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# Cross-sectional correlates of fasting hyperinsulinaemia in post-menopausal women of different ethnic origin

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## Abstract

**Aims** In a large ethnically diverse nationwide sample of post-menopausal women we explored the relationship between fasting insulin levels, ethnicity, and a wide range of anthropometric, socio-economic, and lifestyle factors.

**Methods** Subjects were post-menopausal women aged 50–79 years without diagnosed diabetes mellitus comprising a subsample ($n$ = 3500) of the Women's Health Initiative (WHI) Clinical Trial and Observational Study. In a cross-sectional survey at baseline, we analysed the association between ethnicity and fasting insulin using analysis of covariance procedures and identified independent correlates of hyperinsulinaemia, defined by the 75th percentile cut point for each ethnic group.

**Results** Fasting insulin levels were higher among African-American and Hispanic women than among non-Hispanic White or Asian women. These differences persisted after adjustment for age, educational attainment, total and central body obesity, adult weight change, family history of diabetes, smoking status, alcohol consumption, use of menopausal hormone therapy and physical activity. Higher levels of body mass index, waist–hip ratio, adult weight gain, and lower levels of total and moderate or strenuous recreational activity were independent correlates of fasting hyperinsulinaemia. Habitual walking was also inversely associated with fasting insulin.

**Conclusions** In this cross-sectional analysis, fasting insulin levels were higher among African-American and Hispanic post-menopausal women as compared with non-Hispanic White and Asian women. In addition, obesity, adult weight gain, and low levels of moderate or strenuous physical activity were independently associated with hyperinsulinaemia.

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**Keywords** hyperinsulinaemia, women, ethnicity

**Abbreviations** ACE, angiotensin-converting enzyme; BMI, body mass index; CHD, coronary heart disease; CT, clinical trial; DM, diabetes mellitus; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MET, ratio of metabolic rate during the activity to the resting metabolic rate; MHT, menopausal hormone therapy; OS, observational study; WHI, Woman's Health Initiative; WHR, waist–hip ratio

## Introduction

Several prospective studies suggest that elevated fasting insulin is a predictor of Type 2 diabetes mellitus (DM) [1–7] and may predict coronary heart disease (CHD) [8–10] incidence in both normoglycaemic individuals and those with overt disorders of

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glucose tolerance. Fasting hyperinsulinaemia commonly coexists with other risk determinants for both conditions, including total and abdominal obesity and lifestyle factors such as physical inactivity, alcohol consumption, smoking, and dietary fat and carbohydrate intake. Elucidation of correlates of hyperinsulinaemia may be of particular importance among ethnic minority groups, especially African-Americans and Hispanics, who experience a two- to threefold excess diabetes prevalence [11–14] as compared with non-Hispanic White people. Moreover, age-standardized diabetes prevalence rates among minority women are 25–40% higher than corresponding rates among minority men [15]. Compounding this gender effect, previous studies have shown that menopause and ageing are both associated with diminished insulin sensitivity [16]. It has been hypothesized that loss of this 'insulin advantage' [17,18] may account, in part, for the excess CHD risk observed among post-menopausal women. These intriguing observations underscore the need to identify potentially modifiable risk factors for hyperinsulinaemia, with the ultimate aim of developing strategies for primary prevention in these vulnerable populations.

Few studies have systematically evaluated determinants of fasting hyperinsulinaemia among ethnically diverse cohorts of post-menopausal women. The Women's Health Initiative Clinical Trials (CT) and Observational Study (OS) provide a unique setting in which to examine these issues. In a subsample of 3500 non-diabetic post-menopausal women in whom fasting insulin levels were available, we assessed ethnic difference in fasting insulin and explored potential correlates of fasting hyperinsulinaemia independent of a broad range of measured anthropometric, socio-economic, lifestyle and clinical risk factors.

## Patients and methods

### Women's Health Initiative (WHI) study population

The Women's Health Initiative has both CT and OS components, the objectives and design of which are described in detail elsewhere [19]. In brief, the WHI is a large clinical investigation of strategies for the prevention of several common causes of morbidity and mortality among post-menopausal women. Between 1993 and 1998, eligible post-menopausal women aged 50–79 years were enrolled at one of 40 clinical centres nationwide. Enrollment of racial/ethnic minority groups in proportion to the US population of women 50–79 years of age (18.2% according to the 1990 US census) was a priority.

