Published in final edited form as:

J Hypertens. 2013 May ; 31(5): 1001–1009. doi:10.1097/HJH.0b013e32835f5a83.

Lack of interaction of beta-cell function-associated variants with hypertension on change in fasting glucose and diabetes risk: the Framingham Offspring Study

JM de Miguel-Yanes^a, B Porneala^b, MJ Pencina^c, CS Fox^{d,e}, JC Florez^{e,f,g}, DS Siscovick^h, J Dupuis^{c,d}, and JB Meigs^{b,e}

^aHospital Gregorio Marañón, Universidad Complutense de Madrid, and Hospital del Sureste, Madrid, Spain

^bGeneral Medicine Division, Massachusetts General Hospital, Boston, MA

^cDept. of Biostatistics, Boston University School of Public Health, Boston, MA

^dNational Heart, Lung and Blood Institute's Framingham Heart Study, Framingham, MA

^eHarvard Medical School, Boston, MA

^fDiabetes Unit and Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA

^gProgram in Medical and Population Genetics, Broad Institute, Cambridge, MA

^hCardiovascular Health Research Unit, Departments of Medicine and Epidemiology, University of Washington, Seattle, WA

Abstract

Objective—To test if pancreatic beta-cell genetic frailty and hypertension interact in their associations with change over time in fasting glucose (Δ FG) or type-2 diabetes (T2D) risk.

Methods and results—We pooled data from 3,471 Framingham Offspring Study participants into 6 ~4-yr periods (15,852 person-exams; mean age 52; 54% women). We defined two genetic exposures reflecting beta-cell genetic risk burden: single nucleotide polymorphism (SNP) score counts of FG- and T2D-associated risk alleles at 16 and 33 putative beta-cell loci, respectively; and three hypertension exposures: 1)hypertension vs. no-hypertension; 2)treated vs. untreated-hypertension; and 3)five mutually-exclusive anti-hypertensive categories (beta-blockers, thiazides, renin-angiotensin system agents, combinations, others) vs. untreated-hypertension. We tested ~4-year mean Δ FG or odds of T2D by per-risk allele score change and hypertension category, seeking genetic score-by-hypertension interaction. Genetic scores increased ~4-yr Δ FG (0.6 mg/dl per-risk allele; $p=8.9\times 10^{-16}$) and T2D-risk (~17% per-risk allele; $p=2.1\times 10^{-7}$). Versus no-

Corresponding author (no reprints available): Dr. James B. Meigs. General Internal Medicine Division. Massachusetts General Hospital. 50 Staniford Street, 9th floor. Boston MA 02114. USA. Voice: 617-724-3203. Fax: 617-724-3544. jmeigs@partners.org.

Conflicts of Interest

JMMY has received consulting honoraria from Novartis and sanofi-Aventis. JCF has received consulting honoraria from Novartis, Lilly and Pfizer. For the remaining authors, none were declared. MJP sits on a Board in a trial for a diabetes drug for Theracos. Part of this work was presented in poster form at the AHA EPI/NPAM Scientific Sessions (San Diego, CA, March 13–16, 2012), and at the European Federation of Internal Medicine Congress (Madrid, Spain, October 23–27, 2012).

Contribution statement

J.M.M.Y. researched data and wrote the manuscript. B.P. researched data. M.J.P. contributed to discussion and reviewed/edited manuscript. C.S.F. researched data and reviewed/edited manuscript. J.C.F. contributed to discussion and reviewed/edited manuscript. D.S.S. reviewed/edited manuscript. J.D. contributed to discussion and reviewed/edited manuscript. J.B.M. wrote the manuscript.

hypertension, hypertension conferred higher Δ FG (2.6 vs. 1.7 mg/dl; $p<0.0001$) and T2D-risk (OR=2.9, 95% CI [2.8–3.0]; $p<0.0001$). Versus untreated-hypertension, treated hypertension conferred higher Δ FG (3.4 vs. 3.0 mg/dl; $p<0.0001$) and T2D-risk (OR=1.4 [1.3–1.5]; $p=0.02$). Beta-blockers (OR=1.6 [1.1–2.4]), combinations (OR=1.6 [1.1–2.5]) and others (OR=2.0 [1.4–2.9]) increased T2D-risk (all $p<0.02$). In joint models including interaction terms, all genetic score-by-hypertension interaction terms were $p>0.05$. In joint models without interaction, FG-SNP or T2D-SNP genetic scores (both $p<0.001$) and hypertension ($p<0.0001$) independently increased Δ FG or T2D-risk.

Conclusion—Hypertension, hypertension treatment and common FG-/T2D-SNP genetic scores independently predicted Δ FG and T2D incidence, but did not modify each other's association with Δ FG or T2D risk.

Keywords

hypertension; hypertension treatment; single-nucleotide polymorphisms; genes; genetic risk scores; type 2 diabetes mellitus; fasting glucose; interaction test; Framingham

Introduction

Prevalence of hypertension is high: one out of every three US adults older than 20 years have hypertension (1), and as many as 45 million people are being treated with antihypertensive drugs in the USA (2). In parallel, prevalence of type 2 diabetes was 13% in the 2003–2006 US National Health and Nutrition Examination Survey (NHANES) among adults older than 20 years (3). Presence of combined hypertension and type 2 diabetes is frequent (4). Longitudinal studies have found an increased type 2 diabetes risk associated with hypertension (5,6).

The possibility that antihypertensive drugs worsen glycemic control and increase risk of type 2 diabetes has been examined repeatedly (7–9). Recent clinical trials and meta-analyses suggest that the use of thiazides and beta-blockers is associated with increased type 2 diabetes risk (10–14). Gress *et al* (15) reported a 28% excess risk for type 2 diabetes onset in hypertensive subjects treated with beta-blockers in the Atherosclerosis Risk In Communities (ARIC) Study. Contrarily, renin-angiotensin converting agents (angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB)) could improve glycemic control and lower type 2 diabetes risk (16–18).

By 2012, at least 63 autosomal common single-nucleotide polymorphisms (SNPs) have been shown to increase type 2 diabetes genetic risk in large genome-wide association studies (GWAS) (19–27). Similarly, 36 SNPs have been shown to influence fasting glucose levels (23,28–29). Of these SNPs, by the time our analysis was done, 16 associated with fasting glucose and 33 associated with type 2 diabetes had been reported to act by impairing beta-cell function through different mechanisms, such as beta-cell development, insulin maturation, and insulin storage or secretion (23,24). A greater number of these risk variants across loci would reflect increasing beta-cell genetic frailty. Such genetic frailty can be measured using genetic risk scores that add and weight a group of SNPs (30), with a higher score indicating a greater risk of high trait levels or disease incidence.

