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Variations in Prevalent Cardiovascular Disease and Future Risk by Metabolic Syndrome Classification in the REasons for Geographic And Racial Differences in Stroke (REGARDS) Study

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Abstract

Background—The International Diabetes Federation (IDF) and Adult Treatment Panel (ATP) III define metabolic syndrome (MetSyn) differently, with unclear implications for cardiovascular disease (CVD) risk.

Methods—We examined 22,719 participants in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. We classified participants as: no MetSyn, MetSyn by ATP-III and IDF criteria, MetSyn by ATP-only, or MetSyn by IDF-only. To assess current CVD, we determined the odds of self-reported CVD by MetSyn category using multivariable logistic regression, controlling for socio-demographic and behavioral factors. To estimate future coronary heart disease (CHD) risk, we calculated Framingham risk scores (FRS).

Results—Overall, 10,785 individuals (47%) had MetSyn. Of these, 79% had MetSyn by both definitions, 6% by ATP-only, and 14% by IDF-only. Compared to those without MetSyn, ATP-only individuals had the highest odds of current CVD and of having a FRS >20%. **Also compared to those without MetSyn**, IDF-only individuals had 43% higher odds of current CVD and two-fold increased odds of having a FRS >20%.

Conclusions—Consistent with previous reports, ATP-III MetSyn criteria identified individuals with increased odds of CVD and elevated future CHD risk. However, the IDF definition identified a clinically important number of additional individuals at excess CVD risk.

Introduction

The metabolic syndrome (MetSyn) is highly prevalent in the United States (US) and associated with increased cardiovascular risk.[1–3] The National Cholesterol Education Program Adult Treatment Panel-III (ATP-III) criteria are the most widely utilized MetSyn criteria in the US.[4–5] The International Diabetes Federation (IDF) modified the ATP-III MetSyn classification

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by adopting ethnicity-specific cut-points for elevated waist circumference that are lower than those used by ATP-III and by requiring central obesity.6

While the IDF criteria identify more people as having MetSyn than ATP-III criteria,[7–13] it is unclear whether people identified by only IDF criteria are at increased cardiovascular disease (CVD) risk.[14–23] Some studies suggest that the relatively modest number of individuals identified as having MetSyn by IDF criteria alone have little or no increased CVD risk compared with individuals without MetSyn.[24–29] However, these studies were relatively small and conducted primarily in European and Asian populations and do not reflect the importance of the IDF criteria in the US population. Furthermore, Wang et al[30] concluded that among 6 different MetSyn definitions, the IDF definition best predicted incident stroke, suggesting that the IDF criteria do identify individuals at increased CVD risk.

To examine this issue in the US population, we compared the ATP-III and IDF MetSyn definitions in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study, a nationwide prospective cohort study of 30,228 individuals age 45 years and older, half African American, half female recruited between January 2003 and October 2007. We examine the association between ATP-III and IDF-defined MetSyn and prevalent CVD as well as estimated future coronary heart disease (CHD) risk using 10-year Framingham CHD risk scores (FRS).

Methods

REGARDS has been described previously.[31] The cohort, by design, is 42% African American, and 55% female. Because the primary goals of REGARDS are to elucidate regional and racial differences in stroke, the Stroke Belt, located in the southeastern US, was over-sampled such that 20% of the overall cohort was selected from the "buckle" of the Stroke Belt (the coastal plain region of North Carolina, South Carolina, and Georgia); 30% from the rest of the Stroke Belt (the remaining parts of North Carolina, South Carolina, and Georgia plus Alabama, Mississippi, Louisiana, Arkansas, and Tennessee); and 50% from the remaining 40 contiguous states. Individuals identified by commercially available lists were contacted by mail and telephone. Upon enrollment, individuals underwent a computer assisted telephone interview followed by an in-home examination. During the telephone interview, demographic and self-reported medical information was obtained. During the in-home examination, the participant's blood pressure was measured, an electrocardiogram was performed, and blood and urine samples were obtained.

