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# Insulin Resistance in Healthy U.S. Adults: Findings from the National Health and Nutrition Examination Survey (NHANES)

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## ABSTRACT

**Background:** Insulin is fundamental in two conditions that are epidemic in the United States and globally: obesity and type II diabetes. Given insulin's established mechanistic involvement in energy balance and glucose tolerance, we examined its relationship to common health-related endpoints in a large population-based sample.

**Methods:** The National Health and Nutrition Examination Survey is a cross-sectional study that uses a complex multistage probability design to obtain a representative sample of the United States population. Adult participants were included from 8 successive 2-year data waves (1999–2014), including 9,224 normal individuals, 7,699 prediabetic, and 3,413 diabetic subjects. The homeostatic model for insulin resistance (HOMA-IR) was available for 20,336 participants and its relationship with demographic, anthropometric, and clinical data was analyzed. We examined the relationship of HOMA-IR to 8 groups of outcome variables: general health, anthropometric/metabolic [waist size, body mass index (BMI)], cardiovascular (blood pressure), lipid [triglycerides, high-density lipoprotein (HDL)], hepatic [alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT)], hematologic [white blood cells (WBC), hemoglobin (Hgb), platelets], inflammatory (C-reactive protein), and nutritional (vitamins D and C, serum folate, and pyridoxine) variables.

**Results:** HOMA-IR was generally strongly, monotonically, and highly significantly associated with adjusted outcomes in normal subjects, although clinical laboratory values were generally within normal bounds across insulin quartiles. In the normal subset, the odds ratio and 95% confidence interval for a quartile change in HOMA-IR for obesity (BMI > 30) was 3.62 (3.30–3.97), and for the highest quintile for the triglyceride/HDL the ratio was 2.00 (1.77–2.26), for GGT it was 1.40 (1.24–1.58), and for WBC it was 1.28 (1.16–1.40). The relationship of HOMA-IR to the various outcomes was broadly similar to that observed in prediabetics and diabetics with a few exceptions.

**Conclusions:** HOMA-IR levels in a large sample of normal individuals are associated with poorer general health and adverse changes across a wide range of markers. A similar pattern of alterations is observed in prediabetic and diabetic samples.

**Impact:** Clinically, checking insulin levels may be helpful to identify patients that merit further observation and are candidates for early interventions.

## Introduction

Type II diabetes (T2D) and prediabetes together affect more than half the adults in the United States and rising trends are present globally (1, 2). United States (3, 4) and global trends (5) for obesity exhibit a similar pattern. Obesity and diabetes are associated with cardiovascular disease, cancer (6–8) and overall mortality and are responsible for a large and increasing proportion of health care costs (8–10).

Insulin has a fundamental role in T2D and obesity (11–13). Elevated insulin concentrations are associated with the development of metabolic syndrome [expanded waist size, hypertension, elevated triglycerides and lower high-density lipoprotein (HDL) cholesterol; refs. 14, 15], cardiovascular (16), and overall mortality (17). Insulin resistance (IR) has also been specifically associated with cancer incidence (18) and outcomes (6, 19, 20).

Previous human studies have observed relationships of IR to waist circumference and body mass index (BMI; refs. 21, 22), atherosclerosis (23, 24), adverse lipid profiles (25), altered liver function (26, 27), platelet count (28), elevated inflammatory markers (25, 29, 30), and nutrient levels (26, 31, 32). Some of these studies were conducted in National Health and Nutrition Examination Survey (NHANES; refs. 20, 21, 27, 32–34) but some evaluated IR in smaller clinical subsets (21, 35, 36). These studies generally involved single or selected outcomes apart from one study that described significant cardiovascular, hepatic, inflammatory, and nutrient measurements associated with IR and an independent IR association with decreased thyroid hormones after adjustment (26). Although the relationship between IR and the components of metabolic syndrome have been well-established, our study emphasizes the relationship of IR to a broader group of health-related outcomes in a large, population-based sample after adjustment for demographic and key exposures. Specifically, we selected available health-related measures across 8 domains (general health, anthropometric, cardiovascular, lipid, hepatic, hematologic, inflammatory and nutrition) in subjects that were neither diabetic nor prediabetic to see if increasing IR (as quantified by homeostatic model for insulin resistance) was associated with early changes.

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## Materials and Methods

### Study design and population

The National Health and Nutrition Examination Survey (NHANES) is a cross-sectional study conducted by the National Center for Health statistics (NCHS) that uses a complex multistage probability design involving oversampling of specific groups (ethnic minorities and older individuals) to obtain a representative sample of the United States civilian noninstitutionalized population (see http://www.cdc.gov/nchs/nhanes.htm). NHANES releases data in 2-year intervals and we used the combined data from 8 successive waves (1999–2014) from the publicly available dataset (https://wwwn.cdc.gov/nchs/nhanes/Default.aspx). Initially, participants were interviewed face-to-face in their homes where questionnaire data were collected. A physical examination with further interviews was conducted in a mobile examination center. The procedures for data collection were approved by the NCHS ethics review board, and all participants provided written informed consent prior to data collection. This study was exempt from Institutional Review Board review as the data are deidentified. Our analytic sample included adults 18 years or older who had complete data on homeostatic model for insulin resistance (HOMA-IR) from the 8 data release periods.

### Definitions

HOMA-IR was used to assess insulin resistance based on fasting glucose and insulin concentrations and defined as the fasting plasma glucose (mmol/L) × fasting plasma insulin (μU/mL/22.5; refs. 37, 38). Quartiles of HOMA-IR were calculated on the basis of the entire sample including normal, prediabetic, and diabetic participants. Median (range) values for ascending quartiles were: 0.99 (0.03–1.39), 1.75 (1.39–2.32), 2.84 (2.32–3.80), and 5.58 (3.80–270). Diabetes was defined as having at least one of the following: fasting plasma glucose ≥126 mg/dL, random plasma glucose of ≥200 mg/dL in the presence of symptoms, 2-hour plasma glucose during the 75-g oral glucose tolerance test (OGTT) ≥ 200 mg/dL, and/or HbA1c ≥ 6.5% (39, 40). In addition, subjects that gave a positive response to any of the following questions were classified as diabetic: "Are you taking insulin?," "Did a doctor tell you, you have diabetes?," "Do you take pills to lower blood sugar?" Prediabetes was defined by a fasting plasma glucose between 100 and 125 (impaired fasting glucose) and/or a 2-hour plasma glucose during OGTT 140–199 (impaired glucose tolerance) and/or a HbA1c 5.7%–6.4% (39). Individuals were also classified as prediabetic if they gave a positive response to either: "did a doctor tell you, you had borderline diabetes?" or "did a doctor tell you, you have prediabetes?"

Demographic variables consisted of: age (years, at household interview, continuous), gender (male or female), race/ethnicity (self-reported as non-Hispanic white, non-Hispanic black, Hispanic, and multiethnic), education (less than 9th grade, 9–11th grade, completion of high school, some college or AA degree, college graduate or above), family poverty index (ratio of family income to the poverty level, specific to family size, year, and state). Smoking variables included smoking status (never, former, or current smoking; ref. 38) and pack years smoking, calculated on the basis of an algorithm involving the product of intensity and duration of smoking taking into account years since quitting. Alcohol and caffeine intake were based on daily consumption from a 24-hour dietary recall questionnaire. Dietary supplement use during the last month was based on a question, "Have you used or taken any vitamins, minerals, or other daily supplements in the past month?" Physical activity was a dichotomous variable based on self-report of "10 minutes or more of vigorous or moderate activity in the past week." Body weight and height were measured by trained personnel using standard techniques according to NHANES protocol. BMI was calculated as weight in kilograms divided by the square of height in meters (41). BMI 25–29.9 kg/m$^2$ was classified as overweight and BMI > 30 kg/m$^2$ was obese.

