Insulin Resistance and Risk of Ischemic Stroke Among Nondiabetic Individuals From the Northern Manhattan Study

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Background: Whether insulin resistance predicts ischemic stroke (IS) is still a matter of debate.

Objective: To determine the association between insulin resistance (IR) and risk of first ischemic stroke in a large, multiethnic, stroke-free cohort without diabetes.

Design: Prospective, population-based cohort study.

Setting: Longitudinal epidemiologic study.

Participants: A cohort of 1509 nondiabetic participants from the Northern Manhattan Study (mean [SD] age, 11 [10] years; 64.2% women; 58.9% Hispanics).

Main Outcome Measures: Insulin sensitivity, expressed by the homeostasis model assessment (HOMA) of insulin sensitivity (HOMA index = [fasting insulin × fasting glucose]/22.5). Insulin resistance was defined by a HOMA-IR index in the top quartile (Q4). Cox proportional hazards models were used to determine the effect of HOMA-IR on the risk of incident IS, myocardial infarction (MI), vascular death, and combined outcomes (IS, MI, and vascular death).

Results: The mean (SD) HOMA-IR was 2.3 (2.1), and Q4 was at least 2.8. During mean follow-up of 8.5 years, vascular events occurred in 180 participants; 46 had fatal or nonfatal IS, 45 had fatal or nonfatal MI, and 121 died of vascular causes. The HOMA-IR Q4 vs less than Q4 significantly predicted the risk of IS only (adjusted hazard ratio, 2.83; 95% confidence interval, 1.34-5.99) but not other vascular events. This effect was independent of sex, race/ethnicity, traditional vascular risk factors, and metabolic syndrome and its components.

Conclusions: Insulin resistance estimated using the HOMA is a marker of increased risk of incident stroke in nondiabetic individuals. These findings emphasize the need to better characterize individuals at increased risk for IS and the potential role of primary preventive therapies targeted at IR.

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INSULIN RESISTANCE (IR) IS A METABOLIC disorder characterized by diminished tissue sensitivity to insulin that originates from environmental factors, such as a sedentary lifestyle, central obesity, and genetic predisposition.[1] Insulin resistance is a pivotal pathophysiologic contributor to the increased risk of cardiovascular disease.[2-5] Whether IR predicts ischemic stroke (IS) is still a matter of debate.[4,6-10] We have yet to clarify whether IR is a risk factor for incident IS in the general population after accounting for traditional vascular and metabolic risk factors. The gold standard for direct measurement of insulin sensitivity and secretion are the euglycemic hyperinsulinemic clamp methods, which are cumbersome and unsuitable for epidemiologic studies. The homeostasis model assessment (HOMA) is a widely used clinical and epidemiologic tool for indirect estimates of insulin sensitivity and insulin secretion.[11,12]

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The aim of this study was to determine whether baseline IR estimated using HOMA increases the risk of incident IS, myocardial infarction (MI), and vascular death in a large, multiethnic, population-based, stroke-free cohort without a diagnosis of diabetes. We[13,14] previously observed that impaired fasting glucose levels and metabolic syndrome are powerful predictors of incident IS. The present study extends these results to the predictive effect of IR.

METHODS

PARTICIPANTS

The Northern Manhattan Study (NOMAS) is a prospective, population-based cohort study of stroke incidence, risk factors, and prognosis in a multiethnic urban community. The methods for NOMAS have been extensively described elsewhere.[15,16] A total of 3298 stroke-free individuals were enrolled in NOMAS between 1993 and 2001. After excluding individuals with previously diagnosed diabetes or fasting glucose levels of at least 126 mg/dL (to convert to millimoles per liter, multiply by 0.0555) (n = 705; 21%), those with previous MI (n = 244; 7%), those without blood samples available for fasting insulin and glucose analysis (n = 1464; 44%), and those of a race/ethnicity other than black, white, or Hispanic (n = 79; 2%), a sample of 1509 stroke-free individuals was included in this study.

