Title: Genome-wide association study of the modified Stumvoll Insulin Sensitivity Index identifies *BCL2* and *FAM19A2* as novel insulin sensitivity loci

Running title: Novel insulin sensitivity loci

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Word Count: 3960

Number of Tables: 2

Number of Figures: 3

Abstract

Genome-wide association studies (GWAS) have found few common variants that influence fasting measures of insulin sensitivity. We hypothesized that a GWAS of an integrated assessment of fasting and dynamic measures of insulin sensitivity would detect novel common variants. We performed GWAS of the modified Stumvoll Insulin Sensitivity Index (ISI) within the Meta-Analyses of Glucose and Insulin-related traits Consortium. Discovery was performed in 16,753 individuals, and replication was attempted for the 23 most significant novel loci in 13,354 independent individuals. Association with ISI was tested in models adjusted for age, sex, body mass index (BMI) and in a model ("Model 3") analyzing the combined influence of the genotype effect adjusted for BMI and the interaction effect between the genotype and BMI on ISI. In Model 3, three variants reached genome-wide significance: rs13422522 (*NYAP2*, P=8.87 $\times 10^{-11}$), rs12454712 (*BCL2*, P=2.7$\times 10^{-8}$) and rs10506418 (*FAM19A2*, P=1.9$\times 10^{-8}$). The association at *NYAP2* was eliminated by conditioning on the known *IRS1* insulin sensitivity locus; the *BCL2* and *FAM19A2* associations were independent of known cardio-metabolic loci. In conclusion, we identified two novel loci and replicated known variants associated with insulin sensitivity. Further studies are needed to clarify the causal variant and function at the *BCL2* and *FAM19A2* loci.

Genome-wide association studies (GWAS) have identified common genetic variants that influence risk of type 2 diabetes (1), a disease marked by reduction in beta-cell function and insulin sensitivity (2). While both beta-cell function and insulin sensitivity traits are partly heritable, GWAS have demonstrated relatively few single nucleotide variants (SNPs) associated with insulin sensitivity (3).

Traits used to estimate insulin sensitivity from fasting measurements in prior large GWAS, including fasting insulin and the homeostatic model assessment of insulin resistance (HOMA-IR), demonstrate approximately half the heritability of traits that incorporate both fasting and dynamic assessment of insulin sensitivity following a glucose load (4). Moreover, there is only modest genetic correlation between HOMA-IR and measures of insulin sensitivity by euglycemic clamp, which is considered the gold standard measure of peripheral insulin sensitivity (5,6). Thus, an alternative approach to discover new common genetic variants associated with insulin sensitivity is to perform GWAS using a dynamic measure of whole-body insulin sensitivity. As an example, a recent GWAS identified a novel insulin sensitivity locus at *NAT2* using euglycemic clamp and insulin suppression test techniques in 2,764 subjects with replication in another 2,860 individuals (7). However, these direct, whole-body measures of insulin sensitivity are time- and resource-intensive interventions, which limits the feasible sample size of such experiments. Derived indices from an oral glucose tolerance test (OGTT) that integrate fasting and dynamic measures of insulin sensitivity reasonably approximate euglycemic clamp measures and can be applied in existing large cohorts with glycemic traits, potentially increasing the statistical power to detect novel variant associations.

We tested the hypothesis that a well-powered GWAS would detect common genetic variants for the modified Stumvoll Insulin Sensitivity Index (ISI). Insulin sensitivity assessed by the euglycemic hyperinsulinemic clamp (M/I) has a stronger correlation with the ISI than with HOMA-IR (r=0.79 *vs*. r=0.59, respectively) (8). In addition, the ISI is well correlated (r=0.69) with M/I even when calculated using only fasting insulin values and glucose and insulin values at 120 minutes after a 75-gram oral glucose load (9); this modified version is widely available in existing cohorts providing a larger sample size for association analyses than the sample size that would be available if indices requiring additional time points were used. We further hypothesized that a subset of these common genetic variants would influence the ISI independently or through their effect on body mass index (BMI). Thus, we tested the association of the modified ISI in statistical models without adjustment for BMI, with adjustment for BMI, and in a validated model (10,11) analyzing the combined influence of the genotype effect adjusted for BMI and the interaction effect between the genotype and BMI on ISI.

Research Design and Methods

Cohort Descriptions

The cohorts participating in the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) contributed a total of 30,107 individuals to the analyses. Detailed information on the study cohorts and methods is provided in **Supplemental Table 1**. All participants were of white European ancestry from the United States or Europe and were free of diabetes. All studies were approved by local research ethic committees, and all participants gave informed consent.

Modified Stumvoll Insulin Sensitivity Index (ISI)

Missing trait data were not imputed, and outliers were not excluded from analyses. The ISI was calculated as previously described (9) according to the following formula:

$$0.156-(0.0000459*\text{insulin}_{2\text{hrs[pmol/L]}})-(0.000321*\text{insulin}_{\text{fasting [pmol/L)}})- (0.0054* \text{glucose}_{2\text{hrs [mmol/L]}})$$

Discovery Effort: Genome-Wide Association Studies

Cohorts that were able to contribute genome-wide genotyping results during the course of the project were included in the discovery effort. These were: FHS, Sorbs, FUSION, CHS, LURIC, ULSAM, and METSIM. For the discovery GWAS, all samples with call-rates < 95% were excluded, and SNPs departing from Hardy-Weinberg Equilibrium (at $P < 10^{-6}$), genotype-rate < 95%, or minor allele frequency (MAF) < 1% were excluded. Poorly imputed SNPs were excluded if $R^2 < 0.3$ or proper-info was < 0.4.

Each SNP was tested for association with ISI in three different additive genetic models: Model 1 was adjusted for age and sex; Model 2 was adjusted for age, sex, and BMI; and Model 3 analyzes

the combined influence of the genotype effect adjusted for BMI and the interaction effect between the genotype and BMI on ISI (10,11). The associations in Model 3 result from a test with two degrees of freedom. When no interaction is present, the additional degree of freedom results in a modest loss of statistical power. However, when interaction is present, statistical power of the model is greater (11). To adjust for differences in insulin measurement between cohorts, effect estimates were normalized to the standard deviation (SD) of the ISI in each cohort (**Supplemental Table 1**). A robust estimate of the standard error was calculated in the interaction analysis using ProbAbel, QUICKtest or Generalized Estimating Equations (GEE) using the R geepack package. An inverse variance meta-analysis using METAL was performed on the beta/SD from each cohort.

Following meta-analysis, SNPs with total sample size less than 8,500 (~1/2 of the maximum sample size), or with heterogeneity *P*-values $\leq 10^{-6}$ (a value chosen to take into account multiple hypothesis testing but below the level of strict Bonferroni correction) in the meta-analysis of the discovery cohorts were removed. Genomic correction of cohort-specific association statistics (*i.e.*, correction for each individual study) was performed. In total, up to 2.4 million SNPs were meta-analyzed for association with ISI in the discovery effort.

Selection of SNPs for Replication

Candidate SNPs for replication were identified by their association *P*-value $\leq 10^{-7}$ in one or more of the analysis models. For gene loci with multiple replication candidates, the SNP with the lowest *P*-value and any other SNP in low linkage disequilibrium (LD, $r^2 < 0.5$) with the index SNP in Europeans were retained. Using these filters, 23 unique candidate SNPs from 23 loci

were identified for replication. The SNP Annotation and Proxy Search (SNAP) site was used to find up to three proxies in high LD ($r^2 > 0.8$) in Europeans for each candidate SNP.

Replication Effort

Cohorts that did not contribute to the discovery effort but were able to contribute association results during the course of the project were included in the replication effort. These were: EUGENE2, Amish, RISC, Tuebingen, Inter99, Segovia, Pizarra, Botnia, 1936 Birth Cohort, and Ely Study. Genotype data were obtained using *in silico* data from pre-existing GWAS or *de novo* genotyping. In replication cohorts, SNPs with minor allele count (MAC) < 20 were excluded. Additional details of the replication cohort effort are provided in **Supplemental Table 1**.

Combined meta-analysis

We required the absence of heterogeneity in the combined analysis of discovery and replication cohorts ($P > 10^{-6}$) as well as nominal significance ($P < 0.05$) in the replication effort and genome-wide significance ($P < 5\times10^{-8}$) in the combined meta-analysis for statistical evidence of association between a novel SNP and the ISI. To assess the effect of removing lower frequency SNPs in Model 3, a sensitivity analysis was performed using the MAC < 20 filter on a cohort-wise basis in both the discovery and replication cohorts.

Assessment for association of known insulin sensitivity loci with ISI

The associations of published insulin sensitivity loci were tested for association with the ISI in the discovery cohorts. Loci associated with fasting insulin without (12) and with adjustment for BMI (3,12), with fasting insulin using the approach in Model 3 (10), and with direct measures of

insulin sensitivity were included in these analyses (7). The published results for associations with fasting insulin with or without BMI adjustment (N ≈ 50,000-100,000) (3,12) or exploiting potential BMI by gene interaction (Model 3, N ≈ 80,000) (10) used the same statistical approach as in the current study but were derived in a sample size approximately 3-6 times larger than that of the current study discovery cohort (N ≈16,000). The sample sizes of the published fasting insulin analyses were much greater as only fasting insulin and BMI were required phenotypes for cohort participation. To perform analyses of association with fasting insulin and ISI in a comparable sample, we also examined the subset of discovery cohorts that contributed to the current assessment of ISI and prior assessments of fasting insulin: FHS, Sorbs, FUSION, and CHS. In Model 2 and Model 3, only data from FHS, Sorbs, and FUSION were analyzed as participant level BMI data were not available in CHS. A binomial sign test was used to determine whether the expected direction of effect for these published loci with ISI occurred more often than by chance.

Conditional analyses and assessment for association of top findings with direct measures of insulin sensitivity

Findings that reached genome-wide significance were assessed for association with direct measures of insulin sensitivity in the GENEtics of Insulin Sensitivity (GENESIS) consortium (7). Direct measures of insulin sensitivity were inverse normal transformed M value in cohorts with euglycemic insulin clamp assessments and inverse normal transformation of the steady state plasma glucose from cohorts with insulin suppression test. These two traits are highly correlated (r= -0.85, $P<0.001$) (13), and tests of association with the direct measure of insulin sensitivity showed no evidence of heterogeneity (*P*-value for heterogeneity =0.34 for the *BCL2* variant and

P- value for heterogeneity =0.66 for the *FAM19A2* variant). Therefore, we did not perform separate tests of association in the smaller subsets of data with either the M value or insulin suppression test phenotype. Statistical models were adjusted for age, gender, and BMI.

The top findings of the ISI analyses were also assessed in a MAGIC association analysis from Manning and colleagues (10) with fasting insulin using the approach in Model 3. These ISI variants were only available in the discovery cohort from Manning and colleagues (N=38,649 for rs12454712 and N=45,290 for rs10506418). To perform association analyses with fasting insulin and ISI in a comparable sample, we also performed association analyses with fasting insulin and ISI in a subset of the discovery cohort: FHS, Sorbs, and FUSION.

Approximate conditional analyses were performed to understand whether known loci contributed to the associations of novel findings with the ISI (14). These analyses were based on the summary level statistics from the meta-analysis and the estimated LD using individual-level genotype data from the Framingham Heart Study discovery cohort. The software implementation for this approach does not incorporate the interaction term from Model 3, and therefore conditional analyses were not performed in Model 3.

Results

The demographic characteristics of the participants included in the discovery and replication efforts are presented in **Table 1**. In total, the discovery, replication, and combined meta-analyses included up to 16, 753; 13,354; and 30,107 participants, respectively.

Using a variance component approach implemented in the software SOLAR (15), the heritability of the ISI (H2r ± SE) in related Framingham Heart Study participants (n=2,833) was very similar without or with adjustment for BMI (34.6 ± 6.8%, $P = 2.8 \times 10^{-8}$ and 33.4 ± 6.8%, $P = 1.0 \times 10^{-6}$ respectively). Within the ULSAM discovery cohort, the Spearman correlation between the ISI and M value from the euglycemic hyperinsulinemic was 0.71, (**Figure 1**) consistent with reports from the literature (9); the Spearman correlation between ISI and fasting insulin was -0.49 (**Figure 1**).

When tested in the full discovery cohort, 12 of 13 loci previously associated with fasting insulin in the literature (12) (P=0.002 for binomial sign test) and 13 of 15 loci previously associated with fasting insulin after adjustment for BMI in the literature (3,12) (P=0.004 for binomial sign test) showed the expected direction of effect with the ISI in the discovery cohorts (**Supplemental Table 2**). When these associations were examined in a subset of the current study discovery cohort (**Supplemental Table 2**), statistical significance was reduced but effects at each loci remained in the expected direction (10 of 13 loci for ISI vs. fasting insulin without BMI adjustment, P=0.03 for binomial sign test and 11 of 15 loci for ISI vs. fasting insulin with BMI adjustment, P=0.04 for binomial sign test). Using a variant in LD with rs1208 (rs7815686, r^2 =

0.67), we also found the expected direction of effect with ISI in the discovery cohorts (n=16,753) at the *NAT2* locus (Model 1, β= -0.029, $P=9\times10^{-3}$) (7).

The QQ plots for Models 1, 2, and 3 are shown in **Supplemental Figure 1**, **2**, and **3**, respectively. Measures of genomic control were consistent with low inflation (Model 1 λ_{GC}= 1.015; Model 2 λ_{GC}= 1.006; Model 3 λ_{GC}= 1.079). While genomic control was used to correct for each individual study, no additional corrections were applied to the meta-analysis results. The results of the discovery and replication results, separately, for Model 1 (with age- and sex-adjustment), Model 2 (with age-, sex-, and BMI- adjustment), and Model 3 (with age-, sex-, and BMI- adjustment and analyzing the combined influence of the genotype effect adjusted for BMI and the interaction effect between the genotype and BMI on ISI) are shown in **Supplemental Table 3**. Four SNPs selected from the discovery effort reached nominal significance (P <0.05) in the replication analyses: rs13422522 (*NYAP2*) in Models 1, 2, and 3; rs12454712 (*BCL2*) in Models 2 and 3; rs10506418 (*FAM19A2*) in Model 3; rs6013915 (*PFDN4*) in Model 3. Although the association with rs4548846 (*CDH13*) reached nominal significance in the replication effort for Model 3, the association was in the opposite direction of effect as in the discovery analyses; consequently, the association of this variant also had high heterogeneity combined meta-analysis.

We compared the beta coefficients for the 22 SNPs identified in the discovery effort (rs4548846, *CDH13* was excluded given high heterogeneity) with fasting insulin and ISI in a subset of the discovery cohort. Pearson correlations between the beta for fasting insulin and the beta for ISI were -0.494 in Model 1, -0.797 in Model 2, and -0.461 (for SNP effect) and -0482 (for interaction) in Model 3.

The results of the combined discovery and replication cohort meta-analyses in each of the three models are shown in **Table 2** and in **Supplemental Table 3**. No association reached genome-wide significance in Model 1. In Model 2, rs13422522 (*NYAP2*, P=1.8 ×10^{-11}) and rs12454712 (*BCL2*, P=1.9×10^{-8}) achieved genome-wide significance. In Model 3, rs13422522 (*NYAP2*, P=8.9×10^{-11}), rs12454712 (*BCL2*, P=2.7×10^{-8}), and rs10506418 (*FAM19A2*, P=1.9×10^{-8}) reached genome-wide significance. In Model 3, rs6027072 (*ARHGAP40*, P=4.4×10^{-9}) also reached genome-wide significance but had not achieved nominal significance in the replication cohort, and rs6013915 (*PFND4*) had high heterogeneity in the combined meta-analysis of discovery and replication cohorts (heterogeneity P = 6.03×10^{-7}); therefore associations with these SNPs were not included as trustworthy findings.

Hence, rs13422522 (*NYAP2*), rs12454712 (*BCL2*) and rs10506418 (*FAM19A2*) were the three SNPs that reached our *a priori* requirements for claiming statistical evidence. The association at rs13422522 (*NYAP2*) was in LD (r^2 = 0.7) with previously reported results at the known insulin sensitivity signal rs2943641 (*IRS1*) (10), and the association with the ISI in Model 2 was greatly reduced by conditioning on the published SNP in the discovery cohort (beta = -0.066 ± 0.01, P= 4.29 × 10^{-8} to beta = -0.025 ± 0.01, P=0.01). Thus, this SNP was considered a reflection of the known *IRS1* signal and not an independent signal. The associations for rs12454712 (*BCL2*) and rs10506418 (*FAM19A2*) with the ISI were consistent across the discovery and replication cohorts (**Supplemental Figure 4** and **Supplemental Figure 5**, respectively). When stratifying by BMI, the effect of the minor (A) allele at rs10506418 (*FAM19A2*) on insulin sensitivity was negative at lower BMI and became positive and stronger with increasing BMI (**Figure 2**), and the effect

of the major (T) allele at rs12454712 (*BCL2*) on ISI was more negative with increasing BMI (**Figure 3**).

The genomic inflation of Models 1 and 2 was low and slightly higher in Model 3. Because the same individuals were used in each model, inflation in Model 3 was unlikely to arise from population stratification. We performed an additional sensitivity analysis that applied the MAC < 20 filter on a cohort-wise basis to both discovery and replication cohorts (**Supplemental Table 4**), which tended to reduce the statistical significance of associations with high heterogeneity and slightly reduced the statistical significance of the association at the *FAM19A2* locus in Model 3 without markedly reducing the magnitude of effect or affecting heterogeneity (beta = -0.62 ± 0.13, *P*-value = 1.9×10^{-8}, *P*-value for heterogeneity= 0.11 to beta = -0.58 ± 0.13, *P*-value =8.0×10^{-7}, *P*-value for heterogeneity= 0.07). The sample size for the *FAM19A2* locus association in Model 3 was 462 individuals fewer when the MAC filter was applied in the discovery cohorts versus when the MAF filter was applied, and the resulting loss in power was likely responsible for the slight reduction in statistical significance.

Conditioning the results at either variant with known signals at least 1 Mb away did not attenuate the association with the ISI in the discovery cohorts of Model 2 (full description in **Supplemental Table 5**). The rs10506418 (*FAM19A2*) variant was not associated with fasting insulin using Model 3 in a separate GWAS result (10) or with direct measures of insulin sensitivity in GENESIS. The major (T) allele of rs12454712 (*BCL2*), which was associated with lower insulin sensitivity in this study, was also associated with a trend toward higher fasting insulin in a separate GWAS result using Model 3 (SNP effect -0.006 ± 0.003, interaction effect

0.001 ± 0.001, $P = 5.9 \times 10^{-5}$, N=38,649) (10). Similar trends were observed when the variant was tested for association with ISI and fasting insulin in the same discovery cohort subset (**Supplemental Table 5**).

