

Adiponectin and the Incidence of Type 2 Diabetes in Hispanics and African Americans

The IRAS Family Study

ANTHONY J.G. HANLEY, PHD^{1,2}
LYNNE E. WAGENKNECHT, DRPH³
JILL M. NORRIS, PHD⁴
RICHARD BERGMAN, PHD⁵

ANDREA ANDERSON, MSC³
Y. IDA CHEN, PHD⁶
CARLOS LORENZO, MD⁷
STEVEN M. HAFFNER, MD⁸

OBJECTIVE—A recent meta-analysis of 13 prospective studies reported that higher levels of adiponectin were significantly associated with lower risk of type 2 diabetes. Most previous studies, however, were limited in their ability to adjust for appropriate confounding variables. Our objective, therefore, was to study this association after adjustment for directly measured adiposity and insulin sensitivity, expressed as the insulin sensitivity index (S_I).

RESEARCH DESIGN AND METHODS—The study included 1,096 Hispanic and African American participants free of diabetes at baseline (2000–2002) who returned for follow-up after 5 years. S_I was determined from frequently sampled intravenous glucose tolerance tests with minimal model analysis. Visceral adipose tissue (VAT) area was determined by computed tomography. Diabetes and impaired fasting glucose (IFG) were defined using American Diabetes Association criteria. Multivariate generalized estimating equation logistic regression models were used to account for correlations within families.

RESULTS—A total of 82 subjects met criteria for incident diabetes. After adjustment for age, sex, ethnicity, and smoking, adiponectin was significantly inversely associated with diabetes (odds ratio [OR] 0.54 per 1 SD difference [95% CI 0.38–0.76]). The association remained significant after additional adjustment in individual models for BMI, homeostasis model assessment of insulin resistance, or VAT (all $P < 0.05$). However, adiponectin was no longer associated in separate models adjusted for S_I or IFG (OR 0.81 [0.56–1.16] and 0.75 [0.53–1.06], respectively).

CONCLUSIONS—Adiponectin was inversely associated with incident diabetes after adjustment for conventional anthropometric and metabolic variables or VAT. Adjustment for detailed measures of S_I attenuated this relationship, however, suggesting that the link between adiponectin and diabetes may operate at least in part through insulin resistance.

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Since its discovery in the mid-1990s, the adipocyte-derived protein adiponectin has been reported to have a broad spectrum of effects, including antiatherogenic, anti-inflammatory, and insulin-sensitizing properties (1,2). In addition to the established inverse associations of adiponectin with various

measures of adiposity, one of the most consistent observations in this literature is the prospective association of higher baseline adiponectin levels with reduced risk of type 2 diabetes (3). A recent meta-analysis of 13 prospective studies involving 14,598 participants and 2,623 incident cases of type 2 diabetes reported a robust inverse association of adiponectin with incident type 2 diabetes across diverse populations, with a pooled relative ratio of 0.72 (95% CI 0.67–0.78) per 1-log $\mu\text{L/mL}$ increase (4).

Despite these concordant findings regarding adiponectin and incident diabetes, a number of questions remain unanswered. First, the majority of previous studies have involved Asian populations or Caucasians from Europe or North America (4), with few studies involving African Americans or Hispanics, who are known to be at increased risk of diabetes (5,6). Furthermore, relatively few studies to date have adjusted for HDL cholesterol, which may be an important covariate because HDL is strongly correlated with adiponectin and low HDL is a documented diabetes risk factor (7,8). In addition, the majority of previous reports have adjusted for surrogate measures of insulin resistance and adiposity (4). This is an important limitation in light of the central role of insulin resistance and visceral fat in adiponectin pathobiology (9,10) and the modest validity of the proxy measures of these disorders that have been used to date (BMI and homeostasis model assessment of insulin resistance [HOMA-IR]). In one previous study, the association of adiponectin with incident diabetes was assessed in a cohort of elderly African Americans and whites after adjustment for directly assessed visceral adipose tissue (VAT) (11), although no previous study to our knowledge has used direct measures of both VAT and insulin sensitivity, expressed as the insulin sensitivity index (S_I). Another recent study documented an association of adiponectin with incident diabetes in insulin-resistant subjects but not in those who were insulin sensitive (12).

