Transcription Factor 7-Like 2 (TCF7L2) Polymorphism and Context-Specific Risk of Type 2 Diabetes in African American and Caucasian Adults

The Atherosclerosis Risk in Communities Study

Yu Yan, Kari E. North, Christie M. Ballantyne, Frederick L. Brancati, Lloyd E. Chambless, Nora Franceschini, Gerardo Heiss, Anna Kottgen, James S. Pankow, Elizabeth Selvin, Suzanne L. West, and Eric Boerwinkle

OBJECTIVE—Although variants in the transcription factor 7-like 2 (TCF7L2) gene are consistently associated with type 2 diabetes, large population-based studies of African Americans are lacking. Moreover, few studies have investigated the effects of TCF7L2 on type 2 diabetes in the context of metabolic risk factors of type 2 diabetes.

RESEARCH DESIGN AND METHODS—we investigated the association between the TCF7L2 rs7903146 polymorphism and type 2 diabetes in 2,727 African American and 9,302 Caucasian participants without diabetes who were induced into the Atherosclerosis Risk in Communities study in 1987–1989 and followed for 9 years.

RESULTS—A total of 485 and 923 cases of type 2 diabetes were identified in African Americans and Caucasians, respectively. Compared with homozygous CC individuals, heterozygous CT and homozygous TT individuals had higher cumulative incidence of type 2 diabetes over 9 years of follow-up: 11.3% (95% CI 10.2–12.4) vs. 21.1% (20.8–21.4) and 27.9% (19.3–36.5) in African Americans, respectively, and 9.7% (8.8–10.6) vs. 11.3% (10.2–12.4) and 13.6% (11.1–16.1), respectively, in Caucasians. Individuals with the risk allele had the highest hazards of diabetes if they were obese and had low HDL cholesterol, followed by individuals with any one and none of the traits.

CONCLUSIONS—Our study provides the first significant evidence of association between the TCF7L2 rs7903146 polymorphism and type 2 diabetes risk in a large African American population and also demonstrates that the diabetes risk conveyed by the rs7903146 risk allele is substantially increased in the context of some metabolic risk factors for type 2 diabetes. Our study findings need to be replicated in other large, population-based studies.

Diabetes 58:285–289, 2009

The transcription factor 7-like 2 (TCF7L2) gene is consistently associated with type 2 diabetes, large population-based studies of African Americans are lacking. Moreover, few studies have investigated the effects of TCF7L2 on type 2 diabetes in the context of metabolic risk factors of type 2 diabetes.

The transcription factor 7-like 2 (TCF7L2) gene, a Wnt signaling-associated transcription factor located on chromosome 10q25, has emerged as a consistently replicated susceptibility gene for type 2 diabetes (3–5). The T-allele at single nucleotide polymorphism (SNP) rs7903146 has been described as either the causal risk variant or the closest correlate to an unidentified functional variant (6), possibly impairing glucagon-like peptide-1–induced insulin secretion (7), but the exact mechanism is still under investigation.

Although the TCF7L2 effect is consistently observed across ethnically diverse populations (3,4), studies conducted in African Americans have been of small sample size and results have been inconsistent (4–6,8,9). Moreover, TCF7L2 gene–environment interaction assessment has been limited. Although previous studies have demonstrated effect modification by BMI (8,10), modifications by other metabolic risk factors have been largely unexplored.

In this study, we investigated whether the rs7903146 SNP of the TCF7L2 gene is associated with type 2 diabetes in a large community-based cohort of African American and Caucasian middle-aged adults participating in the Atherosclerosis Risk in Communities (ARIC) study. A second objective was to evaluate whether the risk of type 2 diabetes was associated with the rs7903146 SNP in the context of metabolic impairments.

RESEARCH DESIGN AND METHODS

Study subjects and phenotype definitions. The ARIC study is an ongoing longitudinal cohort study of cardiovascular and other major diseases among 15,792 men and women aged 45–64 years at baseline (1987–1989) and selected from four U.S. communities: Forsyth County, NC; Jackson, MS; the northwest suburbs of Minneapolis, MN; and Washington County, MD. By design, African Americans were oversampled at the Forsyth County site and exclusively sampled in Jackson and thus constituted 27% of the baseline cohort. The sampling procedures and methods used in ARIC have been described in detail elsewhere (11).

