

January 1991

## **Racial differences in the relation between blood pressure and insulin resistance**

Mohammad F. Saad

Stephen Lillioja

*University of Wollongong*, [lillioja@uow.edu.au](mailto:lillioja@uow.edu.au)

B Nyomba

Castillo C

R Ferraro

*See next page for additional authors*

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### **Citation**

Saad, Mohammad F.; Lillioja, Stephen; Nyomba, B; C, Castillo; Ferraro, R; De Gregorio, M; Ravussin, E; Knowler, W C.; Bennett, P H.; Howard, B; and Bogardus, C, 1991, Racial differences in the relation between blood pressure and insulin resistance, 733-739.  
<https://ro.uow.edu.au/medpapers/167>

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## Racial differences in the relation between blood pressure and insulin resistance

### Abstract

**Background.** Insulin resistance and the concomitant compensatory hyperinsulinemia have been implicated in the pathogenesis of hypertension. However, reports on the relation between insulin and blood pressure are inconsistent. This study was designed to investigate the possibility of racial differences in this relation. **Methods.** We studied 116 Pima Indians, 53 whites, and 42 blacks who were normotensive and did not have diabetes; the groups were comparable with respect to mean age (29, 30, and 32 years, respectively) and blood pressure (113/70, 111/68, and 113/68 mm Hg, respectively). Insulin resistance was determined by the euglycemic-hyperinsulinemic clamp technique during low-dose (40  $\mu$ U per square meter of body-surface area per minute) and high-dose (400  $\mu$ U per square meter per minute) insulin infusions. **Results.** The Pima Indians had higher fasting plasma insulin concentrations than the whites or blacks (176, 138, and 122 pmol per liter, respectively;  $P = 0.002$ ) and lower rates of whole-body glucose disposal during both the low-dose (12.7, 17.1, and 19.5 mmol per minute;  $P < 0.001$ ) and the high-dose (38.0, 43.1, and 45.7 mmol per minute;  $P < 0.001$ ) insulin infusions. After adjustment for age, sex, body weight, and percentage of body fat, mean blood pressure (calculated as  $1/3$  systolic pressure +  $2/3$  diastolic pressure) was significantly correlated with the fasting plasma insulin concentration ( $r = 0.42$ ) and the rate of glucose disposal during the low-dose ( $r = -0.41$ ) and high-dose ( $r = -0.49$ ) insulin infusions ( $P < 0.01$  for each) in whites, but not in Pima Indians ( $r = -0.06, -0.02$ , and  $-0.04$ , respectively), or blacks ( $r = -0.10, -0.04$ , and  $0.02$ , respectively). **Conclusions.** The relations between insulinemia, insulin resistance, and blood pressure differ among racial groups and may be mediated by mechanisms active in whites, but not in Pima Indians or blacks.

### Keywords

relation, differences, resistance, racial, insulin, pressure, blood, between

### Disciplines

Medicine and Health Sciences

### Publication Details

Saad, M. F., Lillioja, S., Nyomba, B., C, C., Ferraro, R., De Gregorio, M., Ravussin, E., Knowler, W. C., Bennett, P. H., Howard, B. & Bogardus, C. (1991). Racial differences in the relation between blood pressure and insulin resistance. *New England Journal of Medicine*, 324 (11), 733-739.

### Authors

Mohammad F. Saad, Stephen Lillioja, B Nyomba, Castillo C, R Ferraro, M De Gregorio, E Ravussin, W C. Knowler, P H. Bennett, B Howard, and C Bogardus

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## RACIAL DIFFERENCES IN THE RELATION BETWEEN BLOOD PRESSURE AND INSULIN RESISTANCE

MOHAMMED F. SAAD, M.D., M.R.C.P., STEPHEN LILLIOJA, M.B., B.Ch., F.R.A.C.P.,  
BULANGU L. NYOMBA, M.D., Ph.D., CHARLES CASTILLO, M.D., ROBERT FERRARO, M.D.,  
MICHELE DE GREGORIO, M.D., ERIC RAVUSSIN, Ph.D., WILLIAM C. KNOWLER, M.D., DR.P.H.,  
PETER H. BENNETT, M.B., F.R.C.P., BARBARA V. HOWARD, Ph.D.,  
AND CLIFTON BOGARDUS, M.D.

**Abstract Background.** Insulin resistance and the concomitant compensatory hyperinsulinemia have been implicated in the pathogenesis of hypertension. However, reports on the relation between insulin and blood pressure are inconsistent. This study was designed to investigate the possibility of racial differences in this relation.

**Methods.** We studied 116 Pima Indians, 53 whites, and 42 blacks who were normotensive and did not have diabetes; the groups were comparable with respect to mean age (29, 30, and 31 years, respectively) and blood pressure (113/70, 111/68, and 113/68 mm Hg, respectively). Insulin resistance was determined by the euglycemic-hyperinsulinemic clamp technique during low-dose (40 mU per square meter of body-surface area per minute) and high-dose (400 mU per square meter per minute) insulin infusions.

