Metabolic Syndrome in Healthy Obese, Overweight, and Normal Weight Individuals: The Atherosclerosis Risk in Communities Study

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Objective: There is recent interest in characterizing the subset of obese (OB) individuals who have healthy metabolic profiles yet only two studies have examined this group prospectively but not in racially diverse populations.

Design and Methods: We analyzed factors associated with the prevalence and incidence of metabolic syndrome (MetSyn) among individuals grouped by BMI categories in a multi-center, community-based cohort of 14,663 African-American and white men and women aged 45-64 years at recruitment in 1987-1989, the Atherosclerosis Risk in Communities (ARIC) Study. Logistic and proportional hazards regression were utilized to estimate odds ratios (ORs) for the prevalence and hazard ratios (HRs) for incidence of MetSyn with 95% confidence intervals (CIs).

Results: At visit 1, MetSyn was positively associated with age, female gender, African-American race, and inversely related to education, associations being more pronounced among normal weight (NW) subjects. Among those without MetSyn at visit 1, OB subjects were more likely to develop MetSyn compared with NW (HR (95% CI): 4.53 (4.09-5.01)). Several factors were associated with incident MetSyn among NW, including older age (per year: 1.05 (1.03-1.06)), female gender (vs. male: 1.29 (1.10-1.52)), heavy alcohol intake (vs. never: 0.75 (0.59-0.94)), and physical activity (tertile 3 vs. tertile 1: 0.71 (0.58-0.86)) but not OB. Weight gain (>5%) was also more highly associated with MetSyn in NW (1.61 (1.28-2.02)) compared with OB (1.01 (0.85-1.20)).

Conclusions: We conclude that lifestyle factors may play a stronger role in the development of MetSyn in NW individuals compared with OB and that metabolically healthy obesity may not be a stable condition.

Introduction

A subset of overweight and obese (OB) individuals have been documented to have normal metabolic profiles (1). These individuals, who include over 30% of OB (BMI ≥30 kg/m²) and over 50% of overweight (BMI ≥25 kg/m² and <30 kg/m²) adults, have normal insulin sensitivity, blood pressure, and lipid profiles (2). Some reports have suggested that despite an elevated body size, these “metabolically normal” individuals may have a risk of chronic disease similar to that of normal weight (NW) individuals without metabolic abnormalities (3). Conversely, ~24% of NW US adults (BMI <25.0 kg/m²) are considered metabolically abnormal (2), placing them at elevated risk for chronic diseases that are typically associated with elevated BMI, when compared to metabolically healthy NW individuals. Understanding which individuals are at higher risk for metabolic syndrome, given their body size, could have implications for public health and clinical practice.

Few studies have evaluated correlates of the prevalence of metabolic subtypes within body size categories (2,4,5) and we know of only one reporting on sociodemographic and lifestyle factors (2). The most pressing, yet completely unaddressed question regarding the metabolic subtypes of obesity is their longitudinal patterns (6). To date, only two studies, both in Asian populations, have evaluated the stability of the metabolically healthy phenotype (7,8). Therefore, we know little about the critical question of how common it is for metabolically healthy individuals to remain free from metabolic syndrome, or what factors are associated with the transition from the metabolically healthy condition to the metabolically unhealthy condition over time. There is concern that for some OB individuals, the metabolically healthy condition...
may represent a transition to the higher risk unhealthy phenotype, whereas others may maintain the more favorable metabolic profile indefinitely (6). Characterization of this pattern, including identification of lifestyle and sociodemographic factors will highlight significant areas relevant for public health and clinical interventions.

In the current study, we evaluated factors associated with subgroups of body size defined by metabolic syndrome (MetSyn) at baseline in a cross-sectional analysis. In addition, we examined the course of the metabolically healthy subgroups by examining incident MetSyn among these individuals, including identification of factors associated with this transition, and evaluated whether these associations varied by body size.

**Methods and Procedures**

**Study population**

We used data from the Atherosclerosis Risk in Communities (ARIC) Study, a prospective cohort in four US communities (Forsyth County, NC; Jackson, MS; suburban Minneapolis, MN; Washington County, MD) designed to study the etiology of atherosclerosis in a predominately biracial sample of adult men and women (9). The study was approved by the institutional review boards at each site.