Women were generally eligible for entry into the CT if they were post-menopausal, unlikely to change residence or die within 3 years, not known to have conditions that might affect adherence, and not currently participating in any other clinical trial. Of women screened, 68 133 were enrolled in the four WHI CTs. Women who were found to be ineligible or unwilling for clinical trial enrolment were offered the opportunity to participate in the Observational Study. Recruitment directly into the OS also occurred; 93 676 women enrolled in the OS.

### WHI CT–OS subsample selection

Fasting blood specimens were collected from all women at baseline and, as part of the original protocol design, a subsample [approximately 8.6% of the menopausal hormone therapy (MHT) component, 4.3% of the DM component and 1% of OS participants] was selected for purposes of prospective assessment of WHI core blood analytes, including baseline fasting insulin. Using a pre-specified goal of sixfold oversampling for racial/ethnic minority women, subjects were randomly selected in the stated proportions from each of the WHI components. We excluded women with a history of diabetes and those having missing data for main covariates of clinical interest as predictors of hyperinsulinaemia. A positive history of diabetes was defined as self-reported treatment for diabetes with insulin and/or oral hypoglycaemic agents and/or fasting plasma glucose > 7.0 mmol/l. Based on these criteria, there were 4274 subjects available for analysis, 774 of whom were excluded because of missing values for the following variables: educational level ($n$ = 31), body mass index (BMI) ($n$ = 33), waist–hip ratio (WHR) ($n$ = 20), weight change since age 18 ($n$ = 50), family history of diabetes ($n$ = 253), smoking status ($n$ = 138), physical activity ($n$ = 302), alcohol consumption ($n$ = 41), and MHT use ($n$ = 6), with some women missing data for more than one variable. The mean age (62.2 years), BMI (28.7 kg/m$^2$), and WHR (0.81) for those women excluded were similar to those of the women included in the analysis (mean age = 62.6 years, BMI = 28.6 kg/m$^2$ and WHR = 0.82). The final group included 3500 women. The study was reviewed and approved by Human Subjects Review Committees at each participating institution and signed informed consent was obtained from all women enrolled.

### Ascertainment and definition of clinical variables

During initial screening visits personal information, including demographic characteristics, medical history, medication and vitamin supplement inventories, were reviewed. A personal habits questionnaire for assessment of smoking status, alcohol consumption and physical activity was completed and anthropometric measurements, blood pressure and fasting blood specimens were obtained. Fasting was defined as no food or beverage intake except water in the 12-h period prior to blood collection.

Ethnicity was categorized as non-Hispanic White, African-American, Hispanic, American Indian or Alaskan Native, Asian or Pacific Islander, or unknown (not one of the above) according to self-report. BMI was calculated as the weight in kilograms divided by the height in meters squared. The WHR was calculated as the ratio of the circumference of the waist at the natural waist or narrowest part of the torso and the maximal circumference of the hips measured to the nearest 0.1 cm. A family history of diabetes was coded for individuals with a first-degree relative with diabetes mellitus. Adult weight change was classified according to answers to a question pertaining to change in weight during adult life since age 18 years. Possible responses were (i) weight has stayed about the same (within 10 lb), (ii) steady gain in weight, (iii) lost weight as an adult and kept it off, or (iv) weight has gone up and down again

by more than 10 lb. Systolic and diastolic blood pressures were each measured after subjects had been seated and resting for 5 min. Menopausal hormone therapy status was classified as never, past or current use of unopposed oestrogen and/or oestrogen plus progestin from pills or patches.

Physical activity was quantified according to three separate variables defined as (i) total kcal/kg per week expended from all recreational physical activity (including walking, mild, moderate and strenuous physical activity), (ii) minutes per week of moderate and strenuous recreational physical activity [including walking fairly fast defined as 3.5 miles (5.6 km) per hour or very fast defined as 4.5 miles (7.2 km) per hour, participating in activities such as jogging, aerobics, tennis, swimming, biking, use of an exercise machine, calisthenics, or popular or folk dancing], and (iii) energy expended per week from walking (kcal/kg per week) including fast walking among women reporting no other habitual strenuous physical activity. Those activities requiring an energy expenditure of 4.0–5.9 METs (ratio of metabolic rate during the activity to the resting metabolic rate) were defined as moderate intensity, 6.0 METs as strenuous [20]. For use in regression models, activity level was categorized into approximate quintiles for total energy expenditure from recreational physical activity and quartiles above zero for minutes per week of moderate or strenuous recreational physical activity and expenditure from walking, as there were a large proportion of women reporting no habitual participation in either of these latter activities.

