

# Sex Differences in the Association of Endogenous Sex Hormone Levels and Glucose Tolerance Status in Older Men and Women

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**OBJECTIVE** — Some evidence suggests an inverse association between type 2 diabetes and androgens in men and a positive association between type 2 diabetes and androgens in women. The purpose of this community-based study was to evaluate sex differences in the association between endogenous total and bioavailable estrogen and testosterone levels and glucose tolerance status.

**RESEARCH DESIGN AND METHODS** — We included in this study 775 men and 633 postmenopausal non-estrogen-using women, all  $\geq 55$  years of age (mean ages 72 and 75 years, respectively). A 75-g oral glucose tolerance test (OGTT) was administered to fasting subjects from 1984 to 1987, when sera were frozen for measurement of total and bioavailable hormone levels. Total testosterone and estradiol levels were measured by radioimmunoassay, and bioavailable hormone levels were determined using a modified ammonium-sulfate precipitation method. The association between steroid hormones and glucose tolerance status was tested.

**RESULTS** — In sex-specific age- and BMI-adjusted analyses, men with impaired glucose tolerance (IGT) had significantly lower total testosterone levels. Women with IGT or type 2 diabetes had significantly higher bioavailable testosterone and total and bioavailable estradiol levels than those with normal glucose tolerance. Total testosterone and fasting plasma glucose were inversely associated in men ( $P = 0.0001$ ), whereas bioavailable testosterone and estradiol were positively associated with fasting plasma glucose in women ( $P = 0.0001$  and  $0.001$ , respectively).

**CONCLUSIONS** — Additional studies are needed to further develop the hormone-diabetes connection.

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An association has been shown between sex hormone-binding globulin (SHBG) level and type 2 diabetes and several of its covariates, including total body fat, central obesity, and hyperinsulinemic insulin resistance in men (1–7) and post-

menopausal women (7–13). Because low SHBG levels are associated with increased levels of bioavailable testosterone (14,15), SHBG is thought to be a marker of androgenicity (16). Few studies have measured bioavailable testosterone levels directly, and

those studies that have examined the association between testosterone and type 2 diabetes were limited by small sample size (6,9), were not population-based (5–9), or defined diabetes by history or a single blood glucose measurement (1,5). To our knowledge, there are no large population-based studies of sex differences in total and bioavailable (non-SHBG bound) sex hormones by glucose tolerance status.

The purpose of this cross-sectional study was to examine the sex differences between total and bioavailable endogenous sex hormone levels in a community-based study sample. The sample comprised 775 older men and 633 older women with and without impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or type 2 diabetes, based on an oral glucose tolerance test (OGTT).

**RESEARCH DESIGN AND METHODS** — Between 1984 and 1987, all surviving members of the Rancho Bernardo Heart and Chronic Disease Study (a middle- to upper-middle-class group of older Caucasian adults in Southern California) were invited to a clinic visit. A total of 80% participated (17) and completed a standardized questionnaire, which asked for demographic data and personal history of diabetes, cigarette smoking, alcohol consumption, physical activity, and the use of selected medications. Medication use was validated by the examination of prescriptions or medicine brought to the clinic for that purpose. A 75-g OGTT was performed between 7:00 and 11:00 A.M. after a requested 12-h fast. Plasma glucose levels were measured by a glucose oxidase assay before and 2 h after the glucose load. Height and weight were measured (subjects wore lightweight clothing and no shoes), and BMI was used to estimate obesity (calculated as  $\text{kg/m}^2 \times 100$ ). Waist and hip girth were measured in centimeters over single-layer clothing with the participant standing. Waist was measured both at the bending point (marked where the participant natu-

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**Abbreviations:** IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MRI, magnetic resonance imaging; OGTT, oral glucose tolerance test; OR, odds ratio; PCO, polycystic ovarian disease; SHBG, sex hormone-binding globulin; WHR, waist-to-hip ratio.

