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Fasting and Post-Glucose Load Measures of Insulin Resistance and Risk of Ischemic Stroke in Older Adults

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Abstract

Background and purpose—Few studies have assessed post-glucose load measures of insulin resistance and ischemic stroke risk, and data are sparse for older adults. We investigated whether fasting and post-glucose load measures of insulin resistance were related to incident ischemic stroke in non-diabetic older adults.

Methods—Participants were men and women in the Cardiovascular Health Study, aged 65+ and without prevalent diabetes or stroke at baseline, followed for 17 years for incident ischemic stroke.

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Disclosures None.

The Gutt insulin sensitivity index was calculated from baseline body weight and fasting and 2-hour post-load insulin and glucose; a lower Gutt index indicates higher insulin resistance.

Results—Analyses included 3,442 participants (42% men) with a mean age of 73. Incidence of ischemic stroke was 9.8 strokes per 1,000 person years. The relative risk (RR) for lowest quartile vs. highest quartile of Gutt index was 1.64 (95% confidence interval: 1.24, 2.16), adjusted for demographics and prevalent cardiovascular and kidney disease. Similarly, the adjusted RR for highest quartile vs. lowest quartile of 2-hour glucose was 1.84 (95% CI: 1.39, 2.42). In contrast, the adjusted RR for highest quartile vs. lowest quartile of fasting insulin was 1.10 (95% CI: 0.84, 1.46).

Conclusions—In non-diabetic older adults, insulin resistance measured by Gutt index or 2-hour glucose, but not fasting insulin, was associated with risk of incident ischemic stroke.

Keywords

Non-diabetic older adults; Cohort study; Gutt insulin sensitivity index

Introduction

Insulin resistance is a precursor and mechanism of type 2 diabetes, and is associated with development of atherosclerosis and hypercoagulability.[1] In prospective studies of middle-aged non-diabetic adults, measures of insulin resistance have been associated with coronary heart disease (CHD) and stroke.[1, 2]

Because vascular disease is more strongly associated with impaired glucose tolerance than with impaired fasting glucose,[3] post-glucose load measures of insulin resistance may be important for assessing the relationship between insulin resistance and cardiovascular risk. Although recent studies of insulin resistance and ischemic stroke have examined fasting insulin,[4, 5] there has been little study of ischemic stroke risk in relation to post-glucose load measures of insulin resistance. One such measure is the Gutt insulin sensitivity index, which is derived from body weight and fasting and 2-hour insulin and glucose.[6]

Data are sparse on the association between insulin resistance and ischemic stroke in older adults because in most prior studies insulin resistance was measured in young to middle-aged adults at baseline. We examined a cohort of non-diabetic participants in which measures of insulin resistance were obtained at a mean age of 73 years, with 17 years of follow-up for incident stroke. We hypothesized that insulin resistance, reflected by higher fasting insulin and lower Gutt insulin sensitivity index, would be associated with higher risk of ischemic stroke among non-diabetic older adults.

Methods

Setting and participants

The Cardiovascular Health Study (CHS) is a community-based prospective study of men and women aged 65 years and older.[7] The cohort included 5,201 participants enrolled in 1989/90 at field centers in Washington County, MD; Pittsburgh, PA; Forsyth County, NC; and Sacramento County, CA. The study was approved by institutional review boards at the University of Washington and each field center.

For this analysis we included participants who at baseline had no history of stroke, were free of diabetes, and had fasting and 2-hour oral glucose tolerance test (OGTT) insulin and glucose measurements. An additional cohort of African American participants enrolled later was not included because 2-hour insulin and glucose were not measured at their baseline

visit. Diabetes at baseline was defined as use of insulin or oral hypoglycemic drugs, fasting serum glucose ≥7.0 mmol/L (126 mg/dL), random serum glucose ≥11.1 mmol/L (200 mg/dL), or 2-hour serum glucose ≥11.1 mmol/L (200 mg/dL). History of stroke at baseline was ascertained from participant report and confirmed with medical records.[8] We excluded 199 participants who had a history of stroke, 1,107 who had diabetes, 173 for whom data were incomplete to classify diabetes status, 239 who were missing at least one fasting or 2-hour insulin or glucose measurement, and 41 who had incomplete covariate data, leaving 3,442 participants for analysis.