### Ascertainment of dietary variables

We assessed nutrient intake using a 122-item, semiquantitative food frequency questionnaire (FFQ) which ascertained average consumption of specific foods over the previous 3-month period. We excluded from analysis implausibly low or high scores for total intake of food or energy (less than 600 or more than 5000 kcal per day). The reliability of the FFQ was previously assessed by correlation with 24-h dietary recalls and a 4-day food record [21]. In the current analysis, dietary data were available for 3328 (95.1%) of women.

### Laboratory procedures

Insulin was measured using a step-wise sandwich ELISA procedure on an ES 300 analyser (BMD–Roche Diagnostics, Indianapolis, IN, USA). This assay has 40% cross-reactivity with pro-insulin and 0% cross-reactivity with C-peptide. As part of a monthly quality assurance programme, the assay was monitored by the Diabetes Diagnostic Laboratory at the University of Missouri, Columbia. The coefficient of variation based on 173 blinded duplicates was 8.0%.

### Statistical analysis

Descriptive statistics were first calculated for the entire population. Differences in median fasting insulin levels between each ethnic subgroup and non-Hispanic white people were assessed using the Wilcoxon Rank Sum test. As fasting insulin was non-normally distributed, geometric means and standard deviations were calculated for each ethnic group. Age-adjusted and multivariable-adjusted geometric means were determined using analysis of covariance of log insulin values with adjustment for age alone or with concurrent adjustment for potential confounders. Differences in geometric mean fasting insulin levels between non-Hispanic White people and other ethnic groups were tested by two-sample *t*-tests of least squares means of the log insulin values.

As we found significant differences in mean insulin levels according to ethnic group, we used ethnicity-specific cut points to defined elevated fasting insulin. As reference ranges for insulin differ according to the specific assay employed, no single universal cut point for hyperinsulinaemia has been established. Hyperinsulinaemia was therefore defined as a level in the upper fourth of the distribution for each ethnic group in accordance with the definition proposed by experts in the European Group for the Study of Insulin Resistance [22]. These cut-point values (pmol/l) were as follows for each ethnic group: 85.4 for non-Hispanic White people, 108.7 for African-Americans, 108.3 for Hispanic Americans, 95.1 for American Indian/Alaskan Natives, 84.0 for Asian/Pacific Islanders, and 77.1 for women whose ethnicity was unknown or none of the above. In secondary analyses, we used ethnicity-specific 90th percentile cut points as an alternate definition of hyperinsulinaemia and also repeated the analysis using the total population 75th percentile (93.1 pmol/l) with inclusion of ethnicity as a covariate in multivariable models. Odds ratios according to putative diabetes risk factors were estimated from logistic regression models with elevated fasting insulin as the dependent variable.

We assessed for interactions between ethnicity and risk factors among the three largest ethnic groups (non-Hispanic White people, African-Americans and Hispanics). In these analyses, potential risk factors were dichotomized according to socio-economic or clinically relevant cut points (age > 65 years, education < high school, BMI > 25 kg/m$^2$, WHR > 0.8, steady weight gain or fluctuation > 10 pounds, positive family history of diabetes, current smoking, consumption of less than one alcoholic beverage per week, < 150 min per week of moderate or strenuous physical activity and non-current MHT use).

## Results

Descriptive statistics including the ethnic distribution of the study population are presented in Table 1. As shown, median fasting insulin levels among African-American and Hispanic women were significantly higher than the median for non-Hispanic white women. Age-adjusted and multivariable-adjusted geometric mean insulin levels by ethnicity are presented in Table 2. In age-adjusted models, African-Americans and Hispanics had significantly higher mean insulin levels than non-Hispanic White women. Although Native Americans also appeared to have slightly higher mean fasting insulin levels, this difference did not achieve statistical significance. Fasting insulin levels among Asians were similar to non-Hispanic White women. Additional adjustment for a number of potential confounders and the presence of impaired fasting glucose attenuated the differences between mean fasting insulin levels, however, African-Americans and Hispanics had persistently higher levels compared with non-Hispanic White women.