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

**Table 1—Means (range) of age and other covariates at baseline**

Covariate	Men	Women
<i>n</i>	775	633
Age (years)	71.9 (55.0–89.0)*	74.9 (55.0–89.0)
BMI (kg/m <sup>2</sup> )	25.9 (17.4–42.2)*	24.8 (15.6–40.7)
Waist (cm)	93.8 (64.0–132.0)*	80.2 (57.4–124.9)
WHR	0.92 (0.67–1.18)*	0.81 (0.59–1.01)
Current smokers	10.2	11.7
Daily alcohol	56.6*	42.4
Exercise 3×/week	85.4*	76.6
IFG	7.7	2.8
IGT	26.6	30.8
Type 2 diabetes	15.2	18.0†

Data are *n* or %. \**P* < 0.001; †*P* < 0.05.

rally bends forward and measured after participant has realigned to an upright position) and at the narrowest circumference. Hip circumference was measured both at the iliac crest and at the largest circumference. Both waist and both hip measures were highly correlated; the former was used to calculate waist-to-hip ratio (WHR) to be consistent with our previously reported data. Waist circumference alone was used as an integrated measure of obesity and fat distribution, on the basis of studies suggesting that waist circumference is more highly correlated with both total and visceral body fat when measured by computed tomography or magnetic resonance imaging (MRI) than by WHR (18,19). Plasma was obtained for hormone assays and frozen at –70°C.

Diagnoses of type 2 diabetes, IFG, and IGT were based on World Health Organization criteria (20) as follows: 1) type 2 diabetes: fasting plasma glucose >126 mg/dl, and/or 2-h postchallenge glucose level >200 mg/dl, and/or a history of physician-diagnosed diabetes; 2) IFG: fasting plasma glucose between 110 and 126 mg/dl; and

3) IGT: 2-h plasma glucose between 140 and 199 mg/dl. Reported diabetes was validated by review of medical records in a subset, with >85% confirmation.

In 1992 and 1993, hormones were measured in an endocrinology research laboratory by radioimmunoassay using first-thawed specimens from the 1984–1987 venipuncture. Previous studies have demonstrated no deterioration of total estradiol or testosterone when samples were frozen and stored in tightly sealed containers for 3–10 years (21,22). Non-SHBG-bound bioavailable testosterone and bioavailable estradiol were determined by using a modification of the ammonium-sulfate precipitation method of Tremblay and Dube (23). No data are published on the long-term stability of the bioavailable hormones, but the percent bioavailable testosterone and estradiol levels in this study are comparable to published values (24,25). The sensitivity and intra- and interassay coefficients of variation, respectively, for women were as follows: testosterone, 0.07 nmol/l, 4 and

4.9%; estradiol, 11.0 pmol/l, 5.9 and 7.1%; bioavailable testosterone, 0.07 nmol/l × percentage free, 6.5 and 10.7%; and bioavailable estradiol, 11 pmol/l × percentage free, 6.1 and 7.9%. For men, the sensitivity and intra- and interassay coefficients of variation, respectively, were as follows: testosterone, 1.28 nmol/l, 4 and 6.8%; estradiol, 22 pmol/l, 5.9 and 7.4%; bioavailable testosterone, 1.28 nmol/l × percentage free, 5.8 and 7.6%; and bioavailable estradiol, 22 pmol/l × percentage free, 3.7 and 5.2%. Of the 775 male and 633 female study subjects, the following had hormone levels below the limit of detection: 7 men and 85 women, estradiol; 7 men and 84 women, bioavailable estradiol; and 5 men and 4 women, total and bioavailable testosterone. These subjects were included in the analyses, and undetectable hormone levels were assigned the smallest detectable level.

The 775 men and 633 women in the present study were not using hormone therapy and were ≥55 years of age. We excluded from the study 33 women and 37 men who either had missing values, did not fast for 12 h, or could not be classified according to diabetic status. Also excluded were 5 men and 1 woman who reported insulin use.

Data were analyzed using SAS and SAS/STAT (SAS Institute, Cary, NC). Because hormone levels showed a slightly skewed distribution, median hormone values were used in these analyses. Student's *t* tests were used for continuous variables and  $\chi^2$  tests were used for categorical variables to test for statistically significant differences between men and women and between categories of glucose tolerance status. Analysis of covariance was used to adjust hormone levels by age, BMI, and WHR (or waist circumference) and to compare adjusted median hor-

