical revision of the manuscript for important intellectual content. M.K. contributed to obtaining funding and to the management of the genetic data and revision of the manuscript for important intellectual content. T.L. contributed to obtaining funding and to the management of the genetic data and review of the manuscript. J.S.A.V. contributed to the initial design of Young Finns and critical revision of the manuscript for important intellectual content. O.T.R. leads Young Finns and contributed to obtaining funding and to the study design, data interpretation, and review and editing of the manuscript. N.P. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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