Trends in Hyperinsulinemia Among Nondiabetic Adults in the U.S.

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OBJECTIVE — Insulin resistance and compensatory hyperinsulinemia have been proposed as increasing risk for a variety of abnormalities and clinical syndromes, including type 2 diabetes and cardiovascular disease. Our aim was to assess the trends in the mean concentrations of fasting serum insulin and the prevalence of hyperinsulinemia among nondiabetic adults during the periods of 1988–1994 and 1999–2002 in the U.S.

RESEARCH DESIGN AND METHODS — We conducted analyses of data among men and nonpregnant women without diabetes aged ≥20 years from the Third National Health and Nutrition Examination Survey (NHANES III; 1988–1994; n = 7,926) and NHANES 1999–2002 (n = 2,993). Both surveys were designed to represent the noninstitutionalized civilian U.S. population. We calculated age-adjusted mean concentrations of fasting insulin and the prevalence of hyperinsulinemia defined using the 75th percentile of fasting insulin among nondiabetic individuals as the cutoff value.

RESULTS — The geometric mean concentrations of fasting insulin increased by ~5% from 1988–1994 to 1999–2002 among nondiabetic adults aged ≥20 years in the U.S. Mexican-American men, men and women aged 20–39 years, and non-Hispanic white women had a greater relative increase in the mean concentrations of fasting insulin than their counterparts. The prevalence of hyperinsulinemia increased by 35.1% overall (38.3% among men and 32.1% among women).

CONCLUSIONS — In parallel with the obesity epidemic, concentrations of fasting insulin and prevalence of hyperinsulinemia have increased remarkably among nondiabetic U.S. adults.

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Sensitivity to insulin-mediated glucose disposal varies at least sixfold in the population at large (1). When insulin-resistant individuals cannot maintain the degree of hyperinsulinemia needed to overcome this defect, type 2 diabetes develops (2,3). However, even when insulin-resistant individuals secrete enough insulin to remain nondiabetic, they are at increased risk of developing a cluster of related abnormalities, which lead to a variety of clinical syndromes. For example, in addition to type 2 diabetes, insulin-resistant/hyperinsulinemic individuals are more likely to develop cardiovascular disease, essential hypertension, polycystic ovary syndrome, nonalcoholic fatty liver disease, and certain forms of cancer; the list continues to expand (3).

Although not all obese individuals are insulin resistant, the more overweight/obese a nondiabetic individual, the greater the likelihood that they will be insulin resistant/hyperinsulinemic (4–6). Given the increasing number of individuals in the U.S. who are overweight/obese (7,8), it can be predicted that this would result in an increased prevalence of both insulin resistance and compensatory hyperinsulinemia and the clinical syndromes associated with these metabolic changes. However, to the best of our knowledge, there are no quantitative estimates of the magnitude of this postulated change in insulin resistance/hyperinsulinemia over time. To address this question, we used data from the Third National Health and Nutrition Examination Survey (NHANES III), which was conducted during 1988–1994, and NHANES 1999–2002. In the absence of specific quantitative estimates of insulin-mediated glucose disposal from these epidemiological databases, we used fasting serum insulin concentration as a surrogate estimate of insulin resistance in our analysis (1,9–11).

RESEARCH DESIGN AND METHODS

In both NHANES III and NHANES 1999–2002, the samples were recruited using a multistage, stratified sampling design (12). Both surveys were designed to represent the noninstitutionalized civilian U.S. population. Participants were interviewed at home and were invited to attend the mobile examination center, where they provided a blood sample and were examined. Details about the surveys may be found elsewhere (13–15).

We limited the analyses to men and nonpregnant women aged ≥20 years who attended the morning medical examination and who had fasted ≥8 h. We included only non-Hispanic whites, non-Hispanic blacks, and Mexican Americans in our final analyses. Participants of other races and ethnicities were excluded because of small sample sizes. In addition, all participants who had affirmatively answered the question "Have you ever been told by a doctor that you had diabetes?" or currently had a fasting glucose concentration ≥126 mg/dl were excluded from analyses. The final sample (n = 7,926 for NHANES III and n = 2,993 for NHANES 1999–2002) represents nondiabetic adults aged ≥20 years in the U.S.