Insulin and glucose measures

Serum samples were obtained after an overnight fast of at least 8 hours, and again 2 hours after a 75-g oral glucose challenge. Insulin was measured with a competitive radioimmunoassay (Diagnostic Products Corporation, Malvern, PA), and glucose was measured with an enzymatic method.[9] The Gutt insulin sensitivity index was calculated as $insulin\ sensitivity = m / (G \times I)$, where m is a measure of glucose uptake during the OGTT calculated from body weight and fasting and 2-hour glucose, G is the mean of fasting and 2-hour glucose, and I is a $\log_{10}$ transformation of the mean of fasting and 2-hour insulin. Units for the Gutt index are $mg \cdot L^2/mmol \cdot mU \cdot min$. The complete formula and a correction are reported elsewhere.[6, 10]

Covariates

Age, sex, race, and smoking behavior were determined from participant report. Body weight, waist circumference, and systolic blood pressure (SBP) were measured with standardized protocols. Plasma triglyceride, high density lipoprotein (HDL) cholesterol, and serum creatinine were measured with enzymatic methods.[9] Plasma low density lipoprotein (LDL) cholesterol was estimated with the Friedewald equation.[11] Estimated glomerular filtration rate (eGFR) was estimated with the CKD-EPI equation.[12] Physical activity was measured with a questionnaire.[13] Antihypertensive medication use was measured with a medication inventory.[14] Prevalent CHD (including history of myocardial infarction, angina, coronary angioplasty, or coronary artery bypass graft), congestive heart failure (CHF), and peripheral arterial disease (PAD) were determined from the baseline examination and medical record review.[15] Atrial fibrillation (AF) was determined by 12-lead resting ECG at the baseline examination. Interim development of diabetes was determined from annual medication inventories throughout follow-up and fasting (or random) glucose measurements at three, five, seven, nine, and 16 years after baseline.

Ischemic stroke outcome

The outcome was definite incident ischemic stroke, adjudicated by the CHS cerebrovascular events committee. Incident strokes were ascertained from participant report, questions at annual visits, telephone contacts every six months in between annual visits and after annual visits ended, and screens of hospitalizations for key ICD-9 codes. Strokes were confirmed with information from participant interviews, medical records, test results, and brain images; detailed diagnostic criteria have been described previously.[8] Follow-up for each participant extended from the 1989/90 baseline exam until occurrence of incident ischemic stroke (n = 417), death (n = 1,775), loss to follow-up (n = 149), or end of follow-up on June 30, 2007 (n = 1,101), whichever occurred first.

Statistical analysis

We assessed correlations among Gutt index components with Pearson correlation coefficients. We used Cox proportional hazards models to assess associations of Gutt index and each of its components with incident ischemic stroke. We compared stroke risks across

quartiles of each measure, with the least insulin resistant quartile as reference category (highest quartile for Gutt index; lowest quartile for each component), and tested for trend across quartiles. Relative risks (RR) were adjusted with risk set stratification for baseline age in one year categories; indicator variables for male sex, African American race, eGFR <60 mL/min/1.73 m^2, CHD, CHF, AF, PAD, and antihypertensive medication use; and continuous linear variables for SBP, triglyceride, HDL cholesterol, and LDL cholesterol. We did not adjust for waist circumference or physical activity because they were not associated with ischemic stroke risk in this study. Adjustment for smoking, which was unrelated to measures of insulin resistance, did not affect our results.

In additional analyses we calculated sex-specific RRs and tested whether they were different; and we recalculated RRs using follow-up time and strokes only before interim development of diabetes using models with a time-varying diabetes indicator variable and a multiplicative interaction between diabetes and each baseline measure of insulin resistance.

Results

Participants had a mean age of 73 years at baseline; 42% were men; and 4% were African American. Participants with lower Gutt insulin sensitivity index (more insulin resistant) tended to have a more adverse cardiovascular risk profile (Table 1). During follow-up, 417 participants experienced ischemic stroke, at a mean age of 82 years. Ischemic stroke incidence was 9.8 per 1,000 person years.

Gutt insulin sensitivity index and incident ischemic stroke

Compared with the highest quartile of Gutt index (least insulin resistant), lower quartiles (more insulin resistant) were associated with higher risk of ischemic stroke (Table 2). RRs adjusted for demographics and prevalent diseases were similar to unadjusted RRs. Additional adjustment for blood pressure, antihypertensive medication use, and lipids attenuated the RRs.