We excluded ARIC participants who were not African American or Caucasian (n = 48), African Americans from Minnesota and Maryland field centers (n = 55), participants with prevalent diabetes (n = 1,863), participants with missing information on incident diabetes (n = 1,026), and participants with missing genotype data or who did not provide consent for the use of DNA (n = 771). After these exclusions, 12,029 baseline examination participants (2,727 African Americans and 9,302 Caucasians) were available for analysis.
Selected characteristics of the ARIC study participants at baseline, presented by race and genotype status

|                | African American | Caucasian |
|----------------|------------------|-----------|
|                | CC               | TT        | P        | CC               | TT        | P        |
| n              | 1,381            | 1,133     | 213      | 4,725           | 3,783     | 794      |
| Age (years)    | 53 ± 5.83        | 53 ± 5.69 | 54 ± 5.83| 0.12            | 54 ± 5.66 | 54 ± 5.69| 54 ± 5.75| 0.25 |
| Sex (male)     | 500 (36.21)      | 447 (39.45)| 81 (38.03)| 0.25            | 2,188 (46.31)| 1,746 (46.15)| 379 (47.73)| 0.71 |
| Family diabetes history | 318 (23.03) | 295 (26.04) | 57 (26.76) | 0.16            | 1,006 (21.29) | 846 (22.36) | 178 (22.42) | 0.45 |
| Predicted diabetes risk| 0.23 ± 0.20 | 0.20 ± 0.19 | 0.25 ± 0.22 | 0.01 | 0.15 ± 0.15 | 0.16 ± 0.16 | 0.17 ± 0.15 | 0.27 |
| Ever smoked    | 715 (51.77)      | 610 (53.89) | 117 (54.93) | 0.47            | 2,793 (59.14) | 2,241 (59.27) | 475 (59.82) | 0.94 |
| Leisure-time physical activity | 2.08 ± 0.58 | 2.12 ± 0.59 | 2.05 ± 0.56 | 0.22 | 2.48 ± 0.53 | 2.48 ± 0.53 | 2.46 ± 0.53 | 0.62 |
| Obese          | 522 (37.80)      | 393 (34.75) | 72 (33.80) | 0.02            | 998 (21.12) | 724 (19.16) | 141 (17.76) | 0.02 |
| BMI (kg/m²)    | 29.34 ± 6.11     | 28.86 ± 5.81 | 28.55 ± 5.28 | 0.05 | 26.73 ± 4.58 | 26.52 ± 4.60 | 26.54 ± 4.58 | 0.09 |
| Waist circumference (cm) | 97.97 ± 15.09 | 96.74 ± 14.38 | 96.25 ± 13.28 | 0.06 | 95.37 ± 12.93 | 94.74 ± 12.66 | 94.96 ± 12.67 | 0.08 |
| Hypertension   | 790 (51.02)      | 572 (50.66) | 103 (48.58) | 0.80            | 1,154 (24.57) | 923 (24.51) | 174 (22.03) | 0.09 |
| SBP (mmHg)     | 131.07 ± 21.93   | 132.19 ± 22.43 | 129.08 ± 22.07 | 0.42 | 119.83 ± 16.48 | 119.97 ± 17.18 | 121.17 ± 16.69 | 0.36 |
| DBP (mmHg)     | 77.43 ± 10.34    | 77.44 ± 11.33 | 76.14 ± 11.05 | 0.53 | 70.97 ± 9.17  | 70.91 ± 9.10  | 71.37 ± 9.30  | 0.67 |
| Glucose (mmol/L) | 5.47 ± 0.56     | 5.46 ± 0.54 | 5.47 ± 0.57 | 0.95 | 5.46 ± 0.49  | 5.48 ± 0.50  | 5.52 ± 0.52  | <0.01 |
| Insulin (µU/mL) | 13.82 ± 10.67    | 12.79 ± 8.78 | 12.62 ± 8.68 | 0.02 | 10.24 ± 7.60 | 9.83 ± 7.27 | 9.88 ± 8.10 | 0.04 |
| HOMA-IR†        | 3.45 ± 2.90      | 3.18 ± 2.37 | 3.15 ± 2.33 | 0.03 | 2.54 ± 2.05 | 2.45 ± 1.97 | 2.47 ± 2.18 | 0.12 |
| Triglycerides (mg/dL) | 104.06 ± 62.50 | 105.63 ± 78.38 | 104.88 ± 58.04 | 0.86 | 130.30 ± 76.91 | 128.73 ± 76.80 | 130.75 ± 83.63 | 0.59 |
| Low HDL         | 400 (29.59)      | 321 (28.92) | 59 (28.37) | 0.90 | 1,799 (38.13) | 1,436 (38.36) | 306 (38.59) | 0.95 |
| LDL (mg/dL)     | 56.51 ± 17.77    | 56.45 ± 17.96 | 56.48 ± 17.23 | 0.74 | 51.41 ± 16.78 | 51.75 ± 16.95 | 51.10 ± 16.50 | 0.49 |
| One metabolic risk factor‡ | 526 (38.56) | 436 (39.03) | 83 (39.71) | 0.93 | 1,719 (36.43) | 1,300 (34.42) | 295 (37.20) | 0.10 |
| Two metabolic risk factors‡ | 198 (14.52) | 139 (12.44) | 24 (11.48) | 0.24 | 539 (11.42) | 430 (11.38) | 76 (9.58) | 0.30 |