Serum specimens were frozen at <−70°C, shipped on dry ice, and stored at <−70°C until analysis. From 1988 to

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Abbreviations: NHANES, National Health and Nutrition Examination Survey.

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

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1990, serum concentrations of insulin were measured by using a radioimmunoassay kit from Cambridge Laboratories (Cambridge, MA). (Cambridge Laboratories was later sold to Ventrex.) Starting in November 1990, serum insulin concentration was measured using a radioimmunoassay kit from Pharmacia Diagnostics (Uppsala, Sweden). The cross-reactivity of Pharmacia insulin antibody with proinsulin is ~40% (13–15). All insulin assays for NHANES III and NHANES 1999–2002 were performed at the same laboratory of the University of Missouri at Columbia. Identical laboratory procedures for insulin assays and their quality control procedures were performed in NHANES III and NHANES 1999–2002; therefore, the insulin assay results are compatible throughout the two survey periods. Details of the laboratory procedures for insulin assay are found elsewhere (13–15).

Quality control procedures followed modified Westgard rules and included both within- and between-assay quality control procedures using Levy-Jennings chart plots for means and ranges with monitoring of trend. Four levels of controls, which covered the spectrum of insulin range for both normal and diabetic populations, were used. Three were commercial lyophilized serum controls purchased from Bio-Rad Laboratories (Irvine, CA). The other control was prepared in house and stored at −70°C. The overall coefficients of variation ranged from 5.9 to 13.8% in NHANES III and 3.3 to 5.4% in NHANES 1999–2002. Five percent of the total specimens in NHANES III and 2% in NHANES 1999–2002 were randomly selected and analyzed either within or between assay. If the deviation between duplicates was >10%, the specimen was reanalyzed.

BMI (weight in kilograms divided by the square of height in meters) was calculated using measured weight and height, and BMIs were categorized into three groups (<25, 25–29.9, and ≥30 kg/m^2) according to World Health Organization criteria (16). The waist circumference was measured with a steel measuring tape to the nearest 0.1 cm at the high point of the iliac crest at minimal respiration (13–15). Abdominal obesity was defined as a waist circumference of >102 cm in men and >88 cm in women (17).

Statistical analysis

We calculated the unadjusted and adjusted (for age, BMI, and waist circumference) means and SEs of log fasting insulin by sex, race/ethnicity, age, and BMI status. We directly adjusted our statistics to the U.S. population aged ≥20 years in the year 2000 (weights: 0.183707, 0.212872, 0.215905, 0.155890, 0.102446, 0.082415, and 0.046765 for age-groups 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and ≥80 years, respectively) (18). To adjust for BMI, we calculated the weighted fractions for the three categories of BMI among nondiabetic eligible participants in NHANES III and applied these fractions to the NHANES 1999–2002 survey (weights: 0.4618, 0.3334, and 0.2048 for BMI <25, 25–29.9, and ≥30 kg/m^2, respectively). We also calculated the prevalence of insulin resistance by sex and race/ethnicity for both surveys. The cutoff value for hyperinsulinemia was determined using the weighted 75th percentile of log fasting insulin (19) among nondiabetic eligible participants in NHANES III and was used to calculate the prevalence of hyperinsulinemia for both surveys.

To test the statistical significance of the changes in the mean concentrations of log fasting insulin and the changes in the prevalence of hyperinsulinemia between populations of the two surveys, we performed a pooled *t* test. The pooled SE for the difference in means was calculated by taking the square root of the sum of the squared SEs. The degrees of freedom (df; number of primary sampling units − number of strata) of the two surveys were summed for the pooled *t* test. Finally, multiple regression analysis was conducted to assess the change in the means of fasting insulin adjusting for sex, race or ethnicity, age, and BMI or waist circumference. All analyses were conducted using SUDAAN software (release 9.0; Research Triangle Institute, Research Triangle Park, NC), in order to account for the complex sampling design and calculate estimates that are representative of the civilian noninstitutionalized U.S. population (12,13).