Discussion

In a study of over 30,000 participants, we found novel, independent, genome-wide significant associations for the ISI at rs12454712 (*BCL2*) and rs10506418 (*FAM19A2*). Strengths of the current study's design include a large sample size, well-phenotyped individuals, high-quality genomic data, and use of traditional and contemporary statistical models to account for the influence of BMI on insulin sensitivity. In addition, our approach targeted a phenotype not previously examined in GWAS: the modified Stumvoll Insulin Sensitivity Index. By incorporating glucose and insulin measures before and after a glucose load, this phenotype captures information that fasting assessments such as HOMA-IR or insulin, alone would not. Indeed, the correlation between ISI and M-value is higher than that between M-value and fasting insulin (16), which has been used in prior genetic studies of insulin sensitivity (10,12). At the same time, the use of measures obtained at only two time points (fasting and 120 minutes) during an OGTT permitted assembly of a large sample size required for adequate statistical power.

Several findings serve as positive controls for our results and demonstrate that the ISI is a robust measure of fasting and whole-body insulin sensitivity. First, we observe strong correlation of ISI with direct measures of insulin sensitivity. Second, we show that the ISI can detect genetic influences on measures of fasting insulin sensitivity (3,10,12), generally ascribed to hepatic physiology, as well as on measures of whole-body insulin sensitivity, which also incorporates contributions from muscle and adipose tissue. Integrated measures of insulin sensitivity may have clinical relevance as reduction in peripheral insulin sensitivity may be an early contributor to type 2 diabetes development (17-19).

Consistent with prior genetic explorations of insulin sensitivity (10), the association of variants at the *BCL2* and *FAM19A2* loci became stronger and genome-wide significant after accounting for

the effect of BMI on ISI. Notably, the ISI can be calculated with or without BMI in the formula, and the correlation of the ISI with M/I is greater when BMI is included (r=0.69 vs. r=0.79) (8,9). We note that the effect of these loci on insulin sensitivity is modest, consistent with published findings on other common genetic variants for glycemic traits, such as glucose (12) and fasting insulin (3,10,12). Yet, the findings of the current work are meaningful as they provide a more complete understanding of the contribution of common genetic variation to insulin sensitivity.

Existing literature bolsters our finding of *BCL2* as a novel candidate insulin sensitivity locus. The major (T) allele at rs12454712, which was associated with lower insulin sensitivity in our analysis, has been previously associated with type 2 diabetes in a multi-ethnic GWAS (OR = 1.09, 95% confidence interval (CI), 1.05–1.11, $P = 2.1 \times 10^{-8}$) (20) in analyses adjusted for BMI. Further, this same variant has recently been associated with higher BMI-adjusted waist-hip ratio in women (beta= 0.035, $P= 1.1\times10^{-9}$, N= 96,182), but not men (beta= 0.007, P=0.25, N=73,576) (22). All these findings suggest the metabolically deleterious effects of the *BCL2* locus become more evident after adjustment for BMI. Last, we find that the statistical association of rs12454712 (*BCL2*) is stronger with the ISI than with fasting insulin (10). Notably, the published fasting insulin results were performed in a study much larger than in the current work. The ability of the ISI to detect a genome-wide significant finding in a smaller sample suggests the *BCL2* locus may have a greater influence on insulin sensitivity when fasting and post-prandial phenotypes are assessed together.

The mechanism by which *BCL2* influences insulin sensitivity remains unclear. The *BCL2* family of proteins regulate apoptosis through control of mitochondrial permeability (23). Mouse models

suggest that inhibiting *bcl2* improves glucose tolerance through effects on the pancreatic beta cells (24). Conversely, pharmacological inhibition of the protein BCL2 causes hyperglycemia among a subset of patients with chronic lymphocytic leukemia (25), but the mechanism of this observation is unknown. In contrast, there is little direct published literature to support the role of *FAM19A2* in insulin sensitivity. We found that the association of the minor (A) allele at the *FAM19A2* locus with reduced insulin sensitivity was detected at BMI < 30 kg/m^2. This may suggest the variant is more deleterious among individuals with lower levels of adiposity. While *BCL2* and *FAM19A2* are the closest genes to rs12454712 and rs10506418, respectively, we have not excluded other genes in the region (**Supplemental Figure 6** and **7**). Additional *in silico* findings at the *BCL2* and *FAM19A2* variants are provided in **Supplemental Table 5**.

We recognize limitations to our study. First, analyses were performed exclusively in white individuals of European ancestry. Exploring these loci in other racial and ethnic groups is needed. Second, we used an estimate of whole-body insulin sensitivity derived from post-glucose load measures of glucose and insulin, rather than direct measures of insulin sensitivity. The wide availability of the ISI provided increased statistical power of the association analyses relative to that of other indices which are better correlated with euglycemic measures of insulin sensitivity, such as the Matsuda index (26). Assessment of our novel findings in the GENESIS consortium suggests that the ISI may be capturing different information on insulin sensitivity than that provided by the insulin clamp or the insulin suppression test, or that the power in the GENESIS analyses was limited to detect this association. Third, conditional analyses could not be performed in Model 3, which would have been the best method of assessing the dependence of the signals at *BCL2* and *FAM19A2*. However, the LD for each variant with other known glucose

and insulin loci in the region was low, and the nominally significant associations of the *BCL2* and *FAM19A2* variants with ISI were stable after conditioning in Model 2, suggesting that analyses in Model 3 would have probably confirmed secondary loci. Fourth, given our desire for early dissemination of these results, no experimental attempts at determining the causal gene and mechanisms of action in our novel candidate insulin sensitivity loci were performed here.

In conclusion, we identified two novel candidate insulin sensitivity loci through a GWAS of the modified Stumvoll Insulin Sensitivity Index. Our results demonstrate that ISI is a robust measure of fasting and whole-body measures of insulin sensitivity and suggest that genetic variation in the *FAM19A2* and *BCL2* loci influence insulin sensitivity. While further functional work is needed to clarify the causal genes and mechanisms of action of these loci, our work as well as prior literature provides support for the role of genes in these loci having an effect on human glycemic metabolism.

Acknowledgements

We thank all the participants of each cohort for their cooperation and contribution to this study. For FHS, this research was conducted in part using data and resources from the Framingham Heart Study of the National Heart Lung and Blood Institute of the National Institutes of Health and Boston University School of Medicine; the analyses reflect intellectual input and resource development from the Framingham Heart Study investigators participating in the SNP Health Association Resource (SHARe) project. For CHS, a full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org. For ULSAM, we thank the SNP&SEQ Technology Platform in Uppsala (www.genotyping.se) for excellent genotyping; computations were performed on resources provided by SNIC through Uppsala Multidisciplinary Center for Advanced Computational Science (UPPMAX) under Project b2011036. For Sorbs, we would like to thank Knut Krohn (Microarray Core Facility, University of Leipzig, Institute of Pharmacology) for the genotyping support and Joachim Thiery (Institute of Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics, University of Leipzig) for clinical chemistry services. For LURIC, we thank the LURIC study team either temporarily or permanently involved in patient recruitment and sample and data handling; furthermore, we thank the laboratory staff at the Ludwigshafen General Hospital, and the Universities of Freiburg, Ulm, and Graz. For Amish Studies, we gratefully thank our Amish community and research volunteers for their long-standing partnership in research, and acknowledge the dedication of our Amish liaisons, field workers and the Amish Research Clinic staff, without which these studies would not have been possible. For the Ely Study, we are grateful to the staff of St. Mary's Street Surgery, Ely and the study team.

Author contributions. The study was conceived by GAW (Massachusetts General Hospital, MGH) and JCF (MGH and Framingham Heart Study, FHS). The manuscript was written by GAW (MGH), SG (The Uppsala Longitudinal Study of Adult Men, ULSAM), and DR (FHS) under the guidance of JD (FHS), EI (ULSAM), and JCF (MGH, FHS) and finalized based on detailed comments from other authors. Figures were constructed by SG (ULSAM) and DR (FHS). Meta-analysis of data from all cohorts was performed by SG (ULSAM) and DR (FHS). *In silico* analyses for follow-up studies were performed by SG (ULSAM), AL (FHS), AM (FHS), DR (FHS), XW (Genetics of Insulin Sensitivity, GENESIS), and ZZ (GENESIS). Genotyping within cohorts was performed by ML (Metabolic Syndrome in Men, METSIM); HC, JD, JH, CTL, and DR (Framingham Heart Study, FHS); MLLB, YDC, MOG and JIR (Cardiovascular Health Study, CHS); LL, CML, and APM (The Uppsala Longitudinal Study of Adult Men, ULSAM); NG (Inter99 and Birth Cohort 1936); JPL (Amish Studies , Amish); FM and HS (Tuebingen Family Study for type 2 diabetes, Tuebingen); CL, JL, RAS, and NJW (Ely Study); JMGZ (Pizarra); ACA, MTML, and MSR (Segovia). Phenotyping within cohorts was performed by AS (METSIM; European Network on Functional Genomics of Type 2 Diabetes EUGENE2); JD (FHS); EI (ULSAM); PK and MS (Sorbs); GD, MEK, and GS (Ludwigshafen Risk and Cardiovascular Heath, LURIC); RB, HK, and JT (FUSION); TH, TJ, AL, and OP (Inter99 and Birth Cohort 1936); AF and NS (Tuebingen); CL, RAS, and NJW (Ely Study); and ACA (Segovia). Data analysis was performed within cohorts by AUJ (Finland-United States Investigation of NIDDM, FUSION; METSIM); DR, HC, JH, and CTL (FHS); RAJ and KR (CHS); SG and APM (ULSAM); RM, IP, PS, and AT (Sorbs); EVA and NG (Inter99 and Birth Cohort 1936); JPL, MEM, and JRO (Amish); CL (Botnia Study); HS (Tuebingen); JL (Ely Study); TMF, MNW, MW, and WX (Relationship between Insulin Sensitivity and

Cardiovascular Risk Study, RISC); SM (Pizarra); MTML (Segovia). The cohort principal investigators were JH and ML (METSIM); BMP (CHS); EI (ULSAM); PK and MS (Sorbs); WM (LURIC); MB, RNB, FSC, KLM, and JT (FUSION); TH, TJ, AL, and OP (Inter99 and Birth Cohort 1936); JRO (Amish Studies); LG (Botnia Study); AF, HUH, and NS (Tuebingen); CL, RAS, and NJW (Ely Study); FS (Pizarra); MSR (Segovia); US (EUGENE2).

Conflicts of Interest Statement. WM (LURIC) is employed with synlab Services GmbH and holds shares of synlab Holding GmbH. He has received grants from Siemens Diagnostics, Aegerion Pharmaceuticals, AMGEN, Astrazeneca, Danone, Sanofi/Genzyme, Pfizer, BASF, and Abbott Diagnostics. BMP (CHS) serves in the data safety and monitoring board of a clinical trial funded by the manufacturer (Zoll LifeCor) and the Yale Open Data Access Project Steering Committee funded by Johnson and Johnson. GS (LURIC) is member of an advisory board of AMGEN (Thousand Oaks, CA, USA). MEK (LURIC) has received lecture fees from AstraZeneca. No conflict of interest is reported by the other authors: GAW (MGH), SG (ULSAM), DR (FHS), AS (METSIM, EUGENE2), HC (FHS), CTL (FHS), JH (FHS), RAJ (CHS), KR (CHS), APM (ULSAM), RM (Sorbs), AT (Sorbs), IP (Sorbs), GD (LURIC), AUJ (FUSION, METSIM), EVA (Inter99, Birth Cohort 1936), NG (Inter99, Birth Cohort 1936), JPL (Amish), MEM (Amish), CL (Botnia), HS (Tuebingen), JL (Ely), TMF (RISC), MNW (RISC), WX (RISC), SM (Pizarra), MTML (Segovia), MLB (CHS), YDIC (CHS), ACA (Segovia), KF (Inter99), JMGZ (Pizarra), MOG (CHS), JK (CHS), HAK (FUSION), AL (ULSAM), LL (ULSAM), CML (ULSAM), FM (Tuebingen), AKM (FHS), GMMN (Pizarra), GRM (Pizarra), JIR (CHS), DSS (CHS), JMZ (CHS), ZZ (CHS), MSR (Segovia), US (EUGENE2), FS (Pizarra), TH (Inter99, Birth Cohort 1936), TJJ (Inter99, Birth Cohort 1936), AL (Inter99, Birth Cohort

1936), OP (Inter99, Birth Cohort 1936), MW (RISC), CL (Ely), RAS (Ely), NJW (Ely), AF (Tuebingen), HUH (Tuebingen), NS (Tuebingen), LG (Botnia), JRO (Amish), MB (FUSION), RNB (FUSION), FSC (FUSION), KLM (FUSION), JT (FUSION), PK (Sorbs), MS (Sorbs), JK (METSIM), ML (METSIM), JBM (FHS), JD (FHS), EI (ULSAM), JCF (MGH, FHS).

Guarantor Statement. Dr. Geoffrey Walford is the guarantor of this work and, as such, had full access to the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Funding Sources. This work was supported by DK099249 (GAW). Grant support was provided to cohorts. For METSIM, the study was funded by the Academy of Finland (grants no. 77299 and 124243). For Sorbs, the work was supported by grants from the German Research Council (DFG - SFB 1052 “Obesity mechanisms”; A01, C01, B03 and SPP 1629 TO 718/2-1), from the German Diabetes Association and from the DHFD (Diabetes Hilfs- und Forschungsfonds Deutschland); this work was further supported by the Federal Ministry of Education and Research (BMBF), Germany, FKZ: 01EO1501, AD2-060E to P.K.), and by Boehringer Ingelheim Foundation. For FHS, the study was supported by National Heart, Lung and Blood Institute's contract numbers number N02-HL-6-4278 (supporting its contract with Affymetrix, Inc for genotyping services), N01-HC-25195 and HHSN268201500001I) and National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK): R01 DK078616 to JD, U01-DK085526 to HC and JD, 2R01 DK078616 to JM, and K24 DK080140 to JM; a portion of this research utilized the Linux Cluster for Genetic Analysis (LinGA-II) funded by the Robert

Dawson Evans Endowment of the Department of Medicine at Boston University School of Medicine and Boston Medical Center; AKM was supported by American Diabetes Association grant #7-12-MN-02. For CHS, research was supported by contracts HHSN268201200036C, HHSN268200800007C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, and grant U01HL080295, HL105756, and HL120393 from the National Heart, Lung, and Blood Institute (NHLBI), with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS); additional support was provided by R01AG023629 from the National Institute on Aging (NIA); the content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. For ULSAM, the project was supported by Knut and Alice Wallenberg Foundation (Wallenberg Academy Fellow), European Research Council (ERC Starting Grant), Swedish Diabetes Foundation (grant no. 2013-024), Swedish Research Council (grant no. 2012-1397), and Swedish Heart-Lung Foundation (20120197); APM is a Wellcome Trust Senior Fellow in Basic Biomedical Science (grant number WT098017). For LURIC, the study was supported by the 7th Framework Program (AtheroRemo, grant agreement number 201668 and RiskyCAD, grant agreement number 305739) of the EU and by the INTERREG-IV-Oberrhein-Program (Project A28, Genetic mechanisms of cardiovascular diseases) with support from the European Regional Development Fund (ERDF) and the Wissenschaftsoffensive TMO; MEK and WM are supported by the German Federal Ministry of Education and Research as part of the Competence Cluster of Nutrition and Cardiovascular Health (nutriCARD). For Inter99, the study was financially supported by research grants from the Danish Research Council, the Danish Centre for Health Technology Assessment, Novo Nordisk Inc., Research Foundation of Copenhagen County, Ministry of

Internal Affairs and Health, the Danish Heart Foundation, the Danish Pharmaceutical Association, the Augustinus Foundation, the Ib Henriksen Foundation, the Becket Foundation, and the Danish Diabetes Association. For FUSION, the study was supported by DK093757, DK072193, DK062370, and ZIA-HG000024; HAK has received funding from Academy of Finland (support for clinical research careers, grant number 258753). For Amish Studies, work on this study was supported by NIH awards K23GM102678 to JPL and HL084756 to JRO. For Botnia, the study has been financially supported by grants from the Sigrid Juselius Foundation, Folkhälsan Research Foundation, Nordic Center of Excellence in Disease Genetics, an EU grant (EXGENESIS, GA FP6 2004-005272), Signe and Ane Gyllenberg Foundation, Swedish Cultural Foundation in Finland, Finnish Diabetes Research Foundation, Foundation for Life and Health in Finland, Finnish Medical Society, Paavo Nurmi Foundation, Helsinki University Central Hospital Research Foundation, Perklén Foundation, Ollqvist Foundation, Närpes Health Care Foundation and Ahokas Foundation; the DGI study was further supported by a Linné grant (2006-237) from the Swedish Research Council; the study has also been supported by the Ministry of Education in Finland, Municipal Heath Care Center and Hospital in Jakobstad and Health Care Centers in Vasa, Närpes and Korsholm. For Tuebingen, the study was supported in part by a grant from the German Federal Ministry of Education and Research to the German Center for Diabetes Research (DZD e.V.). For the Ely Study, JAL, CL, RAS and NJW acknowledge support from the Medical Research Council (MC_UU_12015/1); the Ely Study was funded by the MRC (MC_U106179471) and Diabetes UK; genotyping in the Ely and Fenland studies was supported in part by an MRC-GlaxoSmithKline pilot programme grant (G0701863). For Birth Cohort 1936 and Inter99, work was support by the Novo Nordisk Foundation Center for Basic Metabolic Research, an independent Research Center at the

University of Copenhagen partially funded by an unrestricted donation from the Novo Nordisk Foundation (www.metabol.ku.dk). For Pizarra, work on this study was support by ISCIII PI11/00880 and ISCIII PS09/02117. For Segovia, this work was supported by grants FEDER 2FD 1997/2309 from the Fondo Europeo para el Desarrollo Regional, Red de Centros RCMN (C03/08), FIS 03/1618, from Instituto de Salud Carlos III-RETIC RD06/0015/0012, Madrid, Spain, CIBER in Diabetes and Associated Metabolic Disorders (ISCIII, Ministerio de Ciencia e Innovación) and Madrid Autonomous Community (MOIR S2010/BMD-2423), and from Educational Grants from Eli Lilly Lab, Spain, Bayer Pharmaceutical Co., Spain and Fundación Mutua Madrileña 2008, Spain.