From the ¹Departments of Nutritional Sciences and Medicine and Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada; the ²Leadership Sinai Centre for Diabetes, Mt. Sinai Hospital, Toronto, Ontario, Canada; the ³Division of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, North Carolina; the ⁴Department of Preventive Medicine and Biometrics, University of Colorado at Denver and Health Sciences Center, Denver, Colorado; the ⁵Keck School of Medicine, University of Southern California, Los Angeles, California; the ⁶Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, California; the ⁷Division of Clinical Epidemiology, University of Texas Health Science Center, San Antonio, Texas; and the ⁸Department of Medicine, Baylor College of Medicine, Houston, Texas.

Corresponding author: Anthony J.G. Hanley, anthony.hanley@utoronto.ca.

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The objective of the current study, therefore, was to investigate the association of adiponectin with incident type 2 diabetes after adjustment for potential confounders, including directly measured VAT and S_1 as well as HDL, in the Insulin Resistance Atherosclerosis Study (IRAS) Family Study, a prospective cohort study of well-characterized Hispanic and African American adults.

RESEARCH DESIGN AND

METHODS—The methodology of the IRAS Family Study has been described in detail (13,14). Briefly, the study was designed to explore genetic contributions to insulin resistance and visceral adiposity among Hispanic and African American adults using a family-based design (13). Large families were recruited between 2000 and 2002 at centers in San Antonio, TX, San Luis Valley, CO (Hispanics), and Los Angeles, CA (African Americans), with probands identified from the parent study (IRAS) (13) as well as the general population. The present prospective analysis included 1,096 subjects who were free of diabetes at the baseline examination (2000–2002) and who returned for the 5-year follow-up examination, representing a 77% participation rate at follow-up. Subjects who did not return at follow-up were more likely to be male and have slightly better health status than those that returned (including slightly lower levels of subcutaneous adipose tissue [SAT] and VAT and higher S_1). The institutional review boards at the respective institutions approved the protocol, and informed consent was given by each subject.

Fat mass in the abdominal region was measured by computed tomography at both the L2/L3 and L4/L5 vertebral regions (13,14). A standardized protocol was used at each of the three clinical centers. Scans were read centrally at the University of Colorado School of Medicine, Department of Radiology, Bio-Imaging Research Laboratory for SAT and VAT, with bowel fat subtracted out from the measure of VAT. The L4/L5 measure was used in the present analysis. However, 45 subjects had data for the L2/L3 region but not the L4/L5 region. Since adipose tissue areas at the L2/L3 and L4/L5 regions were highly correlated (Spearman correlation: 0.95 for SAT, 0.90 for VAT), data for these latter individuals for the L4/L5 region were imputed using a simple linear model (13,14).

Insulin sensitivity was determined using a frequently sampled intravenous

glucose tolerance test, with two modifications to the original protocol (15). First, an injection of regular insulin, rather than tolbutamide, was used to ensure adequate plasma insulin levels for the accurate computation of insulin sensitivity across a broad range of glucose tolerance (15). Second, a reduced sampling protocol (with 12 rather than 30 samples) was used for efficiency, given the large number of participants (15). S_1 was calculated using minimal model analysis (13–15).

Plasma glucose was measured using the glucose oxidase technique on an auto-analyzer. At both baseline and follow-up examinations, impaired fasting glucose (IFG) was defined as fasting glucose ≥ 100 and < 126 mg/dL, and diabetes was diagnosed as either a fasting glucose ≥ 126 mg/dL or use of antidiabetic medications. Plasma insulin was measured using the dextran-charcoal radioimmunoassay (16), which has a 19% inter-assay coefficient of variation. Fasting indices of insulin resistance and β -cell function were calculated using the HOMA (HOMA-IR and HOMA-B) method of Matthews et al. (17). Lipids were determined using standard laboratory procedures. Height and weight were measured to the nearest 0.5 cm and 0.1 kg, respectively. Duplicate measures were made following a standardized protocol and averages used in the analysis. Ethnicity, smoking, and alcohol consumption were assessed by self-report.

