

## Sex Differences in the Metabolic Syndrome: Implications for Cardiovascular Health in Women

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**BACKGROUND:** The metabolic syndrome is a clinical condition characterized by the presence of multiple interrelated risk factors for type 2 diabetes and cardiovascular disease. Component features include dysglycemia, increased blood pressure, increased triglycerides, decreased HDL cholesterol concentrations, and obesity (in particular, abdominal obesity). The underlying biology, optimal diagnostic criteria, and clinical implications, once diagnosed, have been matter for intense debate. Despite these areas of controversy, there is now general consensus that the observed risk factor clustering signifies heightened cardiovascular risk.

**CONTENT:** The influence of sex on the clinical expression and pathophysiology of the syndrome is underrecognized, and is an issue of increasing importance given the alarming increase in prevalence among young women. This minireview will highlight sex differences in the epidemiology, etiology, biology, and clinical expression of the metabolic syndrome. In particular, key sex differences include distinctions in (a) prevalence of dysglycemia, (b) body fat distribution, (c) adipocyte size and function, (d) hormonal regulation of body weight and adiposity, and (e) the influence of estrogen decline on risk factor clustering.

**SUMMARY:** Accumulated and emerging data convincingly demonstrate that significant heterogeneity exists between men and women developing the metabolic syndrome, in large part related to hormonal regulation of body fat distribution and attendant metabolic abnormalities.

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### From Inception to Codified Clinical Criteria

In 1988, in his seminal Banting award lecture, Reaven (1) proposed that insulin resistance was of fundamen-

tal importance in the clustering of abnormalities that not only increase the risk of type 2 diabetes but also contribute to the development of cardiovascular disease. He speculated that loss or defect in insulin action and compensatory hyperinsulinemia was the linking factor for the condition, which he termed syndrome X. Since that time, an abundance of published data have shown that insulin resistance, detected by various methods, is indeed a key factor associated with the clustering of increased blood glucose, excess body fat, increase in blood pressure, and cholesterol abnormalities, which have alternatively been named the *deadly quartet*, the *insulin resistance syndrome*, the *cardiometabolic syndrome*, and now most commonly, the *metabolic syndrome*.

The first formalized definition of the metabolic syndrome (MetS) was proposed in 1998 and finalized in 1999 by the WHO consultation group on the definition of diabetes (2, 3). The presence of insulin resistance was emphasized as an underlying mechanism, and evidence of insulin resistance or dysglycemia was a requirement. Either central (estimated by waist-to-hip ratio) or total [estimated by body mass index (BMI)] adiposity qualified as 1 of the remaining 5 criteria. As most physicians cannot readily measure direct indices of insulin resistance in routine clinical practice, a simplified diagnostic approach was needed to screen and identify, at low cost, individuals who may have the syndrome. To this end, over the past 15 years the diagnostic criteria have evolved and been endorsed by various organizational bodies including the European Group for the Study of Insulin Resistance (4), the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (5, 6), the American College of Endocrinology (7), the International Diabetes Federation (IDF) (8), and most recently in 2009, in proposing the harmonizing definition, jointly the IDF, National Heart, Lung, and Blood Institute, American Heart Association, World Health Federation, International Atherosclerosis Society, and International Society for the Study of Obesity (9). Contemporary definitions (Table 1) similarly incorporate hyperglycemia (removing measurement of insulin resistance), hypertension, and dyslipidemia, with the main difference being whether abdominal obesity (IDF definition) is obligatory and whether national or regional waist circumference (WC) cut points should be used (IDF and

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Table 1. Recent diagnostic criteria for the metabolic syndrome.