**Data collection**

The initial visit occurred between 1987 and 1989 and included 15,792 men and women aged 45-64 years. Follow-up visits occurred approximately every 3 years (1990-1992, 1993-1995, and 1996-1998) with participation rates of 93, 86, and 81%, respectively. In-home interviews by trained study personnel using standardized questionnaires were conducted at each visit and assessed sociodemographic and lifestyle factors relevant to cardiovascular disease and family medical history. Usual diet was assessed using a 66-item food frequency questionnaire modified from the instrument developed by Willett (10), whereas physical activity was assessed using a modified version of the Baecke questionnaire (11).

Blood pressure, anthropometric measures, and fasting blood samples were collected in clinic visits conducted after the in-home interview. Three repeated blood pressure measurements were obtained using a random-zero sphygmomanometer and the second and third measurements were averaged. Body weight was measured using a calibrated scale with subjects in scrub suits without shoes and height was measured using a ruler. Waist circumference at the umbilicus was measured using a ruler. Waist circumference at the umbilicus was measured using a tape measure. Blood was collected from an antecubital vein into a vacuum tube with ethylenediamine tetraacetic acid (for lipids) or a serum separator gel (for glucose). Triglycerides, high-density lipoprotein (HDL), and serum glucose were assayed using enzymatic methods, dextran-magnesium precipitation and hexokinase/glucose-6-phosphate dehydrogenase, respectively (9).

**Outcome.** The outcome for this study was the presence or incidence of MetSyn as defined by National Cholesterol Program’s Adult Treatment Panel-III (ATP-III) guidelines (12) (three or more of the following risk factors: (i) abdominal obesity, in men: >40, in women: >35; (ii) elevated triglycerides: ≥150 mg/dl; (iii) low HDL cholesterol, men: <40 mg/dl, women: <50 mg/dl; (iv) elevated blood pressure: >130/≥85 mm Hg; (v) elevated fasting glucose: ≥110 mg/dl) within body size subtype defined according to three standard BMI categories (NW: <25 kg/m², overweight: 25-29.9 kg/m², OB: ≥30 kg/m²). The analysis of prevalent MetSyn at visit 1 included 14,663 subjects with adequate information to define or preclude a classification of MetSyn. Subjects were excluded from the analysis due to indeterminate MetSyn (n = 202), missing BMI or BMI <18.5 (n = 164), missing total energy intake or total energy intake outside the ranges 500-3,000 kcal/day for females, 800-4,000 kcal/day for males (13) (n = 529), missing age, education, smoking, alcohol intake or physical activity (n = 130). At visit 1, 10,074 subjects did not meet the criteria for MetSyn, of which 788 had indeterminate MetSyn status at visit 2; thus the analysis of incident MetSyn included the 9,286 subjects without a classification of MetSyn at visit 1. Subjects who were without MetSyn at visit 4, or who failed to participate in a specific visit were right censored.

**Covariates.** Covariates for both aims of this analysis included: age (continuous), sex (male, female), race (white, African-American), education level (less than high school, high school graduate or vocational school, attended college), smoking status (never, former, current), alcohol use (never/rare, former, light, medium, heavy), leisure time physical activity (tertiles of metabolic equivalent task-hours (Met-hours) per week), and total caloric intake (continuous). Weight change was calculated as the percent change between each visit relative to the initial visit (weight in kg in current visit − weight in kg at visit 1)/weight in kg at visit 1).

**Statistical analysis**

We used unconditional logistic regression analysis to estimate odds ratios (OR) and 95% confidence intervals (CIs) for the association of sociodemographic and lifestyle variables with prevalent MetSyn at visit 1. Hazard ratios (HRs) and 95% CI for the association of covariates with development of MetSyn were estimated using interval-censored proportional hazards regression. For analysis of development of MetSyn, BMI and weight change were treated as time-varying covariates. To determine whether the relationship between covariates and MetSyn differed by BMI category, all models included interaction terms and BMI-specific effects were calculated through combination of relevant parameter estimates from these models. The likelihood ratio test with a significance level of 5% was used to determine heterogeneity of association across body size groups for each covariate with prevalence of MetSyn. Each model was adjusted for all other variables. Statistical analysis was conducted in Stata v. 11 (Stata, College Station, TX).

**Results**

**Prevalent metabolic syndrome at visit 1**

At visit 1, prevalence of MetSyn was most common among the OB (Table 1). Nevertheless, a substantial proportion of OB individuals (39.8%) did not meet the ATP-III criteria for MetSyn.