**Results.** The Pima Indians had higher fasting plasma insulin concentrations than the whites or blacks (176, 138, and 122 pmol per liter, respectively;  $P = 0.002$ )

and lower rates of whole-body glucose disposal during both the low-dose (12.7, 17.1, and 19.5 mmol per minute;  $P < 0.001$ ) and the high-dose (38.0, 43.1, and 45.7 mmol per minute;  $P < 0.001$ ) insulin infusions. After adjustment for age, sex, body weight, and percentage of body fat, mean blood pressure (calculated as  $\frac{1}{3}$  systolic pressure +  $\frac{2}{3}$  diastolic pressure) was significantly correlated with the fasting plasma insulin concentration ( $r = 0.42$ ) and the rate of glucose disposal during the low-dose ( $r = -0.41$ ) and high-dose ( $r = -0.49$ ) insulin infusions ( $P < 0.01$  for each) in whites, but not in Pima Indians ( $r = -0.06, -0.02$ , and  $-0.04$ , respectively) or blacks ( $r = -0.10, -0.04$ , and  $0.02$ , respectively).

**Conclusions.** The relations between insulinemia, insulin resistance, and blood pressure differ among racial groups and may be mediated by mechanisms active in whites, but not in Pima Indians or blacks. (*N Engl J Med* 1991; 324:733-9.)

SEVERAL studies have demonstrated insulin resistance in patients with essential hypertension<sup>1-4</sup> and an inverse relation between blood pressure and insulin-mediated glucose disposal.<sup>1,2</sup> Thus, it has been postulated that the compensatory hyperinsulinemia that results from insulin resistance may contribute to the

pathogenesis of hypertension.<sup>5</sup> Indeed, hyperinsulinemia has been reported in patients with hypertension,<sup>6-9</sup> and a strong positive relation between plasma insulin concentration and blood pressure has been documented in some studies.<sup>10-13</sup> Insulin may elevate blood pressure by stimulating the sympathetic nervous system,<sup>14</sup> increasing renal sodium retention,<sup>15</sup> modulating cation transport,<sup>16</sup> or inducing hypertrophy of vascular smooth muscle.<sup>17</sup> Several studies, however, found no relation between insulin concentrations and blood pressure, or only a weak one.<sup>18-26</sup>

Pima Indians commonly have insulin resistance

From the Phoenix Epidemiology and Clinical Research Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Phoenix, Ariz. (M.F.S., S.L., B.L.N., C.C., R.F., M.D.G., E.R., W.C.K., P.H.B., C.B.), and Mediantic Research Foundation, Washington, D.C. (B.V.H.). Address reprint requests to Dr. Saad at DAES, 1550 E. Indian School Rd., Phoenix, AZ 85014.

and hyperinsulinemia,<sup>27</sup> but they have a lower prevalence of hypertension than the general U.S. population, and their plasma insulin concentrations in a fasting state and after carbohydrate loading are not significantly related to blood pressure when there is control for body-mass index (weight in kilograms divided by the square of the height in meters) and plasma glucose concentration.<sup>28</sup> These observations appear to contradict the postulated link between insulin resistance, insulinemia, and blood pressure and raise the possibility of differences in the effects of insulin on blood pressure in different racial or ethnic groups. Consequently, we investigated the relations between plasma insulin concentration, insulin-mediated glucose disposal, and blood pressure in Pima Indians, whites, and blacks.

## METHODS

### Subjects

We studied 116 Pima Indians, 53 whites, and 42 blacks (Table 1). The Pima Indians were recruited from among subjects participating in a longitudinal study on the development of non-insulin-dependent diabetes. The whites and blacks were recruited by advertising in the local community. The whites were American whites whose parents and grandparents were white. The blacks were American blacks whose parents and grandparents were black. Afro-Caribbeans and blacks from countries other than the United States were not included.

The subjects in the three groups were selected to be of comparable age, sex, and body weight. All were required to be healthy, as assessed by medical history, physical examination, and routine hematologic, biochemical, and urine tests. They were not selected on the basis of their blood pressure, but those with hypertension (blood pressure,  $>160/95$  mm Hg)<sup>29</sup> were not included. In addition, subjects who had diabetes (fasting plasma glucose level,  $\geq 7.8$  mmol per liter, or plasma glucose level two hours after oral glucose administration,  $\geq 11.1$  mmol per liter)<sup>30</sup> or were taking any medications were excluded. All subjects gave informed consent, and the studies were approved by the ethics committees of the National Institutes of Health, the Indian Health Service, and the Gila River Indian Community.

### Experimental Protocol

The subjects were admitted to the clinical research unit for 8 to 15 days and followed a weight-maintenance diet calculated initially on the basis of body weight (50 percent carbohydrate, 30 percent fat, and 20 percent protein). The number of calories in the diet was adjusted according to fasting weight measured each morning. The percentage of body fat and fat-free mass were determined by underwater weighing.<sup>31</sup>

#### Blood Pressure

Blood pressure was measured twice by a nurse with a random-zero sphygmomanometer (Hawksley and Sons, Lancing, Sussex, United Kingdom) between 1:30 and 2:30 p.m. on three days with the subjects sitting. The subjects were asked not to drink caffeine-containing beverages or eat for one hour before the measurements. Systolic and diastolic blood pressures were measured at the time of the first and fifth Korotkoff sounds, respectively. The average of the six measurements was taken as the subject's blood-pressure value. A large blood-pressure cuff was used when appropriate. The pulse rate was recorded before each blood-pressure measurement.