Data are means ± SE or n (%) unless otherwise indicated. †Probability of developing diabetes over the 9-year follow-up period was predicted by a model including age at baseline, race, parental history of diabetes, fasting glucose, systolic blood pressure, waist circumference, height, HDL cholesterol, and triglycerides (ref. 22). ‡Calculated as fasting serum insulin (µU/mL) × fasting plasma glucose (mmol/L)/22.5 (ref. 21). ‡Metabolic risk factors refer to obesity or low HDL cholesterol. DBP, diastolic blood pressure; IFG, impaired fasting glucose; SBP, systolic blood pressure.

The institutional review boards at all participating institutions approved the procedures, and all participants included in the analysis gave informed consent.

Individuals were classified as diabetic if any of the following conditions were met: fasting serum glucose levels ≥7.0 mmol/L (126 mg/dL), nonfasting glucose levels ≥11.1 mmol/L (200 mg/dL), current use of hypoglycemic medications (e.g., insulin or sulfonylureas), or a self-reported physician diagnosis of diabetes (12). Individuals without diabetes at baseline who subsequently met any of these criteria at visit two, three, or four were considered to have incident type 2 diabetes.

A positive family history of diabetes was defined by participant report of diabetes in either biological parent. Self-reported cigarette smoking was defined as ever smoking versus never smoking, and the information was obtained by a personal interview. BMI was calculated as kilograms divided by the square of height in meters. Individuals with a BMI ≥30 kg/m² were classified as obese (13). Elevated waist circumference was defined as waist circumference ≥102 cm in men or ≥88 cm in women (14). Blood pressure at baseline was measured three times using a random zero sphygmomanometer, and the average of the last two measurements was used for this analysis. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or antihypertensive medication use (15). Plasma total cholesterol levels, HDL cholesterol, and triglyceride levels were measured by enzymatic methods, and LDL cholesterol was calculated (16). Low HDL was defined as <40 mg/dL in men and <50 mg/dL in women. High LDL was defined as ≥160 mg/dL, and high triglyceride levels were defined as >200 mg/dL (17). Insulin was measured by radioimmunoassay (18). Insulin Rf, Cambridge Medical Diagnostics, Billerica, MA. Physical activity was quantified using a slightly modified version of the Baecke physical activity questionnaire (19) that classified work, sport, and leisure activities into categories ranging from one (low) to five (high). Impaired fasting glucose was defined by a fasting glucose level between 100 and 125 mg/dL (18). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following formula: fasting serum insulin (µU/mL) × fasting plasma glucose (mmol/L)/22.5 (ref. 21). Metabolic risk factors refer to obesity or low HDL cholesterol. DBP, diastolic blood pressure; IFG, impaired fasting glucose; SBP, systolic blood pressure.
The Genotypic distributions were in agreement with Hardy-Weinberg equilibrium in African Americans and Caucasians. *Adjusted for age at baseline, study center, and sex. †P value for HR from additive models.

Variables taking on the values zero for genotype CC, one for genotype CT, and two for genotype TT were used to test for additive genetic effects. The assessment of departure from additivity in gene-environment interaction analyses has been argued to be more indicative of the underlying biologically causal mechanisms than the assessment of multiplicative interaction (23). Among the three measures of additivity (the interaction contrast ratio [ICR], proportion of disease attributable to interaction, and synergy index), ICR performs best when using a proportional hazards model (24).

Variables were considered as potential effect-measure modifiers if either of the following criteria were met: departures from additivity of effect as assessed by the ICR (23) or an indication of context-specific effects in the previous TCF7L2 literature. ICRs were quantified as follows: ICR = HR_AB − HR_A − HR_B + 1, where HR_AB represents the joint effect of metabolic exposure and the SNP and HR_A and HR_B represent the main effects of metabolic exposure and the SNP, respectively (23). Thus, ICR refers to the value for ICR.