RESULTS

Demographic characteristics of the samples

The distribution of sex and racial or ethnic composition of the two analytic samples was similar (49.0% men and 83.9% white in NHANES III; 50.9% men and 81.9% white in NHANES 1999–2002; $P > 0.05$). Participants in NHANES 1999–2002 (mean age 45.2 years [range 20 to ≥90]) were older than those in NHANES III (mean age 43.2 years [range 20–85]) ($P < 0.05$). The overall prevalence of total obesity (26.8%) and abdominal obesity (44.2%) among adults in NHANES 1999–2002 were higher than in NHANES III (21.1 and 36.7%, respectively; $P < 0.001$).

Distribution of fasting insulin concentrations

The shapes of distributions of fasting insulin concentrations were similar for NHANES III and NHANES 1999–2002 (Fig. 1); however, there was an observable shift toward right in the median of fasting insulin or the mean of log fasting insulin from NHANES III to NHANES 1999–2002 (Fig. 1*A* and *B*). The logarithm transformation of fasting insulin improves the distribution and approximates a normal distribution (Fig. 1*B*).

Absolute and relative differences in the mean concentrations of log fasting insulin between NHANES III (1988–1994) and NHANES 1999–2002

The unadjusted means of log fasting insulin concentrations increased by 5.4% from NHANES III to NHANES 1999–2002 ($P < 0.001$) (Table 1). The age-adjusted means increased by 4.9% ($P < 0.001$). The relative change in the means of log fasting insulin concentration was attenuated after adjustment for BMI (2.8%; $P = 0.003$) or waist circumference (2.0%; $P = 0.025$). Overall, men had higher means and relative changes in the means of log fasting insulin concentration than women. Among men, Mexican Americans had higher means and relative changes in the means of log fasting insulin concentration than whites or blacks. Men aged 20–39 years had smaller means but greater relative changes in log fasting insulin concentration than older men. Men who had a BMI ≥30 kg/m^2 had higher means and greater relative increase than those with a BMI between 25 and 29 kg/m^2 or <25 kg/m^2. Men who were abdominally obese had a higher mean log fasting insulin concentration but a smaller relative change. Among women, non-Hispanic whites, individuals aged 20–39 years, and those who were abdominally obese had a greater increase in mean log fasting concentrations than their counterparts.

In multiple linear regression models adjusting for sex, race or ethnicity, and age, the relative change from NHANES III to NHANES 1999–2002 was 5.0% for log