Gutt index components and incident ischemic stroke

The Pearson correlations of Gutt index with each of its components were −0.37 for fasting glucose, −0.36 for fasting insulin, −0.85 for 2-hour glucose, −0.65 for 2-hour insulin, and −0.18 for body weight. For 2-hour glucose, RRs of ischemic stroke comparing higher quartiles (more insulin resistant) with the lowest quartile (least insulin resistant) were similar to RRs observed for Gutt index (Table 2). Two-hour insulin was also positively associated with ischemic stroke; but fasting glucose, fasting insulin, and body weight were not (Table 2). In a model that included all individual Gutt index components simultaneously, only 2-hour glucose was independently associated with stroke risk (data not shown).

Additional analyses

The association between Gutt index and ischemic stroke was stronger in men (lowest quartile vs. highest quartile, RR = 2.39; 95% CI: 1.59, 3.59) than in women (lowest quartile vs. highest quartile, RR = 1.16; 95% CI: 0.79, 1.69; p for interaction = 0.04) adjusted for demographics and prevalent disease. Also for 2-hour insulin, the RR comparing extreme quartiles was higher for men (RR = 1.93; 95% CI: 1.25, 2.97) than for women (RR = 1.11; 95% CI: 0.76, 1.62; p for interaction = 0.009). For other Gutt index components, RRs comparing extreme quartiles were either similar for men and women, or only slightly higher for men. Associations of baseline measures of insulin resistance with stroke before interim development of diabetes were similar to the associations observed when ignoring interim development of diabetes (Table S1; please see http://stroke.ahajournals.org).

Discussion

In this study of non-diabetic older adults, lower Gutt insulin sensitivity index was associated with higher risk of ischemic stroke. Higher 2-hour glucose was as strongly associated with ischemic stroke risk as lower Gutt index. In contrast, higher fasting insulin was not associated with ischemic stroke in this study. This study contributes new information concerning older adults, a group in whom insulin resistance is common and stroke risk is high, and for whom data are relatively lacking from prior studies.

One plausible interpretation of our finding that Gutt index and 2-hour glucose were associated with stroke risk, but fasting insulin was not, is that peripheral rather than hepatic insulin resistance may play a dominant role in cardiovascular risk in older adults. Post-glucose load measures of insulin resistance reflect whole-body or peripheral insulin resistance, because they incorporate information about insulin response to an oral glucose load and glucose uptake during the OGTT by skeletal muscle and fat, in addition to liver. In contrast, fasting insulin reflects hepatic insulin resistance, because fasting insulin concentrations are determined by liver and pancreas. However, hepatic and whole-body (or peripheral) insulin resistance are correlated, so making a sharp distinction based on fasting and post-glucose load measures in epidemiologic studies is difficult.[16]

Other studies have found positive associations between fasting measures of insulin resistance and ischemic stroke risk. Among Atherosclerosis Risk in Communities (ARIC) Study participants without cardiovascular disease or diabetes at baseline, fasting insulin was positively associated with ischemic stroke risk (445 incident ischemic strokes), adjusted for age, sex, race, and study site.[4] Positive associations between fasting insulin and stroke were also observed in smaller studies.[1, 5] The discrepancy between our findings and observations of prior studies that fasting insulin was associated with stroke risk could be that in some prior studies some participants with high fasting insulin also had undiagnosed diabetes that may have been detected if a 2-hour glucose measurement had been made. The association of insulin resistance with ischemic stroke in our study was stronger for post-glucose load measures than for fasting measures, suggesting that the association of insulin resistance and stroke may be underestimated in studies that use fasting measures alone.

We observed a stronger association between Gutt index and stroke in men than in women. However, the p value was not adjusted for multiple comparisons, the sex difference was not significant for 2-hour glucose, and the finding was not consistent with an earlier study which observed a stronger association between fasting insulin and stroke in women than in men.[4]

Insulin resistance may be a mechanism through which characteristics such as age, obesity, and inactivity lead to hypertension, dyslipidemia, and other factors, ultimately increasing stroke risk.[1] We considered demographics, obesity, activity levels, prevalent cardiovascular disease, and kidney dysfunction as potential confounders of the association between insulin resistance and stroke. Hypertension and dyslipidemia may also confound the relationship of insulin resistance with stroke, or they may be intermediate variables. Lower Gutt index and higher 2-hour glucose were associated with higher stroke risk after adjustment for all potential confounding and intermediate variables we considered, and after excluding follow-up time and strokes occurring after interim development of diabetes, suggesting that insulin resistance may influence ischemic stroke risk through mechanisms other than those we considered in this paper.