Adiponectin concentration was measured using a radioimmunoassay (Linco Research, St. Charles, MO), with inter- and intra-assay coefficients of variation of 9.3, 6.9, and 9.3% and 3.6, 6.2, and 1.8%, respectively, at concentrations of 1.5, 3.0, and 7.5 $\mu\text{g/mL}$.

Statistical analysis

SAS version 9.1 (SAS Institute, Cary, NC) was used for all statistical analyses. Data are presented as percent for categorical variables and mean (SD) or median (interquartile range) for normally distributed and skewed continuous variables, respectively. Univariate comparisons of baseline variables across ethnic groups and follow-up diabetes status were calculated from generalized estimating equation (GEE1) models, adjusting for correlations within families. Pearson correlation analysis was used to evaluate the univariate associations of adiponectin with metabolic and anthropometric variables at baseline, with P values adjusted for family structure using GEE models.

GEE1 logistic regression models were used to test for associations of adiponectin with incident diabetes at the 5-year examination, while accounting for familial correlations. GEEs are a standard approach to the analysis of correlated data, such as family data, and are similar to logistic regression models except that they account for the correlation among pedigrees. Newly diagnosed diabetes at the 5-year follow-up examination was the dependent variable for all models. A multistage modeling approach was used to investigate the relationships of adiponectin, treated as a continuous variable, with risk of diabetes. Odds ratios (ORs) were estimated per SD increase in adiponectin. We first determined the associations of adiponectin with risk of diabetes adjusted for age, sex, ethnicity (previous cross-sectional analysis of this cohort documented ethnic differences in adiponectin, VAT, and insulin resistance) (10), and smoking. We then tested (using the same adjustments) for effect modification of sex, ethnicity, baseline glucose tolerance status (normal fasting glucose [NFG] vs. IFG), and insulin resistance (HOMA-IR $<$ vs. \geq median split) on the association of adiponectin with incident diabetes. Effect modification was assumed to be present if the P value for the interaction term was < 0.05 . Finally, we assessed the impact, in separate models, of further adjustment of our initial model for HDL cholesterol, fasting glucose, and indirect and direct measures of adiposity and insulin sensitivity. Specifically, we ran additional models that adjusted for age, sex, ethnicity, and smoking as well as HDL, BMI, VAT, SAT, VAT + SAT, HOMA-IR, S_1 , fasting glucose, and IFG.

RESULTS—Baseline demographic, anthropometric, and metabolic characteristics of participants according to incident diabetes status are presented in Table 1. In addition to being older at baseline, those who had developed diabetes at the 5-year follow-up examination had higher baseline BMI, VAT, and SAT and lower insulin sensitivity (all $P < 0.001$). In addition, converters had higher baseline fasting glucose concentrations and a higher prevalence of IFG (both $P < 0.0001$), although the two groups did not differ by sex or ethnicity. Baseline concentrations of adiponectin were significantly lower in converters compared with nonconverters (10.0 vs. 12.1 $\mu\text{g/mL}$, respectively, $P < 0.001$). At baseline, adiponectin was

Table 1—Baseline characteristics of nondiabetic subjects in the IRAS Family Study stratified by diabetes status at the follow-up examination