As of June 2007, REGARDS had recruited 28,224 participants. Of these, we included the 22,719 participants (80%) with complete data for MetSyn components. Of the 5,505 individuals excluded from this analysis, 4,118 were excluded for not fasting at the time of phlebotomy or because their fasting status was unknown; 1,378 for missing data on a component of the MetSyn; and 9 for missing data on race or gender. Individuals excluded were of similar age (66 vs. 65 years) and gender (55% vs. 55% female) as those included. Individuals excluded were less likely to be from the stroke buckle (16%) than the stroke belt (21%) or non-belt (20%) and were more likely to be African American (23%) than white (17%).

Individuals meeting any 3 of the following criteria were classified as having ATP-III MetSyn: elevated waist circumference (>40 inches in men or >35 inches in women), hypertriglyceridemia (≥150 mg/dL), decreased high density lipoprotein-cholesterol (HDL-C) (<40 mg/dL in men or <50 mg/dL in women), elevated blood pressure (systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg, history of hypertension, or use of medications for elevated blood pressure), or hyperglycemia (fasting glucose ≥100 mg/dL, history of diabetes, or use of medications for diabetes). To meet IDF criteria, individuals had

to have an elevated waist circumference (≥37 inches in men or ≥31.5 inches in women) and 2 of the other 4 ATP-III criteria. Using these criteria, we classified participants into 1 of the following 4 groups: (1) no MetSyn, (2) MetSyn by both ATP-III and IDF criteria, (3) MetSyn by only ATP-III criteria, or (4) MetSyn by only IDF criteria.

We assessed the association between MetSyn classification and prevalent CVD among all 22,719 participants. CVD was defined as a self-reported history of any of the following: myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, stroke, transient ischemic attack, carotid endarterectomy, carotid stenting, or surgery for peripheral arterial disease or abdominal aortic aneurysm. We performed multivariable logistic regression to determine the odds of self-reported CVD for each of the MetSyn classifications, incrementally controlling for demographic variables (age, race, gender, and geographic region), education and income, and behavioral risk factors (smoking status, alcohol use, and physical activity). Because the MetSyn includes individuals with and without diabetes, we performed these analyses in all participants (including those with and without diabetes) and separately in those without diabetes.

In order to compare the estimated future CHD risk of participants in each of the 4 MetSyn classifications, we calculated 10-year FRS for CHD death or myocardial infarction.32 This risk calculator considers diabetes a risk factor for coronary artery disease, but not a risk equivalent as defined by ATP-III.[4] Therefore, we also calculated these FRS assuming that all diabetic participants had a FRS >20%. We then performed multivariable logistic regression to determine the odds of having a FRS >20% for each of the MetSyn classifications, controlling for demographic variables (age, race, gender, and geographic region), education and income, and behavioral risk factors (smoking status, alcohol use, and physical activity). We chose to perform separate models with and without adjustment for age and smoking as they are part of the FRS but not part of the MetSyn definition. This allowed us to assess the impact that MetSyn components have on the FRS. For this portion of the analysis, we excluded the 3,102 participants with a self-reported history of CHD (myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft surgery) and an additional 1,884 participants with evidence of myocardial infarction on their enrollment electrocardiogram who did not report a history of CHD. An additional 63 participants were missing data on other components of the FRS. Therefore, of the 22,719 participants, a total of 17,670 (78%) were included in these models.

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Results

Of the 22,719 participants, 10,785 (47%) met at least one definition for MetSyn. Of these, 8,571 (79%) had MetSyn by both criteria, 686 (6%) by only ATP-III criteria, and 1,528 (14%) by only IDF criteria. Participant characteristics are listed in Table 1. Compared with those meeting only ATP-III MetSyn criteria, individuals meeting only IDF criteria were more often African American, female, slightly better educated, and fewer smoked. Despite being more obese, they had lower overall mean values for fasting glucose and triglycerides, higher mean values for HDL-C, and similar mean values for blood pressure. As a result, fewer individuals

meeting only IDF criteria had low HDL-C, high triglycerides, elevated blood pressure, or hyperglycemia than those meeting ATP-III criteria (Table 1).