Whereas hypertension and hypertension treatment, and genetic background seem to increase fasting glucose and type 2 diabetes risk, it has not been tested whether these factors can modify each other's previously known associations with glycemia. The rationale for this question comes from the view of patient-centered therapeutics: Demonstration of gene-drug interactions might make some basic genetic information useful for clinical practice when selecting anti-hypertensive drugs for patients at risk for developing adverse metabolic

effects. In this context, it is not known if genetic risk scores reflecting aggregate frailty (rather than focusing on single SNP tests) might interact with drug therapy (a potentially strong interactor) to alter physiology (e.g., fasting glucose level) or incident disease risk.

Here, we test the hypothesis that the beta-cell subsets of common SNPs associated with fasting glucose or type 2 diabetes interact with hypertension or antihypertensive drugs in their positive associations with change over time in fasting glucose (Δ FG) or incident type 2 diabetes.

Methods

Study population

We studied Framingham Offspring Study participants. The original prospective Framingham Heart Study was started in 1948 to study predisposing factors for cardiovascular disease. In 1971, the Framingham Offspring Study enrolled 5,124 offspring of the original cohort and the spouses of the offspring, who were followed until 2007 (up to 8 exams) (31). They have been seen in the clinic about every 3–4 years (except for the ~8-year period between exams 1 and 2), to receive a complete medical history, physical exam and blood sample collection. The genetic information needed for this study was available for 3,471 subjects. Participants were essentially all of white European ancestry. All participants gave written informed consent. The Institutional Review Board at the Boston University Medical Center approved the study protocols.

Beta-cell frailty scores

To assess genetic influences on Δ FG, we used the 16 fasting glucose-associated SNPs reported to influence beta-cell function by the time this study was conducted (23,32). For risk of type 2 diabetes, we only used the 33 out of 40 type 2 diabetes-associated SNPs thought to influence beta-cell function by the time this study was conducted (20–26). Eight SNPs overlapped for the Δ FG and the type 2 diabetes analyses. All SNPs were selected from large studies showing robust, replicated statistical associations. We excluded those SNPs that had been suggested to modify type 2 diabetes risk through insulin action (as opposed to insulin secretion), or through other well-defined non beta-cell mechanisms (namely, obesity in case of *FTO*). We also removed from the dataset SNP rs2237892, at *KCNQ1*, associated with type 2 diabetes risk mainly in Asian populations. In addition, no genotyped or imputed data were available in Framingham for rs1800574, at *TCF1/HNF1A*.

Genotypes were obtained from the Affymetrix array data available in the Framingham Heart Study SHARe (SNP Health Association Resource) dataset project, for which genotyping is conducted using approximately 550,000 SNPs (Affymetrix 500K mapping array plus Affymetrix 50K supplemental array), in over 9,300 subjects from the three generations of subjects (33), or from *de novo* genotyping on the iPLEX (Sequenom) platform (34), when not included in the Affymetrix array. Minimum call rates were 97% for Affymetrix and 96.9% for iPLEX SNPs. All SNPs were in Hardy-Weinberg equilibrium ($P > 1 \times 10^{-6}$ for Affymetrix and $P > 0.02$ for iPLEX SNPs). When genes were not actually genotyped, imputation was performed with MACH software (35). For all the imputed SNPs in our study, the variance ratio was > 0.3 , except for rs757210, a type 2 diabetes-associated SNP, at *HNF1B* (variance ratio=0.20); the median variance ratio was 0.94 for the type 2 diabetes-SNPs and 0.98 for the fasting glucose-SNPs.

Using these SNPs we created a 16-fasting glucose beta-cell SNP-genetic score and a 33 type 2 diabetes beta-cell SNP-genetic score. We did not intend to study individual SNPs' main or interaction effects: The genetic scores can be interpreted as a measure of beta-cell frailty continuously distributed, due to having been built by means of counting SNPs with

deleterious effects on glycemia, putatively mediated by impaired beta-cell biology. For the construction of the 16-fasting glucose SNP and the 33-type 2 diabetes SNP-additive weighted genetic risk scores, we counted risk alleles (0,1,2) for each genotyped SNP -or its dosage, when imputed-, and multiplied each SNP genotype by its published beta coefficient for unit increase in fasting glucose or in diabetes risk (23,24). We added up the product of that multiplication at each SNP, divided the sum by twice the sum of the betas and multiplied the result by the number of SNPs. We opted for using weighted scores because some of our analyses explored the main effects of the genetic variants on the traits for which the weights were derived, and typically one gets similar results using weighted versus unweighted scores when testing interaction effects (36). We evaluated the association of the fasting glucose-SNP genetic score with ~4-year Δ FG, and the association of the type 2 diabetes-SNP genetic score with ~4-year risk of incident type 2 diabetes.

Hypertension exposures

We defined three hypertension exposure classifications. We classified individuals at each exam as having or not having hypertension, as having medication- treated hypertension or untreated hypertension, and among those treated, into medication treatment groups. At each exam, we defined “no hypertension” as not on treatment and normal blood pressure, according to the recommendations of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (systolic blood pressure < 140 mm Hg or diastolic blood pressure <90 mm Hg) (2). Untreated hypertension was defined as not on treatment for hypertension but with elevated blood pressure (systolic blood pressure $\geq$ 140 mm Hg or diastolic blood pressure $\geq$ 90 mm Hg) (2). We classified individuals on hypertensive treatment into five mutually exclusive antihypertensive drug exposure groups: thiazides only; beta-blockers only; ACE inhibitors/ARB only; any combination of the previous three classes; and other hypertensive therapies (calcium-channel blockers, reserpine derivatives, methyldopa, alpha-1 agonists, alpha-2 blockers, and peripheral vasodilators). We tested the association of hypertension, hypertension treatment and specific antihypertensive drug exposures with Δ FG and risk of type 2 diabetes.

Clinical outcomes and confounders

We measured fasting glucose in plasma with a hexokinase reagent kit (A-gent glucose test; Abbott, South Pasadena, CA) (37). We defined type 2 diabetes at each exam as having a fasting plasma glucose level $\geq$ 126 mg/dl (7.0 mmol/l) or on diabetes treatment. More than 99% of diabetes cases among the participants in the Framingham Offspring Study have type 2 diabetes (38). We did not use hemoglobin A_{1c} to define diabetes.