**Table 2—Distribution of covariates by sex and diabetes category: Rancho Bernardo men and women, 1984–1987**

	Men				Women			
	Normal	IFG	IGT	Type 2 diabetes	Normal	IFG	IGT	Type 2 diabetes
<i>n</i>	397	60	206	112	326	18	182	107
Age (years)	70.5 ± 8.6	68.6 ± 8.5	74.2 ± 7.5*	74.2 ± 7.6*	74.2 ± 5.9*	72.1 ± 5.7	76.0 ± 6.4*	74.8 ± 7.7*
BMI (kg/m <sup>2</sup> )	25.8 ± 3.3	26.7 ± 2.8	25.7 ± 3.3	26.6 ± 3.5	24.1 ± 3.6	24.2 ± 3.9	25.6 ± 3.5*	25.5 ± 4.6*
Waist (cm)	93.1 ± 8.6	95.1 ± 7.0	93.8 ± 8.8	95.9 ± 10.0†	78.2 ± 8.9	77.9 ± 8.9	81.4 ± 8.1*	82.9 ± 10.8*
WHR	0.91 ± 0.05	0.92 ± 0.06	0.92 ± 0.06	0.93 ± 0.06†	0.79 ± 0.06	0.79 ± 0.05	0.83 ± 0.06*	0.83 ± 0.06*
Current smokers	11.1	15.0	9.2	6.3	11.4	22.2*	11.5	11.2
Daily alcohol	55.7	66.7†	56.2	55.8	43.0	64.7	41.9	35.6
Exercise 3×/week	89.1	86.7	80.6*	80.5*	77.9	83.3	76.4	72.0

Data are *n*, means ± SD, or %. \**P* < 0.001, compared with normal; †*P* < 0.05, compared with normal.

**Table 3—Age- and BMI-adjusted median hormone level by diabetes category for Rancho Bernardo men, 1984–1987**

	Normal	IFG	IGT	Type 2 diabetes	P (trend)
Total estradiol (pmol/l)	74.4	68.9	74.8	77.6	0.74
Bioavailable estradiol (pmol/l)	47.7	48.0	47.3	49.3	0.71
Total testosterone (nmol/l)	11.3	9.8*	10.4†	10.5*	0.002
Bioavailable testosterone (nmol/l)	3.4	3.4	3.0‡	3.1	0.05
Estradiol/testosterone ratio	0.007	0.007	0.008	0.008	0.49

Data are medians. \* $P < 0.01$ ; † $P < 0.001$ ; ‡ $P < 0.05$ , all compared with normal glucose status.

**Table 4—Age- and BMI-adjusted median hormone level by diabetes category for Rancho Bernardo women, 1984–1987**

	Normal	IFG	IGT	Type 2 diabetes	P (trend)
Total estradiol (pmol/l)	20.6	19.6	23.3*	25.4†	0.17
Bioavailable estradiol (pmol/l)	10.3	10.3	11.4*	15.0‡	0.008
Total testosterone (nmol/l)	0.50	0.44	0.64	0.58	0.33
Bioavailable testosterone (nmol/l)	0.15	0.12	0.18†	0.18†	0.03
Estradiol/testosterone ratio	0.04	0.05	0.05	0.05*	0.25

Data are medians. \* $P < 0.01$ ; † $P < 0.05$ ; ‡ $P < 0.001$ , all compared with normal glucose status.

mone level by glucose tolerance status and by clinically relevant categories of body size and behaviors. Adjusted fasting plasma glucose levels were compared by quartile of sex-specific hormone levels to evaluate the presence of a trend. Prevalence rates of IFG, IGT, and type 2 diabetes were calculated according to hormone levels below and above the sex-specific median for each hormone, adjusting for age using the Mantel-Haenszel direct-age adjustment to the entire population included in these analyses. All  $P$  values are 2-tailed. Statistical significance was defined as  $P < 0.05$ .

**RESULTS** — Table 1 shows the characteristics of the 775 men and 633 women aged 55–89 years whose average ages were 72 and 75 years, respectively ( $P < 0.001$ ). Compared with women, men had higher BMI, waist circumference, and WHR; they were also more likely to drink alcohol daily and to exercise at least 3 times a week ( $P < 0.001$ , for each category). Women had a higher prevalence of type 2 diabetes than men (18.0 vs. 15.2%,  $P < 0.05$ ), but this difference was not significant after additional adjustment for age. No significant sex differences in the prevalence of IFG, IGT, or percent of current smokers were seen.