### Outcome variables

To broadly examine the effect of HOMA-IR in normal subjects (with comparison to prediabetic and diabetics) we selected outcome variables in 8 domains: (i) general health, (ii) anthropometric/metabolic (BMI and waist circumference), (iii) cardiovascular (systolic and diastolic blood pressure), (iv) lipids [triglycerides, HDL, and low-density lipoprotein (LDL) cholesterol, total cholesterol, and the triglyceride/HDL ratio], (v) hepatic [alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT)], (vi) hematologic (WBC, neutrophils, lymphocytes, hemoglobin, platelet count), (vii) inflammatory (C-reactive protein, ferritin), and (viii) nutrients (Vitamins B6, B12, C, D, and folate, RBC, and serum). Outcome variable categories were selected for inclusion in the study if they had previous evidence of an association with insulin (components of metabolic syndrome, domains ii, iii, iv), other association evidence (domains i, v, vii) or some data from clinical or population studies indicating a possible relationship with insulin (domains vi and viii).

### Statistical analysis

Using either multiple linear or logistic regression for continuous or binary dependent variables, respectively, potential confounder variables were included in 3 sequentially adjusted models, depicted in **Figs. 1–5** and in Supplementary Table S2 (by HOMA-IR median): basic (Model 1), adjusted for age, age squared, gender, race/ethnicity, standing height, family income, education (less than high school, high school, beyond high school), and data release year (8 categories: 1999–2000 through 2013–2014); partially adjusted (Model 2) adds: smoking status (never/former/current), pack years smoking, caffeine intake (mg/day), alcohol (g/day), and a fully adjusted (Model 3) adds: physical activity, 6-month time period (November–April; May–October), total cholesterol (mg/dL), dietary supplement use (yes/no), and BMI. The outcome variables were transformed into binary variables using various cutoffs (e.g., the top quintile for all the outcomes except BMI, results shown for overweight and obese (BMI > 25 kg/m$^2$) or obese (BMI > 30 kg/m$^2$), and, general health (poor and fair categories vs. others). Adjusted odds ratios (OR) for all the outcome variables using the fully adjusted model are presented in **Table 2**. Adjusted means (with predicted margins) of each variable for each of the three models are shown by HOMA-IR quartiles in **Figs. 1–5** and by median values in Supplementary Table S2. The point estimates and 95% confidence intervals (CI) for the adjusted means of the outcome variables are depicted in **Figs. 1–5** and show the pattern of outcome variable across quartiles of HOMA-IR. The adjusted means are the sample-weighted average of the predicted values from the regression model (multiple linear or logistic regression), if every observation was assigned to a comparison group, which is direct standardization of each comparison group to the entire NHANES analytic sample (42). Interactions were tested by including appropriate cross-product terms into models and evaluating the statistical significance using a Wald test. The addition of terms including HOMA-IR, and combinations of age, gender, and ethnicity categories did not meaningfully change the adjusted means and so they were dropped. In normal individuals (and similarly for diabetics and prediabetics), HOMA-IR levels were strongly correlated (Pearson, weighted) with measured insulin levels ($r$ = 0.996), C-peptide ($r$ = 0.790), and less so with glycohemoglobin ($r$ = 0.096) and 2-hour OGTT results ($r$ = 0.209) with all $P$ values < 0.0001.

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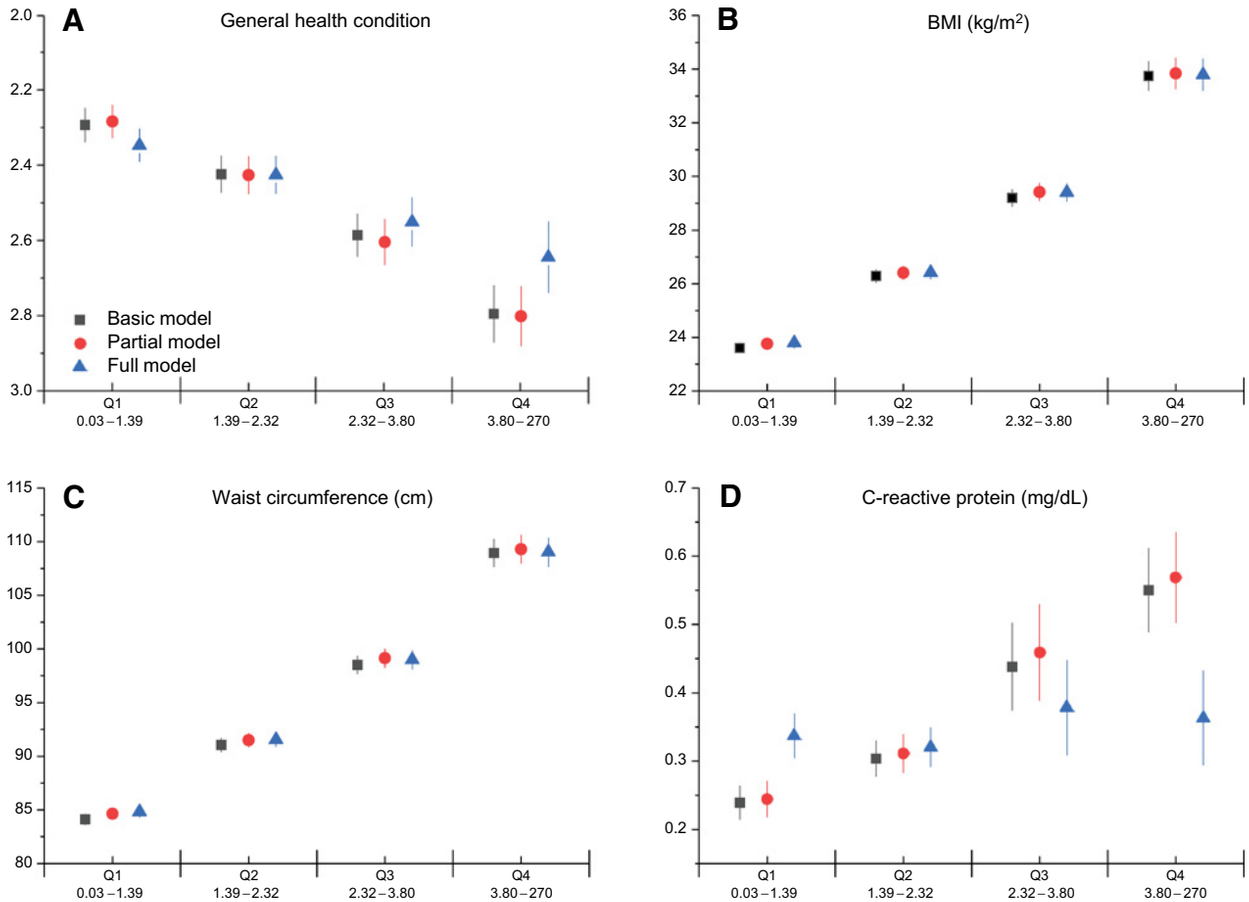


**Figure 1.**

Mean adjusted general health, anthropometric, and inflammatory markers by HOMA-IR quartiles. **A,** General health where 1 = excellent, 2 = good, 3 = fair, 4 = poor. **B,** BMI in kg/m$^2$. **C,** Waist circumference in cm. **D,** C-reactive protein in mg/dL. Shown are HOMA-IR quartile means with 95% CI for each variable, using basic (black rectangle), partial (red circle), and fully adjusted (blue triangle) models. The variables in the latter models include all those in the previous models. The basic (Model 1) is adjusted for age, age squared, gender, race/ethnicity (Mexican-American, other Hispanic, non-Hispanic white, non-Hispanic black, other and multiethnic), standing height, family income, education (less than high school, high school, beyond high school), and data release year (8 categories: 1999–2000 through 2013–2014). The partially adjusted (Model 2) adds smoking status (never/former/current), pack years smoking, caffeine intake (mg/day), and alcohol (g/day). The fully adjusted (Model 3) adds physical activity, 6-month time period (Nov–Apr; May–Oct), total cholesterol (mg/dL), dietary supplement use (yes/no), and BMI. The *x*-axis depicts HOMA-IR quartiles based on the entire study group. The *y*-axis variables and units are listed in the description of each panel (**A–D**).