GCs were wide (Table 3; online appendix Table 1, available at http://dx.doi.org/10.2337/db08-0569). Individuals with one or two T-alleles had the highest HRs of developing type 2 diabetes if they were obese and had low HDL, followed by individuals with any one of these two risk factors and lowest among CC individuals in both races (Table 2). As previously documented, the risk of type 2 diabetes was higher in African Americans than in Caucasians with the same genotype.

We identified obesity and low HDL as important effect-measure modifiers, although 95% CIs of some individual ICRs were wide (Table 3; online appendix Table 1, available at http://dx.doi.org/10.2337/db08-0569). Individuals with one or two T-alleles had the highest HRs of developing type 2 diabetes if they were obese and had low HDL, followed by individuals with any one of these two risk factors and lowest among those with none of the traits (Table 4). Homozygous individuals (TT) with two metabolic risk factors had the highest HR of type 2 diabetes compared with CC individuals with similar frequency in African American and Caucasian individuals but was more common among incident type 2 diabetes cases than noncases in both races (Table 2). The risk of type 2 diabetes was highest among TT individuals, followed by CT individuals, and lowest among CC individuals in both races (Table 2). As previously documented, the risk of type 2 diabetes was higher in African Americans than in Caucasians with the same genotype.

We identified obesity and low HDL as important effect-measure modifiers, although 95% CIs of some individual ICRs were wide (Table 3; online appendix Table 1, available at http://dx.doi.org/10.2337/db08-0569). Individuals with one or two T-alleles had the highest HRs of developing type 2 diabetes if they were obese and had low HDL, followed by individuals with any one of these two risk factors and lowest among those with none of the traits (Table 4). Homozygous individuals (TT) with two metabolic risk factors had the highest HR of type 2 diabetes (6.04 [95% CI 3.70–9.87] in African Americans and 9.35 [6.72–13.00] in Caucasians) compared with CC individuals with none of these two. A similar trend was observed for risk differences and risks of type 2 diabetes (online type status in Table 1. A total of 485 (17.8%) and 923 (9.9%) incident type 2 diabetes cases were identified among African American and Caucasian ARIC participants, respectively (Table 2). The rs7903146 T-allele was observed with similar frequency in African American and Caucasian individuals but was more common among incident type 2 diabetes cases than noncases in both races (Table 2). The risk of type 2 diabetes was highest among TT individuals, followed by CT individuals, and lowest among CC individuals in both races (Table 2). As previously documented, the risk of type 2 diabetes was higher in African Americans than in Caucasians with the same genotype.
appendix Fig. 1; online appendix Table 2). When each effect measure modifier was studied separately, a larger ICR for obesity ($P = 0.02$) in Caucasians and a larger ICR for low HDL cholesterol ($P = 0.004$) in African Americans were observed (Table 3), but testing by bootstrapping (25) did not support significant racial differences (online appendix A).

**DISCUSSION**

**TCF7L2** has been implicated as an important type 2 diabetes susceptibility gene in different populations. Our study replicates the association between the T-allele at rs7903146 and type 2 diabetes risk in Caucasians and provides the first significant evidence of association in a large population-based study of an African American population (4–6,8,). The rs7903146 polymorphism was significantly associated with type 2 diabetes risk in two other African-ancestry studies (4,6), but none of these two studies were population based. Our study also contributes new evidence for additive interaction between **TCF7L2** variants and obesity ($P = 0.02$) in Caucasians and HDL cholesterol ($P = 0.004$) in African Americans (Table 3). Indeed, we demonstrate that the risk of developing type 2 diabetes associated with this **TCF7L2** variant is substantially increased in the context of some of these well-known metabolic risk factors for type 2 diabetes.

When studied separately, the most prominent additive interaction with genotype, indicated by larger ICRs, was for low HDL in African Americans and obesity in Caucasians (Table 3). To our knowledge, no interaction has been reported between low HDL and rs7903146. A multiplicative interaction with obesity and high BMI was observed in two previous studies (8,10). Both studies found that the risk of type 2 diabetes increased in lean individuals, whereas no significant association was noted in obese or overweight individuals, suggesting that the SNP rs7903146 is a much more influential risk factor for lean individuals than for obese individuals. However, in our study the effect in obese Caucasians appears slightly stronger than the effect in lean Caucasians (HR for CT vs. CC 1.25 [1.08–1.45] in obese individuals and 1.20 [1.05–1.36] in nonobese individuals), which is discrepant from the findings of previous studies. The differences in study populations (Caucasian vs. Japanese and men/women vs. men only), analysis methods (additive vs. multiplicative interactions), study designs (cohort vs. case/control and different inclusion/exclusion criteria) may explain these study discrepancies. Moreover, the mechanism of action of **TCF7L2** variants in the context of obesity or other metabolic impairments needs to be studied further.

