Cardiovascular Disease Risk Factors Predict the Development of Type 2 Diabetes

The Insulin Resistance Atherosclerosis Study

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OBJECTIVE — In a few previous studies, cardiovascular disease (CVD) risk factors (RFs) have been shown to predict diabetes. Our objective was to determine whether the presence of CVD RFs predict the eventual development of diabetes after controlling for known RFs, such as directly measured insulin resistance and obesity.

RESEARCH DESIGN AND METHODS — We studied 872 participants with normal or impaired glucose tolerance (IGT) who were enrolled at baseline in the Insulin Resistance Atherosclerosis Study (IRAS). Of these, 143 (16%) developed type 2 diabetes in 5 years. Using these participants, a series of logistic regression models were fit to address the question.

RESULTS — Significant RFs for developing type 2 diabetes included high plasminogen activator inhibitor-1, hypertension, high triglycerides, low levels of HDL cholesterol, and IGT. The 5-year cumulative incidence of type 2 diabetes by the number of RFs (0–5) was as follows: no RFs, 11 of 230 = 5%; one RF, 31 of 278 = 11%; two RFs, 36 of 202 = 18%; three RFs, 41 of 110 = 37%; four RFs, 19 of 42 = 45%; and five RFs, 5 of 10 = 50% ($P < 0.001$). The odds ratio (OR) for conversion to type 2 diabetes for each additional RF was 2.1 (95% CI 1.78–2.46) after adjusting for age, sex, ethnicity, and center. After further adjustment for insulin resistance, determined by the frequently sampled intravenous glucose tolerance test and waist circumference, each additional CVD RF increased the risk of type 2 diabetes significantly (OR 1.81, 95% CI 1.49–2.20).

CONCLUSIONS — Individuals with multiple CVD RFs are at increased risk of type 2 diabetes, which is only partially mediated by insulin resistance or central adiposity. This information should be useful for identifying high-risk patients for developing diabetes through RF assessments.

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The prevalence and incidence of type 2 diabetes is increasing in the U.S. (1). Although the major predictors of type 2 diabetes appear to include glucose levels, obesity (particularly central obesity), insulin resistance, and β-cell dysfunction (2,3), other risk factors (RFs) have also been identified. A number of studies (4–6) have indicated the presence of increased cardiovascular RFs before the onset of diabetes. In 1990, Haffner et al. (5) reported that cardiovascular RFs precede diabetes incidence by as much as 8 years. Similar results have been reported by Feskens et al. (4) in a 25-year follow-up of the Zutphen cohort. It is possible that hyperlipidemia and hypertension, in addition to obesity and cigarette smoking, may not only lead to increased risk of cardiovascular disease (CVD), but also to increased risk of type 2 diabetes. Consequently, the primary prevention of CVD through RF reduction may also be an approach to the primary prevention of type 2 diabetes. Institution of intensive primary prevention of CVD should be considered in the pre-diabetic state. Thus, the presence of CVD RFs in combination with insulin resistance, impaired glucose tolerance (IGT), or impaired fasting glucose is likely a marker for greatly increased risk of the onset of type 2 diabetes relative to those with IGT in the absence of CVD RFs.

Several controlled trials (7–10) have suggested that prevention of type 2 diabetes is possible with intensive lifestyle modifications. In addition, several studies are nearing completion (or recently complete) in which pharmacological interventions to reduce diabetes have been examined (i.e., the Study to Prevent [STOP]-NIDDM Trial [acarbose] and the Diabetes Prevention Program [metformin] [10]). One of the difficulties in developing pharmacological interventions is identifying an at-risk population at which to target the intervention. The risk of conversion to type 2 diabetes

among subjects with IGT is ~30% over 5–6 years (11). In order to justify the primary prevention of type 2 diabetes, particularly with pharmacologic agents, it may be necessary to identify very-high-risk individuals who are likely to have an incidence of diabetes >30%, as is seen in the general population of IGT subjects. Although it is theoretically possible to identify people with high degrees of insulin resistance or secretion defects who have a high probability of diabetes in the near term, such tests are not feasible in routine clinical practice. Unfortunately, direct measurements of insulin resistance in the clinical setting are not practical. An alternate approach might be to determine CVD RFs because they are increased before the onset of diabetes (4,5,12). In addition, evidence is accumulating that reduction of such RFs may reduce the incidence of diabetes (Heart Outcomes Prevention Evaluation [HOPE] [13], Captopril Prevention Project [14], and West of Scotland Coronary Prevention Study [15]). Such an approach raises several questions: does this association between CVD RFs and incidence of diabetes occur in middle-aged subjects, as well as in older ones (12); is the relationship independent of glucose levels and central obesity; and is it explained by increased insulin resistance? These questions form the focus of this report.