HOMA-IR is used to refer to insulin in the report as this was the quantity that was analyzed, but insulin or insulin resistance is occasionally used when referring to insulin more generally.

All analyses were weighted using the NHANES sample weights for survey participants who completed the medical examinations and interviews in the Mobile Examination Centers. The samples and the sample weights were combined according to NCHS guidelines (see https://wwwn.cdc.gov/nchs/data/nhanes/2011-2012/analyticguidelines/analytic_guidelines_11_16.pdf and https://www.cdc.gov/nchs/data/series/sr_02/sr02_161.pdf) to conduct the statistical analyses. The sample weight variable used in the analysis programs is WTSAF2YR (Fasting Subsample Year MEC). SAS statistical software SUDAAN Release 11.0.1, SAS-Callable, 64 bit version was used to account for the sample weighting, sample stratification, and clustering in the NHANES complex sample design. All *P* values for the statistical tests were two-sided. Participants were dropped from a particular analysis if a variable was missing for that subject or because a particular test or data item was not available for a 2-year data wave and this accounts for the smaller numbers of subjects in analyses presented in **Table 2**, **Figs. 1–5**, and Supplementary Tables S1 and S2, compared with **Table 1**. Footnotes are provided in the tables when a particular outcome was unavailable in NHANES for a given period.

## Results

There were 9,224 normal, 7,699 prediabetic, and 3,413 diabetic participants in the analytic sample. In the nondiabetic component, 58% were female, 51% were never smokers, and 32%/23%, respectively, were overweight or obese (**Table 1**). As expected, males, individuals in fair or poor health, with low education, and who were overweight or obese were overrepresented in the diabetic and prediabetic samples.

In a fully adjusted model where the OR represents risk for a one quartile rise in insulin levels for normal subjects, increasing HOMA-IR results in a higher rate of "poor or fair" health (OR = 1.28; 95% CI, 1.10–1.49; **Table 2**). The decline in general health with each quartile

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**Table 1.** Characteristics of study participants.

| Characteristics | Normal (% of total) | Prediabetic (% of total) | Diabetic (% of total) |
|---|---|---|---|
| Total (*n*) | 9,224 | 7,699 | 3,413 |
| Gender | | | |
| Male | 3,853 (41.77) | 4,257 (55.29) | 1,769 (51.83) |
| Female | 5,371 (58.23) | 3,442 (44.71) | 1,644 (48.17) |
| Age at screening | | | |
| 18–29 | 3,627 (39.32) | 1,062 (13.79) | 101 (2.96) |
| 30–39 | 1,899 (20.59) | 1,106 (14.37) | 184 (5.39) |
| 40–49 | 1,432 (15.52) | 1,385 (17.99) | 410 (12.01) |
| 50–59 | 860 (9.32) | 1,299 (16.87) | 608 (17.81) |
| 60–69 | 679 (7.36) | 1,325 (17.21) | 995 (29.15) |
| 70–79 | 419 (4.54) | 912 (11.85) | 705 (20.66) |
| 80–85 | 308 (3.34) | 610 (7.92) | 410 (12.01) |
| Race/ethnicity | | | |
| Mexican-American | 1,764 (19.12) | 1,473 (19.13) | 696 (20.39) |
| Other Hispanic | 618 (6.70) | 618 (8.03) | 293 (8.58) |
| Non-Hispanic white | 4,354 (47.20) | 3,597 (46.72) | 1,412 (41.37) |
| Non-Hispanic black | 1,858 (20.14) | 1,448 (18.81) | 785 (23.00) |
| Other/multi | 630 (6.83) | 563 (7.31) | 227 (6.65) |
| Physical activity | | | |
| Yes | 5,533 (59.98) | 3,891 (50.54) | 1,275 (37.36) |
| No | 3,687 (39.97) | 3,806 (49.43) | 2,137 (62.61) |
| Unknown | 4 (0.04) | 2 (0.03) | 1 (0.03) |
| Education | | | |
| Unknown | 1,216 (13.18) | 327 (4.25) | 33 (0.97) |
| <HS | 1,877 (20.35) | 2,177 (28.28) | 1,323 (38.76) |
| =HS | 1,777 (19.26) | 1,732 (22.50) | 799 (23.41) |
| >HS | 4,354 (47.20) | 3,463 (44.98) | 1,258 (36.86) |
| Smoking status | | | |
| Missing | 1,107 (12.00) | 281 (3.65) | 29 (0.85) |
| Never | 4,700 (50.95) | 3,782 (49.12) | 1,645 (48.20) |
| Former | 1,610 (17.45) | 2,039 (26.48) | 1,161 (34.02) |
| Current | 1,807 (19.59) | 1,597 (20.74) | 578 (16.94) |
| Year of survey cycle | | | |
| 1999–2000 | 1,361 (14.75) | 639 (8.30) | 236 (6.91) |
| 2001–2002 | 1,440 (15.61) | 816 (10.60) | 331 (9.70) |
| 2003–2004 | 1,403 (15.21) | 682 (8.86) | 314 (9.20) |
| 2005–2006 | 1,121 (12.15) | 900 (11.69) | 367 (10.75) |
| 2007–2008 | 862 (9.35) | 1,267 (16.46) | 586 (17.17) |
| 2009–2010 | 1,077 (11.68) | 1,235 (16.04) | 574 (16.82) |
| 2011–2012 | 932 (10.10) | 1,018 (13.22) | 518 (15.18) |
| 2013–2014 | 1,028 (11.14) | 1,142 (14.83) | 487 (14.27) |
| BMI | | | |
| <25 | 4,062 (44.04) | 1,970 (25.59) | 520 (15.24) |
| 25–<30 | 2,918 (31.63) | 2,760 (35.85) | 1,052 (30.82) |
| ≥30 | 2,108 (22.85) | 2,864 (37.20) | 1,743 (51.07) |
| Missing | 136 (1.47) | 105 (1.36) | 98 (2.87) |
| General health condition | | | |
| Missing | 2,007 (21.76) | 1,178 (15.30) | 461 (13.51) |
| Excellent | 986 (10.69) | 585 (7.60) | 114 (3.34) |
| Very good | 2,442 (26.47) | 1,772 (23.02) | 487 (14.27) |
| Good | 2,727 (29.56) | 2,722 (35.36) | 1,127 (33.02) |
| Fair | 948 (10.28) | 1,245 (16.17) | 978 (28.66) |
| Poor | 114 (1.24) | 197 (2.56) | 246 (7.21) |

Note: Data are expressed as the unweighted number of participants and weighted percentages to be nationally representative.
Abbreviation: HS, high school.

rise in insulin is also depicted in **Fig. 1A**, where the adjusted means and their 95% CI for this outcome (and all the others that follow) are shown in basic, partially, and fully adjusted models. The relationship of HOMA-IR to general health are similar in crude correlations (Supplementary Table S1) and the magnitude of change for the adjusted means of each outcome variable in those with HOMA-IR values above or below the median is seen in Supplementary Table S2.