A limitation of our study is that the fasting and 2-hour measures of insulin resistance we used are only modestly correlated with more direct measures of insulin resistance. However, indirect measures of insulin resistance are commonly used in place of invasive tests that place a higher burden on research participants. Another limitation is that we used only

baseline measures of insulin resistance. This study also has strengths, including the focus on older adults who have the highest burden of stroke and insulin disorders, the prospective design with high retention of participants during follow-up, assessment of interim development of diabetes, and adjudicated ischemic stroke outcomes.

In summary, among non-diabetic older adults, lower Gutt insulin sensitivity index, a post-glucose load measure of insulin resistance that mainly reflected higher 2-hour glucose, was associated with a higher risk of ischemic stroke. In contrast, higher fasting insulin was not associated with ischemic stroke risk among non-diabetic older adults. Further research is needed to define clinical and public health implications of these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Kernan WN, Inzucchi SE, Viscoli CM, Brass LM, Bravata DM, Horwitz RI. Insulin resistance and risk for stroke. Neurology. 2002; 59:809–815. [PubMed: 12349850]
2. Sarwar N, Sattar N, Gudnason V, Danesh J. Circulating concentrations of insulin markers and coronary heart disease: A quantitative review of 19 Western prospective studies. Eur Heart J. 2007; 28:2491–2497. [PubMed: 17513304]
3. Smith NL, Barzilay JI, Shaffer D, Savage PJ, Heckbert SR, Kuller LH, et al. Fasting and 2-hour postchallenge serum glucose measures and risk of incident cardiovascular events in the elderly: the Cardiovascular Health Study. Arch Intern Med. 2002; 162:209–216. [PubMed: 11802755]
4. Rasmussen-Torvik LJ, Yatsuya H, Selvin E, Alonso A, Folsom AR. Demographic and cardiovascular risk factors modify association of fasting insulin with incident coronary heart disease and ischemic stroke (from the Atherosclerosis Risk in Communities Study). Am J Cardiol. 2010; 105:1420–1425. [PubMed: 20451688]
5. Rundek T, Gardener H, Xu Q, Goldberg RB, Wright CB, Boden-Albala B, et al. Insulin resistance and risk of ischemic stroke among nondiabetic individuals from the Northern Manhattan Study. Arch Neurol. 2010; 67:1195–1200. [PubMed: 20937946]
6. Gutt M, Davis CL, Spitzer SB, Llabre MM, Kumar M, Czarnecki EM, et al. Validation of the insulin sensitivity index (ISI(0,120)): comparison with other measures. Diabetes Res Clin Pract. 2000; 47:177–184. [PubMed: 10741566]
7. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, et al. The Cardiovascular Health Study: design and rationale. Ann Epidemiol. 1991; 1:263–276. [PubMed: 1669507]
8. Longstreth WT Jr, Bernick C, Fitzpatrick A, Cushman M, Knepper L, Lima J, et al. Frequency and predictors of stroke death in 5,888 participants in the Cardiovascular Health Study. Neurology. 2001; 56:368–375. [PubMed: 11171903]

9. Cushman M, Cornell ES, Howard PR, Bovill EG, Tracy RP. Laboratory methods and quality assurance in the Cardiovascular Health Study. Clin Chem. 1995; 41:264–270. [PubMed: 7874780]

10. Hanley AJ, Williams K, Gonzalez C, D'Agostino RB Jr. Wagenknecht LE, Stern MP, et al. Prediction of type 2 diabetes using simple measures of insulin resistance: Combined results from the San Antonio Heart Study, the Mexico City Diabetes Study, and the Insulin Resistance Atherosclerosis Study. Diabetes. 2003; 52:463–469. [Erratum in *Diabetes*. 2003;52:1306.]. [PubMed: 12540622]

11. 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. 1972; 18:499–502. [PubMed: 4337382]

12. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009; 150:604–612. [PubMed: 19414839]

13. Siscovick DS, Fried L, Mittelmark M, Rutan G, Bild D, O'Leary DH. Exercise intensity and subclinical cardiovascular disease in the elderly. The Cardiovascular Health Study. Am J Epidemiol. 1997; 145:977–986. [PubMed: 9169906]

14. Psaty BM, Lee M, Savage PJ, Rutan GH, German PS, Lyles M. Assessing the use of medications in the elderly: methods and initial experience in the Cardiovascular Health Study. J Clin Epidemiol. 1992; 45:683–692. [PubMed: 1607909]