Among all body size subgroups, MetSyn at visit 1 was more common among older individuals (Table 2; OR (95% CI) per year increase, among NW: 1.08 (1.06-1.10); overweight: 1.06 (1.05-1.07); OB: 1.03 (1.02-1.05); P interaction: <0.005), with greater association with decreasing body size. Women were more likely than men to have MetSyn if they were NW or overweight, yet were less likely if they were OB (P interaction: <0.005), with a similar pattern noted for African-Americans. A higher level of education was generally associated with lower prevalence of MetSyn, with the most pronounced effect among NW subjects (OR (95% CI): 0.48 (0.37-0.63)). Those with MetSyn were
more likely to be current smokers across all body size categories ($P$
interaction: 0.20). Although inverse associations were noted between
both moderate levels of drinking, and the highest level of physical activ-
ity and prevalent MetSyn among NW and overweight individuals, null
associations were observed in the OB group; the heterogeneity of these
effects did not reach statistical significance for either of these covariates.

| TABLE 1 Characteristics of 14,663 subjects from the ARIC cohort with adequate information to define or preclude a classification of metabolic syndrome (MetSyn), according to visit 1 BMI and MetSyn status |
|---|
| | Normal | Overweight | Obese |
| | No MetSyn | MetSyn | No MetSyn | MetSyn | No MetSyn | MetSyn |
| $N$ | 4,380 | 443 | 4,092 | 1,724 | 1,602 | 2,422 |
| Prevalence within BMI category | 90.8 | 9.2 | 70.4 | 29.6 | 39.8 | 60.2 |
| Age (y.o.d.) | 53.6 (5.8) | 56.5 (5.3) | 53.7 (5.7) | 55.8 (5.5) | 53.4 (5.7) | 54.6 (5.6) |
| Female (%) | 62.1 | 68.8 | 42.6 | 50.1 | 65.8 | 60.1 |
| African-American (%) | 15.9 | 19.9 | 24.4 | 23.7 | 42.8 | 35.2 |
| Education (%) |  |  |  |  |  |  |
| Less than high school | 16.6 | 28.4 | 20.7 | 27.2 | 28.1 | 32.0 |
| High school | 42.8 | 42.4 | 39.6 | 41.9 | 39.3 | 41.0 |
| College | 40.6 | 29.1 | 39.7 | 31.9 | 32.6 | 27.0 |
| Smoking (%) |  |  |  |  |  |  |
| Never | 39.5 | 33.4 | 40.9 | 38.9 | 51.1 | 47.7 |
| Former | 28.7 | 24.8 | 36.3 | 33.4 | 32.0 | 33.1 |
| Current | 31.7 | 41.8 | 22.8 | 27.8 | 16.9 | 19.2 |
| Drinking (%) |  |  |  |  |  |  |
| Never/rare | 40.1 | 44.7 | 37.8 | 41.8 | 50.4 | 49.6 |
| Former | 15.8 | 19.6 | 17.2 | 21.8 | 19.7 | 21.8 |
| Light | 10.1 | 7.9 | 11.1 | 8.1 | 8.6 | 7.7 |
| Medium | 17.3 | 12.9 | 20.2 | 15.5 | 11.6 | 11.1 |
| Heavy | 16.7 | 14.9 | 13.6 | 12.8 | 9.7 | 9.8 |
| Physical activity |  |  |  |  |  |  |
| First tertile (0–2 Met-hrs/week) | 35.6 | 42.9 | 37.4 | 42.9 | 49.9 | 50.2 |
| Second tertile (2–7.75 Met-hrs/week) | 31.4 | 28.9 | 30.5 | 30.8 | 28.4 | 29.8 |
| Third tertile (7.75–5 Met-hrs/week) | 33.0 | 28.2 | 32.1 | 26.3 | 21.7 | 20.7 |
| Energy intake (kcal/day) | 1,604.4 (598.4) | 1,547.8 (566.7) | 1,668.5 (606.3) | 1,650.5 (592.5) | 1,614.7 (591.9) | 1,642.8 (619.3) |
| Weight change visit 2–visit 1: |  |  |  |  |  |  |
| $>$5% Loss | 7.3 | 11.4 | 9.3 | 13.5 | 13.0 | 16.5 |
| Within 5% | 66.6 | 64.0 | 69.0 | 69.3 | 62.5 | 66.5 |
| $>$5% Gain | 26.1 | 24.6 | 21.7 | 17.2 | 24.6 | 17.0 |
| Weight change visit 3–visit 1: |  |  |  |  |  |  |
| $>$5% Loss | 7.9 | 15.5 | 9.2 | 15.5 | 11.4 | 19.6 |
| Within 5% | 52.9 | 50.9 | 56.1 | 55.1 | 48.9 | 54.1 |
| $>$5% Gain | 39.2 | 33.6 | 34.6 | 29.4 | 39.7 | 26.2 |

