Insulin Sensitivity and Insulin Secretion Determined by Homeostasis Model Assessment and Risk of Diabetes in a Multiethnic Cohort of Women

The Women's Health Initiative Observational Study

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OBJECTIVE — The homeostasis model assessment (HOMA), based on plasma levels of fasting glucose and insulin, has been widely validated and applied for quantifying insulin resistance and β-cell function. However, prospective data regarding its relation to diabetes risk in ethnically diverse populations are limited.

RESEARCH DESIGN AND METHODS — Among 82,069 women who were aged 50–79 years, free of cardiovascular disease or diabetes, and participating in the Women's Health Initiative Observational Study, we conducted a nested case-control study to prospectively examine the relations of HOMA of insulin resistance (HOMA-IR) and β-cell function (HOMA-B) with diabetes risk. During a median follow-up period of 5.9 years, 1,584 diabetic patients were matched with 2,198 control subjects by age, ethnicity, clinical center, time of blood draw, and follow-up time.

RESULTS — Baseline levels of fasting glucose, insulin, and HOMA-IR were each significantly higher among case compared with control subjects, while HOMA-B was lower (all *P* values <0.0001). After adjustment for matching factors and diabetes risk factors, all four markers were significantly associated with diabetes risk; the estimated relative risks per SD increment were 3.54 (95% CI 3.02–4.13) for fasting glucose, 2.25 (1.99–2.54) for fasting insulin, 3.40 (2.95–3.92) for HOMA-IR, and 0.57(0.51–0.63) for HOMA-B. While no statistically significant multiplicative interactions were observed between these markers and ethnicity, the associations of both HOMA-IR and HOMA-B with diabetes risk remained significant and robust in each ethnic group, including whites, blacks, Hispanics, and Asians/Pacific Islanders. When evaluated jointly, the relations of HOMA-IR and HOMA-B with diabetes risk appeared to be independent and additive. HOMA-IR was more strongly associated with an increased risk than were other markers after we excluded those with fasting glucose ≥126 mg/dl at baseline.

CONCLUSIONS — High HOMA-IR and low HOMA-B were independently and consistently associated with an increased diabetes risk in a multiethnic cohort of U.S. postmenopausal women. These data suggest the value of HOMA indexes for diabetes risk in epidemiologic studies.

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Insulin resistance and progressive pancreatic β-cell dysfunction have been identified as the two fundamental features in the pathogenesis of type 2 diabetes. As a widely validated clinical and epidemiological tool for estimating insulin resistance and β-cell function, the homeostasis model assessment (HOMA) is derived from a mathematical assessment of the balance between hepatic glucose output and insulin secretion from fasting levels of glucose and insulin (1,2). The HOMA model requires only a single measurement of insulin and glucose in the basal state and is thus considered an alternative in large-scale epidemiologic studies to the sophisticated "gold standard" methods that usually require dynamic data via costly and invasive procedures. The HOMA of insulin resistance (HOMA-IR) index, the product of basal glucose and insulin levels divided by 22.5 (1,2), is regarded as a simple, inexpensive, and reliable surrogate measure of insulin resistance, while the HOMA of β-cell function (HOMA-B) index, computed as the product of 20 and basal insulin levels divided by the value of basal glucose concentrations minus 3.5, has been proposed to be a good measure of β-cell function (2).

Previous cross-sectional studies have shown that both high HOMA-IR and low HOMA-B were associated with increased prevalences of impaired glucose tolerance (IGT) and type 2 diabetes in Japanese (3), Mexican-American (4), and non-Hispanic (4) white subjects. Several prospective studies have shown the role of either HOMA-IR or HOMA-B or both in

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Abbreviations: HOMA, homeostasis model assessment; HOMA-B, HOMA of β-cell function; HOMA-IR, HOMA of insulin resistance; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; WHI-OS, Women's Health Initiative Observational Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Baseline characteristics of diabetic case and control subjects