ANNUAL PROSPECTIVE FOLLOW-UP AND OUTCOME CLASSIFICATION

Participants were screened annually by telephone to determine any change in vital status, to detect neurologic and cardiac symptoms and events, and to review interval hospitalizations, risk factor status, medications, and changes in functional status. Persons with positive telephone interview screens were examined in person by the study neurologists and cardiologists. Incident IS was the primary outcome. The secondary outcomes were incident MI, vascular death, and any vascular event, defined as incident IS, MI, and vascular death combined. Follow-up procedures and outcome classifications have been detailed previously.[13,14]

EXPOSURE CLASSIFICATION

Baseline blood samples, collected after at least 12 hours of fasting, were assayed for insulin level using an analyzer (Immulite 2000; Diagnostic Products Corp, Los Angeles, California) and the manufacturer's reagents and a solid-phase, 2-site, chemiluminescent enzyme-labeled immunometric assay.[11,12] The HOMA-IR index was calculated as follows: [fasting insulin × fasting glucose]/22.5.

COVARIATE DEFINITIONS

Race/ethnicity was defined by self-identification based on a series of interview questions modeled after the US census.[15] The race/ethnic categorizations included Hispanic, non-Hispanic white, and non-Hispanic black. Individuals of another race/ethnicity were excluded from the analyses. Hypertension was defined as a self-reported history of hypertension or a measured systolic blood pressure of at least 140 mm Hg or diastolic blood pressure of at least 90 mm Hg. Smoking was categorized as never, former, and current (within 1 year). Moderate alcohol use was defined as current drinking of more than 1 drink per month and 2 drinks or fewer per day. Moderate to heavy physical activity was defined as engaging in recreational activities in a typical 14-day period. Waist circumference, low-density lipoprotein cholesterol level, high-density lipoprotein (HDL) cholesterol level, and systolic and diastolic blood pressures were examined as continuous variables. Metabolic syndrome was defined by the Third Report of the National Cholesterol Education Program Adult Treatment Panel.[17]

STATISTICAL ANALYSES

The HOMA-IR index was examined continuously and as quartiles to investigate a potential dose-response relationship or a threshold effect with vascular outcomes. The prevalence of sociodemographic characteristics (age, sex, race/ethnicity, and education), traditional vascular risk factors, and other baseline variables was stratified by the HOMA-IR status at the cutoff level of the top quartile (Q4) of the HOMA-IR distribution (Q4 = 2.8 or defined as the IR group).

Person-time of follow-up was accrued from baseline to the end of follow-up (January 2008), the time of the outcome event, death, or loss to follow-up, whichever came first. Cox proportional hazards models were used to determine the effect of IR on the risk of incident IS as a primary outcome and on the risk of MI, vascular death, and any vascular event as secondary outcomes. Univariate age-adjusted Cox models were conducted (model 1), as were multivariate-adjusted models controlling for sociodemographic factors (age, sex, race/ethnicity, and high school completion [model 2]), sociodemographic factors and metabolic syndrome (model 3), and sociodemographic factors and risk factors, including waist circumference, systolic and diastolic blood pressure, moderate alcohol consumption, HDL cholesterol level, moderate to heavy physical activity, and current/former smoking (model 4). Last, the 2 interaction terms, sex × HOMA-IR and race/ethnicity × HOMA-IR, were added to model 4 to examine potential effect modification by sex and race/ethnicity. Statistical analyses were conducted using a software program (SAS version 9.1; SAS Institute Inc, Cary, North Carolina).

In addition, we examined the potential for selection bias that can result from the use of a subset of the overall study population if inclusion is jointly affected by IR and risk of cardiovascular events. The population analyzed in this study (n = 1509) represented a subsample of the full NOMAS cohort (N = 3298) with available information on HOMA and meeting all the inclusion criteria. The potential for selection bias was examined by fitting logistic regression models using the observation indicators as response and follow-up times, uncensoring indicators, and risk factors as covariates. Based on this result, we conducted an inverse probability weighting method that adjusts potential selection bias of standard Cox proportional hazards regression variable estimates by weighting each record in the risk set by the inverse of the probability of observation.[18]

RESULTS

In 1509 individuals free of stroke, MI, and the diagnosis of diabetes, the mean (SD) age was 68 (11) years; 36% were male, and 59% were Hispanic, 21% black, and 21% white. The mean (SD) HOMA-IR index was 2.3 (2.1). A value of 2.8 was the cutoff point of the HOMA-IR index Q4 distribution (the IR group). The percentage of individuals in HOMA-IR Q4 was similar for men (23%) and women (26%) but varied across race/ethnic groups (15% for whites, 22% for blacks, and 30% for Hispanics, $P < .05$). A HOMA-IR value greater than 3 was present in 23% of participants (13% white, 18% black, and 69% Hispanic, $P < .05$).