Variable	Diabetes status at follow-up examination		P value
	NGT and IFG	Diabetes	
n	1,014	82	<0.0001
Age (years)	40.6 (13.2)	51.1 (12.8)	<0.0001
BMI (kg/m ²)	28.4 (5.9)	33.3 (7.2)	<0.0001
VAT (cm ²)	98.0 (55.3)	159.7 (53.7)	<0.0001
SAT (cm ²)	334.1 (162.8)	422.3 (170.6)	0.0003
Triglyceride (mg/dL)*	97.7 (70.8–136.7)	126.0 (94.9–166.4)	0.0002
HDL cholesterol (mg/dL)*	43.3 (38.0–50.3)	39.7 (34.5–44.1)	0.0067
Fasting glucose (mg/dL)	92.8 (8.7)	107.8 (11.2)	<0.0001
Fasting insulin (pmol/L)*	12.0 (8.0–18.0)	20.0 (12.0–28.0)	<0.0001
S ₁ × 10 ⁻⁴ (min/UU/mL)*	1.6 (0.9–2.7)	0.7 (0.3–1.1)	<0.0001
Adiponectin (μg/mL)	12.1 (6.3)	10.0 (5.3)	0.0006
HOMA-IR*	47.9 (30.2–76.4)	97.0 (55.7–136.0)	<0.0001
HOMA-B†	151.8 (104.7–219.1)	164.3 (109.4–245.6)	0.5076
Sex (n [%] female)	622 (61.3)	50 (61.0)	0.9962
Ethnicity (n [%] African American/Hispanic)	296 (29.2)/718 (70.8)	22 (26.8)/60 (73.2)	0.7445
Glucose tolerance (n [%] IFG)	194 (19.1)	65 (79.3)	<0.0001

Data are means (SD), medians (interquartile ranges), or proportions. Differences assessed using unadjusted GEE1 models to account for family structure. NGT, normal glucose tolerance. *P values are based on log transformations. †P values are based on square root transformations.

significantly correlated with all anthropometric and metabolic measures (all $P < 0.001$) (Table 2), the strongest correlations being with VAT ($r = -0.31$), HDL ($r = 0.37$), fasting insulin ($r = -0.31$), S₁ ($r = 0.29$), and HOMA-IR ($r = -0.31$).

After adjustment for age, sex, ethnicity, and smoking, baseline adiponectin was significantly inversely associated with risk of incident diabetes (OR 0.54 [95% CI 0.38–0.76] per SD increase). There were no significant interactions of sex,

Table 2—Pearson correlation analysis of adiponectin with baseline metabolic and anthropometric variables in nondiabetic subjects in the IRAS Family Study

	Adiponectin
BMI (kg/m ²)	-0.27
VAT (cm ²)	-0.31
SAT (cm ²)	-0.24
Fasting glucose (mg/dL)	-0.24
Fasting insulin (pmol/L)	-0.31
S ₁ × 10 ⁻⁴ (min/UU/mL)	0.29
HOMA-IR	-0.31
HOMA-B	-0.24
Systolic blood pressure (mmHg)	-0.08
HDL cholesterol (mg/dL)	0.37
Triglyceride (mg/dL)	-0.23

Adjusted for age, sex, and ethnicity. All P values are < 0.0001, except for systolic blood pressure ($P = 0.0006$), and are from GEE models additionally adjusting for family structure.

ethnicity, baseline glucose tolerance status (NFG vs. IFG), or insulin resistance (median split of HOMA-IR) on the association of adiponectin with incident diabetes (all interaction P values ≥ 0.28). Although subgroup associations were not uniformly significant because of reduced power, all ORs were <1.0, indicating a consistent pattern of inverse relationships between adiponectin and incident diabetes within each group (Fig. 1). We also analyzed S₁ as a potential effect modifier by examining subgroups defined by the median split of S₁. There were, however, very few converters to diabetes in the high S₁ (i.e., the most insulin sensitive) group, resulting in nonconvergence of our statistical model for that subgroup (data not shown).

Figure 2 illustrates the impact of further adjustment of our initial model for HDL, glucose, IFG, and indirect and direct measures of adiposity and insulin sensitivity in separate models. The association of adiponectin with incident diabetes remained statistically significant after adjustment for HDL as well as the indirect measures BMI and HOMA-IR (OR 0.64 [95% CI 0.43–0.94], 0.67 [0.46–0.97], and 0.69 [0.49–0.99], respectively; all $P < 0.05$). Notably, models adjusted for SAT, VAT, or both of these variables also maintained statistical significance (OR 0.68 [CI 0.47–0.97], 0.60 [0.41–0.88], and 0.68 [0.46–0.99], respectively; all

$P < 0.05$). However, adjustment for directly measured insulin sensitivity, alone or in combination with VAT, attenuated the association of adiponectin with incident diabetes to nonsignificance (OR 0.81 [0.56–1.16] and 0.85 [0.59–1.24]; both $P > 0.05$). Finally, adjustment for fasting glucose or IFG also attenuated the adiponectin–incident diabetes association to nonsignificance (OR 0.83 [0.58–1.19] and 0.75 [0.53–1.06]; both $P > 0.05$).