#### Oral Glucose-Tolerance Test

A minimum of three days after admission, an oral glucose-tolerance test with a 75-g glucose-equivalent carbohydrate load was performed after an overnight fast. Venous blood samples were col-

Table 1. Physical Characteristics of the Subjects in the Three Groups.\*

CHARACTERISTIC	PIMA INDIANS (N = 116)	WHITES (N = 53)	BLACKS (N = 42)	P VALUE†
Age (yr)	29±6	30±7	31±7	0.26
Sex (M/F)	65/51	27/26	27/15	0.34
Weight (kg)	102±29	96±28	93±24	0.13
Height (cm)	165±8	171±9	173±8	<0.001
Body-mass index	37.2±9.5	32.9±9.3	30.8±7.7	<0.001
Body fat (%)	34±8	30±10	25±10	<0.001
Waist:thigh ratio	1.69±0.18	1.49±0.16	1.37±0.12	<0.001
Blood pressure (mm Hg)				
Systolic	113±10	111±10	113±12	0.43
Diastolic	70±9	68±10	68±11	0.44
Mean	84±9	82±10	83±11	0.44
Pulse (beats/min)	72±9	76±14	71±8	0.05

\*Plus-minus values are means ±SD for continuous variables.

†P values are for comparisons among the three groups by analysis of variance or the chi-square method.

lected for the determination of plasma glucose and insulin concentrations at -15, 0, 30, 60, 120, and 180 minutes. The mean of the samples obtained at -15 and 0 minutes was taken as the fasting concentration of both glucose and insulin.

#### Euglycemic-Hyperinsulinemic Clamp

After 7 to 14 days, a two-step euglycemic-hyperinsulinemic clamp technique was performed after an overnight fast of 10 to 12 hours as previously described.<sup>31</sup> At 6 a.m. an intravenous catheter was placed in an antecubital vein for the infusion of insulin, glucose, and [ $^3$ -H]glucose. Another catheter was placed retrogradely in a dorsal vein of the contralateral hand for the withdrawal of blood. The hand was kept in a warming box at 70°C. A primed continuous infusion of [ $^3$ -H]glucose was begun and continued throughout the first (low-dose) insulin infusion. Two hours after the infusion of [ $^3$ -H]glucose was begun, a primed continuous infusion (40 mU per square meter of body-surface area per minute) of purified porcine insulin (Velosulin, Nordisk, Bethesda, Md.) was started. Five minutes later, an infusion of 20 percent glucose was begun to maintain the plasma glucose concentration at approximately the basal level. One hundred minutes after the start of the first insulin infusion, a second primed continuous infusion of insulin (400 mU per square meter per minute) was started and continued for another 100 minutes. The mean (±SE) plasma glucose and insulin concentrations were  $5.2\pm0.02$  mmol per liter and  $814\pm18$  pmol per liter during the low-dose insulin infusion and  $5.2\pm0.02$  mmol per liter and  $14,803\pm233$  pmol per liter during the high-dose insulin infusion, respectively, and were similar in the three groups. The coefficients of variation of plasma glucose and insulin concentrations during the insulin infusions were calculated for each subject. The mean coefficients of variation of plasma glucose and insulin concentrations for all the subjects were  $2.2\pm0.1$  percent and  $6.6\pm0.5$  percent, respectively, during the low-dose insulin infusion and  $2.8\pm0.1$  percent and  $8.6\pm0.6$  percent, respectively, during the high-dose insulin infusion.

#### Indirect Calorimetry

One hour before the start of the insulin infusion, a ventilated hood made of clear plastic was placed over the subject's head. Room air was drawn through the hood, and the flow rate was measured by a pneumotachograph (Gould, Cleveland). A constant fraction of expired air was withdrawn and analyzed for oxygen and carbon dioxide content. The analyzers and flowmeter were connected to a desktop computer (Hewlett-Packard, Palo Alto, Calif.). Integrated calorimetric measurements were made every five minutes beginning one hour before the insulin infusions and continuing throughout the infusions. The subjects were asked to remain motionless and awake during the base-line period and the last 40 minutes of each insulin infusion. The rate of protein oxidation during the test was estimated by measuring the rate of urinary urea pro-

duction. The rates of carbohydrate and lipid oxidation were calculated with the non-protein respiratory quotient.

### Calculations

The rate of appearance of glucose in the plasma and the rate of endogenous glucose production were calculated from plasma [3-<sup>3</sup>H]glucose-specific activity. Glucose disposal during the low-dose insulin infusion was calculated for each 20-minute interval between 60 and 100 minutes and averaged to estimate the whole-body glucose disposal (expressed as millimoles per minute). Whole-body glucose disposal during the high-dose insulin infusion was calculated similarly during the last 40 minutes (160 to 200 minutes), except that [3-<sup>3</sup>H]glucose was not measured. The rates of glucose uptake were adjusted for steady-state plasma glucose concentrations during the clamp studies. The method of calculation has been described in detail elsewhere.<sup>31</sup> The metabolic rate at rest was determined as the mean energy expenditure during the 40 minutes preceding the insulin infusion. The basal and insulin-stimulated respiratory quotient and substrate use were calculated by averaging the results obtained during the 40 minutes before the insulin infusion was begun and during the last 40 minutes of each insulin-infusion period, as previously described.<sup>32</sup>