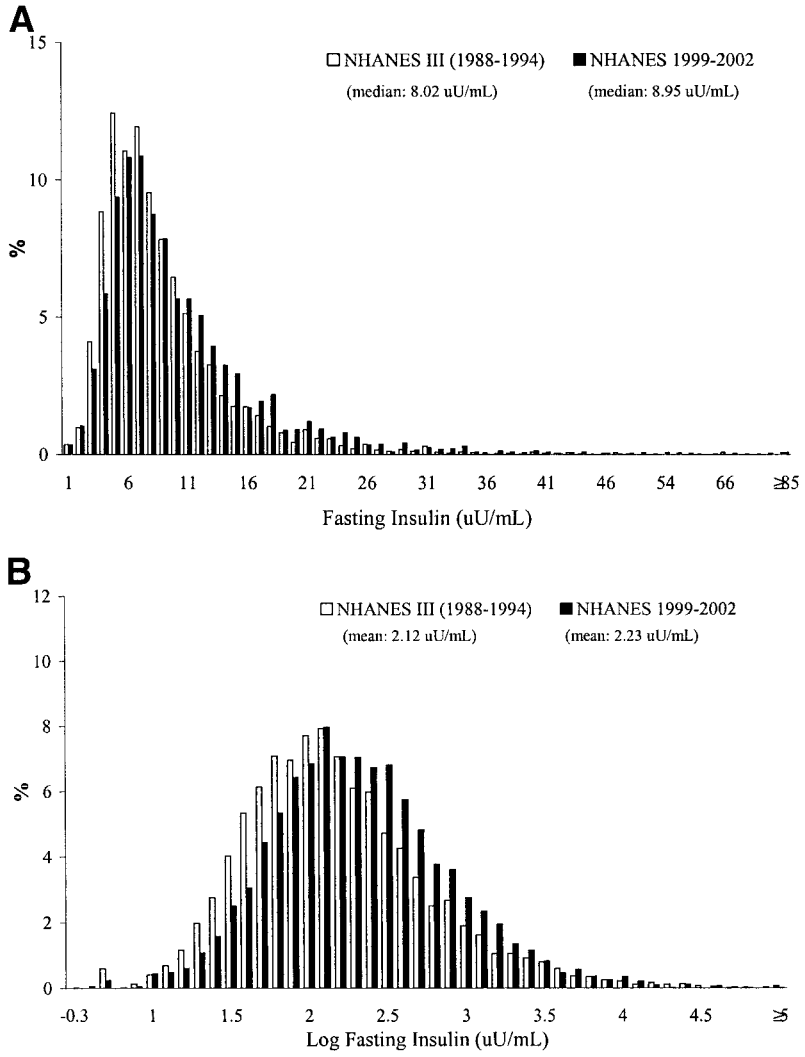

Figure 1—*Distribution of serum fasting insulin concentration* (A) *and natural log scale of fasting insulin* (B) *among nondiabetic U.S. adults, NHANES III and NHANES 1999–2002.*

fasting insulin concentration ($P < 0.001$). This relative change was attenuated to 2.2% ($P = 0.008$) after further adjustment for BMI or 1.8% ($P = 0.03$) after further adjustment for waist circumference. The difference of mean log fasting insulin concentrations between NHANES III and NHANES 1999–2002 decreased by 55.2 or 63.0% after further adjustment for BMI or waist circumference.

Trends in the prevalence of hyperinsulinemia

The weighted 75th percentile of log fasting insulin concentration among nondiabetic individuals in NHANES III was 2.42 μU/ml. The unadjusted prevalence of hyperinsulinemia was 25.0 and 34.8% among participants in NHANES III and NHANES 1999–2002, respectively. The age-adjusted prevalence of hyperinsulinemia increased by 35.1% in total (from 25.8% in NHANES III to 34.8% in NHANES 1999–2002, $P < 0.001$), 38.3% in men (from 27.3 to 37.7%, $P < 0.001$), and 32.1% in women (from 24.4 to 32.2%, $P < 0.001$). Among racial or ethnic subgroups, the prevalence of hyperinsulinemia was the highest among Mexican-American men and women (Fig. 2). The changes in the prevalence of hyperinsulinemia were highest among non-Hispanic white men and women. The changes in the prevalence among non-Hispanic black women ($P = 0.13$) and Mexican-American women ($P = 0.25$) were not statistically significant.

CONCLUSIONS — Using nationally representative samples, we show for the first time that the prevalence of hyperinsulinemia increased greatly in the U.S. during the 1990s. From 1988–1994 to 1999–2002 among nondiabetic adults aged ≥20 years in the U.S., the mean fasting insulin concentrations increased by ~5.0%. Meanwhile, the prevalence of hyperinsulinemia increased by 35.1% overall (38.3% among men and 32.1% among women).

Insulin resistance has been associated with increased risk of type 2 diabetes (2,20), coronary heart disease (2,21), essential hypertension (2,22), congestive heart failure (23), polycystic ovarian disease (24), nonalcoholic fatty liver disease (25), and cancers of certain sites such as prostate (26), colon and rectum (27), and breast (28). These chronic diseases are major causes of death in the U.S. (29) and other regions in the world (30). Furthermore, the burden of these chronic diseases has been growing in the U.S. (31) and worldwide (32). Rapidly increasing trends in insulin resistance and compensatory hyperinsulinemia, if not properly controlled or altered, may predict adverse future courses of many health conditions that are linked to insulin resistance.

The focus on fasting hyperinsulinemia has two advantages. At the simplest level, it is as good a surrogate estimate (1,9,10) of insulin resistance as are various combinations of fasting insulin and glucose concentration such as homeostasis model assessment (33) or quantitative insulin sensitivity check index (34). Perhaps of greater clinical relevance is the pathophysiological role that hyperinsulinemia plays in the development of the abnormalities and clinical syndromes that occur more commonly in insulin-resistant subjects. Not all tissues are equally resistant to the actions of insulin, and the compensatory hyperinsulinemia attempting to normalize muscle glucose uptake and adipose tissue lipolysis in insulin-resistant individuals has adverse effects on tissues, such as the kidney, ovary, sympathetic nervous system, and liver, that retain normal insulin sensitivity (24,35–38). Thus, quantifying the changes in fasting insulin concentration over time provides information regarding both the increasing prevalence of insulin resistance and the potential clinical consequences of this phenomenon.