15. Psaty BM, Kuller LH, Bild D, Burke GL, Kittner SJ, Mittelmark M, et al. Methods of assessing prevalent cardiovascular disease in the Cardiovascular Health Study. Ann Epidemiol. 1995; 5:270–277. [PubMed: 8520708]

16. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care. 1999; 22:1462–1470. [PubMed: 10480510]

Table 1

Baseline characteristics of Cardiovascular Health Study participants without diabetes or history of stroke (n=3,442)*

	← More insulin resistant			Less insulin resistant →
	Quartiles of Gutt insulin sensitivity index (mg·L^2/mmol·mU·min)			
Characteristic, mean (SD) or %	**25.8 to 47 (n = 843)**	**>47 to 60 (n = 874)**	**>60 to 77 (n = 862)**	**>77 to 218.2 (n = 863)**
Age, y	72.9 (5.7)	72.8 (5.6)	72.7 (5.6)	72.1 (5.3)
Male sex, %	44.1%	38.9%	38.5%	47.3%
Black race, %	4.0%	3.2%	5.1%	3.9%
Fasting glucose, mmol/L†	5.8 (0.5)	5.6 (0.5)	5.4 (0.4)	5.3 (0.4)
2-hr glucose, mmol/L†	9.2 (1.0)	7.7 (1.0)	6.5 (0.9)	5.1 (0.9)
Fasting insulin, pmol/L†	121.5 (58.3)	94.5 (42.4)	83.3 (43.8)	72.9 (28.5)
2-hr insulin, pmol/L†	966.7 (486.2)	569.5 (224.3)	402.8 (164.6)	222.9 (93.1)
Body weight, kg	75.3 (14.2)	71.4 (13.8)	68.5 (13.5)	67.7 (12.9)
Waist circumference, cm	97.4 (12.0)	93.4 (12.3)	90.3 (11.8)	88.2 (11.9)
Physical activity, kcal/wk	1,788 (2,141)	1,921 (2,118)	1,847 (2,051)	1,998 (2,008)
eGFR <60 mL/min/1.73 m^2, %	43.7%	42.6%	36.7%	39.6%
Coronary heart disease, %	20.3%	17.3%	14.0%	16.1%
Congestive heart failure, %	5.0%	3.3%	2.3%	1.6%
Atrial fibrillation, %	3.0%	3.1%	1.6%	1.9%
Peripheral arterial disease, %	2.1%	2.5%	1.6%	2.1%
Systolic blood pressure, mmHg	137.2 (21.1)	136.2 (20.6)	133.8 (20.7)	130.0 (21.9)
Antihypertensive medication use, %	52.3%	38.3%	35.4%	32.1%
Triglyceride, mmol/L†	1.7 (0.7)	1.5 (0.6)	1.4 (0.6)	1.3 (0.5)
HDL cholesterol, mmol/L†	1.3 (0.3)	1.4 (0.4)	1.5 (0.4)	1.5 (0.4)
LDL cholesterol, mmol/L†	3.4 (0.9)	3.5 (0.9)	3.4 (0.9)	3.3 (0.9)

*Abbreviations: SD, standard deviation; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; LDL, low density lipoprotein.

†Conversions: glucose, mg/dL = (mmol/L)/0.0555; insulin, μU/mL = (pmol/L)/6.945; triglyceride, mg/dL = (mmol/L)/0.0113; HDL and LDL cholesterol, mg/dL = (mmol/L)/0.0259.

Table 2

Associations of Gutt insulin sensitivity index and its components with incident ischemic stroke, Cardiovascular Health Study, 1989-2007 (n = 3,442; strokes = 417)*