The Insulin Resistance Atherosclerosis Study (IRAS) is well suited to study these questions. Nondiabetic participants were known to be free of diabetes at baseline by standardized oral glucose tolerance test (OGTT) evaluation, and an extensive cardiovascular risk profile was assessed, along with detailed measures of adiposity and insulin resistance (16). A 5-year follow-up examination with a repeat OGTT identified new-onset diabetes and allowed us to test the hypothesis that CVD RFs predicted the new onset of diabetes, independent of central obesity and insulin resistance.

RESEARCH DESIGN AND METHODS

A total of 1,624 individuals participated in the baseline IRAS visit during 1992–1994 (16). Participants were chosen to provide representation across glucose tolerance categories, ethnicity, and sex and were recruited at four clinical centers: San Antonio, Texas, San Luis Valley, Colorado, Oakland, California, and Los Angeles, California. The final study sample included 612 non-Hispanic whites, 548 Hispanics, and 464 African Americans, of whom 56% were women. There were 718 individuals (44%) with normal glucose tolerance (NGT), 537 with type 2 diabetes (33%), and 369 with IGT (23%). A follow-up visit occurred during 1997–1999, and 1,313 participants (81%) returned (the return rate was slightly higher [83%] for the NGT/IGT participants, who are the focus of this report). This report includes the 872 subjects with NGT or IGT at baseline, who had the RFs HDL, triglycerides (TGs), plasminogen activator inhibitor (PAI)-1, and hypertension measured at baseline, and who returned for the follow-up examination.

Each IRAS examination (IRAS-1 and IRAS-2) required two visits conducted ~1 week apart (range 2–28 days), each lasting ~4 h. Participants were asked to fast for 12 h before each visit, to abstain from heavy exercise and alcohol for 24 h, and to refrain from smoking the morning of the examination. Glucose tolerance status was determined during the first visit of the clinical examination using a 75-g OGTT (Orangedex; Custom Laboratories, Baltimore, MD) and classified using 1985 World Health Organization criteria (17). Individuals who were clinically diagnosed with diabetes and taking any hypoglycemic medication or who met World Health Organization criteria for diabetes on their follow-up OGTT were considered to have incident diabetes. Resting blood pressure was measured in the right arm after 5 min in the seated position. A standard mercury sphygmomanometer was used, and three readings were taken according to a standard protocol. The second and third readings were averaged to obtain the blood pressure used in the analyses. Race and ethnicity were assessed by self-report.

Height, weight, and girths were measured following a standardized protocol (18). Minimum waist circumference (WST) was used as a measure of body fat distribution in these analyses.

Insulin sensitivity was assessed at baseline by the frequently sampled intravenous glucose tolerance test (19,20) with minimal model analysis (21). Two modifications of the original protocol were used. An injection of insulin, rather than tolbutamide, was used to ensure adequate plasma insulin levels for the computation of insulin sensitivity across a broad range of glucose tolerance (22). A reduced sampling protocol that requires 12 rather than 30 plasma samples and shows similar results to the full protocol (23) was utilized because of the large number of subjects. Glucose in the form of a 50% solution was injected intravenously (0.3 g/kg) at time zero, followed by regular human insulin (0.03 units/kg) at 20 min. This modified version of the frequently sampled intravenous glucose tolerance test protocol used in the IRAS study has been validated with the hyperinsulinemic-euglycemic clamp (24).