Both BMI > 25, overweight + obese (OR = 3.19; 95% CI, 2.94–3.47) and BMI > 30, obese (OR = 3.62; 95% CI, 3.30–3.97), and waist circumference (OR = 1.52; 95% CI, 1.31–1.78) exhibit strong,

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**Table 2.** Adjusted risk estimates for key outcomes in relation to HOMA-IR.

| Adjusted ORs and 95% CI by HOMA-IR quartiles for key outcomes in fully adjusted model[a] | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Normal | | Prediabetic | | Diabetic | | Overall | |
| Variable | Risk group[b] | *N* | OR (95% CI) | *N* | OR (95% CI) | *N* | OR (95% CI) | *N* | OR (95% CI) |
| General health condition[c] | | | | | | | | | |
| Health | Poor or fair | 5,432 | 1.28 (1.10–1.49) | 5,334 | 1.07 (0.97–1.18) | 2,326 | 0.94 (0.81–1.10) | 13,092 | 1.11 (1.03–1.21) |
| Metabolic | | | | | | | | | |
| BMI (overweight + obese) | >25 kg/m$^2$ | 6,633 | 3.19 (2.94–3.47) | 6,078 | 3.13 (2.86–3.42) | 2,556 | 2.16 (1.87–2.50) | 15,267 | 3.00 (2.84–3.18) |
| BMI (obese) | >30 kg/m$^2$ | 6,633 | 3.62 (3.30–3.97) | 6,078 | 3.27 (3.03–3.53) | 2,556 | 2.19 (1.91–2.51) | 15,267 | 3.23 (3.05–3.42) |
| Waist circumference (cm) | M >90 cm; F >80 cm | 6,556 | 1.52 (1.31–1.78) | 5,986 | 1.68 (1.35–2.08) | 2,481 | 1.64 (1.17–2.32) | 15,023 | 1.58 (1.43–1.73) |
| Cardiovascular | | | | | | | | | |
| Blood pressure (systolic) | ≥132 mm Hg | 6,475 | 1.02 (0.91–1.15) | 5,915 | 1.00 (0.91–1.09) | 2,485 | 1.05 (0.93–1.17) | 14,875 | 1.02 (0.96–1.09) |
| Blood pressure (diastolic) | ≥80 mm Hg | 6,475 | 1.15 (1.04–1.28) | 5,915 | 1.20 (1.09–1.32) | 2,485 | 1.27 (1.09–1.47) | 14,875 | 1.19 (1.12–1.27) |
| Lipids | | | | | | | | | |
| Total cholesterol | 228 mg/dL | 6,633 | 1.21 (1.09–1.34) | 6,078 | 1.06 (0.96–1.16) | 2,556 | 1.02 (0.88–1.19) | 15,267 | 1.13 (1.06–1.20) |
| Triglycerides | ≥176 mg/dL | 6,626 | 1.83 (1.61–2.08) | 6,073 | 1.89 (1.69–2.12) | 2,552 | 1.91 (1.63–2.24) | 15,251 | 1.89 (1.76–2.03) |
| HDL-cholesterol | ≥65 mg/dL | 6,633 | 0.61 (0.55–0.67) | 6,078 | 0.54 (0.48–0.61) | 2,556 | 0.58 (0.51–0.68) | 15,267 | 0.58 (0.54–0.61) |
| LDL-cholesterol | ≥144 mg/dL | 6,550 | 0.98 (0.83–1.15) | 5,942 | 1.19 (1.01–1.41) | 2,423 | 1.05 (0.80–1.38) | 14,915 | 1.08 (0.96–1.20) |
| Triglycerides/HDL | ≥57 | 6,626 | 2.00 (1.77–2.26) | 6,073 | 2.08 (1.84–2.34) | 2,552 | 1.96 (1.68–2.27) | 15,251 | 2.04 (1.89–2.20) |
| Hepatic | | | | | | | | | |
| ALT | ≥31 U/L | 6,625 | 1.58 (1.43–1.75) | 6,059 | 1.59 (1.44–1.77) | 2,552 | 1.76 (1.47–2.11) | 15,236 | 1.62 (1.51–1.74) |
| AST | ≥28 U/L | 6,624 | 1.06 (0.97–1.17) | 6,057 | 1.21 (1.09–1.33) | 2,552 | 1.38 (1.20–1.59) | 15,233 | 1.17 (1.10–1.25) |
| GGT | ≥33 U/L | 6,627 | 1.40 (1.24–1.58) | 6,070 | 1.46 (1.33–1.61) | 2,556 | 1.60 (1.38–1.85) | 15,253 | 1.45 (1.35–1.55) |
| Hematologic | | | | | | | | | |
| White blood cell | ≥8.2 SI | 6,630 | 1.28 (1.16–1.40) | 6,066 | 1.30 (1.19–1.42) | 2,550 | 1.23 (1.07–1.42) | 15,246 | 1.27 (1.20–1.36) |
| Segmented neutrophil number | ≥5.1 | 6,598 | 1.22 (1.12–1.33) | 6,053 | 1.20 (1.09–1.32) | 2,539 | 1.12 (0.98–1.27) | 15,190 | 1.19 (1.11–1.27) |
| Lymphocyte number | ≥2.4 | 6,598 | 1.26 (1.15–1.38) | 6,053 | 1.19 (1.09–1.29) | 2,539 | 1.31 (1.14–1.51) | 15,190 | 1.24 (1.17–1.31) |
| Hemoglobin | ≥15.7 g/dL | 6,630 | 1.23 (1.09–1.38) | 6,066 | 1.34 (1.20–1.48) | 2,550 | 1.37 (1.12–1.67) | 15,246 | 1.30 (1.21–1.40) |
| Platelet count | ≥303% SI | 6,629 | 1.18 (1.09–1.28) | 6,066 | 1.13 (1.02–1.25) | 2,550 | 0.92 (0.81–1.06) | 15,245 | 1.12 (1.06–1.19) |
| Inflammatory | | | | | | | | | |
| C-reactive protein[d] | ≥0.55 mg/dL | 5,130 | 1.10 (0.96–1.27) | 4,354 | 1.03 (0.92–1.15) | 1,782 | 1.23 (1.06–1.44) | 11,266 | 1.11 (1.03–1.19) |
| Ferritin[e] | ≥194 ng/mL | 1,952 | 1.32 (1.04–1.69) | 1,120 | 1.57 (1.27–1.92) | 370 | 2.23 (1.47–3.38) | 3,442 | 1.52 (1.28–1.80) |
| Nutrition | | | | | | | | | |
| Vitamin B6 (pyridoxal 5′-phosphate) | ≥90.7 nmol/L | 3,134 | 0.70 (0.60–0.80) | 3,195 | 0.78 (0.67–0.90) | 1,386 | 1.05 (0.87–1.26) | 7,715 | 0.78 (0.71–0.86) |
| Vitamin B12, serum | ≥660 pg/mL | 4,364 | 0.93 (0.83–1.06) | 3,150 | 0.93 (0.81–1.06) | 1,273 | 0.87 (0.73–1.05) | 8,787 | 0.92 (0.86–1.00) |
| Vitamin C[f] | ≥1.27 mg/dL | 1,744 | 0.65 (0.54–0.79) | 1,243 | 1.11 (0.91–1.34) | 515 | 0.72 (0.56–0.93) | 3,502 | 0.83 (0.73–0.93) |
| Vitamin D (25OHD2+25OHD3)[g] | ≥83.7 nmol/L | 4,806 | 0.87 (0.76–1.00) | 4,550 | 0.86 (0.77–0.96) | 1,979 | 0.86 (0.70–1.06) | 11,335 | 0.87 (0.80–0.94) |
| Folate, RBC[h] | ≥534 ng/mL RBC | 5,784 | 1.00 (0.87–1.14) | 5,136 | 0.99 (0.89–1.10) | 2,163 | 0.88 (0.76–1.03) | 13,083 | 0.98 (0.91–1.05) |
| Folate, serum (ng/mL)[h] | ≥22.3 ng/mL | 5,790 | 0.86 (0.75–0.98) | 5,134 | 0.91 (0.80–1.03) | 2,157 | 0.85 (0.72–1.00) | 13,081 | 0.88 (0.82–0.95) |

Abbreviations: F, females; M, males; RBC, red blood cell.

[a]Fully adjusted model includes age, age squared, gender, race/ethnicity (Mexican-American, other Hispanic, non-Hispanic white, non-Hispanic black, other and multiethnic), standing height, family income, education (less than high school, high school, beyond high school), and data release year (8 categories: 1999–2000 through 2013–2014), smoking status (never/former/current), pack years smoking, caffeine intake per day (mg), alcohol (g/dL), physical activity, 6-month time period (Nov–Apr, May–Oct), total cholesterol, dietary supplement use (yes/no), and BMI.