Vascular risk factor characteristics stratified by IR (HOMA-IR Q4 and Q1-Q3) are presented in **Table 1**. Individuals in HOMA-IR Q4 were younger; were more likely to be Hispanic; had higher blood pressure, waist circumference, body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared), triglyceride levels, and fasting glucose levels; and had lower HDL cholesterol levels. They were less likely to be moderate alcohol users and to be physically active. **Table 2** provides baseline characteristics stratified by

Table 1. Vascular Risk Factor Profile of the Study Population

Variable	Overall Using HOMA (n=1509)	HOMA-IR Q1-Q3 (n=1132)	HOMA-IR Q4 (n=377)	No HOMA (n=747)
Age at baseline, mean (SD), y	67.8 (10.5)	68.1 (10.7)	66.9 (9.8)[a]	70.9 (11.0)[b]
Sex, %				
Male	35.9	37.0	32.4	36.4
Female	64.2	63.0	67.6	63.6
Race/ethnicity, %				
Black	21.0	21.5	17.8[a]	31.3[b]
White	21.0	23.4	12.2[a]	27.6[b]
Hispanic	59.0	55.1	70.0[a]	41.1[b]
Blood pressure, mean (SD), mm Hg				
Systolic	142.6 (21.2)	141.7 (21.4)	145.2 (20.6)[a]	142.9 (20.8)
Diastolic	83.4 (11.2)	82.7 (11.0)	85.7 (11.3)[a]	82.0 (11.5)[b]
Waist, mean (SD), inches	36.3 (4.7)	35.4 (4.4)	38.9 (4.8)[a]	36.4 (5.2)
BMI, mean (SD)	27.6 (5.1)	26.6 (4.5)	30.6 (5.7)[a]	27.2 (5.4)
Fasting glucose, mean (SD), mg/dL	87.7 (15.5)	79.7 (14.9)	87.5 (7.8)[a]	92.1 (24.1)[b]
Cholesterol level, mean (SD), mg/dL				
LDL	130.8 (34.9)	130.9 (34.7)	130.3 (35.9)	126.6 (35.5)[b]
HDL	47.4 (14.4)	48.8 (14.7)	42.9 (12.3)[a]	49.3 (15.6)[b]
Triglycerides, mean (SD), mg/dL	129.4 (69.9)	121.2 (60.9)	153.9 (87.6)[a]	131.7 (63.6)[b]
Current smoking, %	15.6	16.3	13.8	15.8
Former smoking, %	35.9	35.9	35.8	37.3
Moderate alcohol consumption, %	35.9	38.3	28.9[a]	34.1
Moderate-heavy physical activity, %	8.9	10.5	4.3[a]	9.9
Statin use, %	10.9	10.3	12.6	8.2[b]
Antiplatelet drug use, %	20.6	21.0	19.6	20.6

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HDL, high-density lipoprotein; HOMA, homeostasis model assessment; IR, insulin resistance; LDL, low-density lipoprotein; Q, quartile.

SI conversion factors: To convert cholesterol (HDL and LDL) to millimoles per liter, multiply by 0.0259; fasting glucose to millimoles per liter, multiply by 0.0555; triglycerides to millimoles per liter, multiply by 0.0113.

[a] $P<.05$ for the difference between those in HOMA Q1-Q3 vs HOMA Q4.

[b] $P<.05$ for the difference between those in the study cohort with HOMA available and those not included (no HOMA).

sex. Women were older and had a greater BMI and a higher low-density lipoprotein cholesterol level; men were predominantly smokers and moderate alcohol users and had higher diastolic blood pressures and waist circumferences. Although more women used statins, the overall use of statins was low. There was no difference in the use of antiplatelet agents.

Overall, 35% of the participants had metabolic syndrome (61% of those in HOMA-IR Q4 and 27% in the first 3 quartiles). The proportion of individuals in HOMA-IR Q4 was greater in those with vs without metabolic syndrome (43% vs 15%). In addition, the proportion of those in HOMA Q4 was also greater in individuals with vs without each component of metabolic syndrome ($P<.05$), particularly for elevated fasting glucose level (60% vs 23%) and waist circumference (40% vs 15%) (data not shown).