**Table 1** Summary of clinical and biochemical parameters among the study population ($n$ = 3500)

| Characteristic | Mean (SD), median (IQR) or $n$ (%) |
|---|---|
| Age (years), mean (SD) | 62.6 (7.1) |
| Ethnicity, $n$ (%) | |
| Non-Hispanic White | 1910 (54.6) |
| African-American | 728 (20.8) |
| Hispanic | 435 (12.4) |
| American Indian/Alaskan Native | 70 (2.0) |
| Asian/Pacific Islander | 295 (8.4) |
| Unknown/none of the above | 62 (1.8) |
| Education, $n$ (%) | |
| College degree or higher | 1252 (35.8) |
| School after high school | 1363 (38.9) |
| High school diploma or GED | 629 (18.0) |
| Less than high school | 256 (7.3) |
| Body mass index, kg/m$^2$, mean (SD) | 28.6 (6.0) |
| Waist–hip ratio, mean (SD) | 0.82 (0.08) |
| Systolic blood pressure (mmHg) mean (SD) | 127.9 (17.6) |
| Diastolic blood pressure (mmHg), mean (SD) | 76.1 (9.2) |
| Family history of diabetes, $n$ (%) | 1292 (36.9) |
| Smoking status, $n$ (%) | |
| Never smoked | 1943 (55.5) |
| Past smoker | 1296 (37.0) |
| Current smoker | 261 (7.5) |
| Alcohol intake, $n$ (%) | |
| Non-drinker | 474 (13.5) |
| Past drinker | 661 (18.9) |
| < 1 drink per month | 490 (14.0) |
| < 1 drink per week | 781 (22.3) |
| 1–6 drinks per week | 794 (22.7) |
| > 7 drinks per week | 300 (8.6) |
| MHT usage status, $n$ (%) | |
| Never used | 1830 (52.3) |
| Past user | 652 (18.6) |
| Current user | 1018 (29.1) |
| Energy expended from all recreational physical activity (kcal/kg/week), median (IQR) | 7.0 (1.5, 15.5) |
| Minutes per week of moderate/strenuous physical activity, median (IQR) | 20.0 (0.0, 125.0) |
| Energy expended from walking, median (IQR) | 1.9 (0.0, 6.3) |
| All participants | |
| Those not engaging in strenuous physical activity ($n$ = 2718) | 1.5 (0.0, 5.0) |
| Current use of ACE-inhibitors, $n$ (%) | 224 (6.4) |
| Current use of beta-blockers, $n$ (%) | 238 (6.8) |
| Current use of diuretics, $n$ (%) | 460 (13.1) |
| Current use of statins, $n$ (%) | 224 (6.4) |
| Total cholesterol (mmol/l), mean (SD) | 5.75 (0.97) |
| LDL cholesterol (mmol/l), mean (SD) | 3.46 (0.91) |
| HDL cholesterol (mmol/l) mean (SD) | 1.55 (0.40) |
| Triglycerides (mmol/l) mean (SD) | 3.76 (1.9) |
| Total cholesterol to HDL cholesterol ratio, mean (SD) | 4.0 (1.2) |
| Fasting glucose (mmol/l) mean (SD) | 5.2 (0.6) |
| Fasting insulin (pmol/l), median (IQR) | |
| Non-Hispanic White | 61.1 (44.4, 85.4) |
| African-American | 77.1 (56.3, 108.7)*† |
| Hispanic | 72.9 (51.4, 108.3)*† |
| American Indian/Alaskan Native | 68.4 (50.0, 95.1) |
| Asian/Pacific Islander | 59.7 (43.1, 84.0) |
| Unknown/none of the above | 55.9 (43.8, 77.1) |

GED, General Equivalency Diploma.
Means and standard deviations (SD) are presented for normally distributed variables, medians and interquartile ranges (IQR) are presented where indicated. Number of women ($n$) and percentages (%) are presented for proportions.
Differences in median fasting insulin levels between non-Hispanic White women and other ethnic groups were tested using the Wilcoxon Rank Sum test. *$P$ < 0.001.
Differences in median fasting insulin levels compared with the population median were tested using the Signed Rank test. †$P$ < 0.001.

As insulin levels were higher among both African-American and Hispanic women, we used ethnicity-specific cut points in our analysis of risk factors for hyperinsulinaemia rather than a single population-based value. Hyperinsulinaemia was defined as a level above the highest quartile cut point in each ethnic group (Table 1). We found no statistically significant ethnicity by risk factor interactions and therefore did not stratify estimates of main effects according to ethnic background. In age-adjusted analyses, lower educational level, higher BMI and WHR, adult weight gain, a family history of diabetes, less frequent alcohol consumption, non-current MHT use, and all three physical inactivity measures were associated with a greater risk for fasting hyperinsulinaemia (Table 3). Current smoking was also associated with reduced odds of hyperinsulinaemia. These relationships were attenuated in multivariable analyses, but remained significant for indices of obesity, adult weight gain, current smoking and physical inactivity. We observed a progressive reduction in odds for hyperinsulinaemia according to increasing energy expended from all recreational physical activity with women in the highest vs. lowest category having a 47% decrease in odds (95% CI 29 to 60%; $P$-trend < 0.001). Participation in greater than 45 min per week of moderate or strenuous recreational physical activity was associated with significant declines in relative odds across categories. A similar inverse gradient was observed for women who engaged in walking among those reporting no other regular strenuous physical activity ($n$ = 2718, 77.7% of the study population).