The majority of current literature suggests that **TCF7L2** is associated with impaired insulin secretion but not with increased insulin resistance (5,26,27). We found a slightly lower fasting insulin and HOMA-IR concentration among individuals with the T-(risk) allele, suggestive of impaired insulin secretion. A possible explanation of our study findings is that **TCF7L2** may impair β-cell function, which, when combined with insulin resistance caused by other factors, provides a double hit that disproportionately increases the risk for type 2 diabetes. Our study demonstrates that the risk of type 2 diabetes was substantially increased among rs7903146 T-allele carriers with obesity and low HDL cholesterol in comparison with those CC individuals with HDL in the normal range who were lean (online appendix Table 2). There is strong evidence that abnormal metabolic traits including obesity and dyslipidemia aggregate in type 2 diabetic patients and their relatives (28,29). Genetic factors interacting with shared and unique environmental factors may cause this aggregation of metabolic traits (28). Although our study has implicated, for the first time, interesting relationships between these metabolic risk factors, the **TCF7L2** variants, and type 2 diabetes, the mechanism of action of **TCF7L2** variants on type 2 diabetes remains to be determined.

In conclusion, our study provides important new evidence for an association between **TCF7L2** and type 2 diabetes in a large African American population. We also provide estimates of the predicted cumulative incidence of type 2 diabetes over 9 years of follow-up associated with this genetic variant in the context of metabolic impairments that usually precede and coexist with type 2 diabetes. Our study findings need to be replicated in other population-based studies, and further study is needed on the mechanisms by which the **TCF7L2** gene acts in the context of metabolic traits in the pathogenesis of type 2 diabetes.

**ACKNOWLEDGMENTS**

The Atherosclerosis Risk in Communities study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022. E.S. was supported by the National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases Grant K01 DK076595. A.K. was supported by a fellowship from the German Research Foundation, Bonn, Germany.

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

Parts of this study have previously been published in abstract form: *Circulation* 117:e253, 2008.

We are indebted to the staff and participants in the Atherosclerosis Risk in Communities study for their important contributions.

**REFERENCES**

1. Chiasson JL, Rabasa-Lhoret R: Prevention of type 2 diabetes: insulin resistance and beta-cell function. *Diabetes* 53(Suppl. 3):S34–S38, 2004
2. Gerich JE: The genetic basis of type 2 diabetes mellitus: impaired insulin secretion versus impaired insulin sensitivity. *Endocr Rev* 10:491–503, 1989

3. Grant SF, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, Sainz J, Helgason A, Stefansson H, Emilsson V, Helgadottir A, Styrkarsdottir U, Magnusson KP, Walters GB, Palsdottir E, Jonsdottir T, Gundmundsdottir T, Gylfason A, Saemundsdottir J, Wilensky RL, Reilly MP, Rader DJ, Bagger Y, Christiansen C, Gudnason V, Sigurdsson G, Thorsteinsdottir U, Gulcher JR, Kong A, Stefansson K: Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. *Nat Genet* 38:329–333, 2006

4. Cauchi S, El Achhab Y, Choquet H, Dina C, Kremer F, Weigtasser R, Nejjar C, Patsch W, Chikri M, Meyre D, Froguel P: TCF7L2 is reproducibly associated with type 2 diabetes in various ethnic groups: a global meta-analysis. *J Mol Med* 2007

5. Florez JC, Jablonski KA, Bayley N, Pollin TI, de Bakker PI, Shuldiner AR, Knowler WC, Nathan DM, Altshuler D: TCF7L2 polymorphisms and progression to diabetes in the Diabetes Prevention Program. *N Engl J Med* 355:241–250, 2006