Additional exposures used to control confounding included age (in year), sex, body mass index (BMI) (kg/m²), smoking status (current smoker -at least 1 cigarette per day within 1 year-, or non-smoker), plasma HDL cholesterol and triglyceride (TG) levels (both per mg/dl), and self-reported alcohol consumption (ounces per week). Physical activity and potassium levels were not accounted for in the models because they are too sparsely available in Framingham.

Statistical methods

Our main hypotheses were to evaluate whether common SNPs associated with fasting glucose or type 2 diabetes that denote beta-cell genetic frailty interact with hypertension or antihypertensive drugs in their positive associations with: 1) ~4 year Δ FG (calculated as fasting glucose end minus beginning of each time period) and 2) ~4-year risk of incident type 2 diabetes. For descriptive statistics we used the chi-square test for dichotomous variables and the T-test for comparing means for continuous variables. We tested Δ FG and type 2 diabetes risk as a function of baseline hypertension category and genetic status using

a pooled regression approach (39): we pooled clinical data from the 2,922 non-diabetic individuals for whom complete clinical data for all variables were available at every exam into 6 time periods (exams 2–3, 3–4, 4–5, 5–6, 6–7 and 7–8). We thus generated 15,852 person-observations pertaining to 6 time periods, with a mean pool length of 4.15 years over 28.3 years of study follow up. As a result of pooling, the information from each individual for the start point of each time period contributed independently from the information belonging to a different time period. This way, the possibility of switching treatments and changes in other covariates over time can be accounted for. This regression method with pooled repeated measures produces odds ratios that theoretically could overestimate a relative risk ratio if disease prevalence becomes too high, but pooled odds ratios give essentially identical point estimates and variances as time-dependent covariate Cox regression analysis (39,40), as does use of pooled hazard ratios instead of pooled odds ratios. Thus we report odds ratios as the effect size estimate.

We excluded diabetes cases at baseline of each period. For the Δ FG analyses, we additionally excluded people who had started diabetes treatment within a given time period, to fully remove any hypoglycemic drug treatment effects. To test Δ FG, we used age-, sex-, baseline fasting glucose-adjusted Generalized Estimating Equations (GEE) models with the family identity link function (41). For incident type 2 diabetes, we used age-, sex-adjusted pooled logistic regression GEE models (logit link). Use of GEE with family identity as the clustering unit allowed us to account for correlated observations within Framingham families and within individuals.

To analyze whether hypertension categories and genetic scores interacted to influence Δ FG or incident type 2 diabetes beyond main effects, we tested first-order interaction terms between hypertension, antihypertensive treatment or specific drug exposures and each genetic score. Interaction terms took the form: $\text{trait} = \beta_0 + \beta_c \cdot \text{covariates} + \beta_1 \cdot E + \beta_2 \cdot \text{SNP} + \beta_3 \cdot E \cdot \text{SNP} + \epsilon$, where E represented drug exposure and SNP denoted genetic contributions. The result of interest was the p value for the test $H_0: \beta_3 = 0$. In *a priori* specified secondary analyses, we evaluated joint models without interaction terms to test the hypotheses that, in case no interactions were found, hypertension or antihypertensive treatments and the genetic scores had independent associations with Δ FG, or incident type 2 diabetes.

In additional secondary analyses, we tested associations in models with adjustment for additional type 2 diabetes risk factors measured at the baseline of each period (mean blood pressure, body mass index, smoking, HDL cholesterol and triglyceride levels, and alcohol consumption) to see whether these putative confounders altered observed associations.

Statistical analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, NC). An empirical p value <0.05 indicated statistical significance for interaction terms or main effects, as we established one hypothesis for Δ FG, and a separate, correlated one for type 2 diabetes.

Power to detect hypertension-genetic score and drug exposure-genetic score interaction

We generated an empiric power estimate based on our data in order to frame the results in light of what we might expect to see given the Framingham sample size and effect sizes for the exposures known from prior data. We estimated the study statistical power for the gene-environment interaction tests using Quanto software, version 1.2.4 (42), with our known samples sizes, and prior to conducting the association analyses. We estimated statistical power for the hypertension vs. no hypertension analysis, and for the beta-blockers exposure vs. untreated hypertensive, as an example of specific drug exposure analysis. We assumed an additive genetic model using an average per allele effect size of 0.45 mg/dl on fasting

glucose (23), and an average per-allele relative risk of 1.15 for incident type 2 diabetes (24), interacting with binary environmental exposures with effect sizes of 3.24 mg/dl for hypertension and of 0.011 mg/dl for beta-blockers exposure in the change in fasting glucose analyses, and relative risks of 2.4 for hypertension, and 1.28 for beta-blockers exposure in the type 2 diabetes analyses (15). We had 80% statistical power, with a type I error of 0.05 in two-tailed analyses and allele frequencies between 20% and 80%, to detect regression coefficients ranging from 0.04 to 0.05 for the genetic score-hypertension interaction tests, and from 0.10 to 0.12 for the genetic score-beta blockers exposure interaction test in the Δ FG analyses, and coefficients ranging from 1.07 to 1.08 for the genetic score-hypertension interaction tests, and from 1.19 to 1.23 for the genetic score-beta blockers exposure interaction test in the type 2 diabetes analyses.

Results

Base-line characteristics of the study population

Mean age was 51.9 years, and 53.8% of the population were women. As people in the Framingham Offspring Study aged, BMI increased and hypertension and hypertension treatment became more prevalent (Table 1). People with hypertension were older, more frequently male and had higher BMIs and worse lipid profiles than people without hypertension (Supplemental Digital Content Table S1). People with untreated hypertension were younger, more frequently male, and had higher blood pressure values than their treated counterparts (Supplemental Digital Content Table S2). Differences among people treated with different anti-hypertensive drugs are shown in the Supplemental Digital Content Table S3

Association of hypertension, hypertension treatment and specific drug exposures with Δ FG

Versus no hypertension, hypertension was associated with 0.9 mg/dl higher ~4-year Δ FG (Table 2). Versus untreated hypertension, treated hypertension conferred 0.4 mg/dl higher Δ FG (Table 2). Versus untreated hypertension, renin-angiotensin system agents and combined treatment were associated with a higher absolute ~4-year Δ FG, whereas beta-blockers and thiazides were not (Table 3).