During mean follow-up of 8.5 years, 180 participants experienced 1 or more symptomatic vascular events. We observed 46 cases of fatal or nonfatal IS, 45 cases of fatal or nonfatal MI, and 121 vascular deaths. The incidence rate (per 1000 person-years) of IS was 3.5; MI, 3.5; and combined vascular events, 14.0.

Preliminary analyses using HOMA-IR as a continuous variable did not indicate a significant association with the risk of IS (age-adjusted relative risk [RR], 1.04; 95% confidence interval [CI], 0.90-1.19) or combined vascular events (age-adjusted RR, 1.03; 95% CI, 0.97-1.10). Analyses of HOMA-IR quartiles also did not show a dose-response relationship (in **Table 3** for IS only). After adjustment for covariates, a clear dose-response relationship was not apparent for IS (model 4, trend test $P=.08$) or for other events (eg, for combined vascular events in model 4, trend test $P=.74$) (data not shown). A threshold effect was observed in individuals in HOMA-IR Q4, where elevated risks of IS (HOMA-IR Q4 vs Q1 age-adjusted RR, 3.11; 95% CI, 1.25-7.76) and combined vascular events (HOMA-IR Q4 vs Q1 age-adjusted RR, 1.35; 95% CI, 0.91-2.00) (data not shown) were observed.

The HOMA-IR Q4 vs Q1-Q3 was associated with a significant 2.5-fold increased risk of IS in the age-adjusted analysis (RR, 2.47; 95% CI, 1.28-4.77) (Table 3). The association persisted in the model controlling for sociodemographic factors and metabolic syndrome (model 3: multivariate-adjusted RR, 2.43; 95% CI, 1.21-4.91) and in the model controlling for vascular risk factors (model 4: 2.83; 95% CI, 1.34-5.99).

The association between IR and risk of MI and vascular death as secondary outcomes was not significant (model 4: multivariate-adjusted RR for MI, 1.77; 95% CI, 0.88-3.58; for vascular death, 1.10; 0.69-1.74), suggesting that the effect of IR may not be as strong for MI and vascular death as for IS risk (Table 3).

The association between IR and risk of combined vascular events showed that individuals in HOMA-IR Q4 had a 45% increased risk of vascular events in the age-adjusted model (RR, 1.45; 95% CI, 1.04-2.03) (Table 3). This association persisted after controlling for demo-

graphic factors but was attenuated and no longer significant after controlling for metabolic syndrome status (model 3: RR, 1.37; 95% CI, 0.96-1.96) or after adjustment for vascular risk factors (model 4: 1.25; 0.86-1.82).

Table 2. Vascular Risk Factor Profile Stratified by Sex

Variable	Women (n=968 [64.1%])	Men (n=541 [35.9%])
Age at baseline, mean (SD), y[a]	68.8 (10.9)	66.0 (9.4)
Race/ethnicity, %		
Black	21.8	18.3
White	20.0	21.6
Hispanic	58.2	60.1
Blood pressure, mean (SD), mm Hg		
Systolic	143.2 (21.2)	141.5 (21.2)
Diastolic[a]	82.7 (10.9)	84.7 (11.6)
Waist, mean (SD), inches[a]	35.7 (5.0)	37.3 (4.0)
BMI, mean (SD)[a]	28.0 (5.6)	26.9 (4.1)
Fasting glucose, mean (SD), mg/dL	80.1 (15.5)	82.7 (7.6)
Cholesterol level, mean (SD), mg/dL		
LDL[a]	134.2 (35.2)	124.7 (33.7)
HDL[a]	50.4 (14.4)	41.9 (12.5)
Triglycerides, mean (SD), mg/dL	129.2 (66.5)	129.6 (75.7)
Current smoking, %[a]	14.1	18.5
Former smoking, %[a]	28.4	49.2
Moderate alcohol consumption, %[a]	29.0	48.3
Moderate or heavy physical activity, %	8.6	9.5
Statin use, %[a]	12.6	7.8
Antiplatelet drug use, %	20.1	21.7
HOMA Q4, %	26.3	22.6

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HDL, high-density lipoprotein; HOMA, homeostasis model assessment; LDL, low-density lipoprotein; Q4, top quartile.

SI conversion factors: To convert cholesterol (HDL and LDL) to millimoles per liter, multiply by 0.0259; fasting glucose to millimoles per liter, multiply by 0.0555; triglycerides to millimoles per liter, multiply by 0.0113.