ARIC, Atherosclerosis Risk in Communities; MetSyn, metabolic syndrome.
*Sample sizes change over time due to loss to follow-up and removal from risk set due to occurrence of event.

Development of metabolic syndrome among those healthy at visit 1
The prevalence of MetSyn increased over the four follow-up visits among all body size subgroups, with the greatest increase seen among OB individuals (data not shown). Among the 9,286 participants without MetSyn at visit 1 and with sufficient follow-up, the
incidence of MetSyn over 9 years was greatest among the OB (incidence rate (IR) per 1,000 person-years (95% CI): 70.3 (65.8-75.2)), with lower rates noted among overweight (IR: 37.9 (36.0-39.8)) and NW individuals (IR: 15.4 (14.4-16.5)). In adjusted models (Table 3), the metabolically healthy OB (MHO) were much more likely to meet the criteria for MetSyn during the follow-up compared with metabolically healthy NW (MHN) individuals (HR: 4.53 (4.09-5.01)) with a less-pronounced effect noted among the metabolically healthy overweight (MHOw) (HR: 2.73 (2.49-2.99)).

Over the 9 years of follow-up, a weight gain of 5% or greater from visit 1 was associated with an increased risk of developing MetSyn among MHN (Table 3; HR: 1.61 (1.28-2.02)) and MHOw (HR: 1.24 (1.08-1.43)) but not among the MHO (HR: 1.01 (0.85-1.20); P interaction: 0.006). Females were more likely to develop MetSyn, with the effect limited to the MHN and MHOw (P interaction: <0.005). Higher education levels were inversely associated with development of MetSyn, and former and current smoking were positively associated with its development, with fairly uniform effects noted across body size subgroups (P interaction, education: 0.20; smoking: 0.70). Light and moderate alcohol intakes were inversely associated with development of MetSyn overall, with the effect appearing somewhat stronger among MHN (P interaction: 0.06). Similarly, an inverse association between incident MetSyn and physical activity was noted, and it appeared more prominent among those with smaller body size (MHN HR tertile 3 vs. tertile 1: 0.71 (0.79-0.94), MHOw: 0.84 (0.75-0.95), MHO: 1.06 (0.90-1.25); P interaction: 0.02).

### Discussion

In this study of a racially diverse, community-based cohort of men and women, we observed that while a substantial proportion of OB subjects were free of MetSyn at baseline (40%), they were over four times as likely to develop MetSyn over 9 years of follow-up compared with NW adults. Body size emerged as the strongest single factor studied here, although weight gain, age, and female gender were also positively associated with incident MetSyn. Greater physical activity was inversely associated; however, these associations were stronger among those with lower body size. Presence of MetSyn was more common among those of older age and among current smokers for all body size groups, whereas female gender and African-American race were positively associated with MetSyn among NW or overweight individuals only. Similarly, education, moderate drinking, and physical activity were inversely associated with prevalent MetSyn in the non-OB subgroups.

The clustering of cardiometabolic risk factors commonly referred to as the MetSyn has been noted since the 1920s and is hypothesized to be the consequence of an insulin-resistant state (14). The association between MetSyn and chronic disease has been extensively studied, and the condition has been linked to cardiovascular disease, diabetes, and cancer (15,16) which is believed to be due to its effects on dyslipidemia, insulin sensitivity, and chronic systemic inflammation (17). The clinical criterion for identification of MetSyn has gone through a number of iterations, with several