We also assessed waist circumference as opposed to WHR as an alternate measure of abdominal adiposity. In these analyses, the age-adjusted and multivariable ORs according to increasing quartile of waist circumference were 1.0, 2.2, 3.9 and 10.9 ($P$-trend < 0.001) and 1.0, 1.6, 2.2 and 4.1 ($P$-trend < 0.001), respectively, for quartiles defined as < 78.0, 78.0–86.9, 87.0–95.5 and > 95.5 cm. In secondary analyses evaluating the influence of an alternate cut point for the definition of hypersinsulinaemia, we found consistent results using ethnicity-specific 90th percentile thresholds. In brief, all

**Table 2** Age-adjusted and multivariable-adjusted geometric mean fasting insulin levels (pmol/l) by ethnicity

| | Non-Hispanic White ($n$ = 1910) | African-American ($n$ = 728) | Hispanic ($n$ = 435) | American Indian/ Alaskan Native ($n$ = 70) | Asian/Pacific Islander ($n$ = 295) | Unknown/none of the other groups ($n$ = 62) |
|---|---|---|---|---|---|---|
| Model 1 | 63.0 (0.7) | 78.2 (1.4)* | 74.7 (1.7)* | 69.9 (4.0) | 60.0 (1.7) | 60.2 (3.7) |
| Model 2 | 65.2 (0.6) | 70.6 (1.1)* | 71.4 (1.5)* | 68.5 (3.4) | 66.1 (1.7) | 59.3 (3.1) |
| Model 3 | 65.4 (0.6) | 70.3 (1.1)* | 71.7 (1.5)* | 68.0 (3.3) | 65.6 (1.6) | 59.4 (3.1) |

Model 1: age-adjusted in 5 year categories.
Model 2: adjusted for age (5-year categories), education (college degree or greater, school after high school, high school diploma or GED, less than high school), BMI (linear continuous), WHR (linear continuous), weight change (weight gain less than 10 lb, lost weight and maintained, steady gain, or weight fluctuation greater than 10 lb), family history of DM (no/yes), smoking (never, past or current), alcohol consumption (non-drinker, past drinker, < 1 drink/month, < 1 drink/week, 1–6 drinks/week or 7+ drinks/week), total energy expenditure (linear continuous), and MHT use (never/past/current).
Model 3: model 2 additionally adjusted for elevated fasting glucose (6.1–6.9 mmol/l—yes/no).
Differences in geometric mean fasting insulin levels between non-Hispanic white women and other ethnic groups were tested by ANCOVA on the log-transformed levels. *$P$ < 0.001.

findings were similar with BMI, WHR, adult weight gain, smoking status and physical activity remaining the only significant factors after multivariable adjustment. In particular, the multivariable ORs according to increasing quartile of BMI and WHR were 1.0, 0.9, 1.9 and 5.2 ($P$-trend < 0.001) and 1.0, 1.3, 2.3 and 4.2 ($P$-trend < 0.001). Our results were also similar when hyperinsulinaemia was defined by a value in the upper fourth of the overall population distribution of fasting insulin (93.1 pmol/l) with ethnicity included as a covariate in regression models. Using this latter approach, BMI, WHR, adult weight gain, smoking status and exercise measures remained the only significant factors in multivariable analysis.

Adjustment for dietary variables, including total energy consumption, total dietary fibre, total per cent fat and per cent carbohydrates among women with available dietary data ($n$ = 3328, 95.1% of the study population) did not materially alter these results (data not shown). Our findings were also robust to adjustment for lipid levels [total cholesterol to high-density lipoprotein (HDL) ratio and triglycerides level], blood pressure, use of diuretics, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers or statins, and in models adjusting for impaired glucose tolerance defined as a fasting glucose level of 6.1–6.9 mmol/l. In these statistical models, obesity, adult weight gain, smoking status and physical activity remained independent correlates of fasting hyperinsulinaemia.

## Discussion

In this large cross-sectional study conducted among an ethnically diverse nationwide sample of post-menopausal women we found that, as in previous studies of younger men and women [23–25], fasting insulin levels are significantly higher among African-Americans and Hispanics than among non-Hispanic White women. These results were independent of other major correlates of hyperinsulinaemia. We also identified BMI, WHR, adult weight gain, never smoking as opposed to current smoking, and total and moderate or strenuous recreational physical activity as strong independent correlates of elevated fasting insulin. These results agree with previous findings from smaller studies involving older women [26–29], in which BMI, WHR and physical activity were each independently associated with hyperinsulinaemia. In addition, we found that walking, the most common form of physical activity among older adults [30], is associated with lower fasting insulin levels among individuals reporting no regular strenuous recreational physical activity; an observation which suggests that even this form of light-to-moderate physical activity may impart substantial health benefits among post-menopausal women.