[a] $P < .05$ for the difference between men and women.

Effect modification by sex was suggested for the association between HOMA-IR and IS (an interaction term between the HOMA-IR Q4 and sex was significant in the multivariate-adjusted model, $P < .05$). A significant association between IR and risk of IS was observed in men (HOMA-IR Q4 vs Q1-Q3 in model 4: multivariate-adjusted RR, 10.86; 95% CI, 3.04-38.82) but not in women (model 4: 1.27; 0.41-3.92) (data not shown). No effect modification by race/ethnicity was observed.

To test for potential inclusion bias of standard Cox regression parameter estimates, we conducted the analysis by weighting each record in the stroke risk set by the inverse of the probability of observation, which suggested that even after correcting for potential bias due to inclusion of those with available HOMA, the conclusions remained unchanged because the association between IR (HOMA Q4) and risk of IS remained statistically significant.

COMMENT

In this multiethnic, prospective, population-based cohort study of nondiabetic individuals, we report that IR estimated using HOMA in Q4 (vs Q1-Q3) is associated with a 2.8-fold increased risk of first IS but not with other vascular events. Adjustment for established cardiovascular risk factors, including glucose level, obesity, and metabolic syndrome, did not attenuate the association with IS. We also observed a stronger association between IR and first IS in men than in women but not in any specific race/ethnic groups. The potential effect modification of this relationship by sex and race/ethnicity deserves further exploration in larger, ethnically diverse prospective cohorts.

There are several possible reasons for the stronger effect of IR on the risk of IS than of MI in the present study compared within the other studies. First, racial/ethnic dis-

Table 3. Relation Between HOMA-IR Quartiles and Risk of Ischemic Stroke, Myocardial Infarction, Vascular Death, and Combined Vascular Events

	Hazard Ratio (95% CI)			
Adjusted for	Model 1: Age	Model 2: Sociodemographics[a]	Model 3: Sociodemographics and Metabolic Syndrome	Model 4: Multivariate Adjusted[b]
Ischemic stroke				
HOMA	Trend $P = .04$	Trend $P = .06$	Trend $P = .07$	Trend $P = .08$
Q1	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Q2	1.88 (0.72-4.87)	1.87 (0.71-4.89)	1.87 (0.71-4.91)	1.59 (0.58-4.33)
Q3	0.93 (0.29-2.95)	0.87 (0.27-2.81)	0.88 (0.27-2.86)	0.65 (0.18-2.36)
Q4	3.11 (1.25-7.76)	2.98 (1.16-7.62)	3.01 (1.13-8.04)	2.97 (1.05-8.35)
HOMA Q4 vs Q1-Q3	2.47 (1.28-4.77)	2.40 (1.23-4.67)	2.43 (1.21-4.91)	2.83 (1.34-5.99)
Myocardial infarction				
HOMA Q4 vs Q1-Q3	1.87 (1.00-3.48)	1.79 (0.94-3.39)	1.48 (0.76-2.88)	1.77 (0.88-3.58)
Vascular death				
HOMA Q4 vs Q1-Q3	1.27 (0.84-1.93)	1.34 (0.87-2.05)	1.25 (0.80-1.96)	1.10 (0.69-1.74)
Combined vascular events				
HOMA Q4 vs Q1-Q3	1.45 (1.04-2.03)	1.52 (1.08-2.14)	1.37 (0.96-1.96)	1.25 (0.86-1.82)

Abbreviations: CI, confidence interval; HOMA, homeostasis model assessment; IR, insulin resistance; Q, quartile.

[a] Adjusted for age, sex, race/ethnicity, and high school education.

[b] Adjusted for age, sex, race/ethnicity, high school education, waist circumference, diastolic blood pressure, systolic blood pressure, moderate alcohol consumption, high-density lipoprotein cholesterol level, moderate to heavy physical activity, and cigarette smoking (never, former, current).