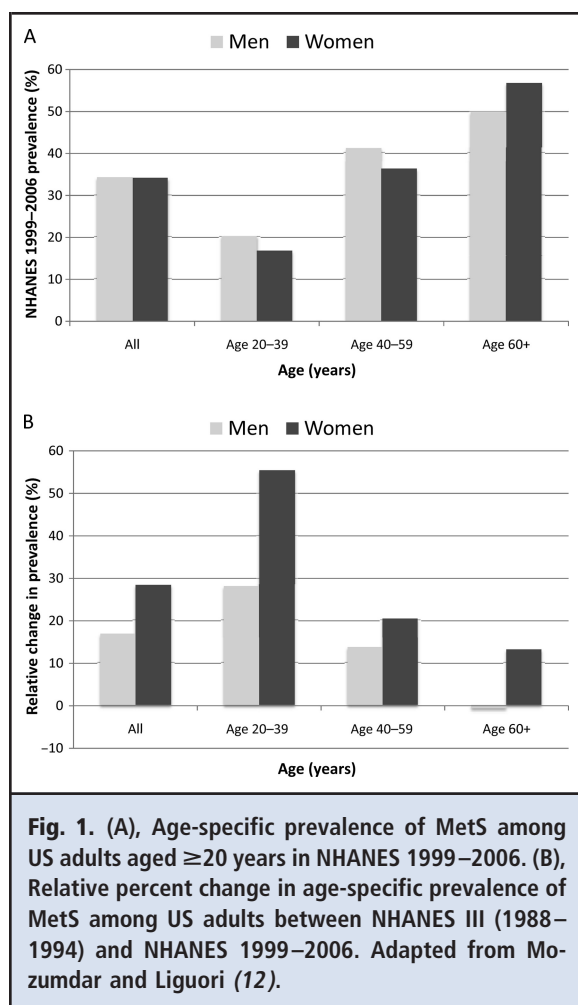
Component	NCEP Adult Treatment Panel III (2002)	American Heart Association/National Heart, Lung, and Blood Institute (2005)	IDF (2005)	Harmonizing definition (2009)
Fasting plasma glucose	>110 mg/dL (>6.1 mmol/L)	>100 mg/dL (>5.6 mmol/L) or drug treatment for increased glucose	>100 mg/dL (>5.6 mmol/L) or previously diagnosed T2D	>100 mg/dL (>5.6 mmol/L) or drug treatment for increased glucose
WC	>40 inches (>102 cm) for men; >35 inches (>88 cm) for women	>40 inches (>102 cm) for men; >35 inches (>88 cm) for women	Ethnic-specific cut points	Population- and country-specific cut points
Blood pressure	>130/85 mmHg	>130 mmHg systolic, >85 mmHg diastolic, or on antihypertensive therapy in a patient with a history of hypertension	>130 mmHg systolic, >85 mmHg diastolic, or treatment of previously diagnosed hypertension	>130 mmHg systolic, >85 mmHg diastolic, or on antihypertensive therapy in a patient with a history of hypertension
TG	>150 mg/dL (>1.7 mmol/L)	>150 mg/dL (>1.7 mmol/L)	>150 mg/dL (>1.7 mmol/L)	>150 mg/dL (>1.7 mmol/L)
HDL cholesterol	<40 mg/dL (<1.0 mmol/L) for men; <50 mg/dL (<1.3 mmol/L) for women	<40 mg/dL (<1.0 mmol/L) for men; <50 mg/dL (<1.3 mmol/L) for women	<40 mg/dL (<1.0 mmol/L) for men; <50 mg/dL (<1.3 mmol/L) for women	<40 mg/dL (<1.0 mmol/L) for men; <50 mg/dL (<1.3 mmol/L) for women
Requirements for diagnosis	>3 of above components	>3 of above components	Central obesity plus >2 other components	>3 of above components

harmonizing definitions). The now universal recommendation (Table 1) to measure WC rather than BMI reflects growing evidence for a critical role of central obesity as an alternate unifying mechanism.

Whether insulin resistance or abdominal obesity is the linking factor, from a practical standpoint, the purpose of a codified definition is to provide a simple means to identify individuals who may have the clinical phenotype. Importantly, as with any clinical syndrome, there is a spectrum of disease that is not fully captured by the criteria devised for use by practitioners. Importantly, other adverse clinical traits not encompassed by the diagnostic criteria include impaired vascular reactivity, altered fatty acid metabolism, heightened inflammatory response, and a prothrombotic state.