[b]Defined risk groups for general health condition and metabolic outcomes; otherwise defined using the highest quintile.

[c]1999–2000 not available; 1, excellent; 2, very good; 3, good; 4, fair; 5, poor.

[d]2011–2012 and 2013–2014 not assayed.

[e]Only available for 1999–2000 and 2001–2002.

[f]Only available for 2003–2004 and 2005–2006.

[g]1999–2000 and 2013–2014 not assayed.

[h]2013–2014 not available.

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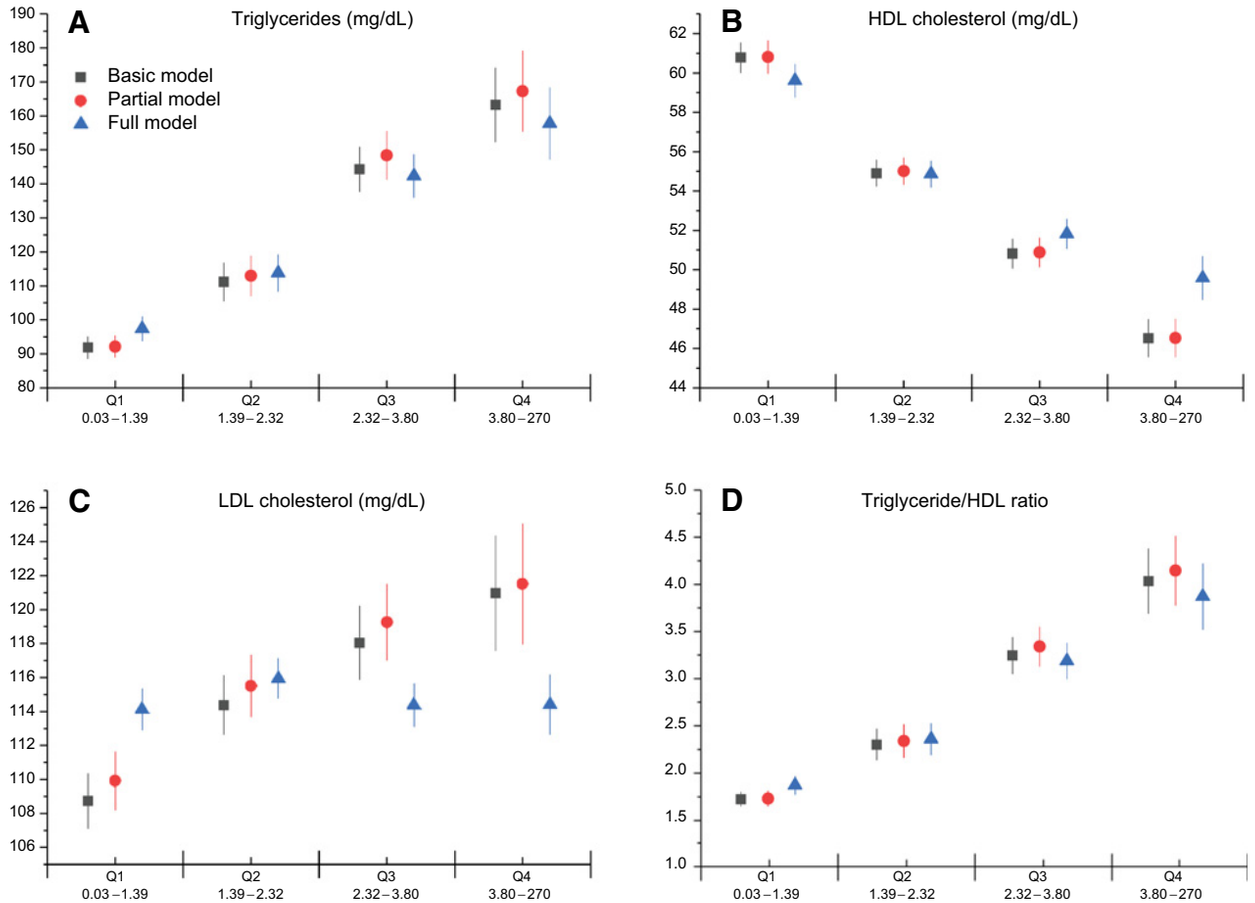


**Figure 2.**

Mean adjusted lipids by HOMA-IR quartiles. **A,** Triglycerides in mg/dL. **B,** HDL cholesterol in mg/dL. **C,** LDL cholesterol in mg/dL. **D,** Triglyceride/HDL ratio, no units. Shown are HOMA-IR quartile means with 95% CI for each variable, using basic (black rectangle), partial (red circle), and fully adjusted (blue triangle) models. The variables in the latter models include all those in the previous models. The basic (Model 1) is adjusted for age, age squared, gender, race/ethnicity (Mexican-American, other Hispanic, non-Hispanic white, non-Hispanic black, other, and multiethnic), standing height, family income, education (less than high school, high school, beyond high school), and data release year (8 categories: 1999–2000 through 2013–2014). The partially adjusted (Model 2) adds smoking status (never/former/current), pack years smoking, caffeine intake (mg/day), and alcohol (g/day). The fully adjusted (Model 3) adds physical activity, 6-month time period (Nov–Apr; May–Oct), total cholesterol (mg/dL), dietary supplement use (yes/no), and BMI. The *x*-axis depicts HOMA-IR quartiles based on the entire study group. The *y*-axis variables and units are listed in the description of each panel (**A–D**).

consistent, and highly significant associations with each quartile rise in HOMA-IR among normal subjects (**Table 2**).

Diastolic (OR = 1.15; 95% CI, 1.04–1.28), but not systolic (OR = 1.02; 95% CI, 0.91–1.15), blood pressure showed significant elevations by adjusted quartile in normal subjects, although the crude correlations (Supplementary Table S1) and analysis based on median threshold (Supplementary Table S2) show highly significant associations of HOMA-IR with both components of blood pressure.

Triglycerides, HDL, and the triglyceride/HDL ratio all show strong and highly significant associations with HOMA-IR in every analysis. LDL-cholesterol is not associated with HOMA-IR in adjusted analyses (OR = 0.98; 95% CI, 0.83–1.15; see **Fig. 2C** for loss of positive trend after full adjustment).

The hepatic markers ALT and GGT show strong and highly significant adjusted associations (OR = 1.58; 95% CI, 1.43–1.75 and OR = 1.40; 95% CI, 1.24–1.58, respectively). The association with AST is not significant for normal subjects only but shows a slight positive trend overall (**Fig. 3B**).

The suite of hematologic markers (WBC, neutrophil and lymphocyte count, hemoglobin, and platelets) were all highly associated with HOMA-IR in every instance in normal subjects and overall (**Fig. 4**).

Among the inflammatory markers, C-reactive protein (CRP) exhibited a tendency to increase (OR = 1.10; 95% CI, 0.96–1.27) with adjusted quartile rises in HOMA-IR (**Table 2**) and the same tendency is present in the other analyses.

Finally, among the suite of nutritional markers, vitamins B6, C, D, and serum folate all exhibit significant associations with HOMA-IR (**Fig. 5**), while vitamin B12 and RBC folate do not (**Table 2**).

The associations observed in the normal subjects are generally recapitulated in the prediabetic, diabetic, and overall group (adjusted for diabetes status) with some exceptions.