parities in the different effects of IR on the risk of stroke or MI may be one of the possible explanations. This population-based study consisted of predominantly Hispanic participants compared with the predominantly white population of the Framingham Offspring Study and the Multi-Ethnic Study of Atherosclerosis.[6,7] Hispanic and black participants in the present population are at particularly greater risk for stroke than are white participants[19] and have a higher prevalence of metabolic syndrome and a greater effect of the metabolic syndrome on the risk of stroke than of MI compared with white participants.[16] Hispanic and black participants also had a higher prevalence of IR than did white participants in this study, which might have had a greater effect on the risk of stroke than of MI. The present study, however, had limited power to explore predictive effect modification of IR by race/ethnicity. Second, we excluded individuals with a history of MI, which may be another explanation for the smaller predictive effect of IR on incident MI compared with other studies that included individuals with prevalent MI. Third, IR has been associated with subclinical atherosclerosis and, therefore, may be more likely linked to IS due to small- or large-vessel atherosclerosis than due to cardioembolism. Small- and large-vessel atherosclerotic strokes were more frequent IS subtypes in Hispanic patients than in white participants in a previous study.[19] Fourth, IR is associated with hypertension, hypertriglyceridemia, and low HDL cholesterol levels (as noted in Table 1), which may be more closely and specifically linked to IS than to MI. This may be especially important in black and Hispanic participants. Because IR drives high triglyceride levels and low HDL cholesterol levels, IR may have a relatively greater effect on stroke than on MI given that low-density lipoprotein cholesterol is less strongly related to stroke. In addition, HDL cholesterol levels are lower in men than in women, which also might have contributed to the stroke sex-specific differential effect of IR in the present study.

The risk of incident IS in the present population (adjusted hazard ratio of 2.8) is higher than that reported in other population-based studies even after adjusting for metabolic syndrome. In large population-based studies[2,4,6,20,21] of nondiabetic participants in the highest 20th to 30th percentile of IR, the adjusted hazard ratio of stroke ranged from 1.5 to 2.6, but in most studies, this effect was lost after adjusting for components of metabolic syndrome. Although a resistance to insulin action may provide the unifying mechanism of metabolic syndrome, the results of the present study suggest that metabolic syndrome (as defined by the Third Report of the National Cholesterol Education Program Adult Treatment Panel) may not capture all the vascular risk associated with IR, raising the possibility that other pathways affected by IR, such as inflammation, may be important.[22]

We observed a greater effect of IR on risk of first IS in men than in women, although the prevalence of IR was similar. Reasons for the sex-specific differential effect remain unclear. Complex interactions between IR and sex-specific vascular risk factor profiles (eg, smoking or higher blood pressure in men),[23,24] sex differences in insulin action,[25] and its biological effects on the atherosclerotic process[26] may have accounted for the observed difference in the risk of stroke between men and women.

The strengths of the present study include a prospective population-based design with thorough case ascertainment, confirmation of diagnosis, a well-documented baseline exposure, and comprehensive prospectively collected data on established risk factors for cardiovascular disease. The aggressive follow-up strategies resulted in less than 1% loss to follow-up. Study participants were seen in person at study enrollment and follow-up, whenever possible, to document outcome events. The inclusion of a large multiethnic, elderly, heterogeneous cohort with similar geographic access to the medical center is generalizable to other multiethnic urban populations and allows for more valid comparisons across race/ethnic categories. However, the power to detect effect modification by race/ethnicity may be limited in the present study. Additional limitations include the potential for residual confounding, the 1-time exposure measurement, and the limited statistical power of the stroke analysis. These results, therefore, must be interpreted with caution. Owing to the lack of a dose-response relation and the possibility of chance findings, further exploration with larger data sets and more end points is necessary. It is likely that because of the small number of end points we did not observe an effect of HOMA-IR on MI. Another possible explanation may be the fact that HOMA-IR is a relatively blunt instrument for estimating reduced sensitivity to insulin, although, in general, HOMA-IR values correlate reasonably well with clamp-derived gold standard values.[27]

The present study provides evidence that IR as measured using HOMA is independently associated with an increased risk of first IS. Insulin resistance may be a novel therapeutic target for stroke prevention. Clinical trials, such as the Insulin Resistance Intervention after Stroke trial[20] in participants with stroke and transient ischemic attack and the Veterans Affairs High-Density Lipoprotein Intervention Trial[5] in patients with coronary heart disease, have shown improved insulin sensitivity and β-cell function after treatment with certain classes of drugs, such as a peroxisome proliferator-activated receptor γ-agonist or cholesterol-lowering drugs. In addition to secondary stroke prevention, future studies are needed to determine whether the treatment of IR can reduce the risk of incident stroke and cardiovascular disease.

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