Characteristic	Case subjects	Control subjects	*P*†
n	1,584	2,198	—
Age (years)	62.7 ± 7.0	62.3 ± 7.0	—
BMI (kg/m^2)	32.3 ± 7.0	27.6 ± 5.9	<0.0001
Waist circumference (inches)	38.2 ± 6.0	32.8 ± 5.0	<0.0001
Waist-to-hip ratio	0.86 ± 0.08	0.80 ± 0.07	<0.0001
Ethnicity			
White	968 (61.1)	968 (44.0)	—
Black	366 (23.1)	732 (33.3)	—
Hispanic	152 (9.60)	303 (13.8)	—
Asian/Pacific Islanders	98 (6.21)	195 (8.85)	—
Family history of diabetes	849 (57.5)	772 (37.9)	<0.0001
Current hormone therapy	34.2	43.7	<0.0001
Smoking status			0.02
Never	50.3	55.8	—
Past	42.0	37.4	—
Current	7.74	6.82	—
Alcohol use			<0.0001
Nondrinker	17.3	16.1	—
Past drinker	27.2	21.5	—
<1 drink/month	15.9	13.1	—
≥1 drink/month to <1 drink/week	20.7	20.3	—
≥1 drink/week	18.9	28.9	—
Physical activity (MET · h^{-1} · week^{-1})	9.84 ± 12.4	12.8 ± 14.4	<0.0001
Biomarkers			
Fasting insulin (μIU/ml)	12.6 (8.14–18.6)	6.40 (4.40–9.61)	<0.0001
Fasting glucose (mmol/ml)	6.78 (5.89–8.17)	5.11 (4.83–5.44)	<0.0001
HOMA-IR	4.03 (2.48–6.28)	1.44 (0.97–2.27)	<0.0001
HOMA-B	75.1 (44.6–118)	81.7 (56.1–120)	<0.0001

Data are means ± SD, *n* (%), percentages, or median (interquartile range) unless otherwise indicated. Medians and interquartile ranges are provided for continuous variables with skewed distributions. *Case and control subjects were matched on age, race/ethnicity, clinical center, time of blood draw, and duration of follow-up. †*P* values for the difference between patients and control subjects were determined by mixed-effects regression for continuous variables and by a matched χ^2 test for variables expressed as percentages.

predicting future risk of type 2 diabetes and/or IGT in diverse populations (5–10). However, whether the relation between HOMA indexes and risk of type 2 diabetes differs by ethnicity is unknown. Furthermore, the comparative importance of HOMA-IR and HOMA-B in relation to risk of type 2 diabetes has been less well studied. In addition, most studies have included both men and women (5–10) and lacked statistical power to detect meaningful results for women.

We therefore prospectively examined whether HOMA-IR and HOMA-B were consistently associated with diabetes risk among apparently healthy American women aged over 50 years from the Women's Health Initiative Observational Study (WHI-OS), an ethnically diverse cohort of postmenopausal women including whites, blacks, Hispanics, and Asian/Pacific Islanders.

RESEARCH DESIGN AND METHODS

— The WHI-OS is an ongoing longitudinal study designed to examine the association between clinical, socioeconomic, behavioral, and dietary risk factors and subsequent incidence of health outcomes, including cardiovascular disease and diabetes. Details of the scientific rationale, eligibility, and other design aspects have been published elsewhere (11). Between September 1994 and December 1998, the WHI-OS enrolled a total of 93,676 women aged 50–79 years at 40 clinical centers throughout the U.S. At baseline, women completed screening and enrollment questionnaires, underwent a physical examination, and provided fasting blood samples (after an overnight fast for at least 12 h). WHI-OS participants were followed by annually mailed, self-administered questionnaires and an additional clinical center visit at 3 years after enrollment.

The study has been reviewed and approved by human subjects review committees at each participating institution, and signed informed consent was obtained from all women enrolled.

Ascertainment of case and control subjects

Among 82,069 (87.6%) postmenopausal women free of cardiovascular disease and diabetes at baseline, 1,584 women who had self-reported first-time use of hypoglycemic medication (oral agents or insulin) during a median follow-up of 5.9 years (mean 5.5 years) were chosen as incident case subjects and matched with 2,198 control subjects on age (±2.5 years), ethnicity (White/Caucasian, Black/African, Hispanic/Latino, and Asian/Pacific Islander), clinical center, time of blood draw (±0.10 h), and length of follow-up. Of these, 968 case subjects among whites were matched with one control subject each, and 366, 152, and 98 case subjects among ethnic minority women were matched with two control subjects each for Black, Hispanic, and Asian/Pacific Islanders, respectively. The 1:2 matching ratio was used for minorities to strengthen the power in these smaller sample sizes of cases. Our study did not include American Indian or native Alaskan women because of their limited sample size.