### Sex Differences in Prevalence of MetS

The prevalence of MetS differs by age, ethnicity, and sex, and according to the definition used and population surveyed. Variable genetic background, diet, levels of physical activity, and levels of over- or undernutrition also influence the prevalence of both the syndrome and its components. Thus, generalized statements regarding sex differences in prevalence may be misleading due to the potential influence of these numerous confounding factors. Further complicating the matter, the syndrome may be diagnosed whenever a threshold of 3 of 5 features is reached. Consequently, any of 16 risk factor combinations may confer a diagnosis, and prevalence estimates do not differentiate between these subtypes, the distribution of which may also be sex and population specific. Nonetheless, a recent analysis (10) of the Third National Health and Nutrition Survey (NHANES III, 1998–1994, NCEP criteria) in the US demonstrated that, in this nationally representative survey, abdominal obesity was the dominant MetS feature in women, whereas risk factor combinations were more varied in men. The most common cluster (16.7%) in younger women was increased triglycerides (TG), low HDL cholesterol, and increased WC. For younger men, the combination of increased TG, low HDL cholesterol, and hypertension was most frequent (18.0%). Notably, the sex difference in subtype distribution was largely abolished in older adults (>65 years) in this cohort, such that the most common subtype, presence of all 5 features, was equally prevalent in older men and women. These observations demonstrate heterogeneity within the syndrome by subtype, by age, and between sexes. Whether simple presence or absence of the syndrome, sum total of risk factors, or a unique risk factor combination more optimally quantifies cardiometabolic risk is not clear from the existing data and requires further study. Some investigators



have suggested that a global MetS calculator with variables treated as continuous factors might address this issue (11).

As obesity rates have continued to surge, more recent data from the NHANES 1999–2006 (12) indicate that in the contemporary era, approximately 68 million US adults (overall prevalence 34.2%) have the condition, with equal prevalence among sexes (age-adjusted prevalence 34.9% and 33.3% in men and women, respectively). Although prevalence rates have increased across all sex and age groups, women, especially young women, appear most affected. Comparative data from NHANES III (1988–1994) and NHANES 1999–2006 are shown in Fig. 1. The greatest increase in MetS prevalence is observed in young women. These trends may be explained in large part by significant increases in abdominal obesity in both sexes, where age-adjusted prevalence grew from 46.0% to 58.0% in women and 30.4% to 41.1% in men, but with concomitant increases in hypertriglyceridemia and fasting glucose in women not seen in men.

### Sex Differences in Etiology, Biology, and Clinical Expression of MetS

Key sex differences in the metabolic syndrome include distinctions in (a) glycemic indices, (b) body fat distribution, (c) adipocyte size and function, (d) hormonal regulation of body weight and adiposity, and (e) the influence of estrogen decline on risk factor clustering. These will be discussed below. The impact of race/ethnicity and related genetic contribution to sex differences in the metabolic syndrome and attendant cardiovascular risk is beyond the scope of this minireview and is the topic of other focused reviews (13, 14).

#### SEX DIFFERENCES IN PREVALENCE OF DYSGLYCEMIA

A diagnosis of abnormal glucose homeostasis in a given individual is most commonly made by establishing presence of impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT). However, it is apparent that IFG and IGT are not interchangeable and represent metabolically distinct abnormalities whose pathophysiological determinants are not the same. Healthy regulation of fasting glucose relies on both adequate levels of basal insulin secretion and insulin sensitivity in the liver to control hepatic glucose output, whereas a healthy response to a carbohydrate load requires a prompt surge in insulin secretion and adequate hepatic and muscle insulin sensitivity to enhance glucose uptake. In particular, IGT is associated with peripheral insulin resistance at the skeletal muscle level, where most postprandial glucose disposal occurs. In most populations, IGT is substantially more prevalent than IFG, with limited overlap between these categories. As has now been established in several diverse populations, the majority of individuals with IGT do not have IFG, and the majority with IFG do not have IGT (15). For example, in the NHANES III study population, the total prevalence of IGT was 14.9%, yet in this group, roughly only 1 in 4 had concurrent IFG (16). Similar differences have been noted in European, Asian, and other ethnic groups (15, 17, 18).

Sex differences in prevalence of IGT and IFG also exist. It is now also clear from analyses of the DECODE/DECODA (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe/Asia) study groups involving data from 13 European and 10 Asian studies that IFG is more common in men than in women in nearly all age groups, typically being 1.5–3 times higher in men, but up to 7–8 times higher in men at older ages (50–70 years). In contradistinction, the prevalence of IGT is higher in women except among those over the age of 60 in Asian populations and over the age of 80 in Europeans (15). Although the underlying explanation for these observations remains to be elucidated, sex differences in lean muscle mass, visceral

adiposity, differential impact of aging, influence of the menopausal transition, and altered susceptibility to free fatty acid-induced peripheral insulin resistance have all been invoked. The implications for screening are highly pertinent, as more recent criteria for the diagnosis of MetS do not include IGT, thus raising concern as to whether current glucose thresholds have equal ability to identify men and women with the syndrome.