### Biochemical Analysis

Plasma glucose concentrations were measured by the glucose oxidase method with a Beckman glucose analyzer (Beckman Instruments, Fullerton, Calif.). Plasma insulin concentrations were determined by radioimmunoassay as previously described<sup>31</sup>; the interassay coefficient of variation was 6 to 8 percent. The tritiated glucose-specific activity was measured after perchloric acid precipitation of plasma proteins, as previously described.<sup>31</sup>

### Statistical Analysis

Statistical analyses were performed with programs of the SAS Institute (Cary, N.C.).<sup>33</sup> The logarithms of the plasma glucose and insulin values and whole-body glucose-disposal rates were used in the statistical analyses to normalize the distributions. Linear regression was used to adjust for differences in age, sex, body weight, and percentage of body fat. Comparisons among the groups were performed by analysis of variance. The relations between variables were analyzed by simple correlation and multiple regression (partial correlation). Racial interaction terms were included in the models to evaluate the racial differences in the relations between blood pressure and various metabolic variables. The statistical significance of differences in the slopes of the relations between blood pressure and other variables among the three racial groups was tested by comparing the regression equations that included these interaction terms with those that excluded them.<sup>33</sup>

## RESULTS

Tables 1 and 2 show the physical and metabolic characteristics of the study subjects. The Pima Indians were more obese, had higher plasma insulin concentrations in a fasting state and after carbohydrate loading, and were more resistant to insulin than the whites and blacks of comparable age and sex, but there was no significant difference in average blood pressure among the three groups.

Systolic and diastolic blood pressure had a similar

Table 2. Metabolic Characteristics of the Subjects in the Three Groups.\*

CHARACTERISTIC	PIMA INDIANS	WHITES	BLACKS	P VALUE†
<b>Base line</b>				
Fasting plasma glucose (mmol/liter)‡§	5.2 (5.1–5.3)	4.8 (4.7–5.0)	4.9 (4.8–5.0)	<0.001
Postload plasma glucose (mmol/liter)‡§	7.2 (6.9–7.5)	5.9 (5.5–6.4)	6.0 (5.5–6.5)	<0.001
Fasting plasma insulin (pmol/liter)‡§	176 (156–199)	138 (118–161)	122 (104–143)	0.002
Postload plasma insulin (pmol/liter)‡§	850 (732–987)	478 (374–610)	419 (334–526)	<0.001
Metabolic rate at rest (kJ/min)	5.4 (5.2–5.6)	5.3 (5.0–5.6)	5.4 (5.1–5.7)	0.680
Respiratory quotient	0.83 (0.82–0.84)	0.84 (0.83–0.85)	0.86 (0.85–0.87)	0.006
<b>Low-dose insulin infusion</b>				
Whole-body glucose disposal (mmol/min)‡	12.7 (12.1–13.3)	17.1 (16.0–18.3)	19.5 (17.6–21.6)	<0.001
Respiratory quotient	0.89 (0.88–0.90)	0.91 (0.90–0.92)	0.91 (0.86–0.96)	0.161
<b>High-dose insulin infusion</b>				
Whole-body glucose disposal (mmol/min)‡	38.0 (36.2–39.9)	43.1 (40.7–45.6)	45.7 (42.8–48.8)	<0.001
Respiratory quotient	0.97 (0.96–0.98)	0.99 (0.98–1.0)	1.0 (0.99–1.1)	<0.001

\*Values (except P values) are means, with 95 percent confidence intervals given in parentheses. Postload denotes measurements obtained two hours after oral glucose administration.

†P values are for comparisons among the three groups by analysis of variance.

‡Means and P values were computed after logarithmic transformation. Antilogs of the mean values (i.e., geometric means) are shown.

§Measurements were made during the oral glucose-tolerance test.

relation to the various metabolic indexes within each racial group. To simplify the presentation of the results, only the relations between mean blood pressure (calculated as  $\frac{1}{3}$  systolic pressure +  $\frac{2}{3}$  diastolic pressure) and metabolic variables are described (Table 3). The fasting plasma insulin concentration correlated with mean blood pressure in whites ( $r = 0.41$ ,  $P = 0.003$ ) but not in Pima Indians ( $r = 0.03$ ,  $P = 0.72$ ) or blacks ( $r = 0.17$ ,  $P = 0.28$ ). After adjustment for age, sex, body weight, and percentage of body fat, the fasting plasma insulin concentration remained significantly related to mean blood pressure in whites ( $r = 0.42$ ,  $P < 0.001$ ) but not in the other two groups (Fig. 1).

Whole-body glucose disposal during low-dose and high-dose insulin infusions was negatively related to mean blood pressure in whites ( $r = -0.37$  and  $-0.43$ , respectively;  $P < 0.01$  for each). These relations, however, were insignificant in blacks ( $r = -0.21$ ,  $P = 0.19$ ; and  $r = 0.01$ ,  $P = 0.93$ , respectively) and in Pima Indians ( $r = 0.09$ ,  $P = 0.36$ ; and  $r = 0.15$ ,  $P = 0.11$ , respectively). After adjustment for age, sex, body weight, and percentage of body fat, whole-body glucose disposal during the low-dose and high-dose insulin infusions remained significantly related to mean blood pressure in whites ( $r = -0.41$  and  $-0.49$ , respectively;  $P < 0.01$  for each) but not in Pima Indians or blacks (Fig. 1).