Among modifiable factors, obesity may play a critical role in the rising levels of insulin resistance among nondiabetic individuals. For adults aged 20–74 years in the U.S., obesity increased by 30.5% overall (34.0% for men and 28.3% for women) between the periods 1988–1994 and 1999–2000 (8,39). As evidenced in

Table 1—*Trends in the means of log fasting insulin concentrations among nondiabetic U.S. adults aged ≥20 years: NHANES III (1988–1994) and NHANES 1999–2002*

	NHANES III		NHANES 1999–2002		Relative change (%)	Absolute change	*P* (df = 78)
	n	Mean ± SE	*n*	Mean ± SE			
Total							
Unadjusted	7,926	2.12 ± 0.02	2,993	2.24 ± 0.02	5.4	0.12	<0.001
Age adjusted	7,926	2.13 ± 0.02	2,993	2.24 ± 0.02	4.9	0.10	<0.001
BMI adjusted	7,926	2.12 ± 0.01	2,993	2.18 ± 0.01	2.8	0.06	0.003
WC adjusted	7,926	2.12 ± 0.01	2,993	2.16 ± 0.01	2.0	0.04	0.025
Men							
Unadjusted	3,849	2.13 ± 0.02	1,503	2.28 ± 0.02	6.9	0.15	<0.001
Age adjusted	3,849	2.15 ± 0.02	1,503	2.28 ± 0.02	6.1	0.13	<0.001
BMI adjusted	3,849	2.13 ± 0.02	1,503	2.21 ± 0.02	3.9	0.08	0.001
WC adjusted	3,849	2.13 ± 0.02	1,503	2.20 ± 0.02	3.1	0.07	0.008
Race/ethnicity*							
Non-Hispanic white	1,589	2.14 ± 0.02	837	2.27 ± 0.02	5.7	0.12	<0.001
Non-Hispanic black	1,067	2.14 ± 0.02	273	2.25 ± 0.04	5.0	0.11	0.014
Mexican American	1,193	2.24 ± 0.03	393	2.43 ± 0.03	8.1	0.18	<0.001
Age (years)							
20–39	1,793	2.08 ± 0.03	556	2.22 ± 0.03	7.2	0.15	<0.001
40–59	969	2.20 ± 0.03	485	2.33 ± 0.03	6.1	0.13	0.002
≥60	1,087	2.21 ± 0.02	462	2.32 ± 0.03	4.9	0.11	0.007
BMI (kg/m^2)*							
<25	1,583	1.86 ± 0.02	488	1.93 ± 0.02	3.5	0.07	0.041
25–29.9	1,532	2.20 ± 0.02	640	2.28 ± 0.02	3.6	0.08	0.013
≥30	734	2.66 ± 0.04	375	2.77 ± 0.04	4.5	0.12	0.024
Abdominal obesity*							
No	2,870	2.00 ± 0.02	956	2.09 ± 0.02	4.8	0.10	<0.001
Yes	979	2.59 ± 0.03	547	2.66 ± 0.03	2.9	0.07	0.124
Women							
Unadjusted	4,077	2.11 ± 0.02	1,490	2.19 ± 0.02	4.1	0.09	0.001
Age adjusted	4,077	2.11 ± 0.02	1,490	2.20 ± 0.02	3.9	0.08	0.003
BMI adjusted	4,077	2.12 ± 0.01	1,490	2.15 ± 0.02	1.7	0.04	0.117
WC adjusted	4,077	2.11 ± 0.01	1,490	2.13 ± 0.02	1.1	0.02	0.262
Race/ethnicity*							
Non-Hispanic white	1,791	2.07 ± 0.02	828	2.15 ± 0.02	3.8	0.08	0.006
Non-Hispanic black	1,215	2.32 ± 0.03	287	2.40 ± 0.04	3.3	0.08	0.113
Mexican American	1,071	2.33 ± 0.02	375	2.41 ± 0.04	3.4	0.08	0.092
Age (years)							
20–39	1,935	2.06 ± 0.02	492	2.21 ± 0.03	7.3	0.15	<0.001
40–59	1,079	2.14 ± 0.03	504	2.15 ± 0.04	0.4	0.01	0.840
≥60	1,063	2.18 ± 0.03	494	2.26 ± 0.03	3.6	0.08	0.034
BMI (kg/m^2)*							
<25	1,696	1.86 ± 0.02	564	1.88 ± 0.02	1.3	0.02	0.406
25–29.9	1,248	2.19 ± 0.02	453	2.23 ± 0.03	1.9	0.04	0.225
≥30	1,133	2.58 ± 0.02	473	2.62 ± 0.02	1.3	0.03	0.322
Abdominal obesity*							
No	1,969	1.89 ± 0.02	630	1.89 ± 0.02	0.1	0.00	0.935
Yes	2,108	2.42 ± 0.02	860	2.47 ± 0.02	2.4	0.06	0.057