CONCLUSIONS—In this cohort of Hispanics and African Americans, adiponectin significantly inversely predicted incident type 2 diabetes after adjustment for demographic variables as well as surrogate measures of body mass and insulin resistance. There were no significant interactions by sex, ethnicity, glucose tolerance, or insulin resistance on this association. Adjustment for VAT or SAT (or both) attenuated the association somewhat, but it remained statistically significant. This inverse association was apparent when models were adjusted for directly measured insulin sensitivity, IFG, or fasting glucose, although the ORs were no longer statistically significant.

These findings contribute novel information to the literature on adiponectin and risk of diabetes. Specifically, this article reports that adiponectin predicts incident diabetes in two ethnic groups for which relatively limited data are available

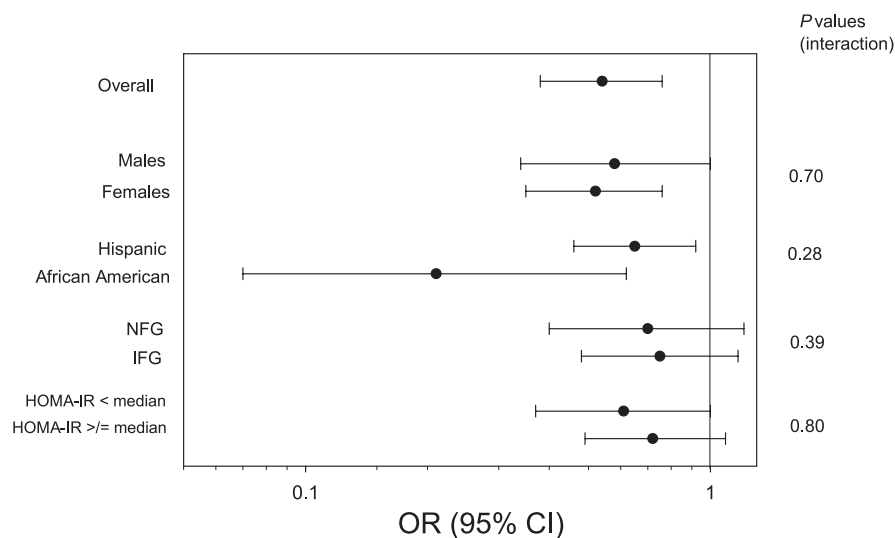


Figure 1—Associations of baseline adiponectin with incident diabetes at the 5-year follow-up examination, overall, and stratified by sex, ethnicity, glucose tolerance status (NFG vs. IFG), and insulin resistance in the IRAS Family Study. ORs (95% CI) are from GEE1 logistic regression, refer to 1 SD changes in adiponectin concentration, and are adjusted for age, sex, ethnicity, and smoking status. Note log scale of x-axis.

on this topic. In addition, important potential confounders, including adiposity and insulin resistance, have been measured with more detailed procedures than in the majority of previous articles.

As reported in the recent meta-analysis by Li et al. (4), higher adiponectin levels

have been shown to be consistently and robustly protective against incident diabetes after multivariate adjustment across a range of populations. Because adiposity is recognized as a key confounder in this relationship, the majority of previous studies adjusted for BMI, waist-to-hip ratio, or

other surrogate measures of body fat and body composition (4). In most cases, associations of adiponectin with diabetes remained significant after adjustment for these indirect measures of adiposity. Our findings are consistent with this literature in that adiponectin remained a significant predictor of diabetes after adjustment for BMI (Fig. 2).