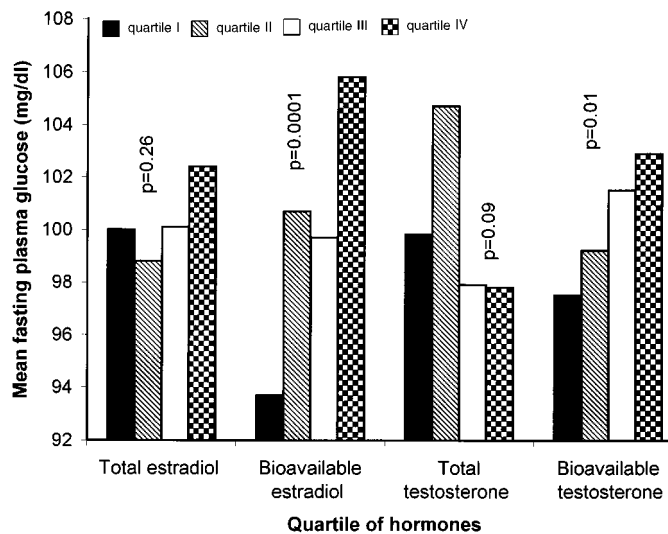
Table 2 shows sex-specific glucose tolerance status and its covariates. Men and women with IGT or type 2 diabetes were

significantly older and had greater central adiposity than normoglycemic men and women. Women with normal glucose tolerance were significantly less obese than those with abnormal glucose tolerance; men with normal glucose tolerance were more likely than those with abnormal glucose tolerance to report exercise  $\geq 3$  times per week. Men with IFG were more likely to drink alcohol daily, and women with IFG were more likely to smoke.

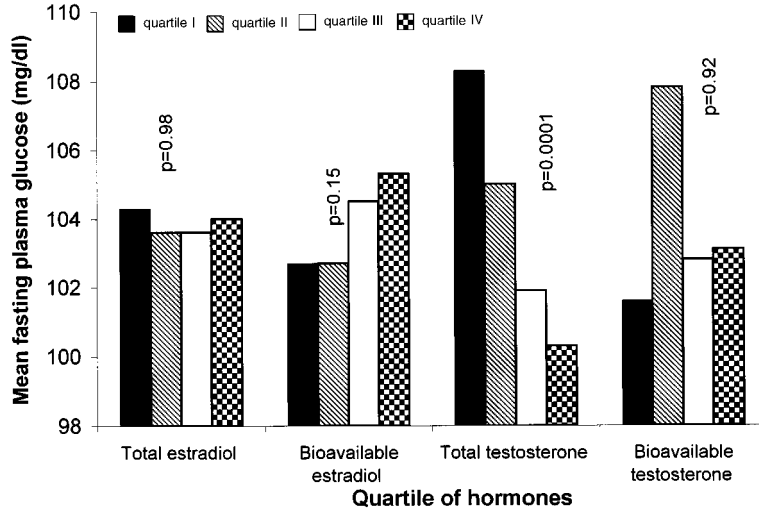
Sex-specific adjusted median hormone levels by glucose tolerance are shown in Tables 3 (men) and 4 (women). Men with IFG, IGT, or type 2 diabetes had significantly lower total testosterone levels compared with men with normal glucose tolerance. Women with type 2 diabetes or IGT had higher levels of total and bioavailable estradiol and bioavailable testosterone than women without diabetes. Women with type 2 diabetes had a significantly higher estradiol/testosterone ratio compared with women with normal glucose tolerance. Results were not materially changed after adjusting for WHR or waist circumference, or after stratification by oophorectomy status, use of diabetes medication, alcohol intake, cigarette smoking, or physical activity (data not shown).

Figures 1 and 2 show the age-adjusted mean fasting plasma glucose levels by quartile of sex-specific hormone level for women and men, respectively. Only total testosterone was significantly and inversely associated with glycemia in men. In women, bioavailable estradiol and bioavailable testosterone levels were positively associated with fasting plasma glucose. Adjustment for BMI did not materially alter these results.

Age-adjusted median hormone levels by clinically relevant categories of body size and behaviors are shown in Table 5. In women, total and bioavailable estradiol were positively associated with BMI and WHR and inversely associated with physical activity, and bioavailable testosterone was associated with BMI only. After additional



**Figure 1—Age-adjusted mean fasting plasma glucose by hormone quartiles: Rancho Bernardo women ( $P$  for trend).**



**Figure 2**—Age-adjusted mean fasting plasma glucose by hormone quartiles: Rancho Bernardo men (P for trend).

adjustment for BMI, the association between total estradiol and physical activity was no longer statistically significant ( $P = 0.17$ ). No association was seen between total testosterone and any diabetes risk factor in women. In men, total and bioavailable testosterone were inversely associated with BMI and WHR. Bioavailable estradiol was positively associated with BMI, physical activity, and current smoking. After additional adjustment for BMI, the association between bioavailable estradiol and smoking was no longer significant ( $P = 0.11$ ). No

association was seen between total estradiol and any diabetes risk factor in men. Limiting all analyses to men and women with hormone levels higher than the sex-specific sensitivity of the assays did not alter the results (data not shown).