Biochemical analysis
Plasma glucose was measured on an automated autoanalyzer (Yellow Springs Instruments, Yellow Springs, OH). Plasma insulin levels were measured with radioimmunoassay (25). Total cholesterol, LDL cholesterol, and HDL cholesterol were measured in plasma by the β-quantification procedure as described by the Lipid Research Clinics. TGs were measured by enzymatic methods with the use of glycerol blanked assays on a Hitachi autoanalyzer. The externally measured coefficient of variation was 4% for LDL cholesterol, HDL cholesterol, and TGs.

PAI-1 was measured in citrated plasma by using a two-site immunoassay that is sensitive to free PAI-1 but not to PAI-1 complexed with tissue plasminogen activator (26). The sample was centrifuged for a minimum of 30,000g min to ensure that there was no contamination from platelet PAI-1; the coefficient of variation was 14%.

Statistical methods
Each of the five CVD RFs of interest was transformed into binary indicator variables identifying the presence or absence of the RF. The following cut points were used: high PAI-1 if PAI-1 was >28 ng/ml (75th percentile among nondiabetic IRAS participants); low HDL if HDL cholesterol was <40 mg/dl for men or <50 mg/dl for women (from National Cholesterol Evaluation Program Adult Treatment Panel III [ATP-III] guidelines); high TGs if TGs were >150 mg/dl (from ATP-III guidelines); hypertension if blood pressure was >140/90 mmHg or if currently on antihypertensive medication; and IGT for participants with fasting glucose <140 mg/dl and 2-h glucose between 140 and 200 mg/dl.

Descriptive statistics (means and SEs

Table 1—*Baseline characteristics of the study population by conversion group*

Characteristic	Nonconverters	Converters	P*
n	729	143	—
Age (years)	54.4 ± 0.32	56.1 ± 0.65	0.02
Sex (% women)	409 (56)	87 (61)	0.30
Ethnicity			
Non-Hispanic white	297 (41)	55 (38)	—
African American	187 (26)	37 (26)	0.85
Hispanic	245 (34)	51 (36)	—
WST (cm)	89.3 ± 0.46	95.8 ± 1.01	<0.001
TG (mg/dl)	130 ± 3.2	155 ± 7.2	0.001
HDL cholesterol (mg/dl)	47.6 ± 0.56	42.7 ± 1.2	0.0003
Systolic blood pressure (mmHg)	121.0 ± 0.61	126.2 ± 1.6	0.003
Diastolic blood pressure (mmHg)	77.6 ± 0.34	78.4 ± 0.81	0.30
PAI-1 (ng/ml)	20.7 ± 0.78	30.0 ± 1.83	<0.001
S_i ($\times 10^{-4} \cdot min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$)	2.35 ± 0.07	1.27 ± 0.14	<0.001
High TGs	201 (27)	60 (42)	<0.001
Low HDL cholesterol	382 (52)	96 (67)	0.0012
Hypertension	209 (29)	63 (44)	<0.001
High PAI-I	153 (21)	57 (40)	<0.001
IGT	195 (27)	97 (68)	<0.001

Data are means ±SE or n (%). *P values for t test or χ^2 test.

or frequencies and percentages) were calculated for participants by whether they developed type 2 diabetes between the IRAS-1 and IRAS-2 visits. Logistic regression models were fit to estimate the association between the binary outcome (developed diabetes by IRAS-2: yes or no) and the five independent potential risk variables. In these five models, we adjusted for baseline demographic characteristics: age, sex, ethnicity, and clinic. Next, we constructed an ordinal variable that took values from 0 to 5, representing the number of CVD RFs present for each participant. We fit three logistic models using this independent variable. The first examined the relationship between the number of CVD RFs and diabetes incidence, adjusting for demographic characteristics; the second adjusted for demographics plus WST; and the third adjusted for demographics plus WST and insulin sensitivity (S_i). The models were fit using PROC LOGISTIC in SAS (version 6.09).

Models were refit stratified by glucose tolerance status or ethnic group (African American, Hispanic, or non-Hispanic white).