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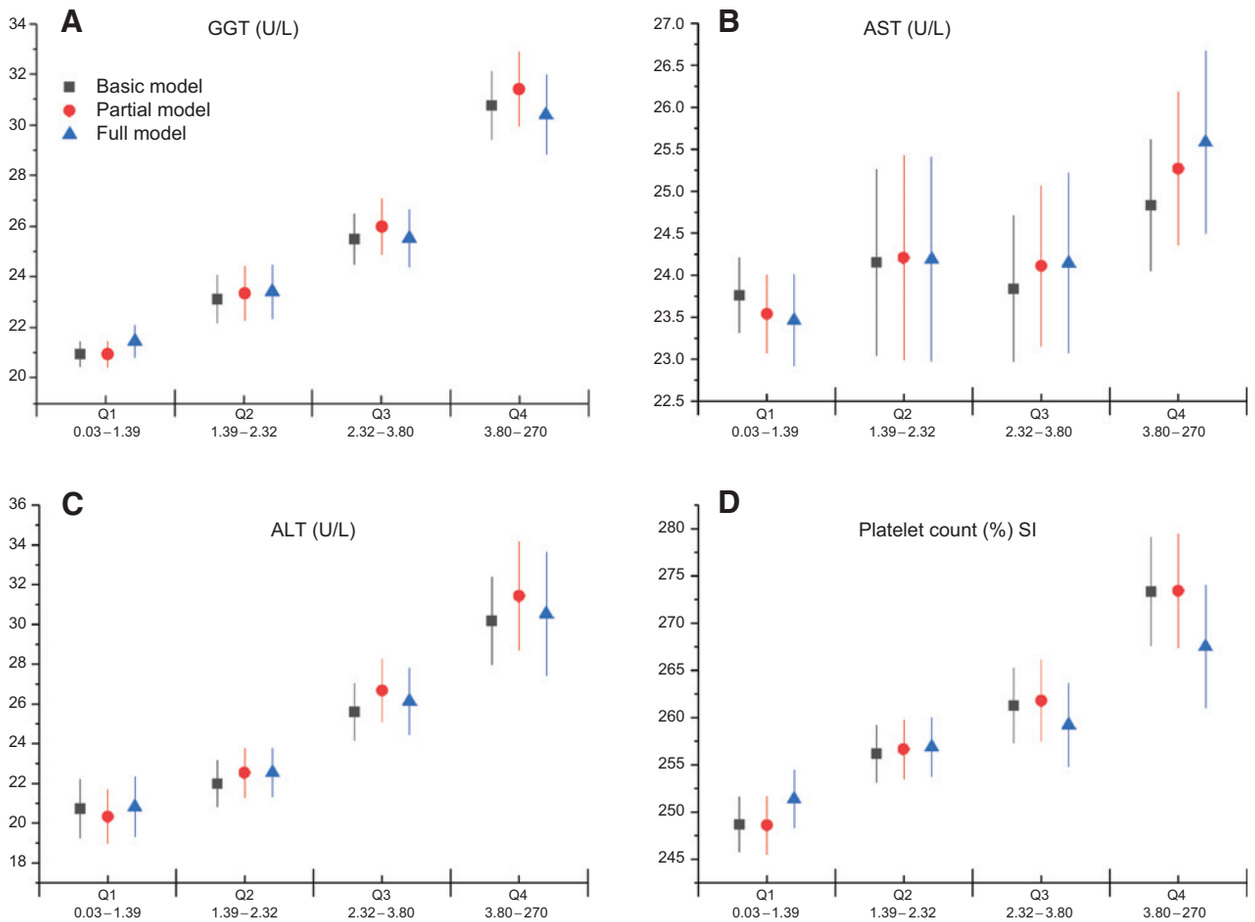


**Figure 3.**

Mean adjusted liver-related markers by HOMA-IR quartiles. **A,** GGT (U/L). **B,** AST (U/L). **C,** ALT (U/L). **D,** Platelet count (%) SI. Shown are HOMA-IR quartile means with 95% CI for each variable, using basic (black rectangle), partial (red circle), and fully adjusted (blue triangle) models. The variables in the latter models include all those in the previous models. The basic (Model 1) is adjusted for age, age squared, gender, race/ethnicity (Mexican-American, other Hispanic, non-Hispanic white, non-Hispanic black, other, and multiethnic), standing height, family income, education (less than high school, high school, beyond high school), and data release year (8 categories: 1999–2000 through 2013–2014). The partially adjusted (Model 2) adds smoking status (never/former/current), pack years smoking, caffeine intake (mg/day), and alcohol (g/day). The fully adjusted (Model 3) adds physical activity, 6-month time period (Nov–Apr; May–Oct), total cholesterol (mg/dL), dietary supplement use (yes/no), and BMI. The *x*-axis depicts HOMA-IR quartiles based on the entire study group. The *y*-axis variables and units are listed in the description of each panel (**A–D**).

## Discussion

It is notable that in a population-based representative sample of noninstitutionalized U.S. adults, more than half meet the criteria for both overweight/obese and for diabetes or prediabetes.

While the varied anthropometric, clinical, and laboratory correlates of diabetes are well documented, the broad nature of insulin-related findings in the NHANES that extend to "healthy" adults are remarkable for a few reasons. Among "normal" subjects, insulin resistance as characterized by HOMA-IR affects diverse body systems including and extending beyond those traditionally recognized in metabolic syndrome, that is, blood pressure, lipids, and waist size. The strong linear relationship of insulin levels with adverse health status and diverse categories of markers (some indirectly associated with adverse outcomes) using a variety of statistical measures including three tiers of adjustment highlights the potential clinical and mechanistic importance. The pattern of association of HOMA-IR with general health was observed in normal, prediabetic, and diabetic groups (Supplementary Table S2) and was present in crude analyses (Supplementary Table S1) and after adjustment (**Table 2**; **Fig. 1A**).

The strongest and most consistent associations with insulin were seen for two categories that are components of metabolic syndrome: lipids (HDL, triglycerides) and the anthropometric measures (BMI and waist circumference). Similarly strong is the association with hepatic markers (ALT and GGT) that are not part of the metabolic syndrome. A pattern of association is seen for another component of metabolic syndrome, blood pressure, but was consistent and significant only for diastolic blood pressure after full adjustment. We did not include fasting glucose level as glucose is a component of HOMA-IR. International bodies have established slightly different thresholds for the components of metabolic syndrome to define the condition (43). For example, the World Health Organization and International Diabetes Federation definitions differ in thresholds for particular components and there are also differences by geography, ethnicity, and gender resulting in differing prevalence estimates, although recent