		Rate per	Unadjusted		Adjusted 1‡		Adjusted 2§	
Measure†	**Strokes**	**1,000 PY**	**RR**	**(95% CI)**	**RR**	**(95% CI)**	**RR**	**(95% CI)**
Gutt index (mg·L^2/mmol·mU·min)								
>77 to 218.2	86	7.7	1.00	(ref)	1.00	(ref)	1.00	(ref)
>60 to 77	90	8.3	1.08	(0.81, 1.46)	1.10	(0.81, 1.48)	1.03	(0.76, 1.39)
>47 to 60	112	10.6	1.38	(1.04, 1.83)	1.37	(1.03, 1.83)	1.24	(0.93, 1.65)
25.8 to 47	129	13.0	1.71	(1.30, 2.24)	1.64	(1.24, 2.16)	1.39	(1.05, 1.86)
p for trend				<0.001		<0.001		0.02
Fasting glucose (mmol/L)#								
3.2 to 5.2	111	9.2	1.00	(ref)	1.00	(ref)	1.00	(ref)
>5.2 to 5.4	99	10.0	1.09	(0.83, 1.43)	1.07	(0.82, 1.41)	1.07	(0.81, 1.40)
>5.4 to 5.8	111	10.1	1.10	(0.84, 1.43)	1.02	(0.78, 1.33)	0.94	(0.72, 1.23)
>5.8 to 6.9	96	10.2	1.12	(0.85, 1.47)	1.07	(0.81, 1.41)	0.94	(0.71, 1.25)
p for trend				0.43		0.73		0.51
Fasting insulin (pmol/L)#								
20.8 to 62.5	121	9.9	1.00	(ref)	1.00	(ref)	1.00	(ref)
>62.5 to 83.3	106	9.2	0.92	(0.71, 1.19)	0.92	(0.71, 1.20)	0.87	(0.66, 1.13)
>83.3 to 111.1	97	10.0	1.00	(0.77, 1.31)	1.04	(0.79, 1.37)	0.93	(0.71, 1.23)
>111.1 to 722.3	93	10.3	1.04	(0.80, 1.37)	1.10	(0.84, 1.46)	0.93	(0.69, 1.25)
p for trend				0.61		0.34		0.83
2-hour glucose (mmol/L)#								
2.1 to 5.8	84	7.4	1.00	(ref)	1.00	(ref)	1.00	(ref)
>5.8 to 7.0	94	8.7	1.19	(0.89, 1.60)	1.23	(0.91, 1.65)	1.13	(0.84, 1.52)
>7.0 to 8.4	100	9.4	1.28	(0.96, 1.71)	1.32	(0.98, 1.77)	1.18	(0.87, 1.59)
>8.4 to 11.0	139	14.4	1.98	(1.51, 2.60)	1.84	(1.39, 2.42)	1.57	(1.18, 2.09)
p for trend				<0.001		<0.001		0.001
2-hour insulin (pmol/L)#								

Measure†	Strokes	Rate per 1,000 PY	Unadjusted RR	Unadjusted (95% CI)	Adjusted 1‡ RR	Adjusted 1‡ (95% CI)	Adjusted 2§ RR	Adjusted 2§ (95% CI)
34.7 to 270.9	87	7.6	1.00	(ref)	1.00	(ref)	1.00	(ref)
>270.9 to 437.5	96	9.2	1.22	(0.91, 1.63)	1.24	(0.93, 1.67)	1.17	(0.87, 1.58)
>437.5 to 687.6	122	11.9	1.57	(1.19, 2.07)	1.57	(1.19, 2.07)	1.41	(1.07, 1.87)
>687.6 to 2,778.0	112	10.9	1.44	(1.09, 1.91)	1.43	(1.08, 1.90)	1.25	(0.93, 1.67)
p for trend				0.01		0.02		0.18
Body weight (kg)								
34.8 to 60	102	10.3	1.00	(ref)	1.00	(ref)	1.00	(ref)
>60 to 70	116	10.3	0.99	(0.76, 1.29)	0.99	(0.75, 1.31)	0.95	(0.72, 1.26)
>70 to 80	95	8.5	0.81	(0.62, 1.08)	0.84	(0.62, 1.15)	0.78	(0.57, 1.07)
>80 to 146.5	104	10.3	1.00	(0.76, 1.31)	1.07	(0.77, 1.48)	0.94	(0.67, 1.31)
p for trend				0.68		0.85		0.55

*Abbreviations: PY, person years; RR, relative risk; CI, confidence interval.

†For each measure, the reference category was the least insulin resistant quartile (highest quartile for Gutt index; lowest quartilefor each component).

‡Adjusted for age, sex, race, estimated glomerular filtration rate, coronary heart disease, congestive heart failure, atrial fibrillation, and peripheral arterial disease.

§Adjusted for all of the above plus systolic blood pressure, antihypertensive medication use, triglyceride, HDL cholesterol, and LDL cholesterol.

#Conversions: insulin, μU/mL = (pmol/L)/6.945; glucose, mg/dL = (mmol/L)/0.0555.