### Table 2

| Sociodemographic and lifestyle factors | Normal | Overweight | Obese | P interaction |
|--------------------------------------|--------|------------|-------|--------------|
| Age (years)                          | 1.08 (1.06–1.10) | 1.06 (1.05–1.07) | 1.03 (1.02–1.05) | <0.005 |
| Female (vs. male)                    | 1.46 (1.18–1.81) | 1.39 (1.24–1.56) | 0.78 (0.69–0.89) | <0.005 |
| African-American race (vs. white)    | 1.36 (0.99–1.87) | 1.00 (0.75–1.00) | 0.72 (0.59–0.94) | <0.005 |
| Education (vs. less than high school)| High school | 0.62 (0.49–0.80) | 0.88 (0.79–1.02) | 0.98 (0.84–1.15) | 0.01 |
|                                      | College    | 0.48 (0.37–0.63) | 0.68 (0.59–0.79) | 0.83 (0.70–0.99) | 0.20 |
| Smoking (vs. never)                  | Former    | 1.06 (0.82–1.38) | 0.99 (0.87–1.14) | 1.24 (1.06–1.44) | 0.52 |
|                                      | Current   | 1.56 (1.23–1.97) | 1.32 (1.14–1.53) | 1.51 (1.28–1.81) | 0.15 |
| Drinking (vs. never/rare)            | Former    | 1.00 (0.76–1.32) | 1.08 (0.92–1.27) | 1.16 (0.98–1.37) | 0.95 |
|                                      | Light     | 0.75 (0.51–1.09) | 0.72 (0.58–0.89) | 0.91 (0.71–1.17) | 0.74 |
|                                      | Medium    | 0.73 (0.54–1.00) | 0.77 (0.65–0.92) | 1.02 (0.82–1.27) | 0.46 |
|                                      | Heavy     | 0.80 (0.59–1.08) | 0.88 (0.73–1.07) | 1.03 (0.82–1.30) | 0.35 |
| Physical activity                    | Second tertile (2–2.75) | 0.79 (0.63–1.01) | 0.90 (0.78–1.03) | 1.03 (0.89–1.20) | <0.005 |
|                                      | Third tertile (2.75–5) | 0.76 (0.59–0.96) | 0.75 (0.65–0.88) | 0.94 (0.80–1.12) | 0.15 |
|                                      | Energy intake (per 100 kcal) | 0.98 (0.96–1.00) | 1.00 (0.99–1.01) | 1.01 (1.00–1.02) | 0.35 |

ARIC: Atherosclerosis Risk in Communities; MetSyn, metabolic syndrome.

*Odds ratios calculated from model with BMI and variable interaction as well as all other covariates listed. *P value from likelihood ratio test for interaction between BMI category and corresponding variable.
organizations separately or jointly releasing four formal definitions between 1998 and 2009 (18,19,20,21,22,23). According to a recent NHANES (National Health and Nutrition Examination Survey) study, nearly a quarter of the US men and women had MetSyn by the most recent 2009 ATP-III definition used here (24). These authors found that prevalence was highest in Mexican-Americans and lowest in African-Americans and was more common with increasing BMI and age, and among current smokers, those with lower income, non-drinkers, and those more physically inactive. We observed similar patterns regarding age, smoking, and alcohol use; however, the lower prevalence among African-Americans was limited to the OB while the inverse association with physical activity was only observed in NW and overweight subjects.

Although body size is strongly correlated with the clustering of cardiometabolic risk factors (24), a substantial number of overweight and OB individuals with normal metabolic profiles have been documented (1) as have NW individuals with abnormal metabolic profiles (2). This latter finding may be particularly noteworthy because metabolically unhealthy NW individuals may be more responsive to dietary and lifestyle interventions, which could significantly reduce their subsequent risk of serious cardiovascular and metabolic complications (25). Although the presence of these subtypes has been documented, detailed data on sociodemographic and lifestyle factors associated with them is lacking. The singular study to examine these issues uses data from the 1999-2004 NHANES (2). Wildman and colleagues report that among overweight and OB adults, the metabolically healthy phenotype was more common in younger adults, moderate alcohol drinkers, non-Hispanic blacks, and those with higher levels of physical activity; associations also observed in the current analysis. Wildman et al. also found that NW individuals were more likely to be metabolically abnormal if they were of older age and male gender, and less likely if they were moderately physically active; they further noted a nonsignificant positive association for current smokers. Our findings are in agreement with regard to age and smoking, yet we found that female gender correlated with prevalent MetSyn where they did not.