The mean metabolic rate at rest was similar in the three groups (Table 2). Independently of age, sex, body weight, and percentage of body fat, the metabolic rate at rest was significantly related to mean blood pressure in whites ( $r = 0.36$ ,  $P = 0.01$ ) but not in Pima Indians or blacks (Fig. 2).

The relations between substrate use and blood pressure differed in the three groups at base line and

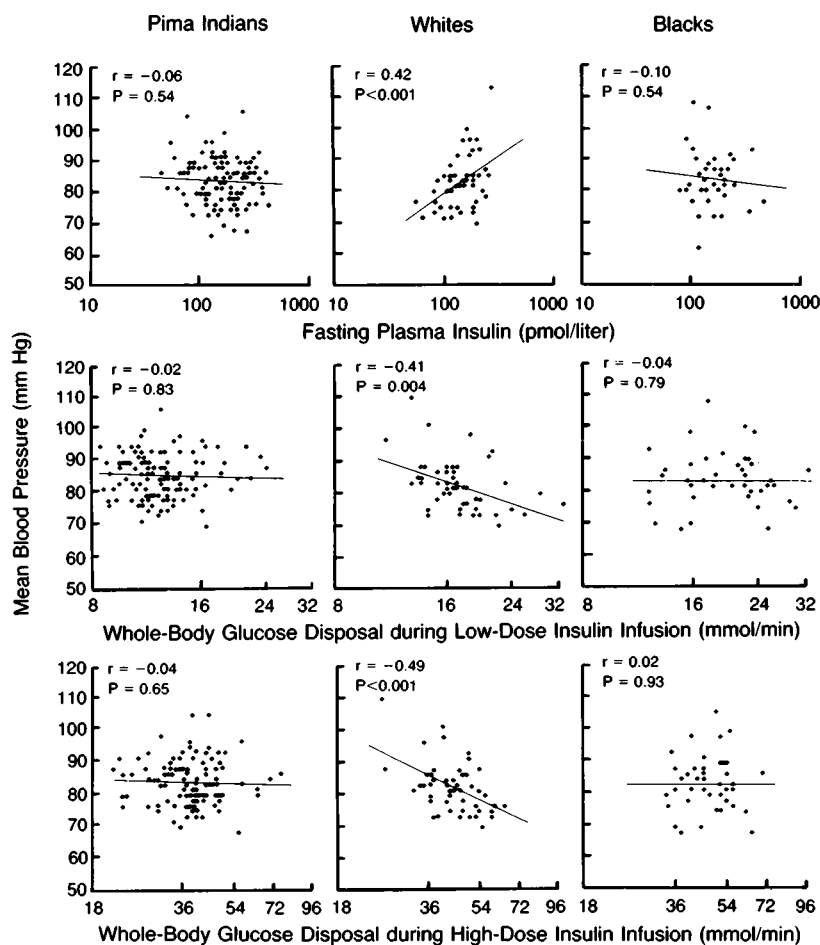


Figure 1. Relation between Mean Blood Pressure and Fasting Plasma Insulin Concentration (Top Panel) and Insulin-Mediated Glucose Disposal during Low-Dose (Middle Panel) and High-Dose (Bottom Panel) Insulin Infusions in Pima Indians, Whites, and Blacks, after Adjustment for Age, Sex, Body Weight, and Percentage of Body Fat.

The differences among the three groups in the slopes of the regression lines between mean blood pressure and the fasting plasma insulin concentration and insulin-mediated glucose disposal during low-dose and high-dose insulin infusions were statistically significant ( $P = 0.001$ ,  $0.017$ , and  $0.025$  for Pima Indians, whites, and blacks, respectively).

Table 3. Simple and Partial Correlations between Mean Blood Pressure and Metabolic Variables.\*

VARIABLE	SIMPLE CORRELATIONS			PARTIAL CORRELATIONS†		
	PIMA INDIANS	WHITES	BLACKS	PIMA INDIANS	WHITES	BLACKS
Base line						
Fasting plasma glucose‡	-0.01	0.33§	0.30	-0.06	0.12	0.20
Postload plasma glucose‡	-0.16	0.18	0.13	-0.10	0.06	-0.07
Fasting plasma insulin‡	0.03	0.41¶	0.17	-0.06	0.42	-0.10
Postload plasma insulin‡	0.06	0.35§	0.29	0.04	0.29	0.18
Metabolic rate at rest**	0.38	0.54	0.38§	0.16	0.36§	0.12
Respiratory quotient**	-0.09	-0.37¶	0.11	-0.04	-0.30§	0.11
Low-dose insulin infusion						
Whole-body glucose disposal**	0.09	-0.37¶	-0.21	-0.02	-0.41¶	-0.04
Respiratory quotient**	-0.19§	-0.55	0.06	-0.01	-0.39§	0.07
High-dose insulin infusion						
Whole-body glucose disposal**	0.15	-0.43¶	0.01	-0.04	-0.49	0.02
Respiratory quotient**	-0.17	-0.55	-0.09	-0.02	-0.35§	0.15

\*Postload denotes measurements obtained two hours after oral glucose administration.