Overall, 22% of participants reported a history of CVD, but this varied significantly by MetSyn classification. Only 17% of participants meeting no criteria for MetSyn reported a history of CVD; whereas, 32% of those meeting only ATP-III criteria, 27% of those meeting both ATP-III and IDF criteria, and 25% of those meeting only IDF criteria reported a history of CVD. **Compared to those without MetSyn**, individuals with MetSyn by any criteria had higher odds of self-reported CVD (adjusted odds ratio [AOR] 1.74 for both ATP-III and IDF, 1.68 for ATP-III-only, and 1.43 for IDF-only, Table 2), after adjusting for socio-demographic and behavioral risk factors. Among non-diabetic participants, individuals with MetSyn by any definition had significantly increased odds of prevalent CVD **compared to those without MetSyn**, although the magnitude was less than among all participants (including diabetics and non-diabetics), with a similar trend across the different MetSyn classifications (Table 2).

We were also interested in whether individuals meeting ATP-III MetSyn criteria had greater odds of self-reported CVD than those identified by the IDF but not the ATP-III criteria. Compared to those meeting only IDF criteria, individuals meeting ATP-III criteria had significantly increased odds of self-reported CVD (AOR 1.22, 95% confidence interval [CI] 1.06–1.40), after adjusting for socio-demographic and behavioral risk factors. When restricting the analysis to only non-diabetic participants, those meeting ATP-III criteria had lower and not significantly increased odds of prevalent CVD than those meeting only IDF criteria (AOR 1.12, 95% CI 0.95–1.32).

Next, we estimated elevated future CHD risk by calculating FRS in those without prevalent CHD (Table 3). Individuals meeting only ATP-III MetSyn criteria had the largest proportion, with 34% having a FRS >20%. However, individuals meeting only IDF criteria, albeit having a lower proportion (13%) than those meeting ATP-III criteria, were twice as likely as those without MetSyn to have a FRS >20%. This pattern persisted when the analysis was restricted to only non-diabetic participants or when all diabetic participants were assumed to have a FRS >20% (Table 3). **Compared to those without MetSyn**, individuals with MetSyn by any criteria had higher odds of a FRS >20% (AOR 7.34 for both ATP-III and IDF, AOR 7.48 for ATP-III-only, and AOR 2.29 for IDF-only), after adjusting for socio-demographic and behavioral risk factors. Among non-diabetic participants, individuals with MetSyn **by any criteria** had significantly increased odds of having a FRS >20% **compared to those without MetSyn**, with a similar trend across the different MetSyn classifications. This trend was also similar when diabetic participants were assumed to have a FRS >20%, although the overall magnitude of the association was greater (Table 3). Additional multivariable models were performed without adjusting for age and smoking with similar results (data not shown).

Discussion

In this nationwide, community-based cohort of African American and White participants, individuals meeting ATP-III MetSyn criteria had the greatest prevalence of CVD and the largest proportion of individuals with elevated future CHD risk. Although less than those meeting ATPIII criteria, individuals meeting only IDF criteria had a 43% increased odds of prevalent CVD and a two-fold increased odds of having elevated future CHD risk compared with individuals without MetSyn. This suggests that in the US, the IDF criteria do identify additional individuals not identified by ATP-III criteria who are at increased risk for prevalent CVD and future cardiovascular events.

Many investigators have reported that the IDF criteria identify more individuals as having MetSyn, but that these individuals had similar cardiovascular risk as those with MetSyn by

ATP-III criteria.[7–23] These studies did not analyze individuals with only IDF MetSyn as a separate group as we have in this analysis. Given that the IDF and ATP-III MetSyn criteria similarly classify most people, it is not surprising that the IDF criteria, overall, did not add much predictive value to the ATP-III criteria in these studies.