### TABLE 3

Hazard ratios (95% confidence intervals) for development of metabolic syndrome (MetSyn) over four visits among 9,203 subjects from ARIC cohort free from MetSyn at visit 1.

| BMI category* | All subjects | Normal | Overweight | Obese | P interactiona |
|---------------|--------------|--------|------------|-------|----------------|
| Overweight (25.0–29.9 kg/m²) | 2.73 (2.49, 2.99) | — | — | — | — |
| Obese (≥30.0 kg/m²) | 4.53 (4.09, 5.01) | — | — | — | — |
| Weight change (vs. within 5% of visit 1 weight) | | | | | 0.006 |
| >5% Loss | 0.91 (0.74, 1.11) | 1.23 (0.92, 1.65) | 0.75 (0.54, 1.05) | 0.67 (0.41, 1.11) | — |
| >5% Gain | 1.21 (1.08, 1.35) | 1.61 (1.28, 2.02) | 1.24 (1.08, 1.43) | 1.01 (0.85, 1.20) | <0.005 |
| Age (years) | 1.02 (1.01, 1.03) | 1.05 (1.03, 1.06) | 1.02 (1.01, 1.03) | 1.00 (0.99, 1.01) | <0.005 |
| Female (vs. male) | 1.14 (1.06, 1.24) | 1.29 (1.10, 1.52) | 1.23 (1.11, 1.37) | 0.90 (0.78, 1.03) | 0.78 |
| African-American race (vs. white) | 0.92 (0.84, 1.01) | 0.86 (0.70, 1.11) | 0.95 (0.84, 1.08) | 0.90 (0.79, 1.04) | 0.20 |
| Education (vs. less than high school) | | | | | 0.70 |
| High school | 0.88 (0.80, 0.97) | 0.83 (0.67, 1.02) | 0.85 (0.74, 0.97) | 0.94 (0.80, 1.11) | — |
| College | 0.79 (0.72, 0.88) | 0.65 (0.53, 0.81) | 0.79 (0.69, 0.91) | 0.88 (0.75, 1.05) | — |
| Smoking (vs. never) | | | | | 0.06 |
| Former | 1.20 (1.11, 1.31) | 1.18 (0.98, 1.42) | 1.18 (1.05, 1.32) | 1.27 (1.09, 1.46) | — |
| Current | 1.29 (1.18, 1.42) | 1.38 (1.15, 1.66) | 1.27 (1.12, 1.45) | 1.23 (1.02, 1.47) | — |
| Drinking (vs. never/rare) | | | | | 0.02 |
| Former | 1.04 (0.94, 1.15) | 1.09 (0.88, 1.34) | 0.97 (0.84, 1.12) | 1.14 (0.96, 1.36) | — |
| Light | 0.87 (0.77, 0.98) | 0.76 (0.57, 1.00) | 0.84 (0.71, 0.99) | 1.03 (0.81, 1.29) | — |
| Medium | 0.86 (0.77, 0.96) | 0.78 (0.62, 0.97) | 0.79 (0.69, 0.92) | 1.13 (0.92, 1.39) | — |
| Heavy | 0.90 (0.80, 1.01) | 0.75 (0.59, 0.94) | 0.94 (0.81, 1.10) | 0.95 (0.75, 1.21) | — |
| Physical activity | | | | | — |
| Second tertile (2–2.75) | 1.02 (0.94, 1.11) | 1.03 (0.87, 1.23) | 0.97 (0.87, 1.09) | 1.07 (0.92, 1.24) | — |
| Third tertile (2.75–5) | 0.86 (0.79, 0.94) | 0.71 (0.58, 0.86) | 0.84 (0.75, 0.95) | 1.06 (0.90, 1.25) | — |
| Energy intake (per 100 kcal) | 1.00 (0.99, 1.00) | 1.00 (0.98, 1.01) | 1.00 (0.99, 1.00) | 1.00 (0.99, 1.01) | — |

Boldsface signifies significance at α = 0.05 level.

ARIC, Atherosclerosis Risk in Communities; MetSyn, metabolic syndrome.