Association of hypertension, hypertension treatment and specific drug exposures with type 2 diabetes risk

Versus no hypertension, hypertension was associated with ~3-fold increased odds of type 2 diabetes (OR=2.9; 95% CI 2.8–3.0) (Table 2). Versus untreated hypertension, treated hypertension conferred 40% increased odds of type 2 diabetes (OR=1.4; 95% CI 1.3–1.5) (Table 2). Versus untreated hypertension, beta-blockers (OR=1.6; 95% CI 1.1–2.4) (Table 3), combined treatment (OR=1.6; 95% CI 1.1–2.5) and others (OR=2.0; 95% CI 1.4–2.9) were associated with increased odds of type 2 diabetes.

Association of the additive genetic scores with Δ FG or risk of type 2 diabetes

The beta-cell derived genetic risk scores reflected frailty. With each additional weighted risk allele in the 16 SNP score, Δ FG increased by 0.55 mg/dl per FG-risk allele ($p=8.9\times 10^{-16}$), and for the 33 SNP score, odds of type 2 diabetes increased 16.6% (95% CI 10.0–23.6) per type 2 diabetes-risk allele. Individuals who developed diabetes had about one half a risk allele more in the score than those who did not (17.3 vs. 16.8; $p=2.1\times 10^{-7}$).

Interaction effect between hypertension or its treatment categories and the genetic scores

All interaction p values in joint models including interaction terms for hypertension, hypertension treatment or specific antihypertensive drug exposures by genetic scores, predicting Δ FG or incident type 2 diabetes, were non-significant (all $p > 0.3$) (Table 4).

Joint models including hypertension, its treatments and genetic scores without interaction terms

In joint models without interaction, hypertension, thiazides and reninangiotensin agents, and per fasting glucose-SNP risk allele independently predicted Δ FG (Supplemental Digital Content Table S6). However, neither hypertension treatment nor beta-blockers predicted Δ FG. In joint models without interaction, hypertension, hypertension treatment, and type 2 diabetes -genetic scores all independently predicted incident type 2 diabetes (Supplemental Digital Content Table S7). No specific hypertension drug predicted incident type 2 diabetes in joint models without interaction terms (all p values > 0.19).

Secondary analyses

To test the possibility that additional type 2 diabetes risk factors measured at the baseline of each period (mean blood pressure, body mass index, smoking, HDL cholesterol and triglyceride levels, and alcohol consumption) could explain the associations, we did the same set of analyses in models with further adjustment for these risk factors. The statistically significant results seen in the age-, sex-adjusted models (with additional adjustment for fasting glucose in the Δ FG analyses) were mostly reproduced (data not shown).

Discussion

We found that hypertension, hypertension treatment, and beta-cell genetic frailty scores derived from fasting glucose- and type 2 diabetes -associated SNPs conferred higher ~4-year Δ FG and risk of incident type 2 diabetes in initially non-diabetic subjects in Framingham. Renin-angiotensin system agents were nominally associated with Δ FG, and exposure to beta-blockers increased ~4-year type 2 diabetes risk in the Framingham participants.

We detected no interaction effect for any hypertension-treatment category-by-genetic score, although hypertension and genetic scores were independently associated with glycemic outcomes. This means that hypertension or antihypertensive specific treatments, and fasting glucose- or type 2 diabetes-associated beta-cell genetic frailty, did not modify each other's association with Δ FG or type 2 diabetes risk. Therefore, the influence that hypertension or its treatment exerted on Δ FG and type 2 diabetes risk was homogeneous irrespectively of the genetic susceptibility conferred by fasting glucose-or type 2 diabetes-associated beta-cell common genetic variation. Reciprocally, the effect of fasting glucose- and type 2 diabetes-associated beta-cell genetic frailty on Δ FG and type 2 diabetes risk was not greater in the presence of hypertension or hypertension treatment. Albeit we only had power to detect relatively large regression coefficients for the interaction effects with our sample size, none of the interaction terms neared statistical significance. We believe that these are truly non-significant interaction effects, and that main effects mostly explain the associations.

In case we had found interaction effects in our study, the implication could have been that, for similar efficacy rates, clinicians might preferentially opt for using drugs with less adverse metabolic effects, which might be more easily anticipated by knowing the genetic susceptibility of the patients and the possible modifying effect on behalf of hypertension treatment to increase their fasting glucose levels or to make patients more likely to develop type 2 diabetes. Our main hypothesis of seeking interaction effects between glucose- and

type 2 diabetes-associated SNPs and hypertension upon Δ FG and type 2 diabetes risk thus seemed plausible and based on a clinical decision making context. Notwithstanding the previous idea, some authors have proposed that the therapeutic or adverse effects of any pharmacological action on glucose metabolism may not be adequately detected by using Δ FG or type 2 diabetes alone, since the interplay of multiple physiologic systems to maintain glycemia in a narrow range may blunt the final effects, and perhaps other phenotypes more closely related to the action of the drug should be defined and tested (43).

Previous work has shown a positive association of hypertension with higher fasting glucose and type 2 diabetes risk (15). These associations have been reported to be stronger in European-ancestry Americans, such as Framingham Study's participants, whereas in African Americans additional risk factors apparently confounded the associations (44). Others have previously evaluated the interaction between genetic background and environmental factors for type 2 diabetes incidence, but few have focused on the possible modifying role of common genetic variation on the effects derived from antihypertensive drugs upon glycemic-related traits. One case-control study including 497 diabetes cases showed that homozygous risk allele carriers for SNP rs1799752, at *ACE* genetic locus, had a 70% increased risk of type 2 diabetes associated with thiazides use (45). Becker *et al* (46), using data from the Rotterdam Study, reported that risk of incident type 2 diabetes was 78% higher among calcium-channel blockers users with the TT genotype for rs10494366, at *NOS1AP* locus, than for calcium-channel blockers users with the TG or GG genotypes. Irving *et al* (47) more recently reported that SNP rs2228576 polymorphism, at the amiloride-sensitive epithelial sodium channel *SCNN1A* locus, modified the association between fasting glucose levels and amlodipine vs. chlorthalidone treatment. To our knowledge, the interaction effect between type 2 diabetes-associated genetic loci and type 2 diabetes risk had mostly been tested for oral antidiabetic drugs (48), and only exceptionally for other kinds of drugs.