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Table 1. Cohort and Participant Demographics

Cohort	N	Female (%)	Age (years)	BMI (kg/m^2)	Fasting Glucose (mmol/l)	Fasting Insulin (pmol/l)	Stumvoll ISI (µmol*pmol/kg*min*l)
Discovery							
FHS	2602	54	54.0 ± 9.9	26.8 ± 4.5	5.2 ± 0.5	28.6 ± 9.9	0.111 ± 0.012
Sorbs	802	60	46.3 ± 15.9	26.5 ± 6.4	5.5 ± 1.2	40.7 ± 26.5	0.105 ± 0.023
FUSION	462	63	66.5 ± 6.7	27.6 ± 4.2	5.1 ± 0.5	68.5 ± 36.0	0.087 ± 0.023
CHS	2761	62	72.3 ± 5.3	26.0 ± 4.3	5.5 ± 0.5	93.3 ± 47.8	0.059 ± 0.038
LURIC	962	24	61.9 ± 27.1	27.1 ± 3.8	5.5 ± 0.6	61.6 ± 49.9	0.065 ± 0.038
ULSAM	962	0	71.0 ± 0.6	26.0 ± 3.2	5.4 ± 0.6	73.0 ± 40.1	0.074 ± 0.031
METSIM	7388	0	57.0 ± 6.96	26.8 ± 3.8	5.7 ± 0.5	49.8 ± 35.3	0.093 ±0.030
Replication							
EUGENE2	885	56	39.4 ± 9.2	26.5 ± 4.8	5.1 ± 0.5	49.0 ± 34.9	0.091 ± 0.028

Amish Studies	334	61	45 ± 12.7	27.4 ± 4.7	4.9 ± 0.5	63.4 ± 26.0	0.09 ± 0.02
RISC	921	56	44 ± 8.37	25.5 ± 4.0	5.1 ± 0.6	34.4 ± 18.7	0.106 ± 0.018
Tuebingen	2470	65	40.2 ± 13.2	30.9 ± 9.6	5.2 ± 0.6	83.4 ± 72.2	0.070 ± 0.049
Inter99	5318	51	45.9 ± 7.9	26.1 ± 4.4	5.5 ± 0.5	41.1 ± 26.3	0.101 ± 0.021
Segovia	420	53	52.1 ± 11.4	26.7 ± 3.8	4.5 ± 0.6	71.2 ± 39.7	0.087 ± 0.025
Pizarra	640	66	43.6 ± 13.0	27.8 ± 4.9	5.4 ± 0.7	46.6 ± 34.2	0.101 ± 0.023
Botnia Study	1235	52	58.3 ± 10.2	27.1 ± 3.9	5.4 ± 0.5	44.7 ± 28.7	0.099 ± 0.020
1936 Birth Cohort	576	54	60.5 ± 0.5	26.5 ± 4.0	5.2 ± 0.5	42.5 ± 23.7	0.098 ± 0.022
Ely Study	1442	54	61.1 ± 9.2	27.3 ± 4.8	5.00 ± 0.56	57.1 ± 35.7	0.088 ± 0.031

Continuous results are shown as mean ± standard deviation. FHS: Framingham Heart Study; FUSION: Finland-United States Investigation of NIDDM; CHS: Cardiovascular Health Study; LURIC: Ludwigshafen Risk and Cardiovascular Heath; ULSAM: The Uppsala Longitudinal Study of Adult Men; METSIM: Metabolic Syndrome in Men; EUGENE2: European Network on Functional Genomics of Type 2 Diabetes; RISC: Relationship between Insulin Sensitivity and Cardiovascular Risk Study; Tuebingen: Tuebingen Family study for type 2 Diabetes; ISI: insulin sensitivity index. Additional information for each cohort can be found in Supplemental Table 1.

Table 2. Meta-Analysis Results for Variant Association with Insulin Sensitivity Index

SNP	Chr	Locus	Allele (Eff/Other)	Freq	Model 1 (β±SE) ***P*-value**	Model 2 (β±SE) ***P*-value**	Model 3 **Main** (β±SE) Int (β±SE) ***Joint P*-value**	N (min,max)
rs13422522	2	*NYAP2*	C/G	0.77	-0.04±0.01 **1.6×10^{-5}**	-0.06±0.01 **1.2×10^{-11}**	0.10±0.06 -0.01±0.002 **8.9×10^{-11}**	30057, 30078.3
rs4078023	16	*GP2*	T/G	0.98	-0.028±0.04 **0.49**	-0.05±0.04 **0.20**	0.80±0.17 -0.03±0.01 **3.2×10^{-7}**	24727, 24742
rs12372926	15	*ARRDC4*	T/C	0.41	-0.03±0.01 **0.001**	-0.03±0.01 **1.6×10^{-5}**	0.11±0.05 -0.005±0.002 **4.2×10^{-4}**	30073, 30095
rs16924527	8	*TOX*	A/C	0.02	0.12±0.04 **0.001‡**	0.07±0.03 **0.02**	-0.08±0.14 0.01±0.01 **$3.7\times10^{-6‡}$**	24994, 25005
rs2828537	21	*MRPL39*	A/T	0.97	-0.04±0.03 **0.12**	-0.03±0.02 **0.16**	0.42±0.10 -0.02±0.004 **2.6×10^{-5}**	29733, 29753.9
rs3900087	4	*ADAMTS3*	T/C	0.98	-0.04±0.05 **0.33**	-0.04±0.04 **0.31**	0.74±0.21 -0.03±0.01 **4.7×10^{-4}**	22350, 22351
rs6027072	20	*ARHGAP40*	A/G	0.03	0.10±0.02 **0.0001**	0.08±0.02 **4.1×10^{-4}**	-0.39±0.12 0.02±0.005 **4.4×10^{-9}**	28877, 28896
rs12454712	18	*BCL2*	T/C	0.58	-0.04±0.01 **0.0003**	-0.05±0.01 **1.9×10^{-8}**	0.04±0.05 -0.003±0.002 **2.7×10^{-8}**	25973, 26761
rs10506418	12	*FAM19A2*	A/G	0.03	0.06±0.03 **0.05**	0.06±0.03 **0.01**	-0.62±0.13 0.03±0.005	26011, 26024

						1.9×10^{-8}	
rs1857095	1	*ELTD1*	T/C	0.98	-0.01±0.03 **0.84**	-0.02±0.03 **0.37**	0.08±0.12 -0.0003±0.005 **7.9×10^{-9}‡**	26596, 26608.9
rs11594101	10	*NRG3*	A/G	0.98	0.02±0.04 **0.57**	-0.002±0.03 **0.94**	0.62±0.14 -0.02±0.005 **9.5×10^{-5}**	27885, 27904
rs12583553	13	*FGF9*	A/T	0.97	-0.04±0.03 **0.19**	-0.05±0.03 **0.04**	0.55±0.12 -0.02±0.005 **3.6×10^{-9}‡**	29195, 29215
rs4548846	16	*CDH13*	T/C	0.02	0.02±0.04 **0.72**	-0.002±0.04 **0.96**	0.59±0.18 -0.03±0.01 **1.1×10^{-5}‡**	18401, 18405.99
rs12522198	5	*FAM134B*	A/G	0.02	-0.03±0.04 **0.48**	0.01±0.04 **0.84**	0.79±0.19 -0.03±0.01 **1.6×10^{-4}‡**	19798, 20589
rs10483182	22	*ISX*	A/G	0.01	0.06±0.04 **0.17**	0.03±0.04 **0.39**	-1.16±0.18 0.05±0.01 **7.8×10^{-12}‡**	20399, 20409
rs10520638	15	*AGBL1*	T/C	0.01	0.004±0.05 **0.93**	-0.01±0.04 **0.77**	0.89±0.19 -0.04±0.01 **1.2×10^{-7}‡**	12369, 12383
rs6013915	20	*PFDN4*	A/G	0.03	0.05±0.03 **0.14**	0.06±0.03 **0.05**	-0.84±0.19 0.04±0.01 **1.5×10^{-9}‡**	23111, 23121.9
rs9658121	6	*PPARD*	A/G	0.02	-0.01±0.04 **0.80**	0.02±0.04 **0.63**	-0.40±0.15 0.02±0.01 **7.3×10^{-4}‡**	16973, 16985
rs10508754	10	*KIAA1462*	A/G	0.08	-0.03±0.02 **0.08**	-0.05±0.02 **0.01**	0.14±0.09 -0.01±0.004 **0.07**	25146, 25150
rs11627967	14	*NPAS3*	T/G	0.016	-0.02±0.05 **0.69**	-0.03±0.04 **0.44**	-0.94±0.21 0.04±0.01	17593, 17595.98

							1.6×10^{-7}‡	
rs10495667	2	*VSNL1*	A/G	0.04	0.02±0.02 **0.32**	0.01±0.02 **0.69**	-0.51±0.12 0.02±0.005 **3.8×10^{-5}**	27332, 27345.9
rs13059110	3	*TXNDC6*	T/G	0.13	-0.05±0.02 **0.0001**	-0.04±0.01 **2.3×10^{-4}**	0.03±0.07 -0.002±0.003 **0.01**	26420, 26425
rs11790816	9	*SH3GL2*	T/C	0.02	0.01±0.03 **0.63**	0.02±0.03 **0.45**	-0.37±0.14 0.02±0.01 **0.001**‡	21814, 21833.92

Model 1 is adjusted for age and sex; Model 2 is adjusted for age, sex, and BMI; Model 3 assesses the combined influence of the SNP effect adjusted for BMI and the interaction effect between the genotype and BMI on ISI. For Model 1 and Model 2, the effect (β), standard error (SE), and *P*-values for the SNP are shown. For Model 3, the β and standard error (SE) are provided for the SNP and the interaction; *P*-value is provided for the joint influence of the SNP and interaction effect. Effect sizes are presented as standard deviation per effect allele. SNP: single nucleotide polymorphism; Chr: chromosome, Eff: effect allele; Freq: frequency of the effect allele); ‡*P*-value for heterogeneity in the combined analysis of discovery and replication cohorts $P\leq10^{-6}$.

Figure Legends

Figure 1. A) Correlation of ISI with M-value from insulin clamp and B) fasting insulin in ULSAM. Insulin sensitivity was measured within the ULSAM discovery cohort (n=1025) using the euglycemic hyperinsulinemic clamp (M-value), the modified Stumvoll ISI, and fasting insulin. The ULSAM cohort contains only men and individuals with known diabetes were excluded from these analyses. For the comparison of the M-value with ISI, the Pearson correlation was 0.69 and the Spearman correlation was 0.71, which are consistent with prior published reports. For the comparison of the ISI with fasting insulin, the Pearson correlation was -0.45 and the Spearman correlation was -0.49.

Figure 2. The effect of rs10506418 (*FAM19A2*) on insulin sensitivity by BMI category. The effect of the minor allele (A) at rs10506418 (*FAM19A2*) on the ISI is shown by body mass index (BMI) category. At low BMI (<20kg/m^2), the effect is negative. At each category of increasing BMI above 20 kg/m^2, the effect is positive and stronger.

Figure 3. The effect of rs10506418 (*BCL2*) on insulin sensitivity by BMI category. The effect of the major allele (T) at rs10506418 (*BCL2*) on the ISI is shown by body mass index (BMI) category. At each category of increasing BMI, the effect is negative and stronger.

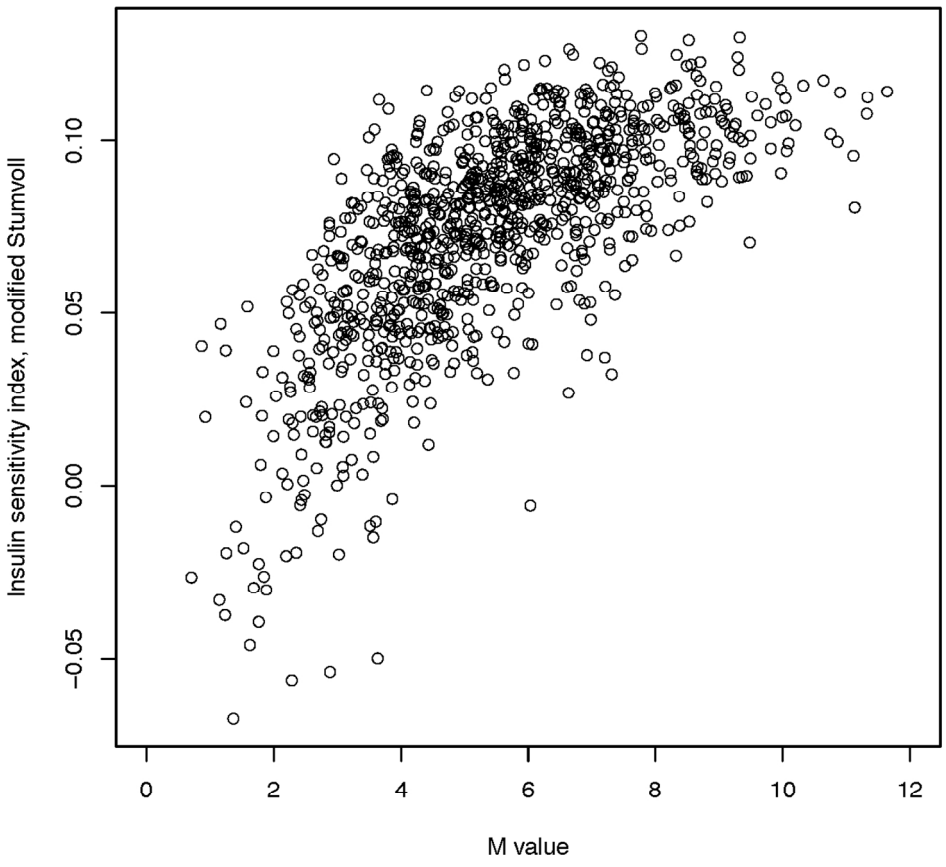


Figure 1A.

177x177mm (200 x 200 DPI)

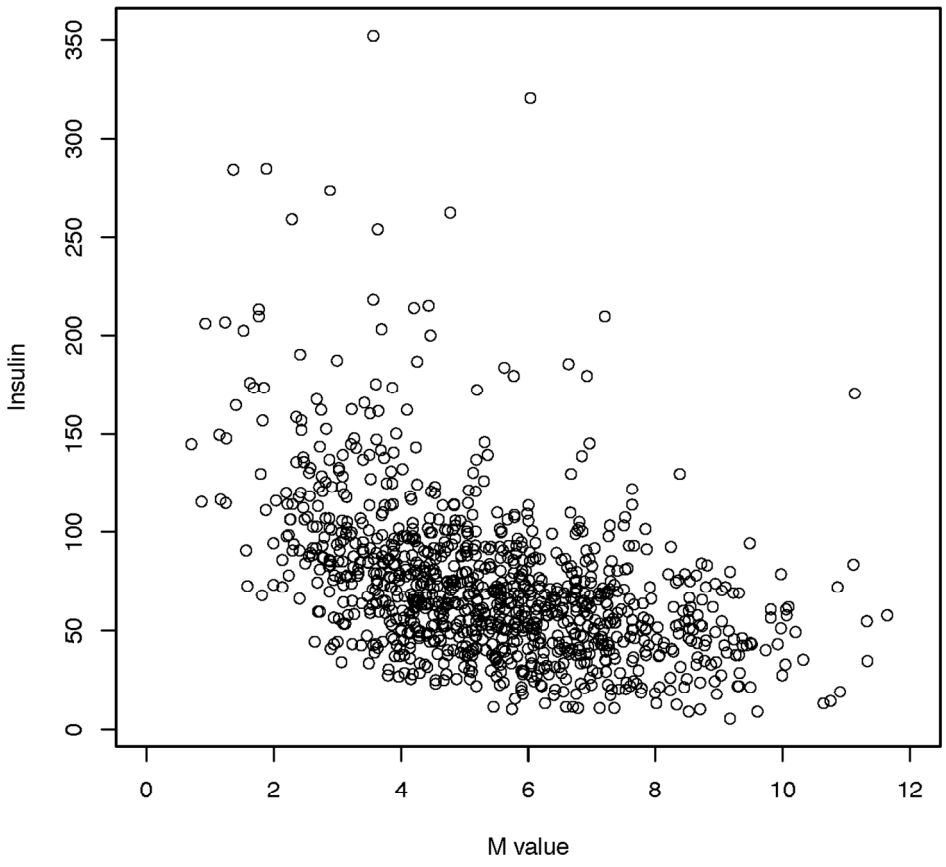


Figure 1B.

177x177mm (200 x 200 DPI)

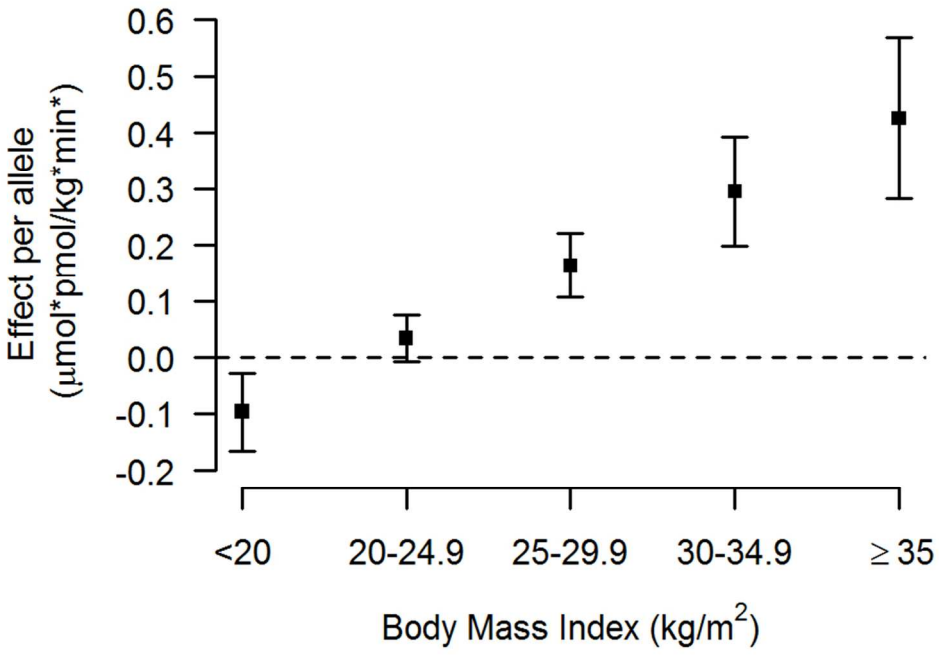


Figure 2.

80x59mm (300 x 300 DPI)

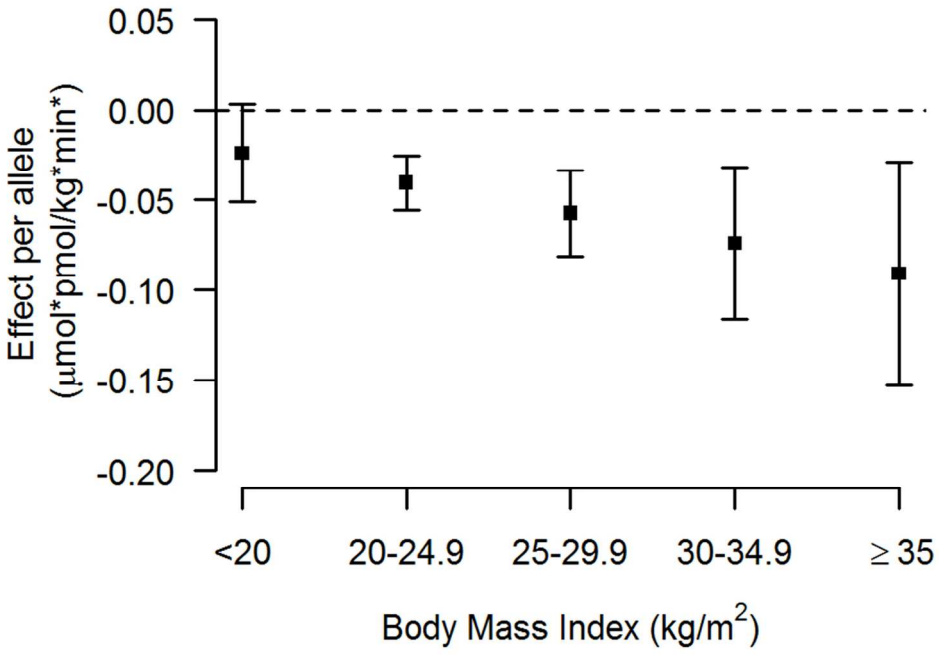


Figure 3.