#### SEX DIFFERENCES IN BODY FAT DISTRIBUTION

*Adipose tissue nomenclature.* Although obesity is a risk factor for insulin resistance, type 2 diabetes, and cardiovascular disease, not all obese patients exhibit the expected metabolic abnormalities despite marked excess body fat, an observation that implies that differences in regional fat distribution rather than total adiposity may have a pathogenic role. Despite intense interest in quantification of regional fat depots, consensus on nomenclature has been lacking. One classification scheme (19) that derives from imaging data and uses anatomic landmarks stipulates that whole-body adipose tissue be subdivided into two main components: subcutaneous adipose tissue (SAT; between dermis and aponeuroses or fascia of muscle) and internal (including visceral) adipose tissue residing within body cavities. Visceral adipose tissue (VAT) from the intra- and extraperitoneal spaces of the abdominopelvic cavity is often combined, yet metabolic properties and venous drainage are distinct. Only intraperitoneal VAT (mainly omental and mesenteric) is drained by the portal vein, a characteristic central to hypotheses linking VAT accumulation to cardiometabolic disease (20).

*Sexual dimorphism in body fat distribution.* Men and women display a conspicuous sex dimorphism in body fat distribution, with substantial variation that may be exclusive to our species (21). In his seminal observations, Vague (22) referred to android and gynoid obesities when describing adipose tissue accrual in the upper body (trunk and abdomen) in men and lower body (hips and thighs) in women, respectively. The teleological explanation for differential fat partitioning is presumably due to evolutionary and sexual selection pressures which favor storage of excess calories in different depots. However, the precise biologic mediators leading to topographical differences in body fat distribution remain to be fully elucidated.

SAT is anatomically and functionally distinct from VAT. Studies that have used imaging techniques to measure SAT have clearly shown that viscerally obese subjects (even in the absence of clinical obesity) represent the subgroup of individuals characterized by the

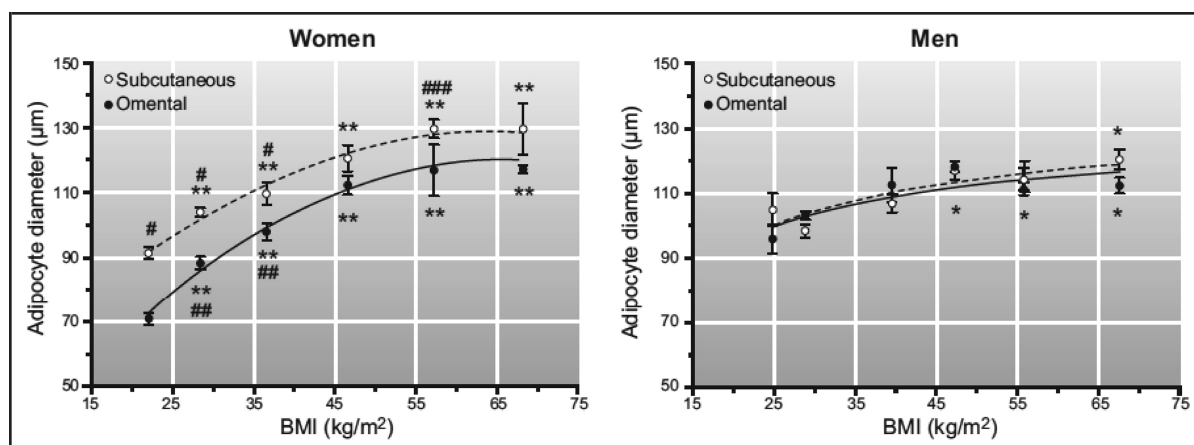
most severe insulin-resistant state (23). Although both SAT and VAT are associated with higher prevalence of IFG, insulin resistance, hypertension, and other features of MetS, several epidemiologic studies have concluded that VAT is a stronger correlate of these metabolic disturbances and of cardiovascular risk (24, 25). Nonetheless, others have argued that SAT may have protective effects (26, 27), and it remains plausible that relative paucity of SAT may be a strong driver of cardiometabolic risk. In support of this hypothesis, recent data suggest that a high VAT/SAT ratio may be a unique risk factor beyond absolute fat volumes (28). Prospective outcomes data are currently unavailable to judge which measure is optimal in predicting future clinical events.