†Adjusted for age, sex, body weight, and percentage of body fat.

‡Measurements were made during the oral glucose-tolerance test.

§ $P < 0.05$ .

¶ $P < 0.01$ .

|| $P < 0.001$ .

\*\*Measurements were made during the euglycemic-hyperinsulinemic clamp study.

during the insulin infusions. In Pima Indians and blacks, the respiratory quotient was not related to blood pressure after adjustment for age, sex, body weight, and percentage of body fat. In whites, however, the mean blood pressure was significantly related to the respiratory quotient at base line, during the low-dose insulin infusion, and during the high-dose infusion ( $r = -0.30$ ,  $-0.39$ , and  $-0.35$ , respectively;  $P < 0.05$  for each). Figure 3 shows the relation between mean blood pressure and the respiratory quotient during the high-dose insulin infusion in the three groups.

## DISCUSSION

The racial differences demonstrated in this study indicate that positive relations between insulinemia, insulin resistance, and blood pressure are not universal. Three studies<sup>1-3</sup> reporting a relation between insulin resistance and blood pressure were performed among whites, and a fourth<sup>4</sup> among Chinese men in Taiwan. In addition, published data on the relation between the fasting plasma insulin concentration (which correlated strongly with glucose disposal after low doses of insulin [ $r = -0.55$ ,  $-0.74$ , and  $-0.56$ , respectively] and high doses of insulin [ $r = -0.48$ ,  $-0.48$ , and  $-0.52$ , respectively] in Pima Indians, whites, and blacks) and blood pressure confirm that the relation between insulin resistance and blood pressure varies according to racial group. In agreement with our data, Voors et al.<sup>34</sup> found no relation between plasma insulin level and blood pressure in black children from 7 to 15 years of age. Manolio and colleagues<sup>21</sup> reported a weak association ( $r = 0.16$ ) in black men and women 18 to 30 years of age, a relation that became much weaker after adjustment for body-mass index ( $r = 0.05$ ). Haffner et al.<sup>23</sup> found plasma insulin concentrations and blood pressure to be weakly related in Mexican American men ( $r = 0.3$ ,  $P < 0.001$ ), but not in women ( $r = 0.1$ ). In addition, Alberti et al.<sup>25</sup> reported that the relation between the plasma insulin concentration and blood pres-

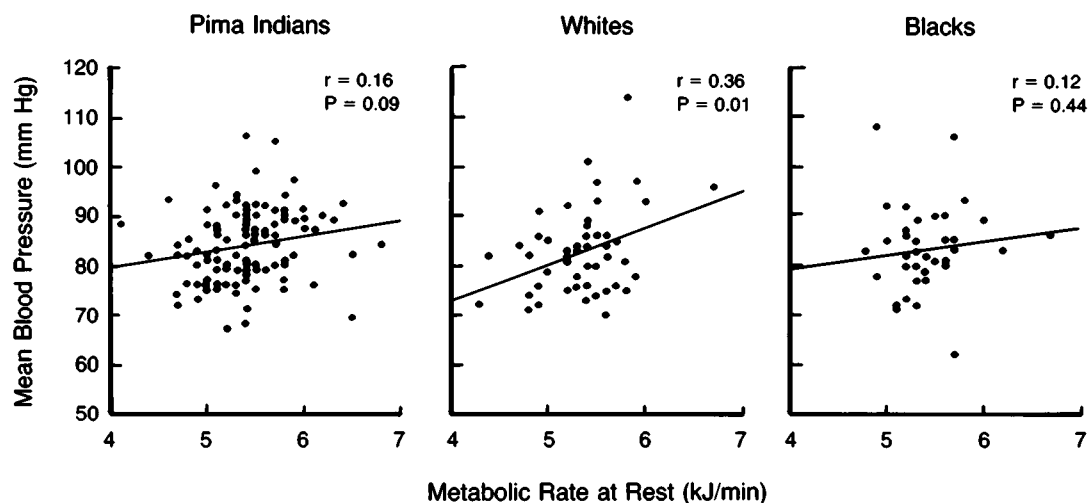


Figure 2. Relation between Mean Blood Pressure and Metabolic Rate at Rest in Pima Indians, Whites, and Blacks, after Adjustment for Age, Sex, Body Weight, and Percentage of Body Fat.

The differences in the slopes of the regression lines among the three groups were statistically significant ( $P = 0.037$ ).

sure was very weak and accounted for 1 percent or less of the variance in blood pressure in 5036 subjects belonging to four different ethnic or racial groups in Mauritius: Hindu and Moslem Indians, Chinese, and Creoles. Moreover, results in whites vary in different studies. Whereas Rose et al.<sup>10</sup> and Lucas et al.<sup>11</sup> reported strong relations between blood pressure and plasma insulin concentrations ( $r = 0.66$ ,  $P < 0.01$ ; and  $r = 0.62$ ,  $P < 0.001$ , respectively), others have reported weaker relations<sup>18-21,26</sup> or none.<sup>22,24</sup>

The reason for the interracial and intraracial differences in the relations between insulinemia, insulin resistance, and blood pressure is unclear. It is possible that the sensitivity to the postulated hypertensive effects of insulin varies among ethnic or racial groups and individuals. In addition, the effect of insulin on blood pressure may depend on its interaction with the other humoral, neural, cellular, myocardial, and

hemodynamic factors involved in the regulation of blood pressure. These factors have not been studied in Pima Indians, but normotensive blacks are more sensitive to salt,<sup>35</sup> secrete less aldosterone,<sup>36</sup> and have lower plasma renin activity<sup>37</sup> and higher intracellular sodium concentrations<sup>38</sup> than normotensive whites.