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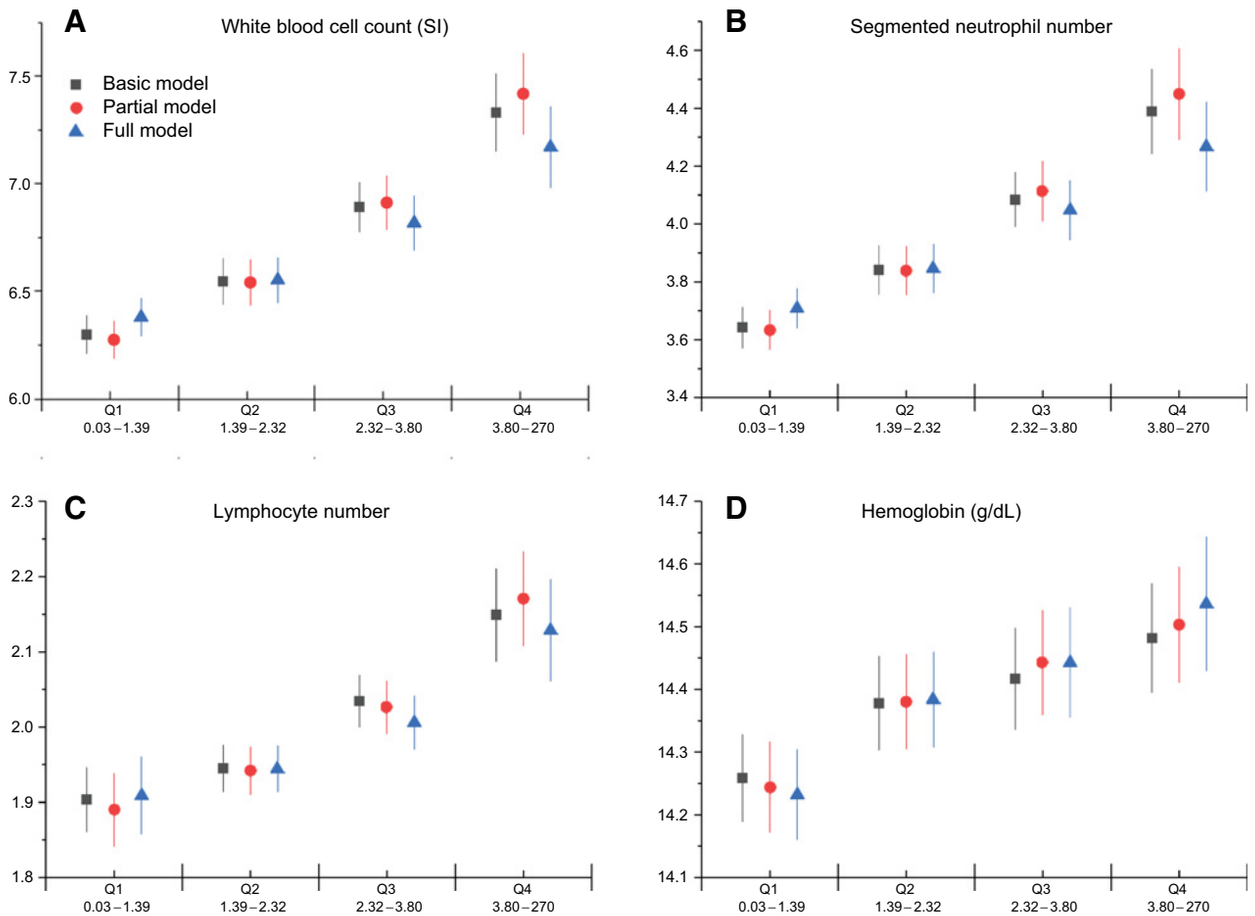


**Figure 4.**

Mean adjusted hematologic markers by HOMA-IR quartiles. **A,** White blood count (SI). **B,** Segmented neutrophils, number. **C,** Lymphocytes, number, thousands. **D,** Hemoglobin, g/dL. Shown are HOMA-IR quartile means with 95% CI for each variable, using basic (black rectangle), partial (red circle), and fully adjusted (blue triangle) models. The variables in the latter models include all those in the previous models. The basic (Model 1) is adjusted for age, age squared, gender, race/ethnicity (Mexican-American, other Hispanic, non-Hispanic white, non-Hispanic black, other, and multiethnic), standing height, family income, education (less than high school, high school, beyond high school), and data release year (8 categories: 1999–2000 through 2013–2014). The partially adjusted (Model 2) adds smoking status (never/former/current), pack years smoking, caffeine intake (mg/day), and alcohol (g/day). The fully adjusted (Model 3) adds physical activity, 6-month time period (Nov–Apr; May–Oct), total cholesterol (mg/dL), dietary supplement use (yes/no), and BMI. The *x*-axis depicts HOMA-IR quartiles based on the entire study group. The *y*-axis variables and units are listed in the description of each panel (**A–D**).

reviews agree that prevalence is increasing (44). The statistical relationships we observed suggest that the components of metabolic syndrome: hypertension, elevated triglycerides, lower HDL, abdominal obesity, and glycemic abnormalities (45) all exhibit highly significant linear relationships with HOMA-IR in "normal" subjects prior to the development of diabetes or the prediabetic state. So, for example, triglycerides, HDL cholesterol, and their ratios are strongly related to HOMA-IR in the literature (46, 47), and our findings show that among apparently normal subjects, HDL, triglycerides, and waist circumference all exhibit smooth increases with rising insulin levels. This pattern is present in crude and adjusted analyses and is also relatively invariant whether HOMA-IR is examined as a quartile, median, or continuous measure. This suggests that elevations in insulin across a wide "normal" range, are associated with adverse changes in these (and the other) categories of markers, well before any of the thresholds for the syndromic definitions of metabolic syndrome or diabetes/prediabetes are diagnosed. The observation that the findings are most prominently observed in normal and prediabetic subjects suggests that insulin exerts broad effects prior to the development of diabetes in what is a latent but apparently "clinically normal" state. Of note, the changes observed exhibit a range and magnitude that generally resides within the normal clinical bounds, as shown in **Figs. 1–5** (by adjusted HOMA-IR quartile) and Supplementary Table S2 (by the median value of HOMA-IR). Although the components of metabolic syndrome exhibit highly significant relationships with insulin in normal subjects, the alterations associated with insulin in our study extend beyond the syndromic definition to the categories of liver function tests, hematologic components, inflammatory markers (CRP), and vitamin levels (inverse). Liver function tests also (ALT and GGT, AST is notably weaker) exhibit strong relationships with HOMA-IR, consistent with the strong associations of non-alcoholic fatty liver disease (NAFLD) with both obesity and T2D (48, 49). Strong relationships were also observed for inflammatory markers and hematologic measures. Strong inverse relationships were observed for a selected group of

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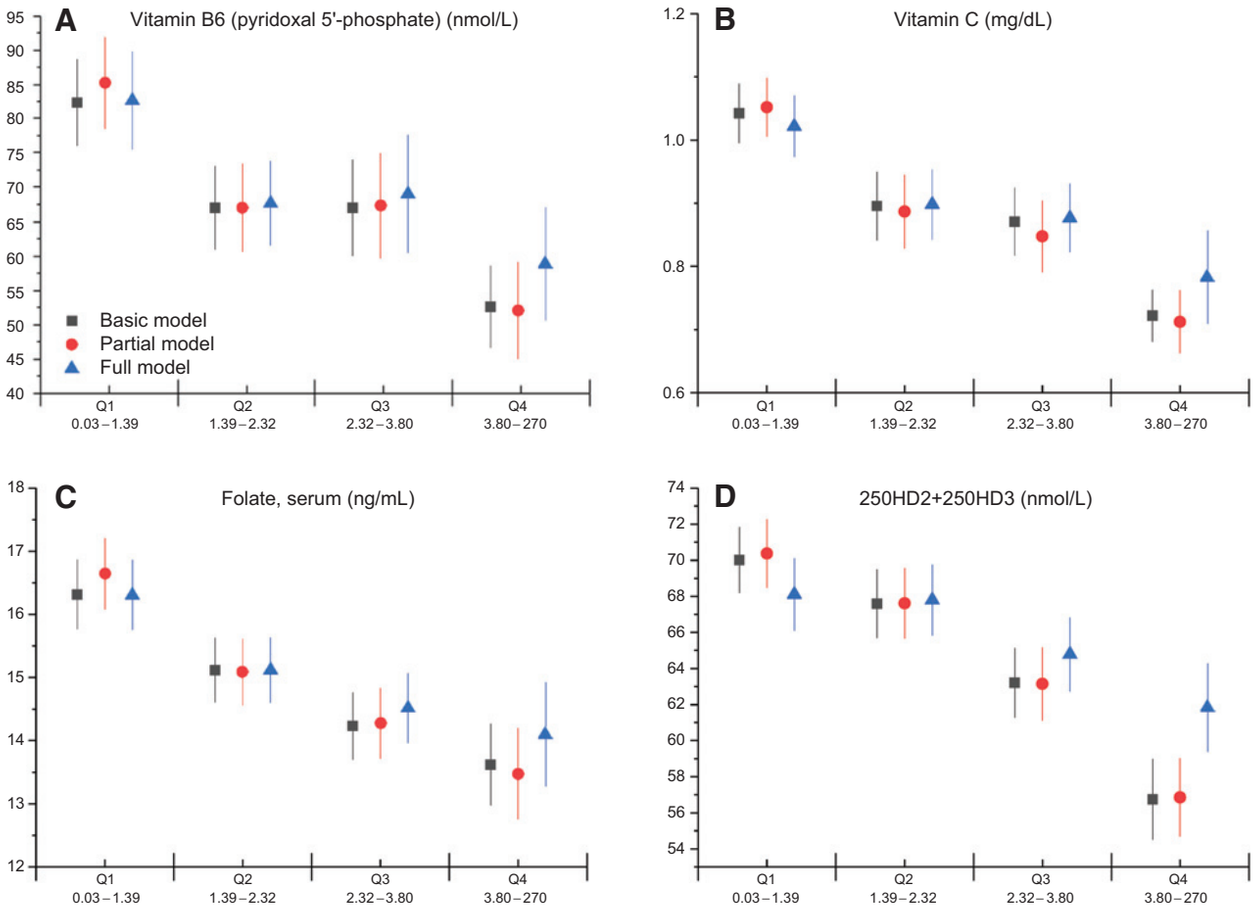