*Adjusted for age. †Abdominal obesity: waist circumference (WC) >102 cm for men and >88 cm for women.

our analyses, the relative change in fasting insulin concentrations was attenuated by >50% after adjusting for BMI or >60% after adjusting for waist circumference. The most dramatic changes in insulin concentrations occurred in the 20- to 39-year-old group for both men and women, suggesting that young people are at a significantly higher risk for diabetes and perhaps cardiovascular disease than in the past. This finding is consistent with data from the Behavioral Risk Factor Surveillance System, which showed that between 1991 and 1998, the greatest increase in the prevalence of obesity was among people aged 18–29 years (40). In addition, increases in the caloric intake (41,42) and sedentary activities (43) in the U.S. population during the period from 1988 to 2002 may have contributed to the increasing trends in fasting insu-

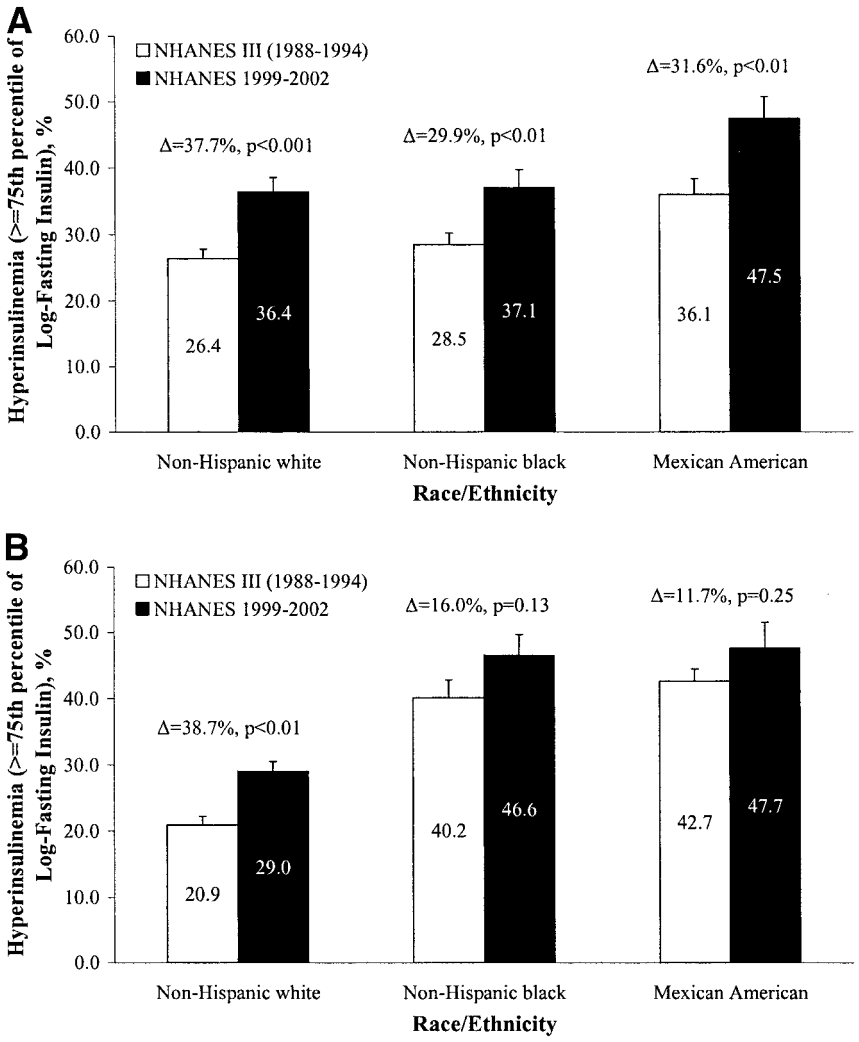

Figure 2—*Trends in age-adjusted prevalence of hyperinsulinemia as defined by 75th percentile of log fasting insulin (2.420 μU/ml; fasting insulin, 11.245 μU/ml) in nondiabetic men* (A) *and women* (B) *aged ≥20 years in the U.S.* Δ*, relative change.*

lin concentrations in the nondiabetic population.

Growing evidence has shown that weight loss and a reduction of carbohydrate intake can improve insulin sensitivity (44). Several clinical trials have demonstrated the effectiveness of both pharmaceutical (e.g., metformin) and nonpharmaceutical (e.g., diet and other lifestyle changes) approaches in the prevention of type 2 diabetes through improving insulin sensitivity (45–47). It may not be feasible to assess insulin resistance using a standard insulin assay (48) in clinical settings. Increased use of relatively simple metabolic markers (49) or simple decision tree algorithms using routine clinical measurements (50) is needed. Examples of metabolic markers that could be used include plasma triglyceride concentration or triglyceride–to–HDL cholesterol concentration ratio (49). Further research is necessary to identify other simple and reliable clinical measurements that highly correlate with insulin resistance. Moreover, health care providers need to reach a consensus on the potential use of simple metabolic markers for insulin resistance.