Surrogate measures of adiposity are limited in their ability to characterize different body fat depots. In light of the specific role of visceral fat in adiponectin pathobiology (18,19), it was of interest to determine whether the adiponectin–diabetes association was independent of directly measured visceral and subcutaneous fat. In the current study, adiponectin significantly predicted incident diabetes after adjustment for VAT, SAT, or VAT and SAT together. A number of potential mechanisms could be proposed to explain the independence of adiponectin in predicting diabetes after adjustment for these variables. Previous research from our group and others has demonstrated that adiponectin variation is not entirely explained by VAT (10,20) and, thus, adiponectin may exert its antidiabetic effects through pathways other than VAT. Previously described risk factors for diabetes, including inflammatory variables, diet, or physical activity, that were not included

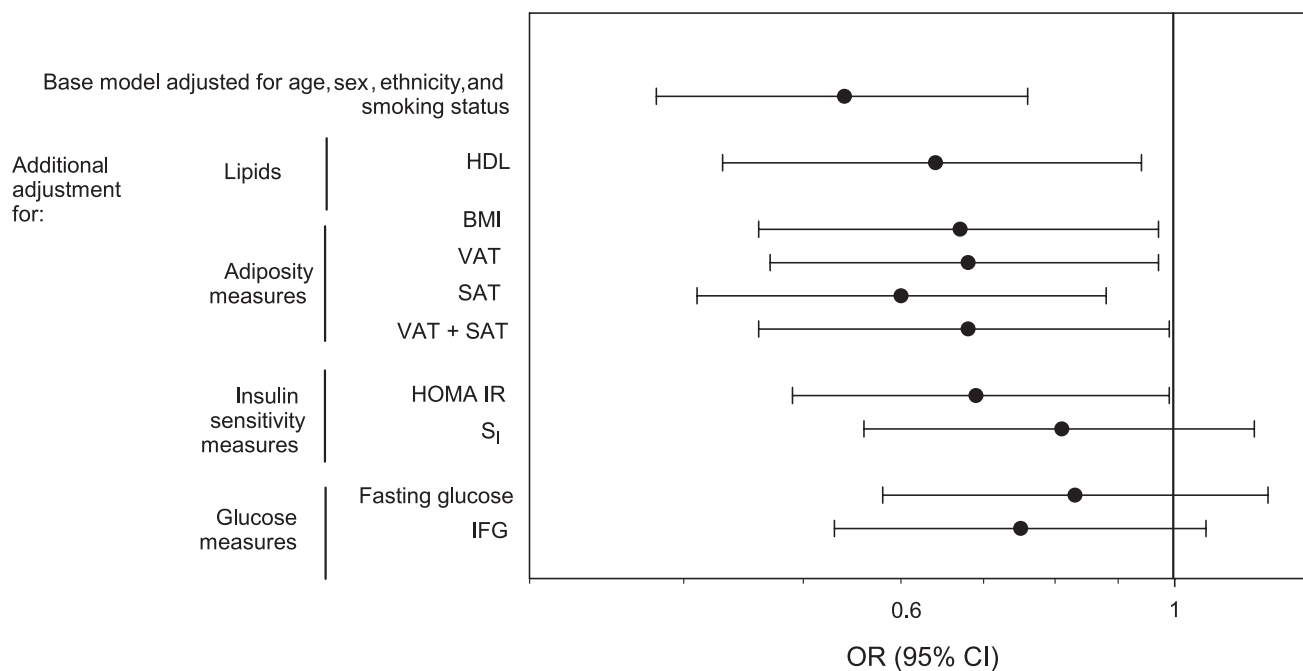


Figure 2—Association of adiponectin with incident diabetes: impact of adjustment for glucose, HDL, and direct and surrogate measures of adiposity and insulin sensitivity. ORs are from GEE1 logistic regression and refer to risk associated with an SD increase in adiponectin, with adjustment for the indicated variables in separate models.

in the present analysis may be related to variation in adiponectin and may help to explain its independence as a diabetes predictor (10,21,22). To our knowledge, only one previous study has used information on VAT as a covariate in modeling the adiponectin–diabetes relationship. In the Health Aging and Body Composition study, a cohort study of older black and white participants, adiponectin was not significantly related to diabetes incidence in a multivariate model that included VAT in addition to conventional cardiometabolic variables, leptin, and PAI-1 (11). Given the inclusion of additional covariates (especially the leptin and PAI-1), it is not possible to isolate the impact of adjustment for VAT from this model.