The menopause transition is associated with a number of metabolic changes which adversely impact risk for both cardiovascular disease and Type 2 diabetes, principally the development of an atherogenic lipid profile and alterations in glucose metabolism. In addition, weight gain, android fat patterning and intramuscular fat deposition, along with unfavourable changes in diet and physical inactivity all occur with greater frequency with ageing and may exacerbate the physiological disturbances attributed to loss of ovarian function. Hyperinsulinaemia in post-menopausal women may therefore be the result of complex interactions between peripheral insulin sensitivity, impaired pancreatic function, less effective inhibition of hepatic glucose output, and decreased insulin clearance [16].

Our findings pertaining to ethnic differences in fasting insulin levels are also of interest. It has commonly been assumed that obesity and low rates of physical activity are the underlying factors which account for ethnic disparities in both hyperinsulinaemia and the incidence of Type 2 diabetes. Precise physiological and radiological estimates of adiposity were not available in this study and therefore residual differences in insulin levels because of obesity beyond that accounted for by BMI and WHR may persist. However, despite this limitation, our epidemiological data and those of others raise the possibility that there may be unexplained, metabolic differences between ethnic groups. For instance, several studies have demonstrated that both African-Americans [31] and Hispanics [24] have lower rates of insulin clearance as well as increased

**Table 3** Crude and adjusted odds ratio for elevated fasting insulin* according to risk factors for Type 2 diabetes

| | Crude (age-adjusted) | | Multivariable adjusted† | |
|---|---|---|---|---|
| Characteristic | Odds ratio | 95% CI | Odds ratio | 95% CI |
| Age (years) | | | | |
| 50–54 | Ref | — | Ref | — |
| 55–59 | 1.05 | 0.81–1.36 | 1.04 | 0.78–1.39 |
| 60–64 | 1.11 | 0.86–1.43 | 1.22 | 0.92–1.62 |
| 65–69 | 0.96 | 0.74–1.24 | 1.07 | 0.80–1.44 |
| 70–74 | 1.08 | 0.81–1.44 | 1.31 | 0.95–1.81 |
| > 75 | 0.97 | 0.65–1.42 | 1.43 | 0.93–2.20 |
| *P*-trend | | 0.93 | | 0.06 |
| Education | | | | |
| College degree or higher | Ref | — | Ref | — |
| School after high school | 1.34 | 1.12–1.61 | 1.16 | 0.95–1.42 |
| High school diploma or GED | 1.42 | 1.14–1.78 | 1.10 | 0.86–1.41 |
| Less than high school | 1.62 | 1.20–2.18 | 1.19 | 0.85–1.67 |
| *P*-trend | | 0.001 | | 0.28 |
| Body mass index (kg/m$^2$; quartiles) | | | | |
| < 24.4 | Ref | — | Ref | — |
| 24.4–27.6 | 1.86 | 1.39–2.49 | 1.33 | 0.97–1.82 |
| 27.7–31.9 | 3.73 | 2.84–4.90 | 2.20 | 1.62–2.99 |
| > 31.9 | 9.77 | 7.48–12.77 | 5.00 | 3.67–6.83 |
| *P*-trend | | < 0.001 | | < 0.001 |
| Waist–hip ratio (quartiles) | | | | |
| < 0.76 | Ref | — | Ref | — |
| 0.76–0.80 | 1.85 | 1.40–2.43 | 1.70 | 1.27–2.28 |
| 0.81–0.86 | 3.42 | 2.63–4.44 | 2.58 | 1.95–3.40 |
| > 0.86 | 6.24 | 4.83–8.05 | 4.06 | 3.09–5.35 |
| *P*-trend | | < 0.001 | | < 0.001 |
| Adult weight change | | | | |
| Maintained weight within 10 lb | Ref | — | Ref | — |
| Maintained weight loss | 0.95 | 0.48–1.88 | 1.23 | 0.60–2.54 |
| Weight fluctuation > 10 lb | 2.46 | 1.97–3.06 | 1.29 | 1.00–1.65 |
| Steady gain in weight | 3.07 | 2.47–3.80 | 1.62 | 1.27–2.07 |
| *P*-trend | | < 0.001 | | 0.001 |
| Family history of diabetes | | | | |
| No | Ref | — | Ref | — |
| Yes | 1.27 | 1.09–1.49 | 1.09 | 0.91–1.29 |
| *P*-value | | 0.002 | | 0.35 |
| Smoking status | | | | |
| Never smoked | Ref | — | Ref | — |
| Past smoker | 0.90 | 0.76–1.06 | 0.81 | 0.67–0.98 |
| Current smoker | 0.55 | 0.39–0.77 | 0.48 | 0.33–0.71 |
| *P*-value | | 0.001 | | < 0.001 |
| Alcohol intake | | | | |
| Non-drinker | Ref | — | Ref | — |
| Past drinker | 1.37 | 1.05–1.79 | 1.35 | 1.00–1.82 |
| < 1 drink per month | 1.26 | 0.94–1.68 | 1.18 | 0.86–1.63 |
| < 1 drink per week | 1.09 | 0.84–1.42 | 1.36 | 1.01–1.83 |
| 1–6 drinks per week | 0.77 | 0.58–1.01 | 1.09 | 0.80–1.49 |
| > 7 drinks per week | 0.66 | 0.46–0.95 | 1.00 | 0.66–1.51 |
| *P*-trend | | < 0.001 | | 0.72 |
| MHT usage status | | | | |
| Never used | Ref | — | Ref | — |
| Past user | 1.09 | 0.89–1.33 | 1.19 | 0.77–1.16 |
| Current user | 0.69 | 0.57–0.83 | 0.94 | 0.96–1.49 |
| *P*-value | | < 0.001 | | 0.17 |
| Energy expended from all recreational physical activity (kcal/kg/week) | | | | |
| 0 | Ref | — | Ref | — |
| 0.10–3.75 | 0.69 | 0.55–0.87 | 0.78 | 0.60–1.00 |
| 3.76–9.25 | 0.61 | 0.48–0.77 | 0.80 | 0.62–1.03 |
| 9.26–17.5 | 0.46 | 0.36–0.58 | 0.69 | 0.53–0.90 |