One limitation of our study was related to the use of the Pharmacia Insulin RIA kit. The cross-reactivity of Pharmacia insulin antibody with proinsulin (~40%) may overestimate the true insulin concentrations in the population, particularly among people with diabetes (51). Proinsulin is disproportionately increased in people with type 2 diabetes (52–54), but its concentration is relatively low among people without diabetes (52). Since we restricted our analyses among people without diabetes, the proportion of proinsulin due to cross-reactivity in our study may be small. Furthermore, because the identical Pharmacia Insulin RIA kit was used for much of NHANES III and NHANES 1999–2002, the cross-reactivity of insulin antibody with proinsulin was stable across the two surveys. Thus, the increasing trends in insulin concentration and hyperinsulinemia, as reported in our study, may not be affected.

The issue of assay drift as a possible explanation for the results deserves comment. Because one survey ended in 1994 and the other started in 1999, the same quality control pools could not bridge the time gap between surveys. Thus, the case against assay drift rests on the technical approach and rigorous quality control procedures implemented by the University of Missouri laboratory. *1*) The same semiautomated method and the same quality control procedures were used throughout the surveys. 2) The same assay method was used for other studies during the time between NHANES surveys, and each new quality control specimen was analyzed along with the previous quality control specimen in that insulin range for at least 20 runs; this overlap insured consistency in assay calibration over time. 3) Periodic reference range studies during and between both studies did not show any upward trend in either fasting or 2-h insulin measurements. That increases in concentrations of insulin occurred in many subgroups during the study period also provides a measure of reassurance against assay drift.

In summary, the high prevalence and rapidly increasing trends of hyperinsulinemia between the periods 1988–1994 and 1999–2002 have important significance in clinical practice and public health services. The alarming increase in hyperinsulinemia, particularly among groups with a lower prevalence of insulin resistance, such as young adults and non-Hispanic white women, underscores the urgent need to address the root causes. Because the major contributing causes of insulin resistance, such as obesity, poor dietary intake, and inadequate physical activity, are modifiable, clinical consultation and public health campaigns aimed to improve these health behaviors are needed.

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