Men with IGT or type 2 diabetes were more likely to have a total testosterone level below the median of 10.3 nmol/l (age-adjusted odds ratios [ORs] = 0.71 and 0.68, respectively;  $P = 0.001$  for each). Women with IGT or type 2 diabetes were more likely to have a total or bioavailable

estradiol level or bioavailable testosterone level above the hormone-specific median of 18.4 pmol/l, 11.0 pmol/l, and 0.13 nmol/l, respectively (age-adjusted IGT ORs = 1.26, 1.52, and 1.41,  $P < 0.01$  for each; age-adjusted type 2 diabetes OR = 1.62 [ $P = 0.09$ ], 1.44 [ $P = 0.002$ ], and 1.44 [ $P = 0.002$ ], respectively).

**CONCLUSIONS** — The results from this large population-based study confirm that men with IFG, IGT, or type 2 diabetes have significantly lower levels of total testosterone (1,5–7,10). Results also confirm that postmenopausal women with IGT or type 2 diabetes have significantly higher levels of bioavailable testosterone (10). Women with type 2 diabetes had significantly higher levels of total and bioavailable estradiol. These differences were independent of total body fat, body fat distribution, physical activity, and smoking, a finding that is inconsistent with a previous study of 50 postmenopausal women (10) that found no association between estradiol level and self-reported diabetes. Small samples, absent direct measurement of bioavailable hormone levels, and/or classification of type 2 diabetes without an OGTT may explain these differences.

Previous studies that evaluated an association between smoking and estrogen have yielded inconsistent results, reporting either a positive association between smoking and estradiol (26–28) or an inverse association

**Table 5**—Age-adjusted median hormone level by categorically defined diabetes covariates: Rancho Bernardo, 1984–1987

	Total estradiol (pmol/l)		Bioavailable estradiol (pmol/l)		Total testosterone (nmol/l)		Bioavailable testosterone (nmol/l)	
	Men	Women	Men	Women	Men	Women	Men	Women
BMI (kg/m <sup>2</sup> )								
<27	74.4 (1.1)	21.2 (0.5)†	46.4 (0.2)†	11.1 (0.1)†	11.4 (0.2)†	0.61 (0.03)	3.26 (0.05)‡	0.16 (0.01) †
≥27	75.8 (1.1)	27.6 (0.9)	49.8 (0.3)	16.3 (0.2)	9.7 (0.2)	0.58 (0.02)	3.16 (0.06)	0.19 (0.01)
WHR								
<0.85 or 0.95*	74.6 (1.0)	22.5 (0.68)‡	47.1 (0.18)	12.1 (0.11)‡	11.1 (0.15)‡	0.60 (0.02)	3.24 (0.04)‡	0.13 (0.005)
≥0.85 or 0.95*	75.0 (1.9)	24.2 (0.67)	48.7 (0.33)	13.6 (0.18)	9.9 (0.27)	0.61 (0.04)	3.11 (0.08)	0.17 (0.01)
Current smoking								
No	74.8 (0.96)	21.5 (0.51)	48.0 (0.17)‡	11.2 (0.10)	11.1 (0.14)	0.60 (0.02)	3.20 (0.04)	0.16 (0.005)
Yes	73.3 (2.8)	21.1 (1.3)	49.0 (0.49)	11.3 (0.26)	11.1 (0.41)	0.58 (0.05)	3.58 (0.11)	0.17 (0.02)
Physical activity (≥3×/week)								
No	74.8 (2.3)	22.6 (0.98)‡	44.2 (0.41)‡	14.6 (0.17)‡	11.1 (0.34)	0.61 (0.03)	3.10 (0.09)	0.16 (0.01)
Yes	75.7 (0.98)	21.4 (0.54)	48.0 (0.17)	11.9 (0.10)	11.1 (0.14)	0.60 (0.02)	3.21 (0.04)	0.16 (0.005)
Daily alcohol								
No	74.8 (1.3)	21.5 (0.60)	47.5 (0.23)	12.9 (0.12)§	11.1 (0.19)	0.60 (0.03)	3.16 (0.05)	0.16 (0.007)
Yes	74.7 (1.3)	21.2 (0.77)	47.5 (0.22)	11.8 (0.15)	11.1 (0.18)	0.60 (0.02)	3.25 (0.05)	0.17 (0.009)

Data are medians. \*0.85 for women and 0.95 for men. † $P \leq 0.001$ ; ‡ $P \leq 0.05$ ; § $P \leq 0.10$ .