80x59mm (300 x 300 DPI)

Supplemental Table 1: Detailed cohort information

COHORT	FHS	Sorbs	FUSION	CHS	LURIC
Discovery or Replication Effort		Discovery	Discovery	Discovery	Discovery
Ethnicity	White	Sorbs (Slavonic origin)	European descent	White	White
Country	USA	Germany	Finland	USA	Germany
Collection Type	Population-based	Population-based	Case-control	Population-based	Case-control
GLUCOSE MEASUREMENTS					
Glucose Sample	Fasting plasma	75g OGTT (fasting, 30 min, 120 min), serum	Fasting plasma	Fasting plasma	Fasting plasma
Glucose Collection method	Venipuncture	Overnight fast, spinning within 1 hour after collection, then immediate quick-freeze on dry ice before transport, further storage in -80°C freezer	Overnight fast and plasma collected in EDTA tubes	Venipuncture	Venipuncture

Glucose Assay	Hexokinase	Hexokinase method (Automated analyser Modular, Roche Diagnostics, Mannheim, Germany)	Glucose oxidase method (Yellow Springs instruments, Yellow Springs, OH and autoanalyser) and hexokinase method	Kodak Ektachem 700 analyzer with reagents (Eastman Kodak, Rochester, NY)	Hexokinase
INSULIN MEASUREMENTS					
Insulin Sample	Fasting and 120 min plasma	75g OGTT (fasting, 30 min, 120 min), serum	Fasting plasma	fasting and 120 min plasma	Fasting, 60 min and 120 min plasma
Insulin Collection method	Venipuncture	Overnight fast, spinning within 1 hour after collection, then immediate quick-freeze on dry ice before transport, further storage in -80°C freezer	Overnight fast and plasma collected in EDTA tubes	Venipuncture	Venipuncture
Insulin Assay	DPC Coat-a-Count Total IRI	AutoDELFIA Insulin assay (PerkinElmer Life and Analytical Sciences, Turku, Finland)	RIA with dextran charcoal separation	competitive radioimmunoassay (Diagnostic Products Corp., Malver, PA)	AIA pack IRI / AIA1200
Insulin Assay sensitivity	> 8 pmol/L	3.0 pmol / L	CV=11% low conc, 13% high conc	5 - 400 mIU/L	
SAMPLES					

EXCLUSIONS	Type 1 diabetes, type 2 diabetes	Known diabetes, FG ≥ 7 mmol/l, 120min glucose ≥ 11.1 mmol/l	Diabetes ascertained by OGTT, medical record review or GAD Ab positivity; diabetes medication, missing phenotype or covariate	Use of diabetes medications or fasting glucose >= 7mmols	History of diabetes, OGTT, fasting glucose > 7mmol
Samples with STUMVOLL phenotype (uniform analysis): N all (%males/%females)	2602 (45.77%/54.23%)	802 (40.3%/59.7%)	462 (37% / 63%)	2761 (38.2 / 61.8)	962 (76.3%/23.7%)
STUMVOLL [Mean (sd)], units			0.0865288 (0.02316)	0.037981	
Age [Mean (sd) males / Mean (sd) females], years	53.94 (9.90)/54.06 (9.82)	47.6(16.7)/48.1(16.1)	69.05(5.36) / 65.10 (6.96)	72.9 (5.6) / 71.9 (5.1)	61.24 (9.90) / 64.03 (9.80)
BMI [Mean (sd) males / Mean (sd) females], kg/m2	27.79 (3.86)/26.05 (4.90)	27.1(3.95)/26.7(5.51)	27.24 (4.12) / 27.84 (4.23)	26.1 (3.4) / 26.0 (4.8)	27.21 (3.57) / 26.77 (4.51)
Fasting PLASMA glucose [Mean (sd) males / Mean (sd) females], mmol/l	5.3542 (0.4639)/5.1228 (0.5027)	5.46(1.10)/5.59(1.20)	5.12 (0.49) / 5.02 (0.44)	5.6 (0.5) / 5.5 (0.5)	5.50 (0.58) / 5.34 (0.56)
Original units for fasting glucose	mg/dl	mmol/l	mg/dl	mg/dl	mg/dl
Conversion factor for glucose to mmol/l	1/18.01	-	0.05551	18-Jan	18-Jan
Fasting insulin [Mean (sd) males / Mean (sd) females], pmol/l	30.186 (10.925)/27.230 (8.739)	40.51(24.89)/41.01(28.02)	66.57 (33.82) / 69.62 (37.25)	94.7 (45.8) / 92.5 (49.0)	62.61 (52.41) / 57.68 (40.73)
Original units for fasting insulin	pmol/l	pmol/l	mU/l	mIU/L	IU/ml
Conversion factor for insulin to pmol/l	1	Not applicable	6	6.945	6
GENOTYPING					

Genotyping platform & SNP panel	Affymetrix 500K and MIPS 50K	500K Affymetrix GeneChip (250K Sty and 250K Nsp arrays, Affymetrix, Inc) and Affymetrix Genome-Wide Human SNP Array 6.0	Illumina HumanHap300	Illumina HumanCNV370-Duo BeadChip	Affymetrix 6.0
Genotyping centre	Affymetrix	Microarray Core Facility of the Interdisciplinary Centre for Clinical Research, University of Leipzig, Germany and ATLAS Biolabs GmbH, Berlin, Germany	Center for Inherited Disease Research	General Clinical Research Center's Phenotyping/Genotyping Laboratory at Cedars-Sinai	LURIC Study nonprofit LLC, c/o Synlab MVZ Heidelberg, Wasserturmstrasse 71, D-69214 Eppelheim
Genotyping calling algorithm	BRLMM	BRLMM algorithm (Affymetrix, Inc) for 500K and Birdseed Algorithm for Genome-Wide Human SNP Array 6.0	Beadstudio	Illumina BeadStudio software	Birdseed v2
SAMPLE QC					
Call rate [filter detail]	97%	> 94%	>97.5%	>95%	>95%
Heterozygosity [filter detail / N individuals excluded]	5 SD from mean (< 25.758% or > 29.958%) / 10	None	None	None	None
Ethnic outliers excluded	None	Ethnic outliers	None	African American excluded	None

Other exclusions	None	duplicates; gender mismatch; known diabetes, FG ≥ 7 mmol/l, 120min glucose ≥ 11 mmol/l	None	1908 persons were excluded from genotyping if they had prevalent cardiovascular disease. Other samples were excluded for sex mismatch and discordance with prior genotyping.	duplicates, sex ambiguity
Individuals for analysis	2602	802	462	3291 available (2761 with phenotype and no DM)	962
SNP QC (prior to imputation)					
MAF [filter detail / N SNPs excluded]	> 1% / 68,953	1%	>1%	none	> 1%
HWE	> 10-6	> 10-6	> 10-6	P > 10-5	> 10-6
Call rate	≥95%	95%	≥ 90%	<97%	≥95%
Other	None	None	NMI or duplicate pair discrepancies <= 3	<=2 duplicate errors or Mendelian inconsistencies (for reference CEPH trios), heterozygote frequency = 0, SNP not found in HapMap.	None
SNP number in QC'd dataset	378163	378513	306791	306655	750437
IMPUTATION STATS					
Imputation software	MACH	IMPUTE to HapMap2 reference panel	MACH 1 to HapMap release 21 CEU (phase I+II) reference panel	BIMBAM v0.99 with reference to HapMap CEU using release 22, build 36	MACH with reference to HapMap CEU Panel 2
Imputation quality metrics	r2hat ≥ 0.3	Proper-info > 0.4	r2hat>0.3	observed/expected variance ratio < 0.01	r2>0.3 and prob>0.9

Other SNP QC filters applied?	MAF ≥ 1%	MAF>1%, HWE<10-4	MAF ≥ 1%	dosage variance <0.01	
DATA ANALYSIS					
Number of SNPs in analysis N imputed	2436797	2531712	2476731	2257780	1800000
Adjustments	sex, age, agesq, PC1-8	sex,age,bmi	sex, age	age, sex, study site	sex, age, age2
Analysis method	Linear mixed effect models, generalized estimating equations (interaction)	linear regression	Linear regression	linear regression	linear regression
Software for analysis	LMEKIN, GEE (R package)	SNPTEST/QUICKTEST	ProbABEL	R	PLINK, QUICKTEST
REFERENCES					
Reference cohort		PMID:21559053	16	PMID: 1669507	
Reference GWAS		PMID:19729412		PMID: 20031568	

Website	http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000007.v2.p1	-	http://fusion.sph.umich.edu	http://www.chs-nhlbi.org/	

ULSAM	METSIM	EUGENE2	Amish Studies	RISC	Tuebingen	Inter99
Discovery	**Discovery**	**Replication**	**Replication**	**Replication**	Replication	**Replication**
Northern European (white, Caucasian)	European descent	White Europeans	European descent	White Europeans	White Europeans	Europeans
Sweden	Finland	Finland, Sweden, Denmark, Germany	USA	Austria, Denmark, Finland, France, Germany, Greece, The Netherlands, Ireland, Italy, Sweden, Spain, Switzerland, United Kingdom, Serbia, Montenegro	Germany	Denmark
Population-based	Population-based	Population-based	Family-based	Population-based	At-risk population (family history, glucose intolerance, overweight, prior gestational diabetes)	Population-based
Fasting plasma	Fasting plasma	Fasting plasma	Fasting fresh venous plasma with sodium floride and potassium oxolate	Serum, 0, 30, 60, 90, 120 min OGTT	Plasma, 0, 30, 60, 90, 120 min OGTT	Plasma; 0, 30, 120 min OGTT
Venipuncture	Venipuncture	Venipuncture	Fasting venous blood collected into sodium floride tubes, plasma frozen and stored at -80oC and thawed immediately before glucose measurement.	Venipuncture	Venipuncture	Venipuncture

Glucose dehydrogenase method (Gluc-DH, Merck, Darmstadt, Germany)	Enzymatic photometric test, Glucose hexokinase.	Glucose oxidase method (Glucose & Lactate Analyzer 2300 Stat Plus, Yellow Springs Instrument Co., Inc, Ohio)	YSI glucose analyzer, Yellow Springs, OH	Glucose oxidase method (Cobas Integra, Roche)	YSI 2300 STAT Plus Glucose Analyzer (glucose oxidase method, Yellow Springs Instruments, OH/USA)	Glucose oxidase method
Fasting plasma, 120 min plasma	Fasting plasma	Serum, 0, 30, 60, 90, 120 min	Fasting venous plasma with heparin	Serum, 0, 30, 60, 90, 120 min OGTT	Serum, 0, 30, 60, 90, 120 min OGTT	Serum; 0, 30, 120 min OGTT
Venipuncture	Venipuncture	Venipuncture	Fasting venous blood collected into sodium heparin tubes, centrifuged at 4oC within 1 hour, plasma frozen and stored at -80oC and thawed immediately before insulin measurement.	Venipuncture	Venipuncture	Venipuncture
Immunoreactive insulin: Enzymatic-immunological assay (Enzymun, Boehringer Mannheim)	Immunoassay, luminometric measurement	Microparticle enzyme immunoassay (Abbott Laboratories, Tokyo, Japan)	Millipore 125 Iodine Human Insulin RA kit	Insulin, proinsulin and C-peptide were measured by a two-sited, time-resolved fluoroimmunoassay (AutoDELFIA Insulin kit, Wallac Oy, Turku, Finland) using monoclonal antibodies	Insulin immunochemiluminometric assay (Advia Centaur XP, Siemens, Germany)	AutoDELFIA insulin kit
	3.0 pmol / L		2-200 mU / L		3 pmol/l	

Use of diabetes medication, fasting plasma glucose >= 7 mmol/L	Diabetes ascertained by OGTT, medical record review or GAD Ab positivity; diabetes medication, missing phenotype or covariate	Diabetes ascertained by OGTT, medical record review	Diabetes (either self-reported or registered as using anti-diabetic drugs), FG >= 7 mmol/l,	Lipid disorders or diabetes, lipid medications, pregnancy	Diabetes ascertained by OGTT, medical record review or GAD Ab positivity; diabetes medication	Self-reported diabetes, treated with anti-diabetic drugs or diabetes at OGTT
962 (100% males)	7388 (100% / 0%)	885 (44.3%, 55.7%)	334 (39%.61%)	921 (44.1%,55.9%)	2470 (35.1% / 64.9%)	5318 (49/51)
0.074 (0.031)	0.0928042 (0.0295312)	0.0914756 (0.0275914)	0.09 ± 0.02	0.106 (0.018)	0.070 (0.049)	0.101 (0.021)
71.0 (0.6) / NA	57.04(6.96) / NA	39.06 (9.27) / 39.72 (9.11)	45.3 (13.6)/ 44.8 (12.1)	43.31 (8.56)/ 44.46 (8.19)	41.5 (14.4) / 39.6 (12.6)	46.1 (7.8)/45.6 (7.8)
26.0 (3.2) / NA	26.84 (3.81) / NA	27.00 (4.37) / 26.07 (5.08)	26.3 (3.5) / 28 (5.2)	26.36 (3.54)/24.78 (4.22)	30.2 (9.0) / 31.4 (9.9)	26.6 (3.9)/25.6 (4.8)
5.38 (0.56) /NA	5.71 (0.48) /NA	5.29 (0.52) / 4.98 (0.44)	5 (0.4) / 4.9 (0.5)	5.20 (0.52) / 4.92 (0.56)	5.24 (0.55) / 5.12 (0.55)	5.61 (0.49)/5.3 (0.49)
mmol/L	mmol/l	mmol/l	mg/dl	mmol/l	mmol/l	mmol/L
No		None	0.0555	NA	None	NA
72.97 (40.10) / NA	49.76 (35.29) / NA	51.95 (37.87) / 46.70 (32.22)	60.9 (22.9) / 64.9 (27.7)	36.80 (19.96)/ 32.5 (17.42)	82.3 (76.2) / 83.9 (69.9)	43.1 (27.8)/39.1 (24.7)
mU/L	mU/l	pmol/l	microU/ml	pmol/l	pmol/l	pmol/L
6	6	Not applicable	6	Not applicable	Not applicable	Not applicable

Illumina Omni2.5+Metabochip	Illumina HumanOmniExpress-12v1	Infinium HumanHap 550k version 3 chips	illumina OmniChip 2.5M, Affy 500K, Affy6.0, Metabochip	Applied Biosystems	Sequenom MassArray	KASP Genotyping
SNP&SEQ Technology Platform, Uppsala	Center for Inherited Disease Research	The Finnish Genome Centre, Helsinki, Finland	Univ of Maryland Division of Endocrinology	Kbioscience	Central Laboratory of the University Hospital Tuebingen	LGC Genomics
GenomeStudio 2010.3	GenomeStudio version 2011.1	Sequenom MassARRAY Typer (version 3)	GeneCall, BRLLM	ABI Prism 7000 sequence detection system	iPLEX software	KlusterCaller
≥ 95%	>98% / 0	99.90%	>95%	>90%	>95%	NA
> 3 s.d.	None	None	None	None	None	NA
MDS analysis performed	non-Finnish, PCA outliers, gender discordance	None	None	None	None	None

Related individuals, missing phenotype values	unexpected duplicates, contamination > 3%, missing phenotype, diabetics	None	mendelian errors	None	None	None
962	7388	885	2872	921	2470	5318
≥1%	none	None	>1%	>5%/0	MAF of replicated SNPs >0.45% / 0	NA
> 10-6	> 10-6	>0.004	0.000001	0.000001/0	$>9.4*10^{-8}$	0.001/0
≥99% (MAF<5%) or ≥95% (MAF≥5%)	95%	>95%	>95%	>95%	>95%	95%/0
None	triallelicmap_score<30 / 5314	None	None	None	None	None
1587454	681789	12	1944974	13	23	20
IMPUTE2	MACH to 1000 Genomes phase 1 integrated variant release (v3) reference panel	Not applicable	**IMPUTE v2 using 1000 Genomes Phase 3 reference panel**	MACH2QTL using 1000 Genomes reference panel	Not applicable	Not applicable
info>0.4	r2hat>0.3	Not applicable	No filtering done post-imputation	Not applicable	Not applicable	Not applicable

MAF≥1%	MAF ≥ 1%	Not applicable	No filtering done post-imputation	MAF >= 1% r2_hat >= 0.3	Not applicable	Not applicable
3178687	9097160	12 (genotyped)	22	24 (13 genotyped, 11 imputed)	23 (none imputed)	20
Age, PC1, PC2	Age, agesq, 3 PCs	Age, sex, center, family	Age, age2, sex	Age, sex, centre, the first two principal components	Age and sex	age, sex
Linear regression	Linear regression	Mixed linear model	Mixed model	Linear regression	Linear regression	Linear mixed effect models, generalized estimating equations (interaction)
SNPTEST v2.4.1/ Quicktest v0.95	ProbABEL	SPSS v.17	MMAP	STATA 10.1	JMP 10.0.0	R
PMID: 16030278	MID: 1922359	; Diabetologia	18440328, 18805900			Jørgensen, T. *et al.* A randomized non-pharmacological intervention study for prevention of ischaemic heart disease: Baseline results Inter99 (1). *Eur J Cardiovasc Prev Rehab* 10, 377-386 (2003)
NA					Böhm A. et al.; PLoS One 2012;7(3):e34035	

http://www2.pubcare.uu.se/ULSAM/			http://medschool.umaryland.edu/endocrinology/amish.asp			www.inter99.dk

Segovia	Pizarra	Botnia Study	Ely Study	1936 Birth Cohort
Replication	Replication	Replication	Replication	Replication
White Europeans	White Europeans	White Europeans	White	Europeans
Spain	Spain	Finland	UK	Denmark
Population based	Population based	At-risk population (family history of T2D)	Population based	population-based
Plasma, 0, 120 min OGTT	Plasma, 0, 120 min OGTT	Plasma, 0, 30, 60, 120 min OGTT	Fasting fresh venous plasma with fluoride	Plasma; 0, 30, 120 min OGTT
Venipuncture	Venipuncture	Venipuncture	Overnight fasting and Plasma centrifuged and analyzed immediately	Venipuncture