RESULTS — Table 1 compares participants who developed diabetes and those who did not. Those who developed diabetes were older, had larger WST, were more dyslipidemic (lower HDL and higher TGs), had higher levels of PAI-I, had higher systolic blood pressure, and were more insulin resistant. Based on the ATP-III cut points for high TGs, 42% of the participants who developed diabetes had high TG levels compared with 27.5% of the participants who remained nondiabetic. Likewise, 40% of participants who developed diabetes had elevated PAI-1 levels compared with 21% who remained nondiabetic. In addition, 69% of the participants who developed diabetes had IGT compared with only 26% of the participants who remained nondiabetic. Similar but slightly less pronounced differences existed for the other cardiovascular RFs (hypertension and low HDL levels).

Among the 872 participants who had NGT (n = 580) or IGT (n = 292) at baseline, 143 (16%) developed type 2 diabetes after 5 years. Of the participants who had NGT at baseline, 46 of 580 (8%) developed type 2 diabetes, whereas 97 of 292 (33%) of individuals with IGT developed type 2 diabetes during the same time period.

Figure 1 displays the 5-year conversion rates by the presence/absence of individual baseline CVD RFs. For each RF, there is nearly doubling of risk for conversion to diabetes when comparing those with and without the RF. Not surprisingly, the strongest RF is IGT, followed by the presence of high PAI-1. Figure 2 displays the relationship between the number of RFs and the proportion of participants who developed diabetes using the unadjusted data overall and then stratified by baseline NGT/IGT status (one of the original five CVD RFs). The unstratified panel (Fig. 2A) suggests a linear increase in the probability of developing diabetes with the addition of each RF, with the largest increase occurring be-
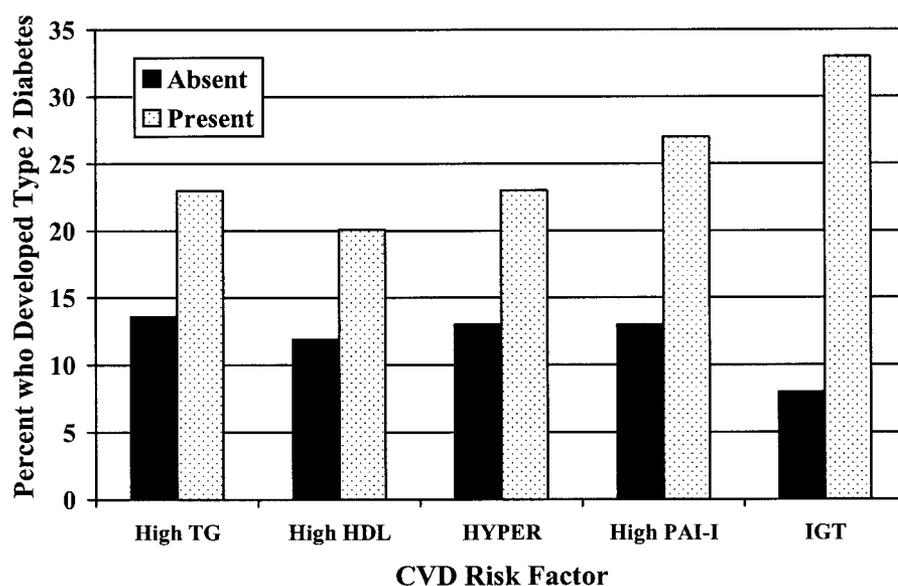