**Table 3** *Continued*

| Characteristic | Crude (age-adjusted) | | Multivariable adjusted† | |
|---|---|---|---|---|
| | Odds ratio | 95% CI | Odds ratio | 95% CI |
| > 17.5 | 0.32 | 0.24–0.41 | 0.53 | 0.40–0.71 |
| *P*-trend | | < 0.001 | | < 0.001 |
| Minutes per week of moderate or strenuous recreational physical activity‡ | | | | |
| 0 | Ref | — | Ref | — |
| 1–45 | 0.91 | 0.73–1.14 | 0.97 | 0.76–1.24 |
| 46–100 | 0.60 | 0.47–0.76 | 0.74 | 0.57–0.96 |
| 101–210 | 0.49 | 0.38–0.63 | 0.72 | 0.54–0.94 |
| > 210 | 0.37 | 0.27–0.49 | 0.60 | 0.43–0.82 |
| *P*-trend | | < 0.001 | | < 0.001 |
| Energy expended from walking (kcal/kg/week)§ | | | | |
| 0 | Ref | — | Ref | — |
| 0.10–2.50 | 0.79 | 0.63–0.99 | 0.80 | 0.62–1.03 |
| 2.51–5.00 | 0.50 | 0.38–0.66 | 0.64 | 0.47–0.86 |
| 5.01–8.75 | 0.54 | 0.40–0.73 | 0.67 | 0.48–0.92 |
| > 8.75 | 0.49 | 0.36–0.66 | 0.73 | 0.52–1.01 |
| *P*-trend | | < 0.001 | | 0.02 |

GED, General Equivalency Diploma; Ref, reference group.

*According to the following ethnicity-specific 75th percentile cut points (pmol/l): non-Hispanic White people 85.4; African-Americans 108.7; Hispanics 108.3; American Indian/Alaskan Native 95.1; Asian/Pacific Islander 84.0; Unknown 77.1.

†Adjusted for age (5-year categories), education (college degree or greater, school after high school, high school, diploma or GED, less than high school), BMI (linear continuous), WHR (linear continuous), weight change (maintained weight within 10 lb, lost weight and maintained, steady gain or weight fluctuation greater than 10 lb), family history of DM (no/yes), smoking (never, past or current), alcohol consumption (non-drinker, past drinker, < 1 drink/month, < 1 drink/week, 1–6 drinks/week or 7+ drinks/week), total energy expenditure (linear continuous), and MHT use never/past/current).

‡This model does not include total energy expended from recreational physical activity.