Confounding by indication, which is a matter of concern in observational studies of drug therapies, has precluded claiming irrefutable evidence for the effect of hypertension and its treatment on glycemic control and risk of incident diabetes. Thus, the fact that genetics do not confound by indication ("Mendelian randomization") gives strength to our study. A limitation is that we only analyzed common genetic variants; eventual incorporation of rare variants with larger effects could further enhance the ability to detect significant interaction effects by constructing more powerfully discriminative genetic scores. Furthermore, genome wide association studies SNPs only tag putative functional variants; had we knowledge of the functional variants at each locus, we might be able to account for a more precise genetic effect and detect interaction. We preferred to use somewhat loose criteria to select the beta-cell frailty genetic loci, despite the possibility that having included loci with unclear or unproven mechanisms leading to Δ FG or increased type 2 diabetes risk may have subtracted power from the study. As an example, we decided to include *GCKR*, formerly thought to act mainly through liver-mediated insulin resistance, because a recent report suggested possible mechanisms influencing beta-cell function, still to be confirmed (49). SNP level effects might be mechanistically more precise, but our sample size prohibited single SNP analyses. Even greater power would be needed to unmask specific SNP effects.

Before drawing definite conclusions, a few additional issues should be pointed out: Framingham Offspring Study subjects were mostly white and of European ancestry. Had we analyzed populations with a different ancestry, we might have seen different results. We were unable to ascertain exact exposure duration or a precise date of type 2 diabetes onset in Framingham participants, since this information was retrieved only at subsequent visits during the scheduled follow-up of the participants. However, we used a robust pooled-regression analysis method that accounted for this limitation. At last, a nominally significant

association was seen for use of beta-blockers and type 2 diabetes risk, although this apparent association should be interpreted with caution, as the lower boundary of the 95% CIs for beta-blockers exposure's OR includes the ORs for some of the exposures that showed non-significant associations with type 2 diabetes risk.

Conclusions

Hypertension, hypertension treatment and common fasting glucose- and type 2 diabetes - SNP genetic scores were independently associated with Δ FG in fasting glucose and type 2 diabetes incidence, but did not modify each other's association with Δ FG or type 2 diabetes risk. Even though we found no significant interaction effects with models using genetic scores, this study hints at the possibility of analyzing individual SNP-by-specific drug category interaction tests in larger samples, or by clustering SNPs according to the biological pathways through which they reportedly operate. Researchers should next design this kind of studies to address whether there is some biological basis for fasting glucose impairment or type 2 diabetes risk associated with anti-hypertensive therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

J.B.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Source of Funding

Supported by National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK) R01 DK078616 and K24 DK080140 and 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, itself supported by the National Heart, Lung and Blood Institute's Framingham Heart Study (Contract No. N01-HC-25195) and its contract from Affimetrix, Inc. for genotyping services (Contract No. N02-HL-6-4278). A portion of this research utilized the Linux Cluster for Genetic Analyses (LinGA – II) funded by the Robert Dawson Evans Endowment of the Department of Medicine at Boston University School of Medicine and Boston Medical Center.

Abbreviations definition list

ACE	Angiotensin converting enzyme
ARB	Angiotensin receptor blockers
BMI	Body mass index
CI	Confidence interval
ΔFG	Change in fasting glucose
GEE	Generalized estimating equations
GWAS	Genome-wide association study
NHANES	National Health and Nutrition Examination Survey
OR	Odds ratio
SNP	Single nucleotide polymorphism
TG	Triglycerides

T2D Type-2 diabetes

References

1. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, et al. Executive summary: heart disease and stroke statistics--2010 update: a report from the American Heart Association. *Circulation*. 2010; 121:948–954. Erratum in: *Circulation* 121:e259. [PubMed: 20177011]
2. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *JAMA*. 2003; 289:2560–2572. [PubMed: 12748199]
3. Cowie CC, Rust KF, Ford ES, Eberhardt MS, Byrd-Holt DD, Li C, et al. Full accounting of diabetes and pre-diabetes in the U.S. population in 1988–1994 and 2005–2006. *Diabetes Care*. 2009; 32:287–294. [PubMed: 19017771]
4. Fryar CD, Hirsch R, Eberhardt MS, Yoon SS, Wright JD. Hypertension, high serum total cholesterol, and diabetes: racial and ethnic prevalence differences in U.S. adults, 1999–2006. *NCHS Data Brief*. 2010; 36:1–8. [PubMed: 20423605]
5. Conen D, Ridker PM, Mora S, Buring JE, Glynn RJ. Blood pressure and risk of developing type 2 diabetes mellitus: the Women's Health Study. *Eur Heart J*. 2007; 28:2937–2943. [PubMed: 17925342]
6. Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. *Circulation*. 2005; 112:3066–3072. [PubMed: 16275870]
7. Shapiro AP, Benedek TG, Small JL. Effect of thiazides on carbohydrate metabolism in patients with hypertension. *N Engl J Med*. 1961; 265:1028–1033.
8. Wilson PW, Anderson KM, Kannel WB. Epidemiology of diabetes mellitus in the elderly. The Framingham Study. *Am J Medicine*. 1986; 80:3–9.
9. Samuelsson O, Hedner T, Berglund G, Persson B, Andersson OK, Wilhelmsen L. Diabetes mellitus in treated hypertension: incidence, predictive factors and the impact of non-selective beta-blockers and thiazide diuretics during 15 years treatment of middle-aged hypertensive men in the Primary Prevention Trial Göteborg, Sweden. *J Hum Hypertens*. 1994; 8:257–263. [PubMed: 7912734]
10. Barzilay JI, Davis BR, Cutler JA, Pressel SL, Whelton PK, Basile JB, et al. Fasting glucose levels and incident diabetes mellitus in older nondiabetic adults randomized to receive 3 different classes of antihypertensive treatment: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med*. 2006; 166:2191–2201. [PubMed: 17101936]
11. Taylor EN, Hu FB, Curhan GC. Antihypertensive medications and the risk of incident type 2 diabetes. *Diabetes Care*. 2006; 29:1065–1070. [PubMed: 16644638]
12. Elliot WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet*. 2007; 369:201–207. [PubMed: 17240286]
13. Bangalore S, Parkar S, Grossman E, Messerli FH. A meta-analysis of 94,492 patients with hypertension treated with beta blockers to determine the risk of new-onset diabetes mellitus. *Am J Cardiol*. 2007; 100:1254–1262. [PubMed: 17920367]
14. Gupta AK, Dahlof B, Dobson J, Sever PS, Wedel H, Poulter NR. Anglo-Scandinavian Cardiac Outcomes Trial Investigators. Determinants of new-onset diabetes among 19,257 hypertensive patients randomized in the Anglo-Scandinavian Cardiac Outcomes Trial--Blood Pressure Lowering Arm and the relative influence of antihypertensive medication. *Diabetes Care*. 2008; 31:982–988. [PubMed: 18235048]
15. Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL. for the Atherosclerosis Risk in Communities Study. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. *New Eng J Med*. 2000; 342:905–912. [PubMed: 10738048]

16. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICROHOPE substudy. *Lancet*. 2000; 355:253–259. Erratum in: *Lancet* 356:860. [PubMed: 10675071]
17. Lindholm LH, Ibsen H, Borch-Johnsen K, Olsen MH, Wachtell K, Dahlöf B, et al. Risk of new-onset diabetes in the Losartan Intervention For Endpoint reduction in hypertension study. *J Hypertens*. 2002; 20:1879–1886. [PubMed: 12195132]
18. McMurray JJ, Holman RR, Haffner SM, Bethel MA, Holzhauer B, Hua TA, et al. NAVIGATOR Study Group. Effect of valsartan on the incidence of diabetes and cardiovascular events. *N Engl J Med*. 2010; 362:1477–1490. Erratum in: *N Engl J Med* 362:1748. [PubMed: 20228403]
19. Sherry ST, Ward MH, Kholodov M, Baker J, Phan L, Smigielski EM, Sirotkin K. dbSNP: the NCBI database of genetic variation. *Nucleic Acid Research*. 2001; 29:308–311.
20. Saxena R, Voight BF, Lyssenko V, et al. Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. *Science*. 2007; 316:1331–1336. [PubMed: 17463246]
21. Zeggini E, Weedon MN, Lindgren CM, Frayling TM, Elliott KS, Lango H, et al. Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. *Science*. 2007; 316:1336–1341. Erratum in: *Science* 317:1035–1036. [PubMed: 17463249]
22. Zeggini E, Scott LJ, Saxena R, Voight BF, Marchini JL, Hu T, et al. Metaanalysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. *Nat Genet*. 2008; 40:638–645. [PubMed: 18372903]
23. Dupuis J, Langenberg C, Prokopenko I, Saxena R, Soranzo N, Jackson AU, et al. New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. *Nat Genet*. 2010; 42:105–116. [PubMed: 20081858]
24. Voight BF, Scott LJ, Steinthorsdottir V, Morris AP, Dina C, Welch RP, et al. Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. *Nat Genet*. 2010; 42:579–589. [PubMed: 20581827]
25. Qi L, Cornelis MC, Kraft P, Stanya KJ, Linda Kao WH, Pankow JS, et al. Genetic variants at 2q24 are associated with susceptibility to type 2 diabetes. *Hum Mol Genet*. 2010; 19:2706–2715. [PubMed: 20418489]
26. Kong A, Steinthorsdottir V, Masson G, Thorleifsson G, Sulem P, Besenbacher S, et al. Parental origin of sequence variants associated with complex diseases. *Nature*. 2009; 462:868–874. [PubMed: 20016592]
27. the DIABetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium, Morris AP, Voight BF, Teslovich TM, Ferreira T, Segrè AV, et al. Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. *Nat Genet*. 2012; 44:981–990.
28. Scott RA, Lagou V, Welch RP, Wheeler E, Montasser ME, Luan J, et al. Largescale association analyses identify new loci influencing glycemic traits and provide insight into the underlying biological pathways. *Nat Genet*. 2012; 44:991–1005. [PubMed: 22885924]
29. Renström F, Shungin D, Johansson I, MAGIC Investigators, Florez JC, Hallmans G, et al. Genetic predisposition to long-term nondiabetic deteriorations in glucose homeostasis: Ten-year follow-up of the GLACIER study. *Diabetes*. 2011; 60:345–354. [PubMed: 20870969]
30. Kathiresan S, Melander O, Anevski D, Guiducci C, Burt NP, Roos C, et al. Polymorphisms associated with cholesterol and risk of cardiovascular events. *N Engl J Med*. 2008; 358:1240–1249. [PubMed: 18354102]
31. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families. The Framingham offspring study. *Am J Epidemiol*. 1979; 110:281–290. [PubMed: 474565]
32. Boesgaard TW, Grarup N, Jørgensen T, Borch-Johnsen K, Meta-Analysis of Glucose and Insulin-Related Trait Consortium (MAGIC), Hansen T, Pedersen O. Variants at *DGKB/TMEM195* *ADRA2A* *GLIS3* and *C2CD4B* loci are associated with reduced glucose-stimulated beta-cell function in middle-aged Danish people. *Diabetologia*. 2010; 53:1647–1655. [PubMed: 20419449]

33. Framingham SNP Health Association Resource (SHARe). [accessed 10 May 2010] 2007. http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000007.v9.p4
34. iPLEX Gold Application Guide. [accessed 10 May 2010] 2009. <http://www.sequenom.com/Home/Products---Services/Genetic-Analysis/Applications/SNP-Genotyping-with-iPLEX-Gold>
35. Marchini J, Howie B. Genotype imputation for genome-wide association studies. *Nat Rev Genet*. 2010; 11:499–511. [PubMed: 20517342]
36. Jensen AC, Barker A, Kumari M, Brunner EJ, Kivimäki M, Hingorani AD, et al. Associations of common genetic variants with age-related changes in fasting and postload glucose: evidence from 18 years of follow-up of the Whitehall II cohort. *Diabetes*. 2011; 60:1617–1623. [PubMed: 21441441]
37. Meigs JB, D'Agostino RB Sr, Nathan DM, Rifai N, Wilson PW. Framingham Offspring Study. Longitudinal association of glycemia and microalbuminuria: the Framingham Offspring Study. *Diabetes Care*. 2002; 25:977–983. [PubMed: 12032102]
38. Meigs JB, Cupples LA, Wilson PWF. Parental transmission of type 2 diabetes mellitus: the Framingham Offspring Study. *Diabetes*. 2000; 49:2201–2207. [PubMed: 11118026]
39. D'Agostino RB, Lee ML, Belanger AJ, Cupples LA, Anderson K, Kannel WB. Relation of pooled logistic regression to time dependent Cox regression analysis: the Framingham Heart Study. *Stat Med*. 1990; 9:1501–1515. [PubMed: 2281238]
40. Wilson PW, Meigs JB, Sullivan L, Fox CS, Nathan DM, D'Agostino RB Sr. Prediction of incident diabetes mellitus in middle-aged adults: the Framingham Offspring Study. *Arch Intern Med*. 2007; 167:1068–1074. [PubMed: 17533210]
41. Diggle, PJ.; Liang, KY.; Zeger, SL. Analysis of longitudinal data. New York: Oxford University Press; 1994.
42. Gauderman, WJ.; Morrison, JM. [accessed 10 May 2010] QUANTO 1.1: A computer program for power and sample size calculations for genetic-epidemiology studies. 2006. <http://hydra.usc.edu/gxe>
43. Watanabe RM. Drugs, diabetes and pharmacogenomics: the road to personalized therapy. *Pharmacogenomics*. 2011; 12:699–701. [PubMed: 21619432]
44. Wei GS, Coady SA, Goff DC Jr, Brancati FL, Levy D, Selvin E, et al. Blood pressure and the risk of developing diabetes in African Americans and Whites: ARIC, CARDIA, and the Framingham Heart Study. *Diabetes Care*. 2011; 34:873–879. [PubMed: 21346180]
45. Bozkurt O, de Boer A, Grobbee DE, de Leeuw PW, Kroon AA, Schiffers P, Klungel OH. Variation in renin-angiotensin system and salt-sensitivity genes and the risk of diabetes mellitus associated with the use of thiazide diuretics. *Am J Hypertens*. 2009; 22:545–551. [PubMed: 19247266]
46. Becker ML, Visser LE, Newton-Cheh C, Witteman JC, Hofman A, Uitterlinden AG, Stricker BH. Genetic variation in the *NOS1AP* gene is associated with the incidence of diabetes mellitus in users of calcium channel blockers. *Diabetologia*. 2008; 51:2138–2140. [PubMed: 18766325]
47. Irvin MR, Lynch AI, Kabagambe EK, Tiwari HK, Barzilay JI, Eckfeldt JH, et al. Pharmacogenetic association of hypertension candidate genes with fasting glucose in the GenHAT Study. *J Hypertens*. 2010; 28:2076–2083. [PubMed: 20577119]
48. Holstein A, Hahn M, Körner A, Stumvoll M, Kovacs P. *TCF7L2* and therapeutic response to sulfonylureas in patients with type 2 diabetes. *BMC Med Genet*. 2011; 12:30. [PubMed: 21349175]
49. Bi M, Kao WH, Boerwinkle E, Hoogeveen RC, Rasmussen-Torvik LJ, Astor BC, et al. Association of rs780094 in GCKR with metabolic traits and incident diabetes and cardiovascular disease: the ARIC Study. *PLoS One*. 2010; 5:e11690. [PubMed: 20661421]