Figure 1—*Five-year conversion rates for developing diabetes by the presence or absence of individual baseline CVD RFs. HYPER, hypertension.*
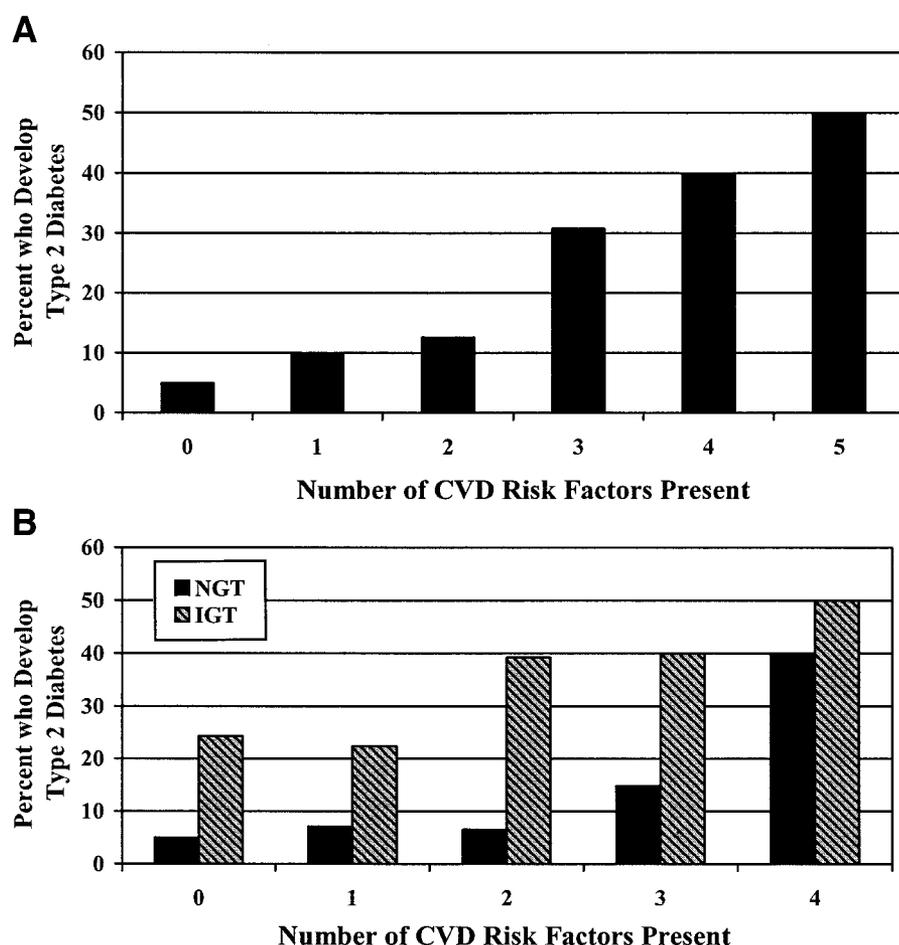
A

B

Figure 2—*Five-year conversion rates for developing diabetes by the number of RFs present at baseline. A: Overall. B: Baseline glucose tolerance status.*

tween two and three RFs. The percentage of participants who developed diabetes rose from 5 to 50% as increasing numbers of RFs became present. The stratified panel (Fig. 2*B*) examined the relationship between the remaining four RFs and the percentage of participants who developed diabetes. The percentage of people with baseline NGT who developed diabetes is nearly the same for those with zero to two RFs (5, 7, and 7%, respectively), but is much higher for those with three (15%) or four (40%) RFs present. The pattern of relationship for participants with IGT is slightly different. Here, 24 and 22% of participants developed diabetes if they had zero or one RF present, respectively. When there were two, three, or four additional RFs present, 39, 40, and 50% of IGT participants developed diabetes, respectively.

We then fit five logistic models, considering each CVD RF indicator separately while adjusting for demographic

characteristics. We found significant ($P <$ 0.001) odds ratios (ORs) for conversion to diabetes for all five RFs considered separately. For hypertension, the OR was 1.9 (95% CI 1.28–2.80); for high TGs, 1.9 (1.32–2.85); for low HDL, 2.1 (1.42–3.14); for high PAI-1, 2.8 (1.86–4.19); and for IGT, 5.7 (3.83–8.47).

Logistic regression models were developed with the number of RFs as the independent variable predicting diabetes

incidence (Tables 2 and 3). For each additional RF that was present, the OR for conversion to diabetes was 2.0 (95% CI 1.70–2.33) in the demographically adjusted model. In the full model, adjusting for demographics plus WST and S_i, the OR remained elevated and was highly significant (1.72, 1.42–2.09). The OR for WST was not statistically significant in this model; however, the OR for S_i was significant (0.745, 0.61–0.91).