In European and Asian populations, individuals meeting only IDF but not ATP-III MetSyn criteria have not demonstrated increased CVD risk compared with individuals without MetSyn. Athyros and others report that among 9,669 Greek adults, individuals meeting only IDF MetSyn criteria did not have an increased prevalence of CVD (10.5%) as compared to the study population as a whole (11.4%).[24] In a cohort of 7,152 German men, Assman et al found that only 5.5% of individuals meeting only IDF MetSyn criteria developed CHD over 10 years of follow-up as compared to 3.4% of individuals without MetSyn (*P*=NS).[25] Tong and associates report that among 4,350 Chinese individuals with diabetes mellitus, the incidence of CHD over a median follow-up of 7.1 years was 3.3 per 1,000 person-years (95% CI 1.2–5.3) in individuals meeting only IDF MetSyn criteria and 4.1 per 1,000 person-years (95% CI 2.8–5.3) in individuals without MetSyn.[26] Monami et al indicate that 3-year survival among **Italians** with only IDF-defined MetSyn (91.8%) was not statistically different than individuals without MetSyn (93.7%).[27] Saely and others report that among 750 **Austrians** referred for coronary angiography, those meeting only IDF MetSyn criteria had no difference in survival free of cardiovascular events than those without MetSyn after a mean follow-up of 3.9 years.[28]

Unlike these previous studies in predominantly European and Asian populations, our findings from a large, **community-based, nationwide** US cohort with large numbers of African Americans indicate that individuals identified as having MetSyn by IDF but not ATP-III criteria have increased odds for prevalent CVD and elevated future CHD risk compared to individuals without MetSyn. These individuals represent a clinically important number of **Americans**, since 14% of individuals in our study identified as having MetSyn only met IDF criteria. Previous smaller **non-US** cohorts were likely unable to assess the true cardiovascular risk of these individuals.

Our findings have important clinical implications. Cardiovascular risk increases prior to the clinical diagnosis of diabetes, and individuals with MetSyn who do not yet have diabetes are at increased CVD risk.[2,33–35] In our analysis, even non-diabetic individuals meeting only IDF MetSyn criteria had significantly increased odds for both prevalent CVD and high risk of future CHD compared to those without MetSyn. These findings suggest that there may be a continuum of risk with those without MetSyn being at lowest risk, those meeting only IDF criteria at higher risk, and those meeting ATP-III criteria at highest risk. Individuals meeting only IDF MetSyn criteria have a lower prevalence of traditional cardiovascular risk factors such as hyperglycemia, elevated blood pressure, and dyslipidemia than individuals meeting ATP-III MetSyn criteria. IDF-only individuals were less obese than those meeting both ATP-III and IDF MetSyn criteria, but more obese than those without MetSyn. Therapeutic lifestyle changes, which modify the MetSyn,[36–40] may be more important than pharmacologic interventions in these patients. However, individuals with MetSyn by only ATP-III criteria tended to be leaner and have more traditional cardiovascular risk factors and higher smoking rates; they might require more intensive pharmacologic intervention to modify cardiovascular risk.

Our analysis has a number of limitations. First, because it is cross-sectional, we are unable to definitively assess the ability of the different MetSyn classifications to predict future cardiovascular events and had to rely upon the FRS to estimate future cardiovascular risk. Although, this tool has been validated in African American populations.[41] Second, we lack detailed knowledge about why patients were taking cholesterol-lowering medications. Therefore, we were not able to include the use of medications for the treatment of hypertriglyceridemia or low HDL-C as criteria for those respective MetSyn components.

However, most patients taking cholesterol-lowering medications receive statins to treat elevated low density lipoprotein-cholesterol, thus this limitation likely had a minimal impact on the results. Third, REGARDS only enrolled African American and White **US** participants, limiting generalizability to other ethnic/racial groups **within the US and in other regions of the world**.