Biochemical measurement

All biochemical assays were carried out by laboratory staff blinded to case/control status. Blood samples from case and their matched control subjects were handled identically, shipped in the same batch, thawed, and assayed in random order in the same analytical run to reduce systematic bias and interassay variation. Glucose was measured enzymatically on the Hitachi 911 analyzer using Roche Diagnostics regents (Indianapolis, IN). Insulin was measured by an ultrasensitive enzyme-linked immunosorbent assay from ALPCO Diagnostics (Windham, NH). The coefficients of variation were 1.7% for glucose and 5.8% for insulin.

Statistical analysis

HOMA-IR was computed as follows: fasting insulin (μIU/ml) × fasting glucose (mmol/ml)/22.5. HOMA-B was calculated using the following formula: 20 ×

Table 2—*RRs of diabetes according to per SD increment of HOMA-based markers*

	RR (95% CI)*				
	Total women	White women	Black women	Hispanic women	Asian/Pacific Islander women
Entirety of case-control samples					
Adjusted for matching factors†					
Fasting glucose	3.65 (3.22–4.14)	4.12 (3.33–5.09)	3.01 (2.49–3.62)	3.37 (2.44–4.64)	6.26 (3.40–11.5)
Fasting insulin	2.72 (2.48–2.99)	3.36 (2.89–3.91)	2.17 (1.86–2.53)	2.31 (1.82–2.93)	2.67 (1.94–3.68)
HOMA-IR	3.57 (3.20–3.98)	4.52 (3.75–5.45)	2.83 (2.39–3.36)	3.17 (2.39–4.19)	3.52 (2.41–5.14)
HOMA-B	0.82 (0.77–0.87)	0.89 (0.82–0.96)	0.69 (0.61–0.78)	0.73 (0.61–0.88)	1.00 (0.79–1.26)
Multivariable model 1‡					
Fasting glucose	3.54 (3.02–4.13)	3.94 (3.03–5.13)	3.18 (2.45–4.14)	3.62 (2.27–5.76)	17.5 (2.74–112)
Fasting insulin	2.25 (1.99–2.54)	2.57 (2.11–3.12)	1.93 (1.56–2.40)	1.79 (1.29–2.48)	3.04 (1.82–5.08)
HOMA-IR	3.40 (2.95–3.92)	4.24 (3.33–5.39)	2.78 (2.20–3.52)	2.85 (1.95–4.15)	4.68 (2.53–8.66)
HOMA-B	0.57 (0.51–0.63)	0.54 (0.47–0.63)	0.53 (0.43–0.64)	0.54 (0.40–0.72)	0.69 (0.48–1.00)
Multivariable model 2§					
Fasting glucose	3.37 (2.88–3.95)	3.76 (2.88–4.92)	3.10 (2.37–4.04)	3.40 (2.14–5.40)	24.2 (1.57–373)
Fasting insulin	1.90 (1.67–2.17)	2.10 (1.70–2.58)	1.72 (1.37–2.16)	1.58 (1.12–2.22)	2.68 (1.52–4.73)
HOMA-IR	3.05 (2.63–3.53)	3.79 (2.94–4.88)	2.59 (2.03–3.30)	2.66 (1.80–3.91)	4.18 (2.18–8.04)
HOMA-B	0.52 (0.46–0.58)	0.50 (0.42–0.59)	0.48 (0.39–0.60)	0.49 (0.35–0.68)	0.59 (0.37–0.93)
After fasting glucose–based exclusion¶					
Adjusted for matching factors†					
Fasting glucose	3.73 (3.21–4.35)	4.14 (3.23–5.32)	3.08 (2.43–3.90)	3.53 (2.42–5.16)	6.05 (3.11–11.8)
Fasting insulin	2.28 (2.04–2.56)	2.78 (2.31–3.35)	1.74 (1.45–2.09)	2.16 (1.59–2.94)	2.70 (1.74–4.19)
HOMA-IR	2.62 (2.32–2.96)	3.18 (2.59–3.89)	2.00 (1.65–2.42)	2.53 (1.82–3.52)	3.37 (2.05–5.55)
HOMA-B	1.25 (1.14–1.38)	1.51 (1.31–1.74)	0.96 (0.81–1.13)	1.14 (0.88–1.48)	1.36 (0.97–1.91)
Multivariable model 1‡					
Fasting glucose	3.54 (2.92–4.30)	3.75 (2.75–5.12)	3.35 (2.34–4.79)	3.80 (2.21–6.55)	15.8 (2.48–100.5)
Fasting insulin	1.88 (1.61–2.19)	2.16 (1.68–2.78)	1.53 (1.16–2.02)	1.62 (1.09–2.40)	3.02 (1.52–5.99)
HOMA-IR	2.30 (1.95–2.71)	2.75 (2.10–3.61)	1.87 (1.40–2.50)	1.96 (1.29–2.98)	3.94 (1.78–8.68)
HOMA-B	0.88 (0.77–1.01)	0.90 (0.74–1.11)	0.71 (0.55–0.92)	0.80 (0.56–1.15)	1.30 (0.78–2.16)
Multivariable model 2§					
Fasting glucose	3.33 (2.74–4.06)	3.53 (2.58–4.85)	3.24 (2.24–4.70)	3.55 (2.05–6.15)	145 (0.19–111,426)#
Fasting insulin	1.62 (1.38–1.91)	1.88 (1.44–2.46)	1.34 (1.00–1.81)	1.38 (0.90–2.11)	4.95 (1.46–16.7)
HOMA-IR	2.03 (1.71–2.41)	2.46 (1.84–3.28)	1.68 (1.24–2.27)	1.73 (1.11–2.71)	10.0 (1.50–66.8)
HOMA-B	0.77 (0.66–0.89)	0.81 (0.65–1.02)	0.62 (0.47–0.83)	0.68 (0.46–1.01)	1.25 (0.61–2.56)