§This model does not include total energy expended from recreational physical activity and is limited to those reporting no other strenuous recreational physical activity ($n$ = 2718).

insulin secretion [23,24] as compared with non-Hispanic White people. Studies among African-American women also implicate differences in resting energy expenditure [24], variable metabolic effects of leptin [32], and increased intramuscular fat deposition [33]. The latter finding is of particular interest, as this body composition characteristic is associated with insulin resistance [34] and participation in a weight loss and structured walking programme (30–45 min on three occasions per week) may lead to beneficial changes in lean tissue fat content among older obese women [35].

Our observations pertaining to BMI and WHR are consistent with prior studies of younger individuals and studies which included smaller numbers of post-menopausal women. In the current analysis, obesity appeared to be the most important independent predictor in all multivariable models. In addition, our findings that adult weight gain is associated with a 30–60% increase in odds for elevated fasting insulin is congruent with results from the Nurses' Health Study [36] in which even modest weight gain (5–6.9 kg) after age 18 years among non-obese women (< 22 kg/m$^2$) was associated with a 2-fold increase in risk of Type 2 diabetes, as compared with women who maintained a stable weight.

Our finding that past and current smokers had lower odds of hyperinsulinaemia in comparison with non-smokers should be interpreted with caution as several, but not all, prospective evaluations have shown a positive and graded association between smoking and the incidence of Type 2 diabetes. While several studies have found strong relationships between smoking and markers of insulin resistance, others have demonstrated lower levels of fasting insulin [37] and suggested a negative effect on pancreatic β-cell function. It is also possible that the current findings may partly reflect residual confounding by obesity as smokers tended to be leaner (BMI among current vs. never smokers: 27.8 vs. 28.6 kg/m$^2$, $P$ = 0.03). Prospective studies utilizing both baseline and follow-up assessment of smoking status, change in weight and fasting insulin may offer additional insight in this regard.

Our data pertaining to physical activity are concordant with a report from the Insulin Resistance Atherosclerosis Study [38], in which both vigorous and non-vigorous physical activity were independently associated with improved insulin sensitivity as measured by intravenous glucose tolerance testing among a multi-ethnic population of middle-aged men and women. Similar associations were noted in the smaller Cross-Cultural Activity Participation Study [39] in which moderate-intensity physical activity was related to declines in fasting insulin among African-American, Native American and Caucasian women. Our findings also concur with those from the Nurses' Health Study [40] in which energy expended from walking was independently associated with a graded decline

in diabetes risk among women aged 30–55 years at baseline. Overall, our observations extend these earlier reports by suggesting that similar benefits might be achieved with regular physical activity among post-menopausal women.

Several important limitations of our analysis merit discussion. First, we interpreted elevated fasting insulin as an indirect measure of insulin resistance and risk for Type 2 diabetes. However, fasting insulin levels are determined not only by the degree of insulin sensitivity but also by β-cell secretory function and insulin clearance. Among non-diabetic subjects, this surrogate index of insulin resistance is moderately well correlated with more direct glucose clamp [41] and minimal model [42] techniques, and is highly correlated with the homeostasis model (HOMA IR, $r = 0.98$) [43]. In addition, our insulin assay had 40% cross-reactivity with pro-insulin which was not directly measured in this study. As ethnic differences in pro-insulin may occur, we cannot precisely determine to what extent elevations in this insulin precursor may have affected our results. However, the overall ratio of fasting pro-insulin to specific insulin in two prior studies of non-diabetic predominantly White [44] and Mexican-American [45] populations has been demonstrated to be low. Second, our use of BMI and WHR as indices of total and central obesity may have introduced non-differential misclassification. BMI may be an imprecise marker of overall adiposity because of unaccounted differences in lean tissue mass and body fat distribution. Also, our use of the WHR as an indicator of abdominal adiposity does not distinguish visceral from subcutaneous adipose depots. However, these indices are practical, non-invasive measures which are more likely to be used as clinical tools for usual risk assessment. Third, as our data are cross-sectional in nature, inferences regarding causality and clinical relevance are hypothesis generating. However, to our knowledge, these data represent one of the largest studies to evaluate potential correlates of hyperinsulinaemia among an ethnically diverse population of post-menopausal women.

In conclusion, in this large ethnically diverse nationwide study of post-menopausal women, we have found ethnicity to be strongly and independently associated with fasting insulin levels and have also identified several modifiable correlates of fasting hyperinsulinaemia. These findings may be helpful in the design of strategies for prevention of both Type 2 diabetes and coronary heart disease among this growing segment of the US population.

## Competing interests

None declared.

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