Alternatively, insulin and blood pressure may not be causally related. Instead, insulin resistance and blood pressure may be linked indirectly through mechanisms of an inherited or acquired nature. A possible link is through the sympathetic nervous system. Enhanced adrenergic tone may lead to increased insulin resistance on the one hand and a rise in blood pressure on the other. Ethnic or racial differences in sympathetic nervous system activity might explain the differences in the relation of insulin resistance to blood pressure. In support of this possibility is our

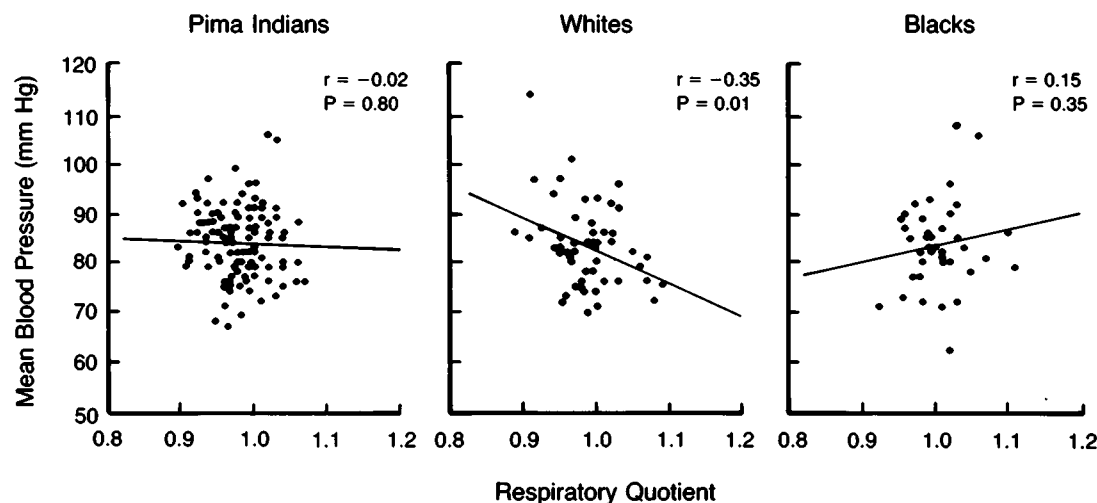


Figure 3. Relation between Mean Blood Pressure and Respiratory Quotient during High-Dose Insulin Infusion in Pima Indians, Whites, and Blacks, after Adjustment for Age, Sex, Body Weight, and Percentage of Body Fat.

The differences in the slopes of the regression lines among the three groups were statistically significant ( $P = 0.048$ ).

finding of variation in the relation between blood pressure and the metabolic rate at rest, which is in part sympathetically mediated, in the three racial groups (Fig. 2).

A further possibility is that a cellular or structural defect, genetic or acquired, may constitute the link between insulin resistance and blood pressure. Reduced activity of sodium-potassium ATPase,<sup>1</sup> decreased intracellular magnesium concentrations,<sup>13</sup> and increased sodium-lithium countertransport<sup>39</sup> have been proposed as possible links. Racial differences in ion regulation have been described<sup>38</sup> and could account for the observed variation in the relation of insulin resistance to blood pressure. Ferrannini and DeFronzo<sup>40</sup> postulated, however, that the association of insulin resistance and blood pressure could be a genetic trait related to the type of muscle fiber present.

Finally, since insulin resistance<sup>31</sup> and high blood pressure<sup>41</sup> each aggregate in families, the conditions may be more likely to occur together in some ethnic or racial groups or persons. Ferrari and Weidmann<sup>42</sup> reported that the normotensive offspring of parents with essential hypertension tended to be more resistant to insulin than those whose parents were normotensive. Furthermore, Berntorp and Lindgärde<sup>43</sup> found that normoglycemic nonobese middle-aged men with a strong family history of non-insulin-dependent diabetes had significantly higher blood pressure than men without such a family history. Thus, if there were different genes contributing to insulin resistance and high blood pressure on the same chromosome — i.e., linked genes — it is conceivable that they could be in linkage disequilibrium in some racial groups (e.g., whites), resulting in an association of the two conditions, but that equilibrium could have been attained in others (e.g., Pima Indians and blacks), resulting in no association.

In summary, plasma insulin concentrations and insulin resistance are related to blood pressure in whites but not in Pima Indians or blacks. The relation between blood pressure and insulinemia or insulin resistance may be mediated by mechanisms active in whites but not in Pima Indians or blacks. Alternatively, blood pressure may not be causally related to either plasma insulin or insulin resistance. A common mechanism, genetic or acquired, such as enhanced adrenergic tone, or a cellular or structural defect may constitute the link between insulin resistance and blood pressure in whites but not in other racial groups.