Plasma glucose was estimated in duplicate by a glucose-oxidase method adapted to analyser	Colorimetric glucose-deshidrogenase method	Glucose oxidase method (Beckman Glucose Analyzer, Beckman Instruments, Fullerton, CA)	Hexokinase	Glucose oxidase method
Serum, 0, 120 min OGTT	Serum, 0, 120 min OGTT	Serum 0, 30, 60, 120 min OGTT	Fasting venous plasma with heparin	Serum 0, 30, 120 min OGTT
Venipuncture	Venipuncture	Venipuncture	Overnight fasting and Fasting venous blood was immediatelly centrifuged and plasma frozen at -80C until measurement	Venipuncture
Human Insulin Specific RIA kit, Linco Research Inc., St Louis MO, USA)	RIA, Coat-a-count Insulin, DPC	Radioimmunoassay (Pharmacia, Uppsala, Sweden), enzyme linked immunoassay (DAKO Diagnostics Ltd, Cambridgeshire, UK), and fluoroimmunometric assay (AutoDelfia, Perkin Elmer Finland, Turku, Finland)	Immunometric assay	ELISA
with a lower detection limit of 2μU/ml.	3.6microU/mL	Pharmacia: CV=5%; DAKO: CV=7.5%	Maximum intra-assay CV of 6.6%	
		SAMPLES		

Diabetes ascertained by OGTT, medical record review	Previous diabetes with insulin or antidiabetic drugs treatment and subjects diagnosed during the OGTT, and/or FPG ≥7 mmol/L. Institutionalized person, pregnant women, and those persons with a severe clinical problem or psychological disorder.	Fasting glucose ≥7.0 mmol/l or 2h glucose ≥11.1 mmol/l, known T2D or GAD Ab positivity, missing phenotype or covariate	Known diabetes, fasting plasma glucose ≥ 7 mmol/l	Self-reported diabetes, treated with anti-diabetic drugs or diabetes at OGTT
420 (46.8%/53.2%)	640 (34.1%/65.9%)	1235 (47.9% / 52.1%)	1442 (46.4 / 53.6)	576 (45.7%/54.3%)
0.0873 (0.02549)	0.10066 (0.023)	0.0988 (0.0204)	0.0875 (0.0311)	0.098 (0.022)
51.74(11.50)/52.41(11.39)	44.2 (13.5) / 43.3 (12.8)	57.6 (10.5) / 59.0 (10.0)	61.3(9.2) / 60.8(9.1)	60.6 (0.41)/60.5 (0.48)
27.0(3.50)/26.4(4.08)	28.1 (4.2) / 27.7 (5.2)	27.0 (3.38) / 27.1 (4.34)	27.3(3.9) / 27.2(5.4)	27.0 (3.5)/26.1 (4.3)
4.66(0.49)/4.41(0.58)	5.5 (0.7) / 5.3 (0.7)	5.5 (0.53) / 5.4 (0.47)	5.13(0.55) / 4.89(0.55)	5.33 (0.52)/5.13 (0.48)
mg/dl	mg/dL	mmol/l	mmol/l	mmol/L
0.05551	0.05551	None	NA	NA
12.03(6.29)/11.72(6.91)	49.5 (36.7) / 44.9 (32.8)	46.9 (31.3) / 42.7 (26.0)	60.4(36.7) / 54.3(34.6)	45.4 (28.6)/40.0 (18.2)
µU/ml	µU/ml	mIU/L	pmol/l	pmol/L
6	6	6.945	Not applicable	Not applicable

Sequenom MassArray	TaqMan® Open Array® Genotyping System (Applied Biosystems)	Affymetrix 500K, some also Illumina HumanOmni2.5-4v1_B	Sequenom	Illumina CoreExome/Illumina HiScan
CEGEN	Sequencing and Genotyping Platform. Hospital Carlos Haya	Broad Institute	MRC-Epid	The Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen
iPLEX software	TaqMan Genotyper Software	BRLMM for 500K and Illumina GenomeStudio v2010.3		Illumina GenCall
>95%	>90%	95%	>95%	95%
None	None	None	None	Rare alleles (MAF<0.05): -0.4<F<0.4, common alleles (MAF>0.05): -0.03<F<0.03 (16 excluded)
None	None	None	None	None

None	None	Genetic fingerprint, gender check	None	None
420	640	1068 with Affy 500K, 1235 when complemented with Omni2.5	1616	656
>1%/0	>1%/0	Monomorphic	None	No filter
$>10^{-2}$ / 0	$>10^{-2}$ / 0	$>10^{-6}$	None	> 10-6
>95%	>90%	95% (Affymetrix) / 98% (Illumina)	>98%	95%
None	None	None	None	None
21	19	9	23	528515
		IMPUTATION STATS		
Not applicable	Not applicable	IMPUTE2 using 1000 Genomes Phase 3 reference panel	Not applicable	IMPUTE2 using 1000 Genomes reference panel
Not applicable	Not applicable	INFO > 0.4	Not applicable	inputeExtract.INFO

Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
		DATA ANALYSIS		
21(none imputed)	19 (none imputed)	47 (9 genotyped, 38 imputed)	23	14
age and sex	age and sex	age, sex, centre; individuals clustered in families	age sex, with/without BMI	age, sex
linear regression	linear regression	Linear regression	linear regression	Linear mixed effect models, generalized estimating equations (interaction)
SPSS 15.0	R and SPSS 17.0	STATA 13.1	Stata v13.0	R
		REFERENCES		
Martinez-Larrad MT et al. Med Clin (Barc). 2005;125(13):481-6	Soriguer F, Rojo-Martínez G, Almaraz MC, Esteva I, Ruiz de Adana MS, Morcillo S, Valdés S, García-Fuentes E, García-Escobar E, Cardona I, Gomez-Zumaquero JM, Olveira-Fuster G. Incidence of type 2 diabetes in southern Spain (Pizarra Study). Eur J Clin Invest. 2008 Feb;38(2):126-33. PubMed PMID: 18226046	PMID: 8866565	PMID: 17257284	PMID: 11251676
		PMID: 17463246		

		http://www.botnia-study.org, https://www.broadinstitute.org/diabetes	http://www.mrc-epid.cam.ac.uk/research/studies/ely/	

Supplemental Table 2. Association of known fasting insulin loci with fasting insulin and ISI in d

			Published Reports for FI (without BMI adjustment)			
SNP	Locus	Eff Allele	Effect	SE	*P*-value	N
rs1421085	*FTO*	C	0.02	0.003	1.9×10^{-15}	104062
rs983309	*PPP1R3B*	T	0.03	0.004	3.8×10^{-14}	103030
rs9884482	*TET2*	C	0.02	0.002	1.4×10^{-11}	108420
rs7903146	*TCF7L2*	C	0.02	0.003	6.1×10^{-11}	103037
rs10195252	*GRB14*	T	0.02	0.003	4.9×10^{-10}	99126
rs1167800	*HIP1*	A	0.02	0.003	2.6×10^{-9}	91416
rs2820436	*LYPLAL1*	C	0.02	0.003	4.4×10^{-9}	104044
rs2745353	*RSPO3*	T	0.01	0.002	5.5×10^{-9}	104075
rs731839	*PEPD*	G	0.02	0.003	1.7×10^{-8}	104636
rs4865796	*ARL15*	A	0.02	0.003	2.1×10^{-8}	100001
rs2972143	*IRS1*	G	0.01	0.003	3.2×10^{-8}	99566
rs1530559	*YSK4*	A	0.02	0.003	3.4×10^{-8}	107281
rs2943645	*IRS1*	T	0.02	0.002	2.3×10^{-19}	99023
			Published Reports for FI (with BMI adjustment)			
SNP	Locus	Eff Allele	Effect	SE	*P*-value	**N**
rs10195252	*GRB14*	T	0.02	0.002	1.3×10^{-16}	98997
rs2126259	*PPP1R3B*	T	0.02	0.003	3.3×10^{-13}	99021
rs4865796	*ARL15*	A	0.02	0.002	2.2×10^{-12}	98314
rs17036328	*PPARG*	T	0.02	0.003	3.6×10^{-12}	98984
rs731839	*PEPD*	G	0.02	0.002	5.1×10^{-12}	103252
rs974801	*TET2*	G	0.01	0.002	3.3×10^{-11}	103489
rs459193	*ANKRD55-MAP3I*	G	0.02	0.002	1.1×10^{-10}	103378
rs6822892	*PDGFC*	A	0.01	0.002	2.6×10^{-10}	103432
rs4846565	*LYPLAL1*	G	0.01	0.002	1.8×10^{-9}	99014
rs3822072	*FAM13A*	A	0.01	0.002	1.8×10^{-8}	99977
rs6912327	*UHRF1BP1*	T	0.02	0.003	2.3×10^{-8}	80010
rs13081389	*PPARG*	A	0.03	0.01	1.6×10^{-6}	52379
rs7578326	*IRS1*	A	0.02	0.003	2.7×10^{-11}	52379
rs780094	*GCKR*	C	0.02	0.003	3.4×10^{-12}	52379

rs972283	*KLF14*	G	0.01	0.003	4.4×10^{-6}	52379
			Published Reports for FI (Model 3)			
SNP	Locus	Eff Allele	SNP Effect Int Effect	SNP SE Int SE	*P*-value	N
rs7607980	*COBLL1- GRB14*	T	-0.06 0.003	0.02 0.001	4.3×10^{-20}	83116
rs2943634	*IRS1*	C	0.02 -0.001	0.02 0.001	2.5×10^{-14}	82318
rs4841132	*PPP1R3B*	A	-0.03 0.00	0.03 0.001	1.7×10^{-10}	82905
rs4691380	*PDGFC*	C	0.004 -0.020	0.02 0.003	5.3×10^{-9}	82075
rs4646949	*UHRF1BP1*	T	-0.02 0.01	0.02 0.003	3.7×10^{-8}	82572
rs2785980	*LYPLAL1*	T	0.01 2.00×10^{-4}	0.02 0.001	2.0×10^{-8}	81598

Association of known fasting insulin (FI) variants were tested for association with fasting insulin and (test of the combined influence of the genotype effect adjusted for BMI and the interaction effect betv adjustment], Nat Genet 2012; 44:991-1005 and Diabetes 2014; 63:2158-2171 [with BMI adjustment], comparable cohort, associations with FI and ISI were performed in a subset of the full discovery coho polymorphism; Int: interaction; SE: standard error.

iscovery cohorts

ISI Full Discovery Cohort (without BMI adjustment)				FI in FHS, Sorbs, FUSION, CHS (wi adjustment)		
Effect	SE	*P*-value	N	Effect	SE	*P*-value
-0.02	0.11	0.12	16753	0.02	0.01	0.02
0.01	0.02	0.55	16753	0.02	0.01	0.04
-0.004	0.01	0.75	16752	0.003	0.01	0.61
-0.02	0.01	0.23	16753	0.01	0.01	0.24
-0.01	0.02	0.49	16752	0.01	0.01	0.07
-0.03	0.02	0.004	16752	0.03	0.01	0.003
-0.03	0.01	0.02	16753	0.02	0.01	0.02
-0.01	0.01	0.22	16753	0.004	0.01	0.51
-0.01	0.02	0.37	13991	0.01	0.01	0.14
-0.04	0.01	0.003	16753	0.01	0.01	0.37
-0.04	0.01	2.00×10^{-4}	16753	0.01	0.01	0.09
-0.01	0.01	0.30	16753	0.02	0.01	0.02
-0.04	0.01	2.00×10^{-4}	16753	0.01	0.01	0.11
ISI Full Discovery Cohort (with BMI adjustment)				**FI in FHS, Sorbs, FUSION (with BMI**		
Effect	SE	*P*-value	N	Effect	SE	*P*-value
-0.03	0.01	0.01	16734	0.02	0.01	0.01
0.03	0.02	0.02	16735	0.01	0.01	0.24
-0.04	0.01	1.00×10^{-4}	16735	0.01	0.01	0.08
-0.07	0.01	1.00×10^{-6}	16725	0.03	0.01	0.003
-0.02	0.01	0.09	13980	0.02	0.01	0.01
-0.01	0.01	0.23	16735	-0.003	0.01	0.65
-0.04	0.01	3.00×10^{-4}	16734	0.03	0.01	5.92×10^{-5}
-0.04	0.01	7.00×10^{-5}	16735	0.02	0.01	0.002
-0.003	0.01	0.79	16735	0.02	0.01	0.002
-0.003	0.01	0.81	16735	0.004	0.01	0.49
-0.02	0.01	0.08	16734	0.02	0.01	0.01
-0.08	0.02	3.00×10^{-5}	16735	0.04	0.01	0.00
-0.06	0.01	6.80×10^{-9}	16735	0.02	0.01	0.00
0.00	0.01	0.70	16725	0.02	0.01	0.00

-0.02	0.01	0.07	16735	0.01	0.01	0.18
ISI Full Discovery Cohort (Model 3)				**FI in FHS, Sorbs, FUSION (Mo**		
SNP Effect Int Effect	SNP SE Int SE	*P* -value	N	SNP Effect Int Effect	SNP SE Int SE	*P* -value
-0.002 -0.002	0.12 0.004	0.002	16685	-0.12 0.01	0.05 0.002	6.18×10^{-5}
0.08 -0.078	0.08 0.005	5.15×10^{-9}	16729	-0.02 0.002	0.03 0.001	1.91×10^{-4}
0.06 0.118	0.12 -0.001	0.13	16735	-0.13 0.01	0.06 0.002	0.03
0.08 -0.078	0.08 0.004	0.001	16735	-0.01 0.001	0.04 0.001	0.002
0.04 0.084	0.08 -0.002	0.25	16726	-0.05 0.003	0.04 0.001	6.15×10^{-5}
0.01 0.081	0.08 0.000	0.99	16735	0.03 -3.72×10^{-4}	0.03 0.001	0.01

the modified insulin sensitivity index (ISI) in different cohorts and in models without adjustment for b
veen the genotype and BMI). Associations of known FI variants with fasting insulin are reported from
, and Nat Genet 2012; 44:659-669 [Model 3]) and in the full discovery cohort of the current work (ISI
rt (FHS, Sorbs, FUSION, and, for analyses without BMI adjustment, CHS). Effect sizes are presented

thout BMI	ISI in FHS, Sorbs, FUSION, CHS (without BMI adjustment)			
N	Effect	SE	*P* -value	**N**
8991	-0.02	0.02	0.32	6627
9584	0.01	0.03	0.65	6627
9223	-0.04	0.02	0.04	6525
9584	0.01	0.02	0.45	6627
9584	-0.01	0.02	0.50	6627
8810	-0.04	0.02	0.05	5825
9312	-0.01	0.02	0.44	6627
9220	0.02	0.02	0.25	6627
9239	-0.01	0.02	0.61	6627
9290	-0.03	0.02	0.08	6627
9584	-0.03	0.02	0.05	6627
8906	-0.01	0.02	0.68	6627
9584	-0.04	0.02	0.04	6627
adjustment)	**ISI in FHS, Sorbs, FUSION (with BMI adjustment)**			
N	Effect	SE	*P* -value	**N**
7851	-0.02	0.02	0.47	3858
7851	0.02	0.03	0.55	3858
7851	-0.05	0.02	0.04	3858
7807	-0.09	0.03	0.005	3848
7851	-0.03	0.02	0.23	3858
7851	-0.03	0.02	0.17	3858
7851	-0.06	0.02	0.02	3858
7851	-0.06	0.02	0.01	3858
7850	-0.02	0.02	0.27	3858
7851	0.02	0.02	0.23	3858
7851	-0.03	0.03	0.19	3858
7851	-0.10	0.04	0.02	3858
7851	-0.03	0.02	0.20	3858
7836	0.01	0.02	0.59	3848

7851	-0.06	0.02	0.004	3858
del 3)	**ISI in FHS, Sorbs, FUSION (Model 3)**			
N	SNP Effect Int Effect	SNP SE Int SE	*P* -value	N
10589	0.04 -0.004	0.15 0.01	0.01	6561
10650	0.15 -0.01	0.11 0.004	0.04	6605
10673	0.26 -0.01	0.18 0.01	0.07	6611
10673	0.07 -0.005	0.10 0.004	0.01	6611
10645	0.06 -0.004	0.11 0.004	0.07	6602
10673	0.03 -0.002	0.11 0.004	0.87	6611

ody mass index (BMI), with adjustment for BMI, and in Model 3 published literature (Nat Genet 2012; 44:991-1005 [without BMI Full Cohort). To compare the association of known FI variants in a as standard deviation per effect allele. SNP: single nucleotide

Supplemental Table 3. Results of Discovery, Replication, and Meta-Analysis for Variant Asso

SNP	Locus		Discovery			
	Model		Effect (Beta)	SE	*P*-value	Het *P*- value
rs13422522	*NYAP2*					
	1		-0.05	0.02	0.003	0.16
	2		-0.07	0.01	4.29×10^{-8}	0.15
	3	SNP	0.13	0.09	1.86×10^{-7}	0.43
		Interaction	-0.01	0.003		
rs4078023	*GP2*					
	1		-0.07	0.05	0.14	0.17
	2		-0.09	0.04	0.04	0.17
	3	SNP	1.31	0.23	3.41×10^{-10}	0.01
		Interaction	-0.05	0.01		
rs12372926	*ARRDC4*					
	1		-0.05	0.01	2.27×10^{-5}	0.01
	2		-0.05	0.01	2.18×10^{-7}	0.02
	3	SNP	0.20	0.08	9.71×10^{-7}	0.06
		Interaction	-0.01	0.003		
rs16924527	*TOX*					
	1		0.14	0.05	0.01	0.06
	2		0.11	0.05	0.02	0.04
	3	SNP	-0.80	0.23	7.6×10^{-10}	0.00
		Interaction	0.04	0.01		
rs2828537	*MRPL39*					
	1		-0.07	0.04	0.06	0.57
	2		-0.06	0.03	0.06	0.41
	3	SNP	1.08	0.17	1.45×10^{-10}	0.20
		Interaction	-0.04	0.01		
rs3900087	*ADAMTS3*					
	1		-0.14	0.08	0.10	0.48
	2		-0.12	0.07	0.09	0.86
	3	SNP	2.29	0.38	9.49×10^{-10}	0.60

		Interaction	-0.09	0.01		
rs6027072	*ARHGAP40*					
	1		0.14	0.03	3.73×10^{-5}	0.95
	2		0.12	0.03	4.3×10^{-5}	0.97
	3	SNP	-0.48	0.18	5.7×10^{-9}	0.37
		Interaction	0.02	0.01		
rs12454712	*BCL2*					
	1		-0.05	0.01	0.0004	0.73
	2		-0.07	0.01	1.39×10^{-7}	0.69
	3	SNP	0.12	0.10	5.39×10^{-7}	0.95
		Interaction	-0.01	0.004		
rs10506418	*FAM19A2*					
	1		0.11	0.04	0.01	0.16
	2		0.14	0.04	0.001	0.19
	3	SNP	-0.80	0.25	2.09×10^{-8}	0.11
		Interaction	0.04	0.01		
rs1857095	*ELTD1*					
	1		0.02	0.05	0.69	0.48
	2		0.01	0.04	0.91	0.20
	3	SNP	0.88	0.25	5.4×10^{-16}	0.06
		Interaction	-0.03	0.01		
rs11594101	*NRG3*					
	1		0.04	0.05	0.41	0.61
	2		0.00	0.04	0.98	0.71
	3	SNP	1.61	0.25	8.38×10^{-10}	0.09
		Interaction	-0.06	0.01		
rs12583553	*FGF9*					
	1		-0.05	0.04	0.18	0.04
	2		-0.06	0.03	0.08	0.10
	3	SNP	1.02	0.19	1.41×10^{-10}	4.39×10^{-5}
		Interaction	-0.04	0.01		
rs4548846	*CDH13*					