Data are RRs (95% CIs). *RRs for predictors as continuous variables were RR per 1 SD for log-transformed values; each SD was equivalent to each increase of 1.11 mmol/l in fasting glucose, 1.84 uIU/ml in fasting insulin, 1.93 in HOMA-IR, and 1.79 in HOMA-%B. †Matching factors included age, race/ethnicity, clinical center, and time of blood draw. ‡Model 1 was adjusted for matching factors, BMI, alcohol intake, level of physical activity, cigarette smoking status, the use or nonuse of postmenopausal hormone therapy, and family history of diabetes. §Model 2 made additional adjustment for waist-to-hip ratio in model 1. ¶After excluding women who had a single measure of fasting glucose ≥126 mg/dl at baseline. #Due to very low statistical power, this RR estimate and its variability became unusually large.

fasting insulin (μIU/ml)/fasting glucose (mmol/ml) − 3.5. Basal fasting glucose, insulin, and two derived HOMA indexes were not normally distributed and were thus logarithmically transformed. Age- and ethnicity-adjusted Pearson's partial correlation coefficients were calculated to evaluate associations between these markers among control subjects. We performed a conditional logistic regression model to estimate the odds ratio (OR) per each SD increment in each of markers (in log scale) because there was a significant linear relationship with diabetes risk for each of them. Since risk-set sampling was used for our matched case-control pairs, the ORs yield unbiased estimates of the relative risks (RRs). In the matched analyses, we adjusted for matching factors such as age, ethnicity, clinical center, and time of blood draw. In multivariate analyses, we adjusted for BMI (modeled as a continuously distributed covariate), family history of diabetes (yes or no), smoking (never, past, or current), alcohol intake (never, past, or current), physical activity (quintiles), and current postmenopausal hormone use (yes or no). A likelihood ratio test was used to test statistical significance of interactions by ethnicity.

We also conducted subgroup analyses to examine potential interactions by levels of prespecified factors including BMI (<25 and ≥25 kg/m^2), waist (<35 and ≥35 inches), hormone use (yes/no), physical activity (less than and more than/equal to the median), and family history of diabetes (yes/no). A likelihood ratio test was performed to test significances.

To evaluate the joint relationship between HOMA-IR and HOMA-B, we divided the study population into four groups according to their median cut points in control subjects (HOMA-IR <1.44 and ≥1.44; HOMA-B <81.7 and ≥81.7) and estimated each subgroup-specific OR.