We are indebted to the residents of the Gila River Indian Community and the staff of the Indian Health Service for their help and cooperation; to Drs. Idamar Raz, Boyd Swinburn, and Francisco Zurlo for their assistance; to Ms. Carol Lamkin, head nurse of the Clinical Research Unit, for her help; to Ms. Vicky Boyce and the dietary staff for their work; to Mr. James Smart (Nordisk USA) for supplying the insulin; to Ms. Charlene K. Gishie and Ms. Susan Elson for secretarial assistance; and to Daryl Allis, Thomas Anderson, John Brown, Aileen Coyne, Revina Frank, Margie Goldsmith, Inge Harper, Christina Hendricks, Jeanetta Impson, Donna Judd-Padillo, Pat Moulsoff, Harlan Osife, Victoria Ossowski, Vera Rodriguez, Donna Rush, Joy Seumtewa, Karen Stone, Pam Thuillez, Dorothy Willer, and Debbie Wolfe-Lopez for technical and nursing assistance.

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## SMOKING CESSATION AND SEVERITY OF WEIGHT GAIN IN A NATIONAL COHORT

DAVID F. WILLIAMSON, M.S., PH.D., JENNIFER MADANS, PH.D., ROBERT F. ANDA, M.D., M.S.,  
JOEL C. KLEINMAN, PH.D., GARY A. GIOVINO, PH.D., AND TIM BYERS, M.D., M.P.H.

**Abstract Background.** Many believe that the prospect of weight gain discourages smokers from quitting. Accurate estimates of the weight gain related to the cessation of smoking in the general population are not available, however.

**Methods.** We related changes in body weight to changes in smoking status in adults 25 to 74 years of age who were weighed in the First National Health and Nutrition Examination Survey (NHANES I, 1971 to 1975) and then weighed a second time in the NHANES I Epidemiologic Follow-up Study (1982 to 1984). The cohort included continuing smokers (748 men and 1137 women) and those who had quit smoking for a year or more (409 men and 359 women).

**Results.** The mean weight gain attributable to the cessation of smoking, as adjusted for age, race, level of education, alcohol use, illnesses related to change in weight, base-line weight, and physical activity, was 2.8 kg in men and 3.8 kg in women. Major weight gain (>13 kg) occurred

in 9.8 percent of the men and 13.4 percent of the women who quit smoking. The relative risk of major weight gain in those who quit smoking (as compared with those who continued to smoke) was 8.1 (95 percent confidence interval, 4.4 to 14.9) in men and 5.8 (95 percent confidence interval, 3.7 to 9.1) in women, and it remained high regardless of the duration of cessation. For both sexes, blacks, people under the age of 55, and people who smoked 15 cigarettes or more per day were at higher risk of major weight gain after quitting smoking. Although at base line the smokers weighed less than those who had never smoked, they weighed nearly the same at follow-up.

**Conclusions.** Major weight gain is strongly related to smoking cessation, but it occurs in only a minority of those who stop smoking. Weight gain is not likely to negate the health benefits of smoking cessation, but its cosmetic effects may interfere with attempts to quit. Effective methods of weight control are therefore needed for smokers trying to quit. (*N Engl J Med* 1991; 324:739-45.)

**D**ESPITE the well-publicized adverse health effects of tobacco and the declining prevalence of smoking in the United States, slightly more than one in four adults continue to smoke cigarettes.<sup>1</sup> Some smokers may be reluctant to stop smoking because the disadvantages of smoking cessation are realized soon after they quit, whereas the advantages are less certain and occur in the future.<sup>2</sup> One potential disadvantage of smoking cessation — weight gain — is a widely held concern of both the public at large and health professionals.<sup>3,4</sup> In fact, surveys of both smokers and nonsmokers report that concern about body weight is related to starting and continuing to smoke and may be related to the resumption of smoking in those who quit.<sup>5-8</sup>

There is an inverse relation between smoking and

body weight.<sup>9</sup> Several mechanisms by which smoking decreases body weight have been proposed, including alterations in insulin homeostasis,<sup>10</sup> lipoprotein lipase activity,<sup>11</sup> the activity of the sympathetic nervous system,<sup>12</sup> physical activity,<sup>13,14</sup> and preferences in food consumption.<sup>15</sup>

The recent report of the Surgeon General<sup>16</sup> reviewed 15 prospective epidemiologic studies and estimated that the average weight gain attributable to the cessation of smoking was about 1.8 kg (4 lb) in both sexes. Such studies have limitations, however, including high attrition rates, short duration, lack of appropriate controls, self-reports of body weight, and the participation of subjects with previously diagnosed heart disease, subjects enrolled in risk-reduction programs, paid volunteers, and pregnant women.<sup>16,17</sup> In addition, neither the relative risk of gaining various amounts of weight nor smokers' perceptions of unwanted cosmetic change have been studied.

Because of these limitations, accurate estimates of the weight gain attributable to the cessation of smok-

From the Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control, Atlanta (D.F.W., R.F.A., G.A.G., T.B.), and the National Center for Health Statistics, Hyattsville, Md. (J.M., J.C.K.). Address reprint requests to Dr. Williamson at the Division of Nutrition, M.S. A-41, Centers for Disease Control, Atlanta, GA 30333.