**Figure 5.**

Mean adjusted nutritional markers by NOMA-IR quartiles. **A,** Vitamin B6 (pyridoxal 5′-phosphate) in nmol/L. **B,** Vitamin C in mg/dL. **C,** Serum folate in ng/mL. **D,** Vitamin D as 25OHD2+25OHD3 in nmol/L. Shown are HOMA-IR quartile means with 95% CI for each variable, using basic (black rectangle), partial (red circle), and fully adjusted (blue triangle) models. The variables in the latter models include all those in the previous models. The basic (Model 1) is adjusted for age, age squared, gender, race/ethnicity (Mexican-American, other Hispanic, non-Hispanic white, non-Hispanic black, other, and multiethnic), standing height, family income, education (less than high school, high school, beyond high school), and data release year (8 categories: 1999–2000 through 2013–2014). The partially adjusted (Model 2) adds smoking status (never/former/current), pack years smoking, caffeine intake (mg/day), and alcohol (g/day). The fully adjusted (Model 3) adds physical activity, 6-month time period (Nov–Apr; May–Oct), total cholesterol (mg/dL), dietary supplement use (yes/no), and BMI. The *x*-axis depicts HOMA-IR quartiles based on the entire study group. The *y*-axis variables and units are listed in the description of each panel (**A–D**).

micronutrients (vitamins D, C, serum folate, and pyridoxine), but not for some others (RBC folate, vitamin B12). In general, and as noted earlier, the associations of insulin with general health, weight, lipids, liver function, and inflammatory markers are consistent with previous work. Associations of insulin with hematologic parameters (50–52) and specific nutrients [vitamin D (53), vitamin C and pyridoxine (54)] are reported but generally in smaller studies. While these associations achieve statistical significance, clinical significance requires further study because the quartiles generally reside within standard bounds for the clinical laboratory studies and replication in other settings is needed. The associations of these markers with HOMA-IR are present with quartiles (**Fig. 5**) and in dichotomous categories (Supplementary Table S2). Spline graphs of risk factors plotted against population percentile of HOMA-IR show that the generally linear relationships extend across the range of variation of HOMA-IR (Supplementary Figs. S1 and S2).

The broad nature of the observed associations and the general lack of strong attenuation when various adjustment variables are incorporated into the models raise the question of where insulin resistance resides on the causal pathway in relation to the outcomes reported. It must be emphasized that based on the population data presented here, even with the substantial size, representativeness, and adjustment for diverse cofactors, distinct limitations preclude any such conclusion. NHANES is a cross-sectional study and so formal assessment of causality is not possible. Moreover, the role of plausible and closely related hormonal, inflammatory, dietary, nutritional, metabolic, and anthropometric factors require further study in prospective or clinical trial settings. It may be difficult to separate the effect of insulin from associated cofactors like obesity and its subsets (e.g., visceral fat), obesity-related hormones (glucagon, ghrelin, leptin and adiponectin), sex hormones (estrogen), growth factors (IGF family), coagulopathy, circadian disruption, and inflammation. Moreover, while smoking, BMI, physical activity and others are included as adjustment variables, a degree of residual confounding and measurement error are likely. Confounder variables are based on self-report and unknown confounders could exist. That said, NHANES is among the largest, most

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representative, highest quality, and best documented population-based studies available. Finally, even if insulin were established to be causal, additional studies would be required to demonstrate that interventions that lowered insulin had therapeutic effects on the endpoints studied here. Also, the associations of outcome variables with insulin in quartiles and beyond generally vary within the normal range of laboratory values, emphasizing the distinction between statistically significant changes and clinical significance. Although we were able to adjust for many other factors associated with the physical findings and laboratory markers studied, fully describing how insulin interacts with other factors that plausibly modify mortality such as physical activity, obesity, circadian disruption, other hormones, inflammation, and secondary associated conditions such as hypertension will require further study.

While mindful of the noted limitations, a substantial body of previous mechanistic and population data support a central role for insulin. Insulin is implicated in the components of metabolic syndrome (55, 56) and insulin resistance is often noted as a closely related entity. Genetic instruments of insulin secretion implicate it in higher BMI consistent with a role in promoting obesity (12). Previous work has established that elevated insulin levels predict future development of diabetes and may coexist with normal fasting glucose studies (57, 58). Insulin levels have been independently related to cardiovascular parameters (59, 60), cancer risk (20), cancer (17), and overall mortality (19).

A few of the associations present in normal and prediabetics are absent or less prominent in diabetics, for example, total cholesterol, platelet count and vitamin B6, segmented neutrophils, and general health. Power issues may contribute as the diabetic group is the smallest. It is also plausible that the loss of beta cell function and mass in established diabetics attenuates insulin levels in this group (61).

Although cardiovascular and metabolic disease endpoints are associated with IR, evidence suggests that insulin may also contribute to established associations of obesity with diverse cancers (62). General obesity and visceral adiposity, lipid profiles (63), lack of physical activity or inactivity, vitamin D status (64), sleep/circadian rhythm disruption (65, 66), and inflammatory mediators (67) are all plausible cofactors that could contribute to adverse health associations with insulin. Further investigation into the role of insulin and cancer is also supported by work implicating dietary sugar as a metabolic driver of cancer (68), studies of the roles of caloric restriction and cancer/longevity, metformin as a cancer-protective agent (7, 69), and studies associating diabetes and cancer risk (6) and mortality (18, 20). Organ-specific factors may contribute to particular cancers, that is, fatty liver/NAFLD and hepatocellular carcinoma (70) or polycystic ovarian syndrome and endometrial cancer (71).

With the cautions noted, this work supports further investigation of insulin as an informative biomarker, therapeutic target, and risk stratification tool. Our findings suggest that insulin monitoring may be a useful adjunct to glucose screening studies because we show that insulin resistance (elevated HOMA-IR) is associated with adverse changes in markers across multiple categories, both in subjects with normal glucose profiles and those who are prediabetic. This suggests that such studies could identify subjects at high risk of progression where lifestyle, pharmacologic, or surgical interventions may delay or avert the progression of short-term metabolic abnormalities and improve health outcomes (72, 73). We suggest that monitoring of insulin may have clinical relevance in facilitating effective interventions including subjects with fasting serum glucose results in the normal range.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

## Authors' Contributions

**Conception and design:** N.E. Caporaso, R.Z. Stolzenberg-Solomon
**Development of methodology:** N.E. Caporaso, R.R. Jones, B.I. Graubard
**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** N.E. Caporaso
**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** N.E. Caporaso, R.R. Jones, R.Z. Stolzenberg-Solomon, L.L. Kahle, B.I. Graubard
**Writing, review, and/or revision of the manuscript:** N.E. Caporaso, R.R. Jones, R.Z. Stolzenberg-Solomon, D.N. Medgyesi, L.L. Kahle, B.I. Graubard
**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** N.E. Caporaso, D.N. Medgyesi, L.L. Kahle
**Study supervision:** N.E. Caporaso

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