Table 1

Base-line characteristics of the Framingham Offspring Study population at each exam after excluding exam 1.

	Exam 2 (1979–1983)	Exam 3 (1983–1987)	Exam 4 (1987–1991)	Exam 5 (1991–1995)	Exam 6 (1995–1998)	Exam 7 (1998–2001)
	Mean or n (SD) ^b or %	Mean or n (SD) or %	Mean or n (SD) or %	Mean or n (SD) or %	Mean or n (SD) or %	Mean or n (SD) or %
Number of subjects (n)	2,622	2,841	2,867	2,681	2,581	2,273
Age, years	43.4 (9.9)	47.6 (9.9)	50.6 (9.8)	54.0 (9.8)	57.9 (9.6)	59.8 (9.1)
Male sex, (%)	1,243 (47.4)	1,353 (47.6)	1,339 (46.7)	1,218 (45.4)	1,167 (45.2)	1,000 (44.0)
Family history of diabetes, (%)	469 (17.9)	508 (17.9)	515 (18.0)	482 (18.0)	468 (18.1)	388 (17.1)
Systolic blood pressure, mmHg	121 (16)	122 (16)	125 (18)	125 (18)	127 (9)	125 (18)
Diastolic blood pressure, mmHg	77 (10)	79 (10)	79 (10)	74 (10)	76 (5)	74 (10)
Blood pressure medication, (%)	232 (8.9)	400 (14.1)	432 (15.1)	428 (16.0)	631 (24.5)	640 (28.2)
Hypertension, (%)	520 (19.8)	775 (27.3)	910 (31.8)	819 (30.6)	973 (37.7)	903 (39.8)
BMI ^a , kg/m ²	25.7 (4.2)	26.0 (4.5)	26.6 (4.8)	27.1 (4.7)	27.5 (4.9)	27.7 (5.0)
Smoking, (%)	955 (36.5)	887 (31.3)	729 (25.5)	509 (19.0)	450 (17.5)	333 (14.9)
HDL cholesterol, mg/dl	49.0 (13.4)	51.9 (14.8)	50.2 (14.7)	51.0 (15.0)	52.2 (16.1)	55.4 (17.0)
Triglycerides, mg/dl	100.5 (83.2)	115.5 (89.7)	117.2 (88.1)	140.7 (105.3)	134.3 (88.6)	128.6 (80.4)
Fasting glucose, mg/dl	95.9 (9.4)	91.1 (9.2)	90.8 (9.1)	94.8 (9.6)	96.7 (9.8)	96.8 (9.6)
Alcohol, ounces/week	3.6 (4.8)	3.3 (4.7)	2.9 (4.2)	2.6 (3.7)	2.4 (3.6)	2.7 (3.7)
Prevalent cardiovascular disease, (%)	74 (2.8)	146 (5.1)	161 (5.6)	177 (6.6)	209 (8.1)	197 (8.7)
Prevalent coronary heart disease, (%)	54 (2.1)	107 (3.8)	117 (4.1)	118 (4.4)	143 (5.5)	132 (5.8)
Prevalent chronic heart failure, (%)	1 (0.0)	4 (0.1)	4 (0.1)	8 (0.3)	15 (0.6)	12 (0.5)
Prevalent intermittent claudication, (%)	16 (0.6)	31 (1.1)	37 (1.3)	50 (1.9)	52 (2.0)	45 (2.0)
Beta-blockers users, (%)	56 (2.1)	190 (6.7)	189 (6.6)	147 (5.5)	214 (8.3)	252 (11.1)
Thiazides users, (%)	170 (6.5)	235 (8.3)	186 (6.5)	73 (2.7)	102 (4.0)	148 (6.5)
Renin-angiotensin system users, (%)	-	8 (0.3)	90 (3.1)	152 (5.7)	246 (9.6)	291 (12.8)
Incident diabetes cases by end of period	32	39	75	91	70	115

^aBMI: body mass index.

^bSD: standard deviation.