	1		0.04	0.06	0.46	0.07
	2		0.04	0.05	0.46	0.22
	3	SNP	1.56	0.28	1.53×10^{-9}	3.90×10^{-15}
		Interaction	-0.06	0.01		
rs12522198 *FAM134B*						
	1		-0.04	0.05	0.38	0.56
	2		-0.04	0.04	0.37	0.61
	3	SNP	1.80	0.28	1.18×10^{-10}	6.13×10^{-6}
		Interaction	-0.07	0.01		
rs10483182 *ISX*						
	1		0.06	0.05	0.27	0.23
	2		0.01	0.05	0.78	0.31
	3	SNP	-1.98	0.26	7.32×10^{-15}	1.4×10^{-5}
		Interaction	0.08	0.01		
rs10520638 *AGBL1*						
	1		-0.001	0.08	0.99	0.03
	2		-0.004	0.07	0.95	0.03
	3	SNP	2.01	0.33	8.27×10^{-14}	1.96×10^{-6}
		Interaction	-0.08	0.01		
rs6013915 *PFDN4*						
	1		0.05	0.05	0.35	0.06
	2		0.07	0.04	0.13	0.15
	3	SNP	-0.96	0.27	6.32×10^{-8}	2.6×10^{-5}
		Interaction	0.04	0.01		
rs9658121 *PPARD*						
	1		0.09	0.07	0.25	0.003
	2		0.13	0.07	0.06	0.003
	3	SNP	-0.49	0.33	1.54×10^{-7}	3.06×10^{-6}
		Interaction	0.03	0.01		
rs10508754 *KIAA1462*						
	1		-0.14	0.03	1.07×10^{-5}	0.30
	2		-0.15	0.03	2.55×10^{-7}	0.10
	3	SNP	0.19	0.22	2.64×10^{-5}	0.14

		Interaction	-0.01	0.01		
rs11627967 *NPAS3*						
	1		-0.04	0.06	0.53	0.10
	2		-0.04	0.05	0.46	0.08
	3	SNP	-1.46	0.28	1.01×10^{-9}	1.42×10^{-13}
		Interaction	0.06	0.01		
rs10495667 *VSNL1*						
	1		0.09	0.04	0.01	0.50
	2		0.09	0.03	0.01	0.71
	3	SNP	-0.90	0.18	3.83×10^{-9}	0.12
		Interaction	0.04	0.01		
rs13059110 *TXNDC6*						
	1		-0.10	0.02	1.6×10^{-6}	0.18
	2		-0.09	0.02	3.69×10^{-7}	0.12
	3	SNP	0.20	0.14	8.84×10^{-5}	0.08
		Interaction	-0.01	0.01		
rs11790816 *SH3GL2*						
	1		0.03	0.06	0.59	0.06
	2		0.03	0.05	0.52	0.15
	3	SNP	-1.38	0.26	3.56×10^{-9}	2.06×10^{-4}
		Interaction	0.06	0.01		

Model 1 is adjusted for age and sex; Model 2 is adjusted for age, sex, and BMI; Model 3 assesses t
the effect, SE, and *P*-values for the SNP are shown. For Model 3, the effect (beta) and SE are prov
deviation per effect allele. SNP: single nucleotide polymorphism; Het *P*-value: heterogeneity *P*-va

ɔciation with Insulin Sensitivity Index

	Replication					
N	**Effect (Beta)**	**SE**	***P*-value**	**Het *P*- value**	**N**	**Effect (Beta)**
16752.3	-0.05	0.02	0.00	0.19	13326	-0.04
16735	-0.05	0.01	5.53×10^{-5}	0.51	13322	-0.06
16735	0.07	0.07	3.00×10^{-4}	0.29	13322	0.10
	0.00	0.003				-0.01
13185	0.07	0.07	0.36	0.45	11557	-0.03
13171	0.04	0.06	0.51	0.06	11556	-0.05
13171	0.11	0.25	0.79	0.13	11556	0.80
	-0.003	0.01				-0.03
16753	-0.0004	0.01	0.98	0.27	13342	-0.03
16735	-0.01	0.01	0.54	0.07	13338	-0.03
16735	0.07	0.06	0.57	0.05	13338	0.11
	-0.002	0.002				-0.005
13523	0.10	0.05	0.05	1.48×10^{-7}	11482	0.12
13514	0.04	0.04	0.40	0.30	11480	0.07
13514	0.38	0.17	0.05	8.07×10^{-6}	11480	-0.08
	-0.01	0.01				0.01
16752.9	-0.01	0.04	0.74	0.05	13001	-0.04
16735	-0.004	0.03	0.90	0.29	12998	-0.03
16735	0.02	0.13	0.92	0.30	12998	0.42
	-0.001	0.005				-0.02
10784	-0.003	0.05	0.96	0.46	11567	-0.04
10784	-0.01	0.05	0.91	0.42	11566	-0.04
10784	-0.02	0.25	0.79	0.03	11566	0.74

	-8.87×10^{-5}	0.01				-0.03
16753	0.04	0.04	0.28	0.21	12143	0.10
16735	0.02	0.03	0.53	0.09	12142	0.08
16735	-0.30	0.16	0.07	0.08	12142	-0.39
	0.01	0.01				0.02
13190	-0.02	0.01	0.11	0.62	12783	-0.04
13982	-0.03	0.01	0.01	0.26	12779	-0.05
13982	0.02	0.07	0.01	0.06	12779	0.04
	-0.002	0.003				-0.003
13992	0.01	0.04	0.74	0.83	12032	0.06
13982	0.01	0.04	0.73	0.61	12029	0.06
13982	-0.51	0.15	0.004	0.26	12029	-0.62
	0.02	0.01				0.03
13991.9	-0.02	0.04	0.57	0.03	12617	-0.01
13982	-0.04	0.03	0.23	0.08	12614	-0.02
13982	-0.17	0.14	0.04	0.01	12614	0.08
	0.004	0.01				-2.82×10^{-4}
16753	-0.01	0.05	0.91	0.91	11151	0.02
16735	-0.01	0.05	0.90	0.80	11150	0.00
16735	0.08	0.18	0.83	0.92	11150	0.62
	-0.004	0.01				-0.02
16753	-0.02	0.04	0.69	0.81	12462	-0.04
16735	-0.04	0.04	0.31	0.74	12460	-0.05
16735	0.19	0.16	0.16	0.07	12460	0.55
	-0.01	0.01				-0.02

8811.99	-0.03	0.08	0.75	0.31	9594	0.02
8810	-0.07	0.07	0.29	0.63	9591	-0.002
8810	-0.43	0.29	0.05	0.19	9591	0.59
	0.01	0.01				-0.03
13190	0.01	0.08	0.93	0.70	6608	-0.03
13982	0.11	0.06	0.09	0.51	6607	0.01
13982	-0.41	0.28	0.14	3.37×10^{-15}	6607	0.79
	0.02	0.01				-0.03
13992	0.06	0.08	0.43	0.76	6417	0.06
13982	0.07	0.06	0.29	0.75	6417	0.03
13982	-0.27	0.26	0.21	0.87	6417	-1.16
	0.01	0.01				0.05
7601	0.12	0.09	0.17	0.77	4782	0.004
7587	0.05	0.07	0.47	0.35	4782	-0.01
7587	0.38	0.26	0.22	0.10	4782	0.89
	-0.01	0.01				-0.04
13991.9	0.05	0.05	0.25	3.30×10^{-4}	9130	0.05
13982	0.05	0.04	0.23	0.01	9129	0.06
13982	-0.56	0.29	0.04	0.004	9129	-0.84
	0.02	0.01				0.04
6142	-0.05	0.05	0.27	0.97	10843	-0.01
6132	-0.03	0.04	0.51	0.98	10841	0.02
6132	-0.33	0.16	0.10	0.93	10841	-0.40
	0.01	0.01				0.02
12363	0.03	0.02	0.26	0.83	12787	-0.03
12363	0.01	0.02	0.72	0.72	12783	-0.05
12363	0.17	0.10	0.17	0.55	12783	0.14

	-0.01	0.004				-0.01
8811.98	0.02	0.09	0.79	0.60	8784	-0.02
8810	-0.02	0.07	0.79	0.57	8783	-0.03
8810	-0.10	0.32	0.95	0.38	8783	-0.94
	0.003	0.01				0.04
13991.9	-0.01	0.03	0.73	0.74	13354	0.02
13982	-0.03	0.03	0.34	0.97	13350	0.01
13982	-0.13	0.17	0.51	0.21	13350	-0.51
	0.004	0.01				0.02
13984	-0.01	0.02	0.52	0.13	12441	-0.05
13982	-0.01	0.02	0.77	0.65	12438	-0.04
13982	-0.04	0.09	0.79	0.06	12438	0.03
	0.001	0.003				-0.002
9364.92	-0.01	0.04	0.84	0.39	12469	0.01
9347	0.01	0.04	0.89	0.90	12467	0.02
9347	0.13	0.17	0.45	0.42	12467	-0.37
	-0.004	0.01				0.02

he combined influence of the SNP effect adjusted for BMI and the interaction effect between the ge
ided for the SNP and the interaction; *P*-value is provided for the joint influence of the SNP and int
alue for the model.

Combined Meta-Analysis			
SE	***P*-value**	**Het *P*- value**	**N**
0.01	1.64×10^{-5}	0.14	30078.3
0.01	1.20×10^{-11}	0.26	30057
0.06	8.87×10^{-11}	0.29	30057
0.002			
0.04	0.49	0.18	24742
0.04	0.20	0.03	24727
0.17	3.17×10^{-7}	4.23×10^{-5}	24727
0.01			
0.01	0.001	0.002	30095
0.01	1.16×10^{-5}	4.35×10^{-4}	30073
0.05	4.20×10^{-4}	0.001	30073
0.002			
0.04	0.001	2.57×10^{-7}	25005
0.03	0.02	0.05	24994
0.14	3.72×10^{-6}	2.29×10^{-15}	24994
0.01			
0.03	0.12	0.12	29753.9
0.02	0.16	0.28	29733
0.10	2.60×10^{-5}	3.19×10^{-4}	29733
0.004			
0.05	0.33	0.42	22351
0.04	0.31	0.52	22350
0.21	4.66×10^{-4}	1.75×10^{-5}	22350

0.01			
0.02	9.43×10^{-5}	0.41	28896
0.02	4.05×10^{-4}	0.18	28877
0.12	4.36×10^{-9}	0.02	28877
0.005			
0.01	2.80×10^{-4}	0.64	25973
0.01	1.87×10^{-8}	0.21	26761
0.05	2.67×10^{-8}	0.19	26761
0.002			
0.03	0.05	0.30	26024
0.03	0.01	0.10	26011
0.13	1.92×10^{-8}	0.01	26011
0.005			
0.03	0.84	0.08	26608.9
0.03	0.37	0.08	26596
0.12	7.91×10^{-9}	7.83×10^{-10}	26596
0.005			
0.04	0.57	0.87	27904
0.03	0.94	0.90	27885
0.14	9.46×10^{-5}	0.001	27885
0.01			
0.03	0.19	0.22	29215
0.03	0.04	0.35	29195
0.12	3.60×10^{-9}	6.92×10^{-8}	29195
0.005			

0.04	0.72	0.35	18405.99
0.04	0.96	0.65	18401
0.18	1.12×10^{-5}	1.21×10^{-16}	18401
0.01			
0.04	0.48	0.79	19798
0.04	0.84	0.38	20589
0.19	1.57×10^{-4}	8.00×10^{-27}	20589
0.01			
0.04	0.17	0.53	20409
0.04	0.39	0.57	20399
0.18	7.82×10^{-12}	1.18×10^{-7}	20399
0.01			
0.05	0.93	0.09	12383
0.04	0.77	0.08	12369
0.19	1.21×10^{-7}	6.78×10^{-13}	12369
0.01			
0.03	0.14	4.64×10^{-4}	23121.9
0.03	0.05	0.01	23111
0.19	1.52×10^{-9}	6.03×10^{-7}	23111
0.01			
0.04	0.80	0.02	16985
0.04	0.63	0.02	16973
0.15	0.001	1.65×10^{-8}	16973
0.01			
0.02	0.08	0.01	25150
0.02	0.01	0.001	25146
0.09	0.07	0.004	25146

0.004			
0.05	0.69	0.31	17595.98
0.04	0.44	0.29	17593
0.21	1.55×10^{-7}	3.90×10^{-15}	17593
0.01			
0.02	0.32	0.37	27345.9
0.02	0.69	0.32	27332
0.12	3.76×10^{-5}	1.58×10^{-4}	27332
0.010			
0.01	1.10×10^{-4}	0.01	26425
0.01	2.26×10^{-4}	0.01	26420
0.07	0.01	0.002	26420
0.003			
0.03	0.63	0.15	21833.92
0.03	0.45	0.63	21814
0.14	0.001	2.72×10^{-7}	21814
0.01			

enotype and BMI on ISI. For Model 1 and Model 2,
eraction effect. Effect sizes are presented as standard

Supplemental Table 4. Results of Meta-Analysis for Variant Association with Insulin Sensitiv

SNP	Locus		Combined Meta-Analysis using MAC < 20 filter in Cohorts			
	Model		Effect (Beta)	SE	*P*-value	Het *P*- value
rs13422522	*NYAP2*					
	1		-0.04	0.01	1.64×10^{-5}	0.14
	2		-0.06	0.01	1.20×10^{-11}	0.26
	3	SNP	0.10	0.06	8.87×10^{-11}	0.29
		Interaction	-0.01	0.002		
rs4078023	*GP2*					
	1		-0.02	0.04	0.65	0.34
	2		-0.04	0.04	0.30	0.08
	3	SNP	0.46	0.18	0.03	0.05
		Interaction	-0.02	0.01		
rs12372926	*ARRDC4*					
	1		-0.03	0.01	0.001	0.002
	2		-0.03	0.01	1.61×10^{-5}	4.35×10^{-4}
	3	SNP	0.11	0.05	4.20×10^{-4}	5.59×10^{-4}
		Interaction	-0.005	0.002		
rs16924527	*TOX*					
	1		0.12	0.04	0.001	8.10×10^{-7}
	2		0.07	0.03	0.02	0.13
	3	SNP	0.18	0.14	0.01	9.95×10^{-7}
		Interaction	-0.004	0.01		
rs2828537	*MRPL39*					
	1		-0.04	0.03	0.13	0.10
	2		-0.03	0.02	0.17	0.23
	3	SNP	0.41	0.10	3.56×10^{-5}	1.45×10^{-4}
		Interaction	-0.02	0.004		
rs3900087	*ADAMTS3*					
	1		-0.04	0.05	0.33	0.42
	2		-0.04	0.04	0.31	0.52

		3	SNP	0.74	0.21	4.66×10^{-4}	1.75×10^{-5}
			Interaction	-0.03	0.01		
rs6027072	*ARHGAP40*						
		1		0.10	0.02	9.43×10^{-5}	0.41
		2		0.08	0.02	4.05×10^{-4}	0.18
		3	SNP	-0.39	0.12	4.36×10^{-9}	0.02
			Interaction	0.02	0.005		
rs12454712	*BCL2*						
		1		-0.04	0.01	2.80×10^{-4}	0.64
		2		-0.05	0.01	1.87×10^{-8}	0.21
		3	SNP	0.04	0.05	2.67×10^{-8}	0.19
			Interaction	-0.003	0.002		
rs10506418	*FAM19A2*						
		1		0.05	0.03	0.09	0.54
		2		0.06	0.03	0.02	0.20
		3	SNP	-0.58	0.13	7.96×10^{-7}	0.07
			Interaction	0.02	0.005		
rs1857095	*ELTD1*						
		1		-0.01	0.03	0.84	0.06
		2		-0.02	0.03	0.36	0.05
		3	SNP	0.09	0.12	0.09	0.001
			Interaction	-0.01	0.005		
rs11594101	*NRG3*						
		1		0.02	0.04	0.57	0.87
		2		-0.002	0.03	0.94	0.90
		3	SNP	0.62	0.14	9.46×10^{-5}	0.001
			Interaction	-0.02	0.01		
rs12583553	*FGF9*						
		1		-0.04	0.03	0.17	0.69
		2		-0.05	0.03	0.04	0.76
		3	SNP	0.21	0.13	0.01	0.18
			Interaction	-0.01	0.01		

rs4548846	*CDH13*					
	1		0.02	0.04	0.63	0.49
	2		0.002	0.04	0.96	0.75
	3	SNP	-0.45	0.21	0.08	0.20
		Interaction	0.02	0.01		
rs12522198	*FAM134B*					
	1		-0.03	0.04	0.52	0.74
	2		0.01	0.04	0.80	0.32
	3	SNP	0.79	0.19	1.66×10^{-4}	9.26×10^{-28}
		Interaction	-0.03	0.01		
rs10483182	*ISX*					
	1		0.06	0.04	0.16	0.46
	2		0.03	0.04	0.39	0.47
	3	SNP	-0.41	0.21	0.07	0.44
		Interaction	0.02	0.01		
rs10520638	*AGBL1*					
	1		0.01	0.05	0.78	0.13
	2		-0.01	0.04	0.88	0.08
	3	SNP	0.15	0.21	0.76	0.03
		Interaction	-0.01	0.01		
rs6013915	*PFDN4*					
	1		0.05	0.03	0.18	0.001
	2		0.05	0.03	0.07	0.02
	3	SNP	-0.26	0.22	0.03	0.02
		Interaction	0.01	0.01		
rs9658121	*PPARD*					
	1		-0.01	0.04	0.80	0.02
	2		0.02	0.04	0.63	0.02
	3	SNP	-0.40	0.15	0.001	1.65×10^{-8}
		Interaction	0.02	0.01		
rs10508754	*KIAA1462*					
	1		-0.03	0.02	0.08	0.01
	2		-0.05	0.02	0.01	0.001
	3	SNP	0.14	0.09	0.07	0.004