*Hazard ratios calculated from model with BMI and variable interaction. P value from likelihood ratio test for interaction between BMI category and corresponding variable.
There has been a significant lack of study regarding the stability of the metabolically healthy OB condition, and particularly if the effects of factors associated with the transition from healthy to unhealthy obesity vary between OB and NW individuals (6). Two recent analyses, both in Asian populations, have reported that metabolically healthy OB individuals have a much greater risk of developing metabolic syndrome when compared to healthy NW subjects (7,8). In the smaller of the two studies, which included 1,547 Taiwanese men and women, increased rates of MetSyn were observed with greater BMI, with a greater than 24-fold rate of metabolic syndrome among those with BMI 27 or greater, compared to <23 (8). Chang et al. reported that in a population of Korean men the rate of development of MetSyn was 68% greater among those with BMI >25 compared to those with BMI between 18.5 and 22.9; when limited to weight-stable subjects the rate of MetSyn in this BMI group increased to more than five times the rate in the lower BMI category. Notably, both the Taiwanese and Korean studies included younger subjects than were in our cohort (18-59 years and 30-59 years, respectively) and both had less follow-up (average 5.4 and 5.1 years, respectively). Our findings, which are the first to be reported in a racially diverse sample of men and women, are in agreement with these previous works that indicate that obesity is a significant factor in the development of MetSyn. Furthermore, within the OB subgroup we observed a moderate, yet statistically insignificant inverse association of incident MetSyn with weight loss. However, previous work has suggested that weight loss among OB women achieved through caloric restriction may decrease insulin sensitivity among the metabolically healthy, while improving insulin sensitivity among those with impaired metabolism (26). This apparent discrepancy with our results may be due to differences in classification of metabolic health; however, this could have implications for clinical and public health interventions aimed at weight reduction. Our findings of a positive association with age, and an inverse association with alcohol intake that appears stronger among NW and overweight individuals is unique and should be explored in more depth in future analyses. The observation that smoking increased the risk of MetSyn across all body size groups is consistent with its hypothesized effect on blood pressure (27,28), lipids, and systemic inflammation. However, we did not note a difference in the effect of smoking across body size despite previous findings that may suggest otherwise (29). The inverse association between MetSyn and physical activity was similarly expected (30,31), particularly since a previous analysis in this population reported a favorable relationship between physical activity and lipid levels, specifically HDL and triglycerides, among all individuals (32). Yet the lack of association among OB individuals was somewhat surprising given the known beneficial effects of increased activity. However, it has recently been suggested that the amount of exercise needed to improve metabolic health may vary by specific risk factor (33). Therefore, since OB individuals, even those who fail to meet the classification of MetSyn, typically possess more of these factors than NW or overweight individuals, then the association with activity may be more evident in the latter two groups. Further investigations to identify individual characteristics associated with the transition from metabolically healthy to unhealthy obesity could identify which interventions would provide the greatest impact for this high-risk subgroup. Our analysis benefitted from repeated assessments of anthropometric and biologic measurements from a racially diverse community-based population of middle-aged men and women. A notable limitation of our study lies in the lack of a consistent definition for metabolic health. Here, we utilized the currently accepted definition of MetSyn (23); however, other studies examining metabolic subtypes of obesity have utilized alternative criteria, some of which include direct measures of insulin resistance (4,34,35), whereas others used schemes similar to the ATP-III definition (36,37,38,39), which vary considerably from study-to-study. Despite its limitations, we elected to focus our analysis on the ATP-III definition since it is straightforward in its application, relevant for both NW and overweight individuals, and is an established clinical standard. Finally, although the majority of the covariates examined here were objective measures, the use of questionnaires to assess physical activity and total energy intake have known disadvantages including recall bias and measurement error. However, the Baecke physical activity questionnaire used in this study has been reported to be accurate and reliable in this population (40), and food frequency questionnaires are useful for examining correlations based on ranking of individuals relative intake, as was performed in this analysis (13).

In conclusion, we found that metabolically healthy obesity may not be a stable condition, as body size was a significant factor associated with development of the cluster of cardiometabolic abnormalities among those considered here. Among the NW individual, lifestyle factors, specifically weight maintenance, physical activity, and moderate alcohol intake, appear to offer more protection against the development of this condition compared to those individuals of greater body size. These findings suggest that specific subsets of NW individuals may be more likely to develop this cluster of cardiometabolic abnormalities and they may benefit from lifestyle interventions, whereas OB subjects may benefit most from interventions related to attainment of a healthy body size. Additional efforts are needed to clarify the definition of metabolic health, particularly within apparently high-risk groups, which will improve our ability to identify factors to prevent or reverse the clustering of these conditions among all body size groups.

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