(29). In the present study, the association between smoking and total estradiol in men was not statistically significant after adjusting for BMI; only 10% of these older men were current smokers. Differences in age of the study population (26,27), sample size (26,27), or lack of adjustment for obesity (27) may explain these inconsistencies.

As expected, less body fat was associated with lower total and bioavailable estradiol levels in women (30–33), whereas total and bioavailable testosterone levels in men were inversely associated with total body fat (4,34–36). Because obesity may be involved in the causal pathway between hormones and diabetes, adjusting for BMI may be “overadjusting.” Adjustment for BMI in our analyses reduced but did not eliminate most of the hormone–diabetes associations. Because of the relatively crude measurements of obesity used, residual confounding cannot be excluded.

The present study documents important sex differences in the association between central adiposity and endogenous steroid hormones, with a positive association between central obesity and total and bioavailable estradiol in women and an inverse association between central obesity and total and bioavailable testosterone in men. Although WHR has been shown to predict diabetes in both men (37–39) and women (38,39), the association appears to be stronger in women than in men (39). Adjustment for WHR or waist circumference did not, however, eliminate the hormone–diabetes associations in either sex.

Others have suggested that diabetes is associated with hyperandrogenicity in women and hypogonadism in men (10). An association between hyperandrogenicity, hyperinsulinemia, and type 2 diabetes in women is supported by the higher prevalence of IGT and type 2 diabetes seen in women with polycystic ovarian disease (PCO) (41), who often have male-pattern (central) obesity and hyperandrogenicity (42). Women with PCO typically have marked peripheral insulin resistance and hyperinsulinemia, independent of obesity (43–45). We have previously shown in this cohort an association between type 2 diabetes and SHBG (45), presumed to reflect hyperandrogenicity in women (16). In addition, insulin levels have been shown to be directly associated with bioavailable testosterone (46) and inversely associated with SHBG in women (47,48). Fasting insulin levels are higher in postmenopausal than in premenopausal women, which

suggests that low estrogen may permit insulin resistance (49). Clinical trial data in nondiabetic women regarding the effect of estrogen replacement therapy on glucose and insulin levels are contradictory, with the results varying with dose and type of estrogen (50–54). Small studies reported an improvement in glucose homeostasis and glycemic control with exogenous estrogen replacement in postmenopausal women with type 2 diabetes (55,56).

Several lines of evidence support an association between hypogonadism and insulin resistance in men. Insulin resistance, a hallmark of type 2 diabetes, can be produced by castration of male rats and is reversed with subsequent testosterone replacement (57). Testosterone treatment of men with abdominal obesity reduces insulin resistance (58). Cross-sectional studies have shown that insulin concentration is inversely associated with SHBG (16,59) and inversely associated with total and bioavailable testosterone in nondiabetic men (35,60,61). This association may be modified largely by total body fat or visceral adiposity (62).

This study is limited by the use of a single hormone measurement. Testosterone, however, shows a high intraclass correlation, suggesting that a single measure reliably characterizes an individual (63). Although estradiol has wide intra-individual variation, such that a single assay characterizes an individual poorly (63,64), this study found the expected associations between estradiol and measures of body fat, body fat distribution, and physical activity. Some investigators have remarked on the limited sensitivity of the estrogen assays, and although >13% of women (87 of 633) in this cohort had estradiol levels below the level of sensitivity, exclusion of these women did not alter the results. Potential nondifferential misclassification of hormone levels would be expected to bias the results toward the null, and any true association would be stronger than reported. Although hormone analyses were performed using sera that had been frozen for an average of 8 years, previous studies have demonstrated no hormone deterioration when sera were frozen and stored for up to 10 years in tightly sealed containers (22,23). And, as noted above, hormone levels were those expected for age according to a leading textbook of endocrinology (24).

This study supports an association between type 2 diabetes and hypogonadism in men and hyperandrogenism in

women. The cross-sectional nature of the study cannot determine the direction of the hormone–type 2 diabetes association, i.e., whether hormone levels precede diabetes or vice versa. Prospective studies are therefore needed to determine the direction of these hormone–type 2 diabetes associations and whether hormone differences by sex are related to the etiology and optimal treatment of type 2 diabetes in elderly men and women.

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