		Interaction	-0.01	0.004		
rs11627967 *NPAS3*						
	1		-0.03	0.05	0.54	0.70
	2		-0.04	0.04	0.33	0.76
	3	SNP	0.30	0.26	0.52	0.28
		Interaction	-0.01	0.01		
rs10495667 *VSNL1*						
	1		0.02	0.02	0.32	0.37
	2		0.01	0.02	0.69	0.32
	3	SNP	-0.51	0.12	3.76×10^{-5}	1.58×10^{-4}
		Interaction	0.02	0.005		
rs13059110 *TXNDC6*						
	1		-0.05	0.01	1.10×10^{-4}	0.01
	2		-0.04	0.01	2.26×10^{-4}	0.01
	3	SNP	0.03	0.07	0.01	0.002
		Interaction	-0.002	0.003		
rs11790816 *SH3GL2*						
	1		0.01	0.03	0.80	0.33
	2		0.02	0.03	0.58	0.84
	3	SNP	-0.06	0.15	0.44	0.21
		Interaction	0.003	0.01		

In a sensitivity analysis, the combined meta-analyses were repeating removing all SNPs with a min
to when a minor allele frequency (MAF) < 1% was applied to the discovery cohorts and MAC < 2(
Table 2 and Supplemental Table 3 and repeated here for comparison), application of the MAC filte
reduced the heterogeneity of some results in the Model 3 and for the results of the *PFDN4* locus as
statistical significance of associations with high heterogeneity. It also slightly reduced the statistica
markedly reducing the magnitude of effect or affecting heterogeneity. The sample size for the *FAM*
filter was applied in the discovery cohorts versus when the MAF filter was applied. Model 1 is adju
the combined influence of the SNP effect adjusted for BMI and the interaction effect between the g
for the SNP are shown. For Model 3, the effect (beta) and SE are provided for the SNP and the inte

ɪty Index Using Minor Allele Count Filter

Discovery	Combined Meta-Analysis using MAF <1% filter in Discovery Cohorts (repeated from Table 2 and Supplemental Table 3)				
N	**Effect (Beta)**	**SE**	***P*-value**	**Het *P*- value**	**N**
30078.3	-0.04	0.01	1.64×10^{-5}	0.14	30078.3
30056.3	-0.06	0.01	1.20×10^{-11}	0.26	30057
30056.3	0.10 -0.01	0.06 0.002	8.87×10^{-11}	0.29	30057
21844	-0.03	0.04	0.49	0.18	24742
21829	-0.05	0.04	0.20	0.03	24727
21829	0.80 -0.03	0.17 0.01	3.17×10^{-7}	4.23×10^{-5}	24727
30095	-0.03	0.01	0.001	0.002	30095
30073	-0.03	0.01	1.16×10^{-5}	4.35×10^{-4}	30073
30073	0.11 -0.005	0.05 0.002	4.20×10^{-4}	0.001	30073
25005	0.12	0.04	0.001	2.57×10^{-7}	25005
24993	0.07	0.03	0.02	0.05	24994
24993	-0.08 0.01	0.14 0.01	3.72×10^{-6}	2.29×10^{-15}	24994
29291.9	-0.04	0.03	0.12	0.12	29753.9
29270.9	-0.03	0.02	0.16	0.28	29733
29270.9	0.42 -0.02	0.10 0.004	2.60×10^{-5}	3.19×10^{-4}	29733
21557	-0.04	0.05	0.33	0.42	22351
22350	-0.04	0.04	0.31	0.52	22350

21557	0.74 -0.03	0.21 0.01	4.66×10^{-4}	1.75×10^{-5}	22350
28896	0.10	0.02	9.43×10^{-5}	0.41	28896
28877	0.08	0.02	4.05×10^{-4}	0.18	28877
28877	-0.39 0.02	0.12 0.005	4.36×10^{-9}	0.02	28877
25973	-0.04	0.01	2.80×10^{-4}	0.64	25973
25961	-0.05	0.01	1.87×10^{-8}	0.21	26761
25961	0.04 -0.003	0.05 0.002	2.67×10^{-8}	0.19	26761
25562	0.06	0.03	0.05	0.30	26024
25549	0.06	0.03	0.01	0.10	26011
25549	-0.62 0.03	0.13 0.005	1.92×10^{-8}	0.01	26011
26146.9	-0.01	0.03	0.84	0.08	26608.9
26133.9	-0.02	0.03	0.37	0.08	26596
26133.9	0.08 -2.82×10^{-4}	0.12 0.005	7.91×10^{-9}	7.83×10^{-10}	26596
27904	0.02	0.04	0.57	0.87	27904
27885	0.00	0.03	0.94	0.90	27885
27885	0.62 -0.02	0.14 0.01	9.46×10^{-5}	0.001	27885
27951	-0.04	0.03	0.19	0.22	29215
27933	-0.05	0.03	0.04	0.35	29195
27933	0.55 -0.02	0.12 0.005	3.60×10^{-9}	6.92×10^{-8}	29195

23124	0.02	0.04	0.72	0.35	18405.99
23111	-0.002	0.04	0.96	0.65	18401
23111	0.59	0.18	1.12×10^{-5}	1.21×10^{-16}	18401
	-0.03	0.01			
19336	-0.03	0.04	0.48	0.79	19798
20127	0.01	0.04	0.84	0.38	20589
19336	0.79	0.19	1.57×10^{-4}	8.00×10^{-27}	20589
	-0.03	0.01			
19947	0.06	0.04	0.17	0.53	20409
19937	0.03	0.04	0.39	0.57	20399
19937	-1.16	0.18	7.82×10^{-12}	1.18×10^{-7}	20399
	0.05	0.01			
19309	0.004	0.05	0.93	0.09	12383
19295	-0.01	0.04	0.77	0.08	12369
19295	0.89	0.19	1.21×10^{-7}	6.78×10^{-13}	12369
	-0.04	0.01			
22659.9	0.05	0.03	0.14	4.64×10^{-4}	23121.9
22648.9	0.06	0.03	0.05	0.01	23111
22648.9	-0.84	0.19	1.52×10^{-9}	6.03×10^{-7}	23111
	0.04	0.01			
16985	-0.01	0.04	0.80	0.02	16985
16973	0.02	0.04	0.63	0.02	16973
16973	-0.40	0.15	0.001	1.65×10^{-8}	16973
	0.02	0.01			
24359	-0.03	0.02	0.08	0.01	25150
24345	-0.05	0.02	0.01	0.001	25146
24345	0.14	0.09	0.07	0.004	25146

	-0.01	0.004			
17134	-0.02	0.05	0.69	0.31	17595.98
17131	-0.03	0.04	0.44	0.29	17593
17131	-0.94	0.21	1.55×10^{-7}	3.90×10^{-15}	17593
	0.04	0.01			
30106.9	0.02	0.02	0.32	0.37	27345.9
30084.9	0.01	0.02	0.69	0.32	27332
30084.9	-0.51	0.12	3.76×10^{-5}	1.58×10^{-4}	27332
	0.02	0.010			
26425	-0.05	0.01	1.10×10^{-4}	0.01	26425
26412	-0.04	0.01	2.26×10^{-4}	0.01	26420
26412	0.03	0.07	0.01	0.002	26420
	-0.002	0.003			
28759.9	0.01	0.03	0.63	0.15	21833.92
28739.9	0.02	0.03	0.45	0.63	21814
28739.9	-0.37	0.14	0.001	2.72×10^{-7}	21814
	0.02	0.01			

ıor allele count (MAC) < 20 in the discovery and replication cohorts. As compared
) was applied to replication cohorts in the combined meta-analysis (as shown in
ɾ to both the discovery and replication cohorts in the combined meta-analysis
ssociation in Model 1. The application of this MAC filter tended to reduce the
ıl significance of the association at the *FAM19A2* locus in Model 3 without
419A2 locus association in Model 3 was 462 individuals fewer when the MAC
ıusted for age and sex; Model 2 is adjusted for age, sex, and BMI; Model 3 assesses
genotype and BMI on ISI. For Model 1 and Model 2, the effect, SE, and P-values
ɾraction; P-value is provided for the joint influence of the SNP and interaction

Supplemental Table 6. ***In silico*** **findings for rs12454712 (*BCL2*) and rs10506418 (*FAM19A2*)**

rs12454712 (*BCL2*)

located 3 Mb away (LD $r^2 < 0.0001$), did not attenuate the association with the ISI in the discovery cohorts of Model 2 (beta = -0.067 ± 0.01, *P* = 1.4 × 10-7 to beta = -0.067 ± 0.01, *P* =1.6 × 10-7), and no other genome-wide significant findings for glycemic traits are present on chromosome 18.

sensitivity as measured by M value from direct measures of insulin sensitivity in the GENESIS consortium (beta = -0.0275 ± 0.03, P=0.41, N=2,764). When the variant at BCL2 was tested in the same subset of discovery cohorts (FHS, Sorbs, FUSION), the associations with fasting insulin and ISI were not significant (for fasting insulin SNP effect = -0.11 ± 0.07, interaction effect 0.004 ± 0.003, P=0.25, N=7,819 and for ISI SNP effect = -0.03 ± 0.22, interaction effect -0.001 ± 0.01, P=0.24,

factor binding (RegulomeDB score 2b = TF binding + any motif + DNAse footprint + DNAse peak). Using the UCSC Genome Browser, binding motifs to several transcription factors are evident (MYC,

phosphatase that mediates dephosphorylation of AKT1, AKT2, and AKT3, which has a role in regulation of apopotosis and insulin signaling (www.Uniprot.org). Thus, this locus may play a role in

rs10506418 (*FAM19A2*)

and insulin loci within 100 Mb did not attenuate the association with the ISI in the discovery cohorts of Model 2 (beta = 0.139 ± 0.04, P= 4.50 × 10-4 (unconditioned) to beta = 0.139 ± 0.04, *P* = 4.57 × 10-4 when conditioned on rs35767 (IGF1, LD $r^2 = 0.0005$), to beta = 0.139 ± 0.04, P= 4.54 × 10-4 when

associations with fasting insulin and ISI were not significant (for fasting insulin SNP effect = 0.33 ± 0.13, interaction effect -0.01 ± 0.13, *P* =0.06, N=7,851 and for ISI SNP effect = -0.17 ± 0.48, interaction effect -0.01 ± 0.01, *P* =0.85, N=3,396). However, for the fasting insulin and ISI analyses,

acting as regulators of immune and nervous cells primarily in the brain.

diabetes and fasting insulin, although these are not in LD with our finding at rs10506418. The genomic region containing FAM19A2 also contains USP15, a hydrolase that removes ubiquitin from target proteins and regulates several pathways, including TGF-beta receptor signaling and NF-kappa-B

Supplemental Table 3: Association for rs12454712 (*BCL2*) and rs10506418 (*FAM19A2*) w

	rs12454712			
	ISI		Fasting Insulin	
BMI (kg/m^2)	Full Cohort	FHS, Sorbs, FUSION	Manning *et al*	FHS, Sorbs, FUSION
< 20	-0.02	-0.05	0.01	-0.03
20-24.9	-0.04	-0.06	0.02	0.00
25-29.9	-0.06	-0.06	0.02	0.02
30-34.9	-0.07	-0.07	0.03	0.04
≥35	-0.09	-0.08	0.03	0.06

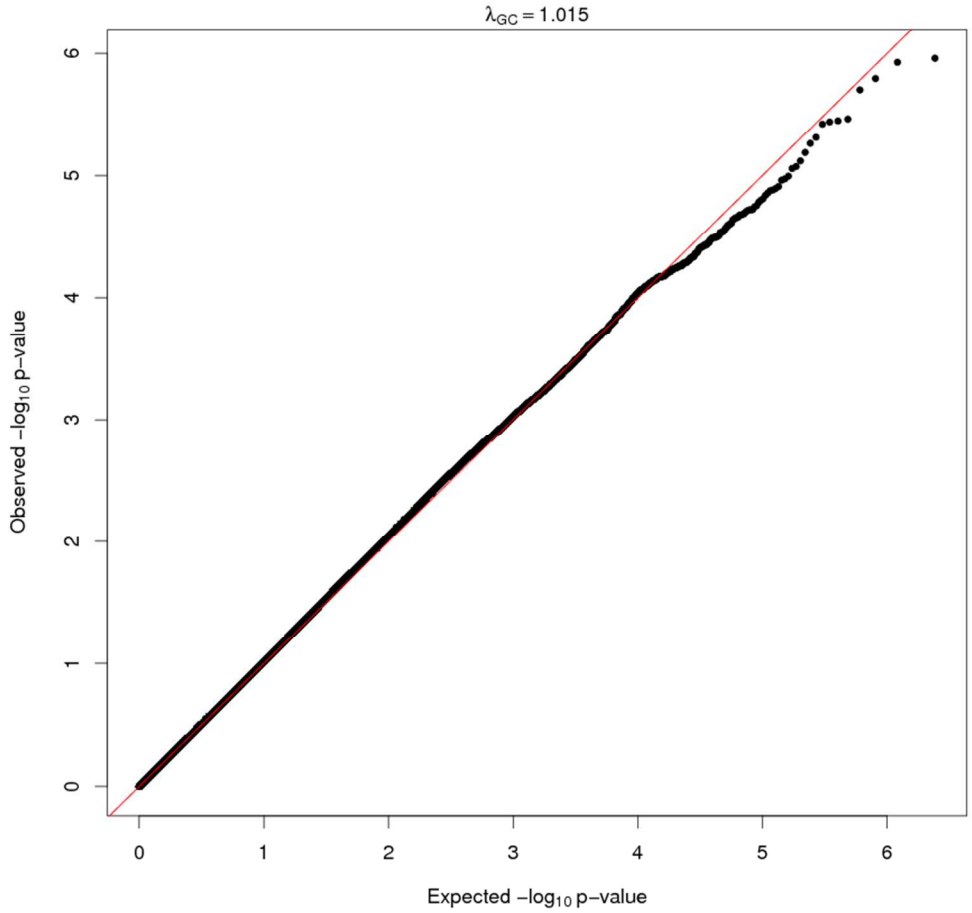
The association of the T allele rs12454712 (*BCL2*) and the A allele rs10506418 (*FAM19A2*
(BMI). The effect (beta) is derived from the Model 3 analyses in the full cohort of the curre
dataset for fasting insulin (Nat Genet 2012; 44:659-669). To compare the effects in the same
the same subset of discovery cohorts (FHS, Sorbs, FUSION). Effect sizes are presented as s
combined influence of the SNP effect adjusted for BMI and the interaction effect between th

ith ISI and fasting insulin at different strata of body mass index

rs10506418			
ISI		Fasting Insulin	
Full Cohort	FHS, Sorbs, FUSION	Manning *et al*	FHS, Sorbs, FUSION
-0.10	-0.02	0.01	0.10
0.03	0.02	0.00	0.04
0.16	0.06	-0.01	-0.01
0.30	0.09	-0.03	-0.06
0.43	0.13	-0.04	-0.11

) with ISI and fasting insulin is shown at different strata of body mass index
ıt study for ISI (the same data in Figure 2 and Figure 3) and from a published
ɛ cohorts, the Model 3 associations for ISI and fasting insulin were performed in
tandard deviation per effect allele at each strata of BMI. Model 3: test of the
ıe genotype and BMI on ISI.

Supplemental Figure 1: QQ plot of association statistics in genome-wide scan for discovery effort (n= 16,753 participants) in Model 1 (adjusted for age and sex only).