There were no significant interactions between ethnic group and the number of RFs or baseline NGT/IGT status and the number of RFs ($P > 0.15$ for each test). We estimated the ORs stratified by these two variables to examine whether there appeared to be any clinically meaningful differences among these groups. Tables 2 and 3 also show the ORs (with CIs) for developing diabetes for each additional RF present stratified by NGT/IGT status and by ethnic group, respectively. In the models stratified by baseline NGT/IGT status, there were significantly elevated ORs for all four models, with ORs being slightly higher for subjects with NGT (ranging from the highest ORs [1.64] for the demographically adjusted model [$P = 0.001$] to the lowest ORs [1.44, $P = 0.02$] in the fully adjusted model) than for subjects with IGT (highest OR [1.45, $P = 0.004$] in the demographically adjusted model to the lowest OR [1.38, $P = 0.03$] in the fully adjusted model).

There were significant effects for all three ethnic groups for all models fit. In the demographic model, the ORs were 1.6 (95% CI 1.28–2.08) for Hispanics, 2.2 (1.56–2.96) for African Americans, and 2.4 (2.01–3.60) for non-Hispanic whites. When we further adjusted for WST and S_i, the ORs became 1.6 (1.2–2.1) for Hispanics, 2.3 (1.5–3.6) for African Americans, and 1.8 (1.2–2.5) for non-Hispanic whites.

Table 2—*ORs and (CIs) for conversion to type 2 diabetes for the number of RFs present: overall and stratified by NGT/IGT status*

Model	Overall	NGT	IGT
Demographic (demog model)*	2.00 (1.7–2.3)†	1.64 (1.2–2.2)†	1.45 (1.1–1.9)‡
Demog plus WST	1.84 (1.5,2.2)†	1.44 (1.05–2.0)§	1.40 (1.1–1.8)§
Demog plus WST‖ and S_i¶	1.72 (1.4,2.1)†	1.43 (1.03–2.0)§	1.38 (1.0–1.8)§

Data are OR (95% CI). *Demographic model adjusts for age, sex, clinic, and ethnic group; †$P < 0.001$; ‡$0.001 < P < 0.01$; §$0.01 < P < 0.05$; ‖OR for WST in the overall model is 1.003 (0.984–1.022); ¶OR for S_i in the overall model is 0.745 (0.611–0.908).

Table 3—ORs (and CIs) for conversion to type 2 diabetes for the number of RFs present: stratified by ethnic group

Model	Non-Hispanic white	African American	Hispanic
Demographic (demog model)*	2.4 (1.8–3.3)†	2.2 (1.6–3.0)†	1.6 (1.3–2.1)†
Demog plus WST	2.1 (1.5–2.9)†	2.2 (1.5–3.2)†	1.5 (1.2–2.0)‡
Demog plus WST and S_i	1.8 (1.2–2.5)‡	2.3 (1.5–3.6)†	1.6 (1.2–2.1)‡

Data are OR (95% CI). *Demographic model adjusts for age, sex, clinic, and ethnic group; †$P < 0.001$; ‡$0.001 < P < 0.01$.

CONCLUSIONS — We have confirmed in the IRAS population that the presence of CVD RFs (high PAI-1, low HDL, high TGs, hypertension, and IGT) predict the incidence of type 2 diabetes in a multiethnic cohort. The relationship between conventional CVD RFs and the development of type 2 diabetes was independently associated despite adjustment for age, sex, and ethnic group. Additionally, this relationship was only modestly attenuated by adjusting for traditional diabetes RFs, including a direct assessment of insulin resistance (S_i) and WST. Consideration of the clustering of CVD RFs may considerably improve the prediction of type 2 diabetes and may be useful in identifying individuals at high risk of diabetes who may benefit by both behavioral and pharmacological interventions to delay the onset of type 2 diabetes.

This relationship occurred in the entire study group and when examined separately by ethnicity. When we examine the ethnicity-specific estimates, in the demographically adjusted models it appears that the relationship may be strongest among non-Hispanic whites, intermediate in African Americans, and lowest in Hispanics; however, this difference among ethnic groups was not statistically significant. Interestingly, after adjusting for the traditional diabetes RFs (S_i and WST), the African-American group appeared to be at highest risk for developing diabetes and the difference between non-Hispanic white and Hispanic groups was greatly reduced. Specifically, the non-Hispanic white OR for each additional RF was reduced from 2.4 to 1.8, while there was a very modest change in the OR for Hispanics and a slight increase in the OR for African Americans (the OR increased from 2.2 to 2.3). This suggests that in Hispanics, the information gathered from traditional diabetes RFs and CVD RFs may be independent (and additive), whereas in non-Hispanic whites, the information from these two types of RFs may share some common predictive ability (and not being fully additive). In African Americans, the increase in the OR may suggest that once the traditional diabetes RFs are adjusted for, the impact of CVD RFs is even larger than what may have been previously estimated.