In addition to adiposity, insulin resistance is another key covariate in the adiponectin–diabetes relationship, considering that the insulin-sensitizing effects of adiponectin have been demonstrated previously (3). A limited number of prior studies have adjusted for surrogate measures of insulin resistance, usually by using fasting insulin or indices derived from this variable, and in most cases, but not all, the association of adiponectin with incident diabetes remained statistically significant (4). The results of the current study are consistent with these findings because the association of adiponectin with diabetes development remained significant after adjustment for HOMA-IR. However, the association was attenuated and became nonsignificant after adjustment for directly measured insulin sensitivity. This observation suggests that a primary antidiabetic aspect of adiponectin may be its effect on increasing insulin sensitivity. Previous cross-sectional analysis in this cohort has shown that adiponectin and insulin sensitivity are independently associated (10), and it has been demonstrated in other studies that low plasma adiponectin concentrations at baseline precede declines in insulin sensitivity over time (23–25). In contrast to a recent study by Hivert et al. (12), the association of adiponectin with incident diabetes was not modified by insulin resistance, an inconsistency which may be the result of marked ethnic and metabolic differences between the participants in the two studies. Additional research is needed on the potential modifying effect of insulin resistance on adiponectin's role in diabetes pathogenesis.

Finally, the association of adiponectin with diabetes onset was evaluated after HDL adjustment, given that relatively few

previous studies had considered this covariate. This question was of interest since strong associations between HDL and adiponectin had previously been documented (7), including a strong loading of HDL and adiponectin together in a factor analysis of metabolic syndrome variables and a prospective association of baseline adiponectin with increases in HDL (23). However, our finding of a significant association of adiponectin with incident diabetes after HDL adjustment suggests that these two variables may be linked through mechanisms that are not directly related to diabetes pathogenesis.

The strengths of this study include the availability of direct measures of insulin sensitivity and body composition in a well-characterized prospective cohort of Hispanics and African Americans, two ethnic groups that are known to be at increased risk of diabetes and for whom little is known regarding the prospective association of adiponectin with diabetes. Limitations include the lack of oral glucose tolerance tests, which possibly resulted in the misclassification of subjects who would have been diagnosed as having diabetes based on elevated post-challenge glucose levels. In addition, the period of follow-up was relatively short and there were relatively few incident cases of diabetes, resulting in limited power to detect statistical interactions and/or associations with diabetes in fully adjusted models. In light of ethnic differences in adiponectin levels, future studies with sufficient power to examine ethnic-specific effects are needed. Finally, the assay used for determination of adiponectin concentrations measured “total” adiponectin and, thus, was not able to differentiate the different isoforms of the protein, the distributions of which have been shown to differ by ethnicity. It has been demonstrated that the high molecular weight isoform of adiponectin is responsible for its insulin-sensitizing effects (3).

In conclusion, adiponectin significantly predicts the 5-year incidence of type 2 diabetes after adjustment for covariates including demographic variables, HDL, surrogate measures of body mass and insulin resistance, and direct measures of visceral and subcutaneous fat. However, adjustment for directly measured insulin sensitivity, IFG, or fasting glucose attenuated this association to nonsignificance. These observations suggest that while derived from adipose tissue, adiponectin exerts its antidiabetic

effect in part independently of the visceral and subcutaneous fat mass. The attenuating effect of a precise measure of insulin sensitivity on this relationship may indicate that the antidiabetic effect of adiponectin is derived primarily through the amelioration of insulin resistance.

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A.J.G.H. wrote the manuscript. L.E.W., J.M.N., and R.B. researched data, contributed to discussion, and reviewed and edited the manuscript. A.A. conducted the statistical analysis and reviewed and edited the manuscript. Y.I.C., C.L., and S.M.H. researched data, contributed to discussion, and reviewed and edited the manuscript.

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