To address the concern about undiagnosed diabetes at baseline, we conducted secondary analyses by excluding case and control subjects with a fasting glucose ≥126 mg/dl at baseline. We further excluded incident case subjects diagnosed

Table 3—*RRs of diabetes according to HOMA-based markers stratified by BMI, waist, physical activity, hormone therapy use, and family history of diabetes*

Variable	Fasting glucose		Fasting insulin		HOMA-IR		HOMA-B	
	RR (95% CI)*	*P* for interaction‡	RR (95% CI)*	*P* for interaction‡	RR (95% CI)*	*P* for interaction‡	RR (95% CI)*	*P* for interaction‡
BMI (kg/m^2)								
<25	15.5 (2.09–115)	0.53	1.36 (0.85–2.17)	0.03	2.61 (1.46–4.66)	0.03	0.24 (0.12–0.50)	0.06
≥25	3.53 (2.88–4.32)	—	2.31 (1.97–2.70)	—	3.66 (3.02–4.44)	—	0.56 (0.50–0.64)	—
Waist circumference (inches)								
<35	4.21 (2.99–5.94)	0.94	1.90 (1.51–2.38)	0.42	3.04 (2.33–3.97)	0.28	0.45 (0.36–0.56)	0.40
≥35	5.35 (3.29–8.70)	—	2.43 (1.87–3.14)	—	4.26 (3.05–5.96)	—	0.53 (0.43–0.65)	—
Physical activity (MET · h^{-1} · week^{-1})†								
<Median	3.98 (2.86–5.53)	0.98	2.11 (1.70–2.62)	0.86	3.12 (2.44–3.97)	0.87	0.53 (0.44–0.64)	0.36
≥Median	3.01 (2.26–3.98)	—	1.92 (1.49–2.46)	—	2.92 (2.20–3.88)	—	0.52 (0.42–0.64)	—
Current hormone use								
Yes	3.05 (2.19–4.23)	0.41	2.10 (1.56–2.84)	0.43	2.98 (2.14–4.15)	0.96	0.61 (0.48–0.78)	0.16
No	3.40 (2.69–4.29)	—	2.12 (1.78–2.53)	—	3.20 (2.60–3.93)	—	0.54 (0.47–0.63)	—
Family history of diabetes								
Yes	3.60 (2.63–4.94)	0.39	1.98 (1.58–2.48)	0.83	3.10 (2.39–4.03)	0.29	0.44 (0.36–0.55)	0.12
No	3.39 (2.53–4.54)	—	2.08 (1.67–2.58)	—	3.02 (2.35–3.90)	—	0.58 (0.49–0.70)	—

RRs for predictors as continuous variables were RR per 1 SD for log-transformed values; each SD was equivalent to each increase of 1.11 mmol/l in fasting glucose, 1.84 uIU/ml in fasting insulin, 1.93 in HOMA-IR, and 1.79 in HOMA-B. *The multivariable model was adjusted for matching factors, BMI, alcohol intake, level of physical activity, cigarette smoking status, the use or nonuse of postmenopausal hormone therapy, and family history of diabetes. †Median for physical activity was 8.333 metabolic equivalent (MET) · h^{-1} · week^{-1}. ‡Log likelihood ratio test was performed to test interactions.

during the 1st year of follow-up who were more likely to have undiagnosed diabetes at baseline.

All analyses were performed with the use of SAS software (version 9.1; SAS Institute, Cary, NC). All *P* values were two tailed.

RESULTS — Overall, diabetes case subjects had a higher prevalence of traditional diabetes risk factors at baseline than control subjects (Table 1). As expected, women with diabetes had significantly higher levels of baseline fasting insulin, glucose, and HOMA-IR and lower HOMA-B than their matched control subjects (all *P* values < 0.0001).

Fasting insulin levels were almost completely correlated with HOMA-IR ($r = 0.99$) and highly correlated with HOMA-B ($r = -0.84$). Fasting glucose was strongly associated with HOMA-IR ($r = 0.51$) and modestly associated with HOMA-B ($r = -0.17$). The two HOMA indexes were also correlated with each other ($r = -0.76$). HOMA-IR was more strongly correlated with BMI and waist-to-hip ratio than was HOMA-B.

After adjustment for matching factors, increasing levels of fasting glucose, insulin, and HOMA-IR were significantly associated with an increased risk of diabetes, while HOMA-B was significantly associated with a lower risk of diabetes (Table 2). Further adjustment for BMI, alcohol intake, physical activity, smoking, postmenopausal hormone use, and family history of diabetes attenuated the positive associations of fasting glucose, insulin, and HOMA-IR but strengthened the inverse association of HOMA-B (model 1). When waist-to-hip ratio was further adjusted, similar changes were observed (model 2).