6. Helgason A, Palsson S, Thorleifsson G, Grant SFA, Emilsson V, Gunnarsdottir S, Adeyemo A, Chen Y, Chen G, Reynisdottir I, Benediktsson R, Hinney A, Hansen T, Andersen G, Borch-Johnsen K, Jorgensen T, Schafer H, Faruque M, Dommatey A, Zhou J, Wilensky RL, Reilly MP, Rader DJ, Bagger Y, Christiansen C, Sigurdsson G, Hebebrand J, Pedersen O, Thorsteinsdottir U, Gulcher JR, Kong A, Rotimi C, Stefansson K: Refining the impact of TCF7L2 gene variants on type 2 diabetes and adaptive evolution. *Nat Genet* 39:218–225, 2007

7. Cauchi S, Froguel P: TCF7L2 genetic defect and type 2 diabetes. *Curr Diab Rep* 8:149–155, 2008

8. Humphries SE, Gable D, Cooper JA, Ireland H, Stephens JW, Hurel SJ, Li KW, Palmen J, Miller MA, Cappuccio FP, Elkeles R, Goddard I, Miller GJ, Talmud PJ: Common variants in the TCF7L2 gene and predisposition to type 2 diabetes in UK European Whites, Indian Asians and Afro-Caribbean men and women. *J Mol Med* 84:1–10, 2006

9. Elbein SC, Chu WS, Das SK, Yao-Borengasser A, Hasstedt SJ, Wang H, Rasouli N, Kern PA: Transcription factor 7-like 2 polymorphisms and type 2 diabetes, glucose homeostasis traits and gene expression in US participants of European and African descent. *Diabetologia* 2007

10. Horikoshi M, Hara K, Ito C, Nagai R, Froguel P, Kadowaki T: A genetic variation of the transcription factor 7-like 2 gene is associated with risk of type 2 diabetes in the Japanese population. *Diabetologia* 50:747–751, 2007

11. The ARIC investigators: The Atherosclerosis Risk in Communities (ARIC) study: design and objectives. *Am J Epidemiol* 129:687–702, 1989

12. American Diabetes Association: Diagnosis and classification of diabetes mellitus (Position Statement). *Diabetes Care* 30 (Suppl. 1):S82–S87, 2007

13. U.S. Department of Health and Human Services: The Practical Guide—Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. Bethesda, MD, National Institutes of Health (NIH publ. no. 00-0484)

14. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Kraus RM, Savage PJ, Smith SC Jr, Spretus JA, Costa F: Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement: executive summary. *Cardiol Rev* 13:322–327, 2005

15. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ, the National High Blood Pressure Education Program Coordinating Committee: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 42:1206–1252, 2003

16. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 18:499–502, 1972

17. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285:2486–2497, 2001

18. Baecke JA, Burema J, Frijters JE: A short questionnaire for the measurement of habitual physical activity in epidemiological studies. *Am J Clin Nutr* 36:936–942, 1982

19. American Diabetes Association: diagnosis and classification of diabetes mellitus (Position Statement). *Diabetes Care* 28 (Suppl. 1):S37–S42, 2005

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

21. Schmidt MI, Duncan BB, Bang H, Pankow JS, Ballantyne CM, Golden SH, Folsom AR, Chambless LE: Identifying individuals at high risk for diabetes: the Atherosclerosis Risk in Communities study. *Diabetes Care* 28:2013–2018, 2005

22. Pencina MJ, Larson MG, D’Agostino RB: Choice of time scale and its effect on significance of predictors in longitudinal studies. *Stat Med* 26:1343–1359, 2007

23. Rothman KJ, Greenland S: *Modern Epidemiology*. Philadelphia, Lippincott-Raven, 1998

24. Li R, Chambless L: Test for additive interaction in proportional hazards models. *Ann Epidemiol* 17:227–236, 2007

25. Carpenter J, Bithell J: Bootstrap confidence intervals: when, which, what? A practical guide for medical statisticians. *Stat Med* 19:1141–1164, 2000

26. Lyssenko V, Lupi R, Marchetti P, Del Guerra S, Orho-Melander M, Almgren P, Sjogren M, Ling C, Eriksson KF, Lethagen AL, Mancarella R, Berglund G, Tuomilehto J, Nilsson P, Del Prato S, Groop L: Mechanisms by which common variants in the TCF7L2 gene increase risk of type 2 diabetes. *J Clin Invest* 117:2155–2163, 2007

27. Loos RJ, Frankis PW, Francis RW, Barroso I, Gribble FM, Savage DB, Ong KK, O’Rahilly S, Wareham NJ: TCF7L2 polymorphisms modulate proinsulin levels and β-cell function in a British Europid population. *Diabetes* 56:1041–1047, 2007

28. Li JK, Peng Y, Chambless LE: Asian populations. *Ann Epidemiol* 19:1141–1164, 2000