With regard to sex differences in central obesity, as shown by computed tomography measurements, the amount of VAT is up to 2-fold higher in men than in premenopausal women (29). In men, VAT accrual generally increases with the amount of total body fat, whereas in women, VAT accumulation is less a function of total adiposity. It has been convincingly demonstrated that even after accounting for total body fat mass, premenopausal women have a lower ratio of VAT to total body fat than men. Women had less visceral fat despite having a higher total body fat, BMI, and abdominal SAT (30). Premenopausal women therefore appear to accumulate a substantial amount of total body fat before increases in visceral fat are observed. Moreover, it has been demonstrated that for the same waist circumference, men have more VAT than women (31). Thus, a large waistline alone, although a convenient measure, may not be an accurate indicator of visceral obesity.

Although data have been controversial due to small sample size and methodologic issues, several reports suggest that among obese subjects, men lose relatively more VAT than women despite similar total body weight loss. In a relatively large study, Kuk and Ross (32) evaluated 81 men [mean (SD) age 44.3 (8.3) years] and 72 women [40.2 (6.7) years] with BMI >27 kg/m<sup>2</sup> who had participated in various diet and exercise programs for weight loss. Whole-body magnetic resonance imaging was performed to assess body composition before and after 12–16 weeks of intervention. For a given reduction in body weight or WC, men experienced greater reductions in VAT and smaller re-

<sup>2</sup> Nonstandard abbreviations: MetS, metabolic syndrome; BMI, body mass index; NCEP, National Cholesterol Education Program; IDF, International Diabetes Federation; WC, waist circumference; NHANES III, Third National Health and Nutrition Survey; TG, triglycerides; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; E<sub>2</sub>, 17 $\beta$ -estradiol; ER, estrogen receptor.





**Fig. 2. Subcutaneous and omental adipocyte diameter in men and women according to BMI category.**

Mean (SE) are shown. The analysis included 54 men and 207 women. #Statistically significant depot difference within each BMI group ( $P < 0.05$ ). Statistically significant sex differences in the corresponding BMI group within each adipose tissue depot, ## $P < 0.05$  and ### $P < 0.001$ . Statistically significant differences compared with the lowest BMI group for that depot, \* $P < 0.05$  and \*\* $P < 0.001$ . Reproduced with permission from Tchernof and Despres (23).

ductions in SAT even after adjustment for baseline values. These sex differences progressively increased with greater magnitude of weight loss. Factors responsible for these observations require further study, as does the impact of type of intervention (caloric restriction vs exercise), yet these data and corroborative findings from a more recent metaanalysis (33) suggest that men experience greater reductions in visceral fat and potentially greater improvements in metabolic profile than women despite similar levels of weight loss.

#### SEX DIFFERENCES IN ADIPOCYTE SIZE AND FUNCTION

The volume of any given adipose tissue compartment is largely determined by adipocyte size and number. However, marked interindividual variation in these variables is observed. In general, in both sexes and all anatomical regions, mean adipocyte size increases with adiposity level but plateaus in markedly obese individuals (Fig. 2) (23). This leveling of adipocyte size with extreme obesity suggests that presence of large adipocytes may stimulate adipocyte proliferation to accommodate additional weight gain. We now know that sex is an additional modulator of adipose tissue cellularity in specific anatomic locations. Gluteofemoral compartments of obese women contain more adipocytes than those of leaner women in a sex-specific manner not seen in men (34). Consistent with this finding, longitudinal studies performed during weight gain suggest that lower-body adipose tissue tends to expand through hyperplasia in women but through hypertrophy in men, and accordingly that for any given obesity level, lower-body SAT adipocytes of women

tend to be larger than men. This relationship appears to be depot specific in that sex differences in abdominal SAT adipocyte size are less apparent (23, 34).