In the same multivariable models stratified by ethnicity (Table 2), fasting glucose, insulin, and HOMA-IR appeared to be strongly associated with diabetes risk in each of four ethnic groups, while HOMA-B retained significant associations with diabetes in whites, blacks, and Hispanics in all models but not in Asian/Pacific Islanders because of small sample size. The RR estimates for fasting glucose also tended to be unstable, with a wide 95% CI in Asian/Pacific Islanders. However, the ethnic differences in these associations did not reach statistical significance when tested for a formal interaction.

After we excluded 736 case and 26 control subjects with a fasting glucose ≥126 mg/dl at baseline (Table 2), fasting

Table 4—*RRs of diabetes according to different levels of HOMA-IR and HOMA-B*

HOMA-IR	HOMA-B	Case/control subjects	Matching factor adjusted*	Model 1†	Model 2‡
Low	High	21/236	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Low	Low	140/861	1.72 (1.02–2.92)	1.92 (1.91–4.29)	2.01 (1.09–3.68)
High	High	696/860	9.97 (5.99–16.6)	5.34 (2.96–9.62)	3.97 (2.19–7.19)
High	Low	721/236	36.9 (21.7–62.8)	24.9 (13.4–46.2)	19.5 (10.5–36.3)

Data are RRs (95% CIs) unless otherwise indicated. High and low levels of HOMA-IR and HOMA-B were based on a median split among controls; the median cut points were 1.439 for HOMA-IR and 81.7 for HOMA-B. *Matching factors included age, race/ethnicity, clinical center, and time of blood draw. †Model 1 was adjusted for matching factors, BMI, alcohol intake, level of physical activity, cigarette smoking status, the use or nonuse of postmenopausal hormone therapy, and family history of diabetes. ‡Model 2 additionally adjusted for waist-to-hip ratio in model 1.

insulin and HOMA-IR remained significantly associated with diabetes risk with stable estimates in all women and all ethnic groups, although the association strength was stronger for HOMA-IR than for insulin. Notably, due to decreased statistical power, the RR estimate variability became unusually large for fasting glucose, and the direction for the association of HOMA-B and diabetes risk was even changed after additional controlling for diabetes risk factors (Table 2).

The positive associations with diabetes were evident for HOMA-IR and fasting insulin in women with a BMI ≥25 kg/m^2 (both *P* values for interaction = 0.03). No significant effect modifications were observed for other factors (Table 3).

Compared with women who had low HOMA-IR and high HOMA-B, those with high HOMA-IR and low HOMA-B had the highest RRs (Table 4). Low HOMA-B was consistently associated with an increased risk of diabetes regardless of HOMA-IR levels. Likewise, HOMA-IR was positively associated with diabetes risk among women with either low HOMA-B or high HOMA-B.

CONCLUSIONS — In this prospective, nested, case-control study from a large-scale, multiethnic cohort of postmenopausal women, we confirm that both HOMA-IR and HOMA-B derived from basal levels of fasting insulin and glucose were consistently associated with diabetes risk. These associations were independent of BMI and waist-to-hip ratio as well as other conventional diabetes risk factors. No statistically significant multiplicative interactions by ethnicity were noted. When evaluated jointly, the associations of HOMA-IR and HOMA-B with diabetes risk tended to be independent and additive, with the highest RR of diabetes associated with high HOMA-IR and low HOMA-B.