Furthermore, CVD RFs predicted type 2 diabetes in subjects who had NGT or IGT at baseline. Importantly, the presence of other CVD RFs increases the risk of type 2 diabetes, even in participants with IGT who are already at high risk of developing diabetes. Participants with NGT who had all four CVD RFs had a risk of developing diabetes similar to IGT participants with four CVD RFs. This suggests that we can even identify a group of participants at very high risk of developing diabetes (and probably coronary heart disease) in some subjects with NGT.

It has previously been shown (27,28) that hypertension is predictive of the development of type 2 diabetes. However, there is little previous work linking dyslipidemia to the development of type 2 diabetes. Mykkanen et al. (27) included lipids in their analyses; however, their population consisted of older participants, and therefore, little was known about the impact for middle-aged adults before this study.

Recently, more attention has been given to the role of inflammatory markers, such as PAI-I and C-reactive protein, and their ability to predict the onset of diabetes. Festa et al. (29) demonstrated using IRAS data that PAI-1 is a strong predictor of the development type 2 diabetes. Their work focused specifically on the relationship between inflammatory markers and diabetes and did not consider the constellation of CVD RFs as a whole. In addition, Freeman et al. (30) recently reported that C-reactive protein is an independent pre-dictor of diabetes. Additional analyses using the IRAS data have shown that acute insulin response and proinsulin are strong independent predictors for the development of type 2 diabetes (31), but that work did not focus specifically on other CVD RFs.

Our results confirm that in a middle-aged population CVD RFs predict the development of type 2 diabetes. More recent data (32) suggest that increased prevalence of nonfatal CVD events precede the onset of type 2 diabetes. These data, combined with our results, suggest the need for aggressive treatment of glycemia and insulin resistance, and the treatment and control of CVD RFs in the pre-diabetic stage may also be an important public health initiative.

A question that remains is whether the CVD RFs developed due to insulin resistance per se and thus are related to the future development of diabetes only as epiphenomena. The fact that the results from the multiple logistic regression models indicated that the CVD RFs remained significant even after adjustment for insulin resistance is encouraging, although not completely conclusive, since both the progression to diabetes and the development of CVD RFs may arise independently as a result of insulin resistance. Nevertheless, in a clinical setting, where assessment of CVD RFs is easier to obtain than a direct measure of insulin resistance (such as the one used in these analyses), the presence of additional CVD RFs should provide the clinician with information useful for identifying patients who may be at higher risk for developing diabetes, even if the underlying cause is related to insulin resistance. In general, once a person has been identified as potentially at high risk for developing diabetes, more aggressive RF management should begin and insulin resistance should be included as an additional RF to be managed as well. This work suggests that even absent of a direct assessment of insulin resistance, one can identify patients at high risk for developing diabetes based on easily measured CVD RFs.

Gu, Cowie, and Harris (33) have suggested, based on analyses from the follow-ups of the National Health and Nutrition Examination Survey data, that individuals with diabetes have had a much more modest decline in coronary artery disease mortality relative to nondiabetic individuals. This observation, coupled with the

rising prevalence of type 2 diabetes and obesity (34) in the U.S., suggests that the problem of CVD in type 2 diabetes is going to be increasingly important. Clearly, primary prevention of type 2 diabetes is an important approach; recent behavioral interventions (10) have shown a 58% reduction in type 2 diabetes over 4 years. Because intensive behavioral interventions and pharmacological interventions are expensive to implement, defining a high-risk group for developing type 2 diabetes is imperative. Our results suggest that the identification of subjects with several CVD RFs may be an important way to identify such a target for intervention as well as identifying subjects with a high risk for CHD.

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