With regard to visceral adipocyte size, in women, omental adipocytes are 20%–30% smaller than abdominal subcutaneous adipocytes over a broad range of obesity levels (Fig. 2). Intriguingly, as women reach menopause, depot differences in adipocyte size are attenuated due to express increase in omental cell size. The propensity of postmenopausal women toward visceral fat accumulation and presence of larger adipocytes suggest that estrogen decline may stimulate adipocyte hypertrophy in this depot (35). In men, adipocytes of the visceral and abdominal subcutaneous fat compartments have similar sizes across the range of adiposity values (Fig. 2).

Adipocyte size is an important determinant of adipocyte function and metabolic activity, irrespective of obesity level. Adipocyte size is closely correlated with measures of insulin resistance and alterations in lipid metabolism, including hydrolysis of triglyceride-rich lipoproteins and triglyceride synthesis. Analyses of adipocyte populations separated by cell size show that larger adipocytes have higher basal and stimulated rates of lipolysis. Adipocyte morphology is also an important determinant of adipokine secretion, with increasing size resulting in a shift toward a predominance of proinflammatory adipokines (36). Although further studies will be required, sex-specific differences in adipocyte size and metabolic function may therefore contribute to the development of MetS, MetS subtype distribution, and associated cardiometabolic risk in men and women.

## SEX DIFFERENCES IN HORMONAL REGULATION OF BODY WEIGHT AND ADIPOSITY

Body weight is regulated by the complex interaction of negative feedback loops, which typify most homeostatic systems. These include peripheral signals called adiposity signals, such as leptin, insulin, and also estrogen, which act to convert hormonal input into neurobiologic responses. Signals act in the brain, specifically the hypothalamus, to regulate food intake, energy expenditure, and ultimately regional and total body fat stores. Negative feedback is engaged to keep overall adiposity levels relatively static.

*Leptin.* Leptin is secreted from adipose tissue in direct proportion to body fat mass and interacts with leptin receptors in the hypothalamus and brainstem, where it provokes a powerful catabolic signal to inhibit food intake, suppress insulin secretion, and increase lipolysis, thermogenesis, and energy expenditure in part through interactions with the sympathetic nervous system. Leptin expression is greater in subcutaneous than in visceral adipocytes. Moreover, subcutaneous adipocyte size is associated with plasma leptin concentrations independent of total adiposity, suggesting that hyperleptinemia in obesity is likely a function of both subcutaneous adipocyte hypertrophy and hypersecretion. As women generally have more subcutaneous fat than men, an important correlate is that the adiposity signal transmitted to the brain differs in males and females and relates to fat distribution. Importantly, regulation of leptin activity by estrogen has been proposed as 1 theoretical framework for how female sex hormones regulate fat distribution, i.e., through stimulating leptin-mediated lipid mobilization from visceral to subcutaneous fat depots (37).

*Insulin.* Insulin has also been designated a catabolic adiposity signal, although distinct from leptin in several important ways. Insulin is secreted from pancreatic  $\beta$ -cells in response to increases in circulating glucose. Insulin is 1 afferent neural input that provides information about the calorie stores in adipose tissue and, in contradistinction to leptin, is a better marker of visceral fat. Although plasma concentrations of both hormones relate to adiposity and metabolic activity, insulin is less stable, having a shorter half-life (approximately 2–3 min) than that of leptin (approximately 45 min) and responding to marked fluctuation in glucose concentrations rather than more stable metabolic activity of adipocytes.

*Estrogen.* Estrogens are a class of structurally similar, hormonally active molecules that regulate cell signaling pathways critical to cell proliferation, differentiation, and homeostasis and comprise 1 major group of female sex hormones. The endogenous forms of estrogen are  $17\beta$ -estradiol ( $E_2$ ), estrone, and estriol, with  $E_2$  being