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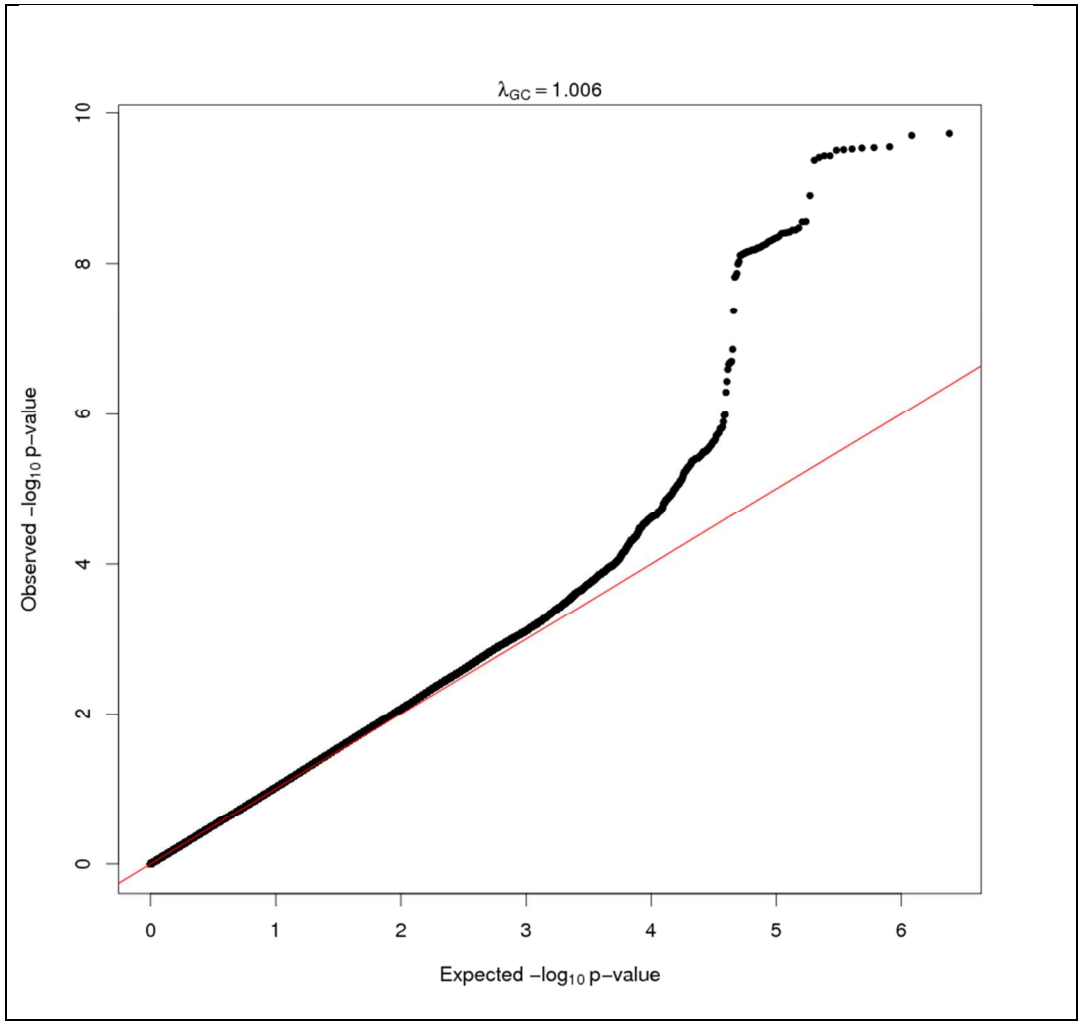
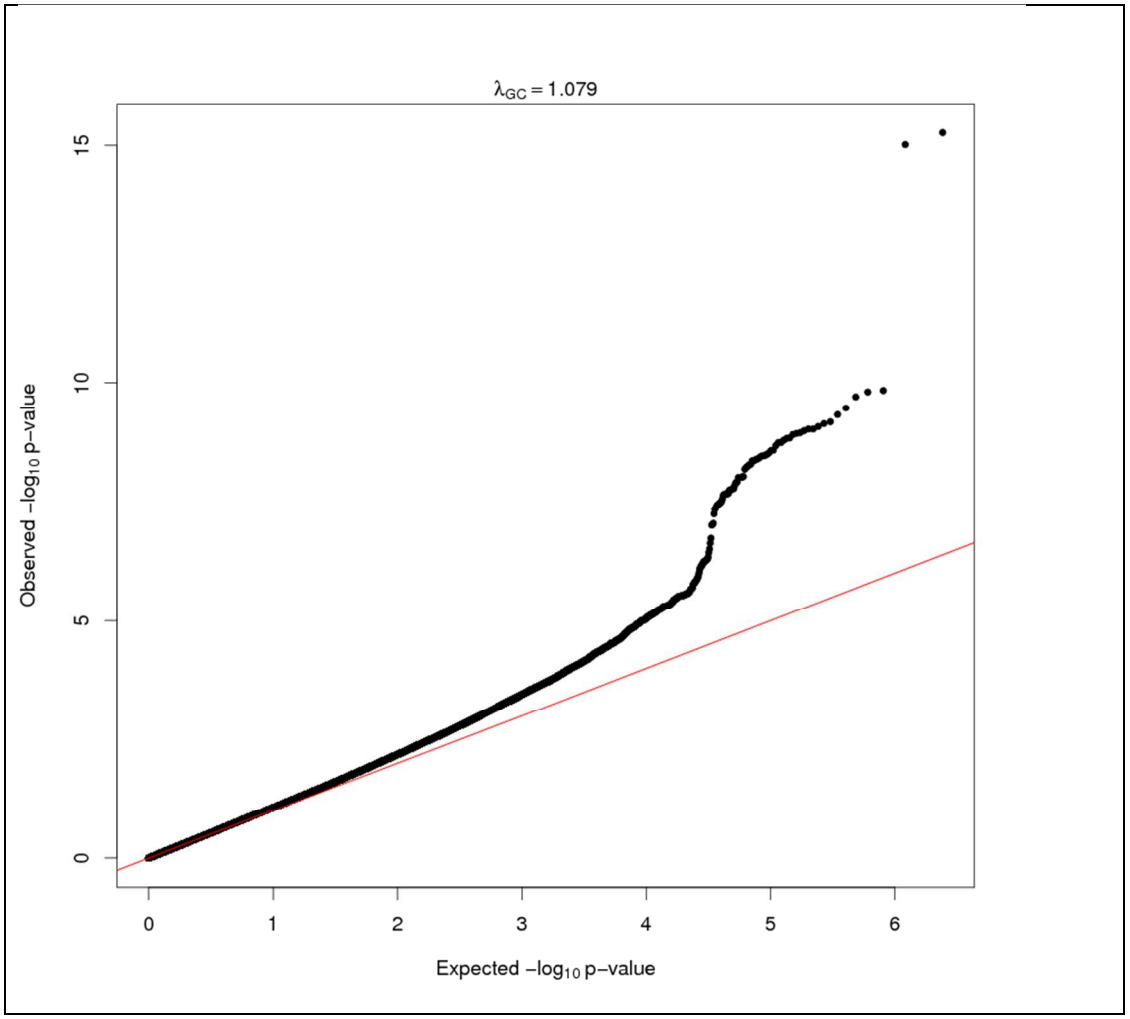
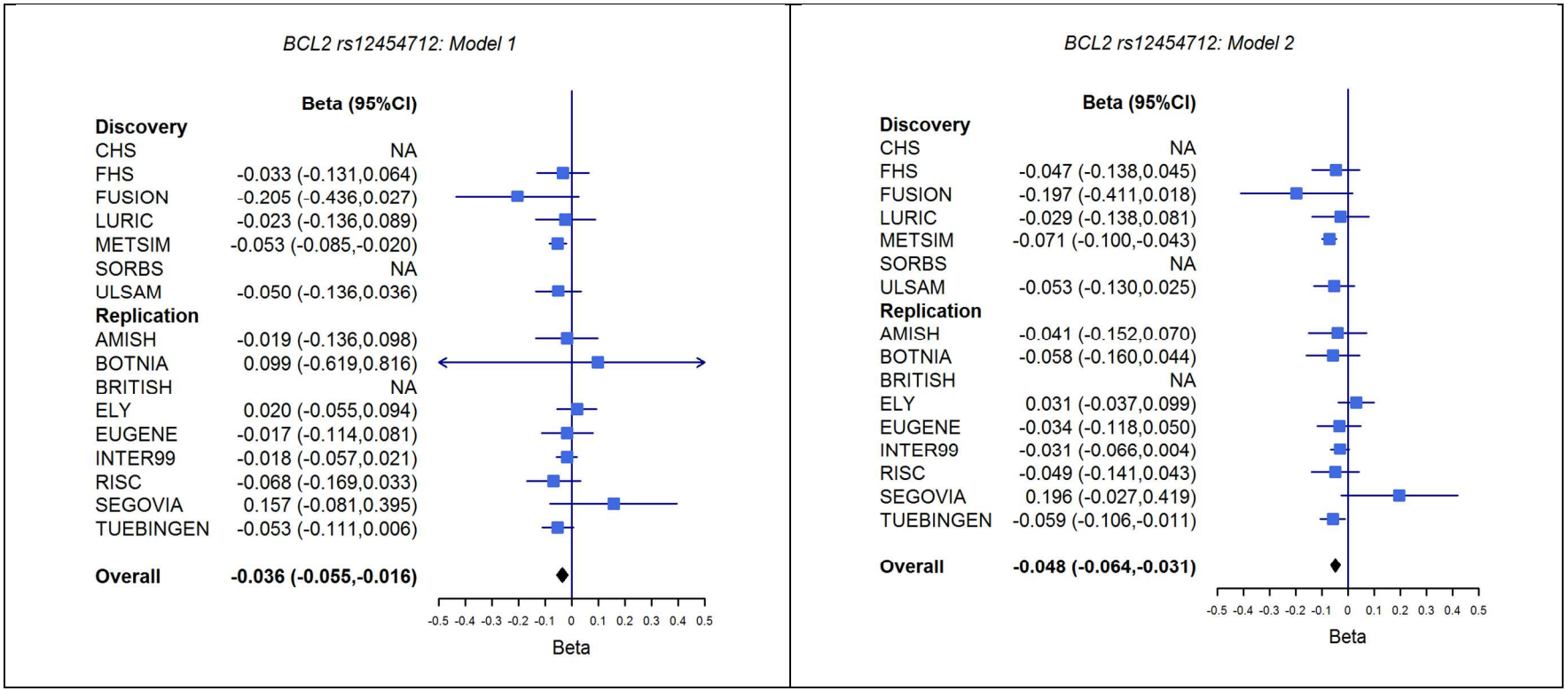
Supplemental Figure 2: QQ plot of association statistics in genome-wide scan for discovery effort (n= 16,735 participants) in Model 2 (adjusted for age, sex, and body mass index).



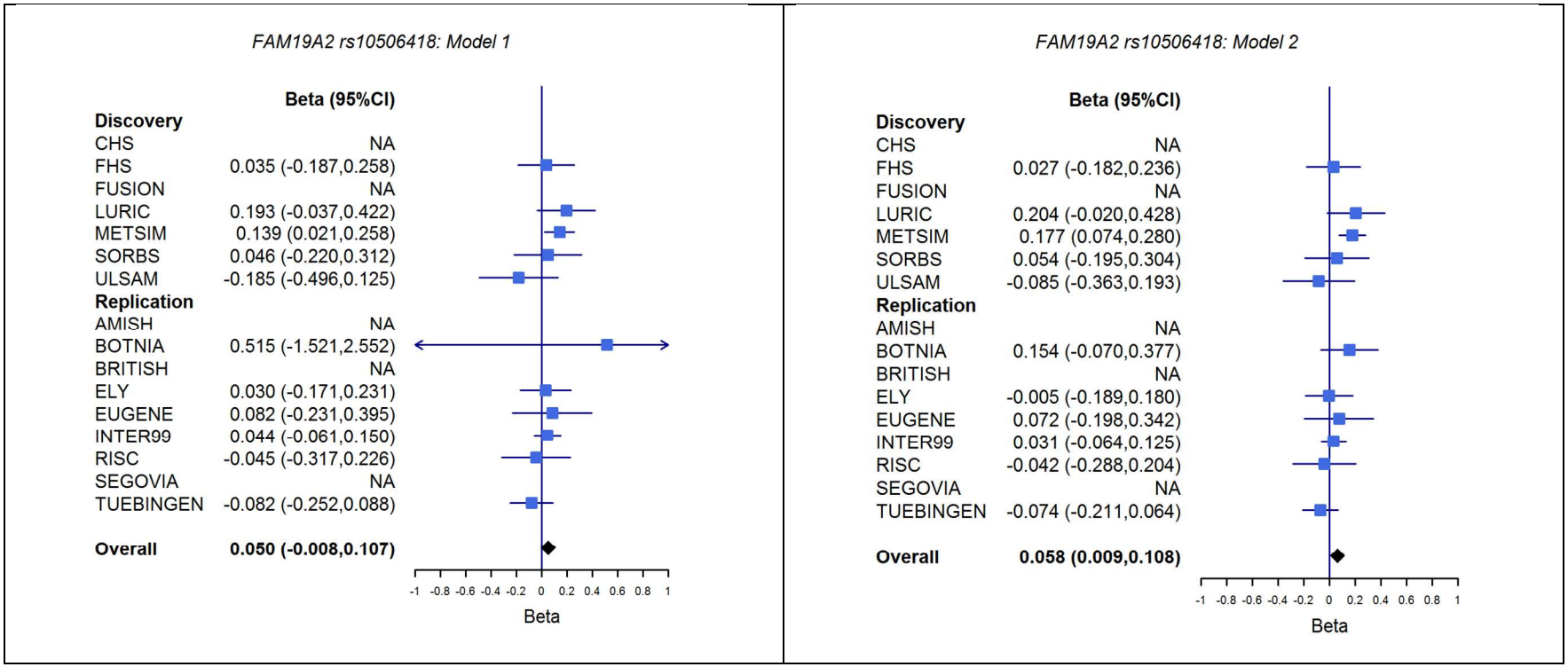
Supplemental Figure 3: QQ plot of association statistics in genome-wide scan for discovery effort (n= 16,735) participants in Model 3 (adjusted for age and sex and analyzing combined influence of the SNP effect adjusted for body mass index [BMI] and the interaction effect between genotype and BMI on ISI).



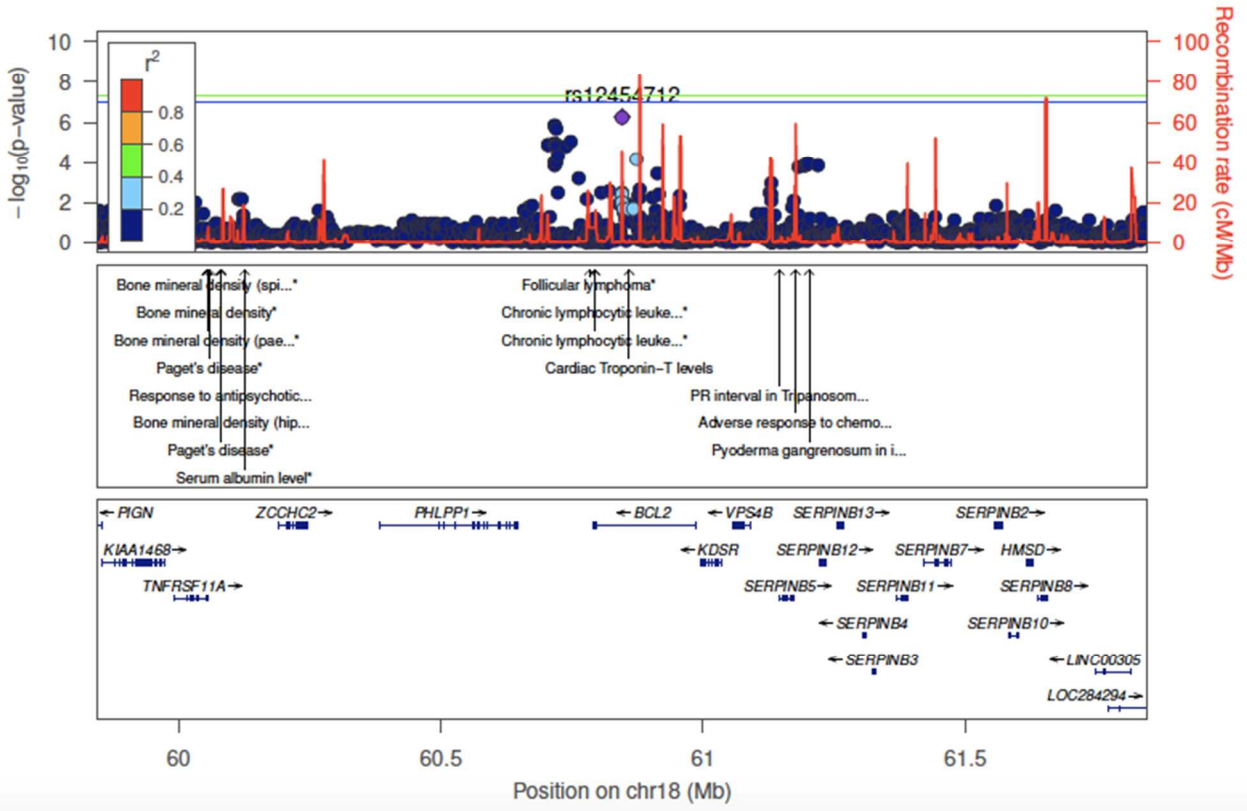
Supplemental Figure 4: Forrest Plot for association of rs12454712 (*BCL2*) with the ISI in Model 1 and Model 2 of the discovery and replication cohorts.



Supplemental Figure 5: Forrest Plot for association of rs10506418 (*FAM19A2*) with the ISI in Model 1 and Model 2 of the discovery and replication cohorts

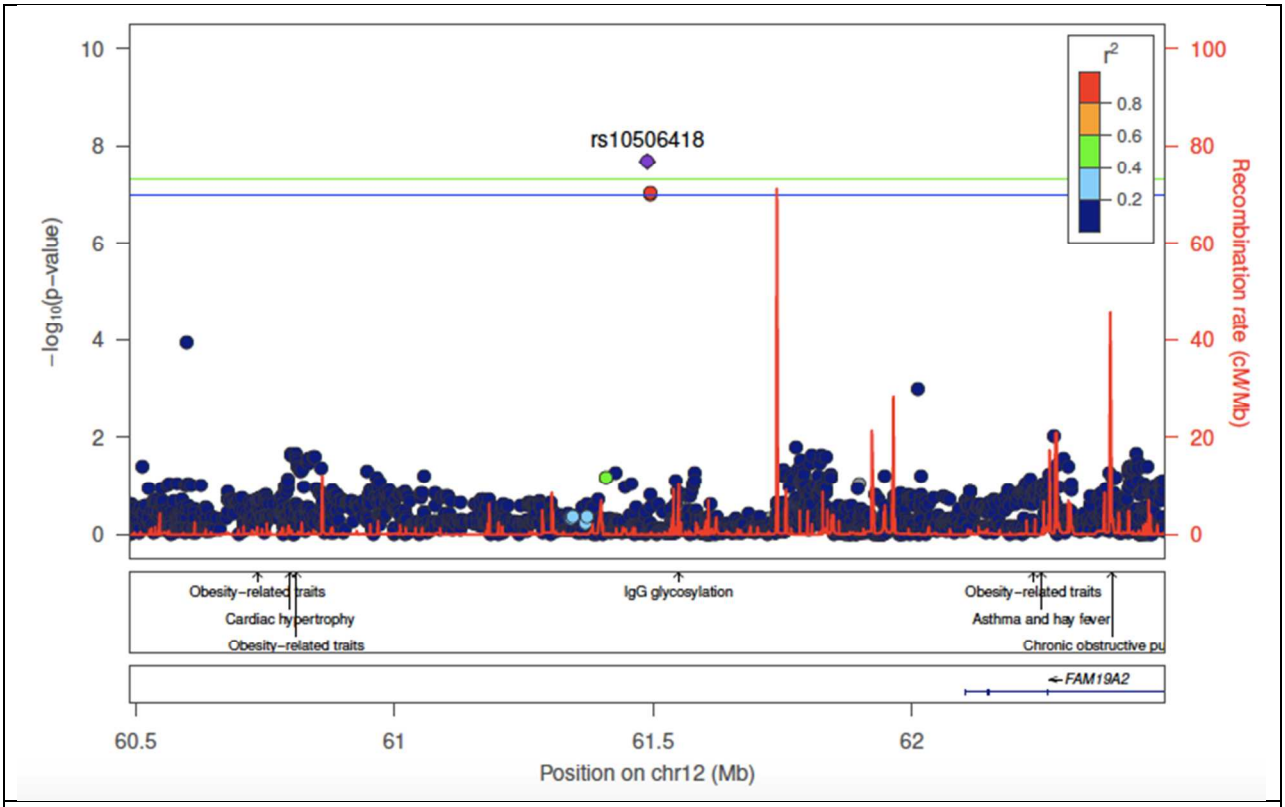


Supplemental Figure 6: Locus Zoom plot for associations at rs12454712 (*BCL2*)



The LocusZoom plot (1) is shown for rs12454712 (*BCL2)* and other SNPs within 1MB for association with ISI in Model 3 (adjusted for age, sex, and BMI and tested the interaction between genotype and BMI) in the discovery cohorts. GWAS catalog traits are presented at the bottom and those traits with a genome-wide significant association ($P<5\times10^{-8}$) are marked with *. The green horizontal line indicates $P=5\times10^{-8}$ and the blue horizontal line indicates $P=1\times10^{-7}$. Pruim RJ, Welch RP, Sanna S, Teslovich TM, Chines PS, Gliedt TP, Boehnke M, Abecasis GR, Willer CJ. LocusZoom: regional visualization of genome-wide association scan results. Bioinformatics 2010; 26:2336-2337

Supplemental Figure 7: Locus Zoom plot for associations at rs10506418 (*FAM19A2*)



The LocusZoom plot (1) is shown for rs10506418 (*FAM19A2)* and other SNPs within 1MB for association with ISI in Model 3 (adjusted for age, sex, and BMI and tested the interaction between genotype and BMI) in the discovery cohorts. GWAS catalog traits are presented at the bottom and those traits with a genome-wide significant association ($P<5\times10^{-8}$) are marked with *. The green horizontal line indicates $P=5\times10^{-8}$ and the blue horizontal line indicates $P=1\times10^{-7}$. Pruim RJ, Welch RP, Sanna S, Teslovich TM, Chines PS, Gliedt TP, Boehnke M, Abecasis GR, Willer CJ. LocusZoom: regional visualization of genome-wide association scan results. Bioinformatics 2010; 26:2336-2337