The HOMA model is the most widely used surrogate measure for assessing insulin resistance and β-cell function in clinical and epidemiologic studies (2,7). The HOMA model was initially proposed by Matthews et al. (1) in 1985 and was considered a structural model of the underlying physiological basis for the feedback loop between the liver and the β-cell in fasting (2). The simplified formulae were derived from a mathematical assessment of the balance between hepatic glucose output and insulin secretion from basal levels of both glucose and insulin (1,2). The validity of HOMA-IR has been evaluated by comparison with the physiologic measures of insulin sensitivity by some gold standard methods in individuals with normal glucose tolerance (NGT), those with IGT, and diabetic patients. HOMA-IR has been shown to correlate well with insulin resistance index derived from the euglycemic clamp (NGT individuals: $r = 0.40–0.58$ [12,13], diabetic patients: $r = 0.57–0.73$ [12,14,15], and combined diabetic and nondiabetic individuals: $r = 0.56–0.82$ [12,16]) and from directly measured insulin sensitivity, estimated using the minimal model from the frequently sampled intravenous glucose tolerance test (NGT individuals: $r = -0.49$ to -0.70 [7,17–19], IGT individuals: $r = -0.83$ [18], and nonobese diabetic patients: $r = 0.50$ [20]). Overall, there were good correlations between HOMA-IR and insulin resistance assessed from those well-validated methods. In contrast, it remains controversial whether HOMA-B is an accurate reflection of pancreatic β-cell function. In both nondiabetic and diabetic individuals, HOMA-B has been shown to correlate moderately well with those sophisticated measures of insulin secretion using the hyperglycemic clamps ($r = 0.62–0.69$) (1,13), continuous infusion glucose model assessment ($r = 0.87$) (1), the acute insulin response (AIR) estimated from the intravenous glucose tolerance test ($r = 0.65$) (21), and the ratio of change in insulin to change in glucose over the first 30 min of an oral glucose tolerance test ($r = 0.38$ in nondiabetic participants, $r = 0.64$ in diabetic patients, and $r = 0.44$ for the overall population) (4).

The ability of the HOMA model to predict the development of type 2 diabetes has been evaluated in both cross-sectional and cohort studies. Previous cross-sectional studies have shown the relationships between HOMA-IR and HOMA-B and the prevalence of IGT and type 2 diabetes in Japanese (3), Mexican-American (4), and non-Hispanic white subjects (4). HOMA-IR significantly predicted risk of incident IGT in 128 Japanese Americans with NGT with >10 years of follow-up (8) and 10-year diabetes incidence in the Bruneck Study of 1,000 Italians (5). In a recent study of combined prospective data involving a total of 3,574 participants including non-Hispanic white, African-American, Hispanic-American, and Mexican subjects with 5–8 years of follow-up, HOMA-IR displayed a more consistent ability to predict type 2 diabetes compared with other insulin resistance indexes (7). In line with these findings, our study has confirmed that HOMA-IR was a robust surrogate compared with fasting glucose, insulin, or HOMA-B in each of four ethnic groups of American women with different diabetes risk factor profiles.

A few prospective studies have evaluated the role of both HOMA-IR and HOMA-B in predicting future risk of type 2 diabetes and/or IGT (6,9,10). Increased HOMA-IR and decreased HOMA-B have been shown to significantly predict type 2 diabetes among 1,449 Mexicans during a 3.5-year follow-up (6), 644 Chinese followed for 4.5 years (9), and 81 healthy first-degree relatives of African-American patients with type 2 diabetes followed for 6 years (10). With similar findings, our large prospective data further showed the independent and additive associations of

HOMA-IR and HOMA-B with diabetes risk, indicating the importance of assessing both insulin resistance and β-cell function in relation to diabetes risk. Of note, our secondary analyses showed limited utility of HOMA-B, most likely because its independent association with diabetes risk seemed to be very sensitive to statistical power loss and specification of multivariable model.

The strengths of our multiethnic study include its prospective study design, large sample size, and detailed measures of variables. Nonetheless, several limitations of the present study merit consideration. First, bias from the inclusion of undiagnosed diabetes may be a concern. However, when the analyses were restricted to all case and control subjects with a fasting glucose <126 mg/dl at baseline, the findings were not appreciably altered. We also had similar results after further excluding all the case subjects occurring in the first follow-up year who were likely to have undiagnosed diabetes. These results suggest that bias due to undiagnosed diabetes was unlikely to be substantial. Also, we cannot exclude the possibility of residual confounding by incompletely measured or unmeasured physiologic covariates; it seems unlikely that more complete statistical adjustment would fully eliminate the observed associations or the consistency of our findings across diverse populations.

In summary, our prospective data showed that the basal levels of HOMA indexes, especially HOMA-IR, were independently and consistently associated with diabetes risk in a multiethnic cohort of U.S. postmenopausal women. These prospective associations appeared to be robust across diverse ethnic groups. Our findings suggest the utility of the HOMA indexes for assessing insulin resistance and β-cell function in identifying individuals who are at high risk and who may benefit from interventions for diabetes prevention.

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