the major physiologic form. Estrogen is released primarily by the ovaries in premenopausal women. However, in both men and women, estrogens are also generated through peripheral aromatization in several tissues, especially fat. Peripheral estrogen sources are especially important in men and postmenopausal women. Estrogens primarily exert their physiological effects through activation of 2 major estrogen receptor (ER) subtypes,  $ER\alpha$  and  $ER\beta$ , that belong to the nuclear receptor family of ligand-activated transcription factors. Estrogens also exert nongenomic effects through membrane-localized ERs.  $E_2$  secretion and action is now implicated in a variety of processes involved in adipocyte biology and glucose and lipid metabolism. Several excellent reviews on the topic have recently been published (38, 39), with the balance of data supporting several critical metabolic functions including (a) anorexigenic action via central nervous system control of feeding behavior, (b) augmented glucose disposal in skeletal muscle via actions on several proteins in the insulin signaling pathway and by increased glucose transporter type 4 translocation, (c) prevention of visceral fat accumulation and decreased lipogenic activity of lipoprotein lipase in adipose tissue, and (d) antiapoptotic effects on pancreatic  $\beta$ -cells. In some tissues, such as adipose tissue,  $ER\alpha$  and  $ER\beta$  appear to have opposing actions, for instance  $ER\alpha$  agonism decreases adipocyte proliferation and hypertrophy, whereas  $ER\beta$  promotes adipose tissue expansion. It has thus been hypothesized that imbalance of  $ER\alpha/ER\beta$  ratio may contribute to the development of MetS in women (38).

## INFLUENCE OF ESTROGEN DECLINE ON EMERGENCE OF MULTIPLE RISK FACTORS IN MetS

As previously well detailed (40), features of MetS (insulin resistance, abdominal obesity, and dyslipidemia) commonly emerge with the estrogen decline experienced during menopause. As noted above, we now know that  $E_2$  is involved in a plethora of mechanisms regulating body fat distribution and glucose and lipid metabolism. Menopause may be best defined as the cessation of menses for 12 consecutive months, with perimenopause consisting of the period of menstrual irregularity and hormonal variability lasting on average 4 years and ending 1 year after the final menstrual period. Thus, the metabolic and hormonal changes of menopause occur over several years, extending into the postmenopausal period, and vary widely among women. In contrast, fluctuation in nonreproductive hormones produced by the thyroid, parathyroid, and pancreas noticeable after menopause are considered a result of chronological aging without a significant relationship to menopause itself (41).

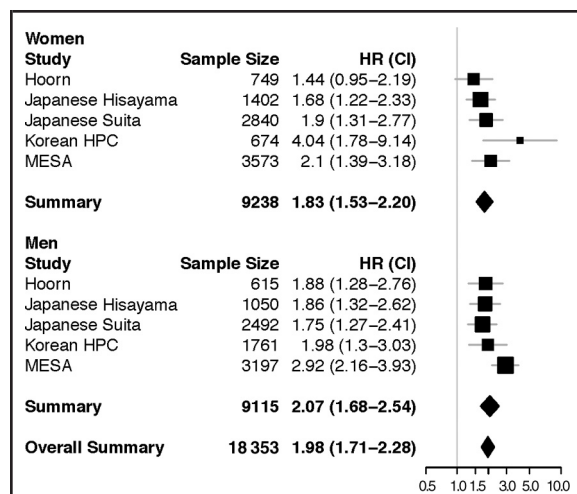
Although middle-aged women on average gain approximately 0.55 kg (approximately 1 lb) per year, this

effect appears to be independent of menopause. However, even in the absence of weight gain, postmenopausal alterations in fat partitioning occur with a preferential increase in visceral adiposity even after accounting for age and baseline total adiposity. Lovejoy et al. (35) demonstrated that among initially healthy premenopausal women followed longitudinally, all women gained subcutaneous adipose tissue with age, irrespective of menopausal status, whereas visceral adipose tissue increased only in women who became postmenopausal and in parallel with a decline in E<sub>2</sub>. Furthermore, this increase in visceral fat has been shown to correlate positively with an adverse inflammatory and thrombotic profile and to correlate negatively with concentrations of adiponectin (42).

Weight gain with menopause is a concern for many women, as is the perception that hormone therapy may increase appetite and thereby aggravate weight gain. However, several prospective studies indicate that energy intake is unaffected by hormone therapy, (43, 44) and a metaanalysis of data from 22 randomized clinical trials did not show evidence of significant weight gain or BMI change with estrogen alone or in combination with progestin (45). Rather, most randomized controlled trials show a reduction in central adiposity with menopausal hormone therapy compared with untreated women (46, 47).