Association of hypertension and hypertension treatment with change over time in fasting glucose (Δ FG) and estimated risk of incident diabetes

Table 2

	Age-, sex-adjusted: hypertensive vs. non-hypertensive			Age-, sex-adjusted: treated vs. untreated hypertensive		
	Hypertension status			All hypertensive		
	Yes	No		Treated hypertensive	Untreated hypertensive	
Number of subjects (n) (person-exams)	4,900	10,952		2,763	2,137	
Age, years	Mean (Std. Error) ^a 57.8 (10.0)	Mean (Std. Error) 49.3 (10.7)	p-value <.0001	Mean (Std. Error) 59.5 (9.4)	Mean (Std. Error) 55.7 (10.3)	p-value <.0001
Male sex, %	52.1 (0.5)	43.5 (0.5)	<.0001	50.6 (0.5)	54.1 (0.5)	0.013
Incidence of diabetes model, %	3.6 (1.5)	1.2 (0.5)	<.0001	4.9 (0.7)	3.6 (0.5)	0.023
Number of subjects (n) (person-exams)	4,492	10,181		2,517	1,985	
Fasting glucose, mg/dl	Estimates (Std. Error) 96.5 (0.1)	Estimates (Std. Error) 93.0 (0.1)	p-value <.0001	Estimates (Std. Error) 98.4 (0.2)	Estimates (Std. Error) 96.7 (0.2)	p-value <.0001
Δ FG, mg/dl	2.6 (0.2)	1.7 (0.1)	<.0001	3.4 (0.3)	3.0 (0.3)	<.0001

Fasting glucose and Δ FG are mean values across all exams. Δ FG was additionally adjusted for base-line fasting glucose at the beginning of the corresponding time period. Subjects who started antidiabetic treatment during a given time period were excluded from the fasting glucose analysis, so number of subjects for the fasting glucose analyses was lower than for the type 2 diabetes analyses.

^aStd Error: standard error.

Association of specific antihypertensive drug exposures with change over time in fasting glucose (Δ FG) and estimated risk of incident diabetes.

Table 3

	Age-, sex-, other treatments-adjusted: each medication group compared to reference untreated HTN									
	Untreated HTN ^a			Beta-blockers only			Thiazides only			ACE-I / ARB ^b only
Number of subjects (person-exams)	2,137			676			527			516
Age, years	Mean (Std. Error) ^c			Mean (Std. Error)			Mean (Std. Error)			Mean (Std. Error)
Male sex, %	55.7 (10.3)			60.2 (9.2)		<.0001	55.4 (9.4)		<.0001	60.5 (8.8)
Incidence of diabetes (%)	54.1 (0.5)			59.0 (0.5)		0.0001	42.3 (0.5)		<.0001	56.8 (0.5)
Odds Ratio, reference untreated HTN	4.1			6.6		0.010	5.8		0.205	5.7
Number of subjects (person-exams)	NA			1.6			1.3			1.3
Fasting glucose, mg/dl	Estim. ^d (Std Error)			Estim. (Std Error)			Estim. (Std Error)			Estim. (Std Error)
Δ FG, mg/dl	96.7 (0.2)			98.8 (0.4)		<.0001	98.0 (0.4)		0.008	96.5 (0.5)
	2.8 (0.3)			3.4 (0.5)		0.351	2.0 (0.6)		0.237	4.2 (0.6)
										0.037

p-values and ORs compare each column to the untreated group. Data for “combination” and “others” not included.

^aHTN: Hypertension.

^bACE-I / ARB: Angiotensin converting enzyme inhibitors / angiotensin receptor blockers.

^cStd. Error: Standard Error.

^dEstim.: Estimate

Table 4

Interaction effect by fasting glucose or type 2 diabetes mellitus (type 2 diabetes) genetic scores on hypertension (HTN) or its treatment categories for change over time in fasting glucose (Δ FG, mg/dl) and ~4-year incident type 2 diabetes risk.

	Δ FG		Type 2 diabetes	
	Beta (per mg/dl)	p-value	OR (GEE) ^a	p-value
Interaction_Hypertension $\times$ Genetic score; age-, sex-adjusted model (additional fasting glucose-adjustment for ΔFG only)				
Number of subjects	14,683		15,852 (422 diabetes cases)	
Age, years	0.18	<.0001	1.03	<0.0001
Sex, male	1.60	<.0001	1.34	0.004
Fasting glucose, mg/dl	-0.36	<.0001	NA	NA
Hypertension	1.25	0.35	4.76	0.14
Mean fasting glucose / type 2 diabetes genetic score	0.54	3.2×10^{-11}	1.19	0.0004
HTN $\times$ Mean fasting glucose / type 2 diabetes genetic score	0.10	0.53	0.98	0.70
Interaction_Treatment $\times$ Genetic score; age-, sex-adjusted model (additional fasting glucose-adjustment for ΔFG only)				
	Beta (per mg/dl)	p-value	OR (GEE)	p-value
Number of subjects	4,502		4,900 (272 diabetes cases)	
Age, years	0.09	<.0001	1.01	0.06
Sex, male	0.70	0.07	1.22	0.11
Fasting glucose, mg/dl	-0.22	0.0002	NA	NA
Treated hypertensive	1.69	0.46	1.18	0.90
Mean fasting glucose / type 2 diabetes genetic score	0.52	0.01	1.14	0.038
HTN Treated $\times$ Mean fasting glucose / type 2 diabetes genetic score	-0.11	0.67	1.02	0.83
Interaction_Specific drug category $\times$ Genetic score ; age-, sex-adjusted model (additional fasting glucose-adjustment for ΔFG only)				
	Beta (per mg/dl)	p-value	OR (GEE)	p-value
Number of subjects	4,502		4,900 (272 diabetes cases)	
Age, years	0.08	<.0001	1.01	0.10
Sex, male	0.63	0.10	1.23	0.10
Fasting glucose, mg/dl	-0.22	<.0001	NA	NA
Mean fasting glucose / type 2 diabetes genetic score	0.52	0.004	1.14	0.038
Hypertensive exposed to beta-blockers only ^b	1.01	0.77	2.80	0.58
Beta-blockers $\times$ Mean fasting glucose / type 2 diabetes genetic score	-0.05	0.91	0.97	0.76
Hypertensive exposed to thiazides only ^b	-1.30	0.74	0.26	0.56
Thiazides $\times$ Mean fasting glucose / type 2 diabetes genetic score	0.06	0.90	1.10	0.48
Hypertensive exposed to ACE-I/ARB ^c only ^b	2.39	0.57	2.47	0.69
ACE-I/ARB $\times$ Mean fasting glucose / type 2 diabetes genetic score	-0.11	0.82	0.96	0.77

Subjects who started antidiabetic treatment during a given time period have been excluded from the Δ FG analysis. Betas reflect the mg/dl Δ FG by each unit increase in the covariate.

^aOR: Odds Ratio. GEE: generalized estimating equations.

^bPeople exposed to each specific antihypertensive drug vs. reference untreated hypertensive group. Data for “combination” and “others” not included

^cACE-I: angiotensin converting enzyme inhibitors. ARB: angiotensin receptor blockers