Visceral fat accumulation, when it does occur, is generally accompanied by insulin resistance, increased free fatty acid concentrations, and secretion of apolipoprotein B-containing particles, leading to hypertriglyceridemia and increased hepatic lipase activity. This cascade ultimately results in a preponderance of small, dense LDL particles and a reduction in large anti-atherogenic HDL<sub>2</sub> particles. A similar pattern emerges with menopause, in that LDL particle composition shifts from a low prevalence of small, dense atherogenic LDL particles in premenopausal women (10%–13%) increasing to as much as 30%–49% after menopause. These lipid changes (increased TG, low HDL cholesterol, and increased small, dense LDL) are indicative of increased cardiovascular risk and contribute to the number of women meeting a diagnosis of MetS. However, it should be emphasized that recent intervention trials to raise HDL cholesterol have led to either conflicting or disappointing results, with no reduction in coronary heart disease events or mortality benefit and perhaps potential harm (48). These findings have led, in part, to a shift in focus to clinical evaluation and targeting of HDL functionality rather than plasma HDL cholesterol alone. At the current time, therapeutic strategies to address the lipid abnormalities characteristic of MetS remain unproven.

Studies of the relationship between menopause and hypertension have been equivocal, showing either an in-



**Fig. 3. Association of MetS with cardiovascular events.** Results of a random-effects metaanalysis of data from 5 cohort studies. All hazard ratios (HRs) are minimally adjusted for age, smoking, and total or LDL cholesterol (except Japanese Suita). The size of each box is proportional to weight (inverse-variance method) of each study. In metaregression analysis of for a moderating effect of sex, no significant effect was detected ( $P = 0.47$ ) and no significant heterogeneity when results were combined across sexes ( $I^2 = 30.5\%$ ;  $Q$  statistic = 13.5,  $P = 0.14$ ). References: Hoorn [Dekker et al. (51)], Japanese Hisayama [Ninomiya et al. (52)], Japanese Suita [Kokubo et al. (53)], Korean HPC [Hwang et al. (54)], and MESA [Hari et al. (55)].

crease or no change in systolic and diastolic blood pressure when adjusted for age. However, evaluation of blood pressure differences may be confounded by initiation of antihypertensive therapy as women age. Nonetheless, several mechanisms may contribute to the development of hypertension in postmenopausal women including endothelial dysfunction, inappropriate activation of the renin-angiotensin and sympathetic systems, oxidative stress, and inflammatory mediators. To date, few studies have evaluated the relationship between changes in blood pressure and menopause in a way that allows separation of the independent effects of age, body composition, and blood pressure treatment.

### MetS and Incidence of Diabetes and Cardiovascular Disease in Men and Women

Data from multiple prospective cohorts and meta-analysis (49) of these results now unequivocally demonstrate that MetS is a strong predictor of incident diabetes. Although significant heterogeneity exists across

populations, the estimated relative risk by use of any of the more recent definitions is roughly 3.5–5.0. In contrast, the association of MetS with cardiovascular events is weaker, with a recent metaanalysis (50), suggesting a roughly 2-fold increase in risk. Data with regard to effect modification by sex are sparse, few studies having provided sex-specific incidence rates by use of similar modeling approaches and the same definition for the syndrome. In this regard, Fig. 3 shows results from a random-effects metaanalysis incorporating results from 5 major prospective cohorts that have provided sex-stratified results, with similar multivariable adjustment, with the NCEP definition to characterize baseline MetS. Within these constraints, no apparent heterogeneity for incidence of cardiovascular events is observed.

### Conclusion

The currently available data support sex-specific pathophysiological differences in MetS arising from several factors including distinctions in prevalence of dysglycemia and MetS subtype distribution, fat partitioning and adipocyte biology, hormonal regulation of body weight and adiposity, and prominent effects of estrogen. Yet data regarding clinical significance of this

heterogeneity on cardiovascular risk remain understudied, and the syndrome continues to be viewed largely as a singular entity irrespective of sex. The burgeoning population of young women affected by the condition underscores the need to further examine sex-specific mechanisms and tailored therapies to ameliorate long-term cardiometabolic risk. Whether MetS in aggregate confers additional risk beyond the individual components remains an active area of debate which may be resolved with continued refinement of measurable indicators of high-risk abdominal obesity. Importantly, in this area, as highlighted in this review, sex differences in etiologic factors for both development and chronic progression of the syndrome must be considered.

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