Our study indicates important differences between the ATP-III and IDF MetSyn criteria in the US. Those meeting only ATP-III criteria are an especially high risk, clinically distinct group appropriate for aggressive targeting. Contrary to previous reports, our findings suggest that in the US, the IDF MetSyn criteria identify a clinically important number of individuals at increased cardiovascular risk who may benefit from risk factor modification.

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Table 1

Participant Characteristics by Metabolic Syndrome Classification in the REasons for Geographic And Racial Differences in Stroke (REGARDS) Study.

	Neither (n=11,934)	Both (n=8,571)	ATP-Only (n=686)	IDF-Only (n=1,528)
Age (years)	65.0±9.7	65.1±8.9	66.5±9.3	66.3±9.2
Female	54%	60%	28%	44%
African American	38%	46%	33%	39%
Region				
Non-Stroke Belt	46%	42%	39%	44%
Stroke Belt	35%	37%	39%	37%
Stroke Buckle	20%	21%	22%	19%
Education				
Less than high school	10%	15%	11%	12%
High school graduate	25%	29%	29%	26%
Some College	26%	28%	29%	26%
College or postgraduate	39%	28%	30%	36%
Smoking Status				
Never	47%	44%	34%	42%
Past	39%	42%	44%	43%
Current	14%	15%	22%	15%
Alcohol Use				
Never	27%	35%	26%	26%
Past	16%	21%	20%	18%
Current	58%	44%	53%	56%
Physical Activity (days/week)				
0	30%	41%	32%	31%
1–4	45%	41%	41%	44%
5–7	25%	18%	27%	25%
Body Mass Index (kg/m^2)				
Men	26.5±4.2	32.3±4.8	25.9±2.8	27.9±2.7
Women	27.3±6.1	33.6±6.6	24.5±3.9	26.8±3.6
Waist Circumference (inches)				
Men	37.1±4.5	43.9±4.9	35.3±1.7	38.8±0.9
Women	33.6±5.7	40.6±5.5	29.5±1.7	33.1±0.9
Lipid Profile				
Total Cholesterol (mg/dL)	195±38	191±43	190±43	189±42
HDL-C (mg/dL)	59±16	45±13	39±11	49±14
Triglycerides (mg/dL)	100±50	167±105	207±110	131±78
LDL-C (mg/dL)	116±34	114±36	111±38	113±35
Blood Pressure				
Systolic (mmHg)	124±16	133±17	131±16	129±17
Diastolic (mmHg)	75±9	79±10	77±10	77±9
Diabetes	5%	40%	31%	21%

	Neither (n=11,934)	Both (n=8,571)	ATP-Only (n=686)	IDF-Only (n=1,528)
Fasting Glucose (mg/dL)	92±18	117±41	115±45	103±29
Individual MetSyn Components				
ATP Waist Circumference	29%	88%	0%	0%
IDF Waist Circumference	50%	100%	0%	100%
Low HDL-C	12%	63%	83%	41%
Hypertriglyceridemia	8%	49%	77%	29%
Elevated Blood Pressure	50%	89%	91%	81%
Hyperglycemia	13%	72%	73%	49%

Values expressed as mean±standard deviation or %.

ATP, Adult Treatment Panel; HDL-C, high density lipoprotein-cholesterol; IDF, International Diabetes Federation; LDL-C, low density lipoprotein-cholesterol; MetSyn, Metabolic Syndrome.

Table 2

Odds of Prevalent Cardiovascular Disease* by Metabolic Syndrome Classification in the REasons for Geographic And Racial Differences in Stroke (REGARDS) Study.

	Model 1† OR (95% CI)	Model 2‡ OR (95% CI)	Model 3§ OR (95% CI)	Model 4□ OR (95% CI)
All Participants (n=22,719)				
No MetSyn	Referent	Referent	Referent	Referent
MetSyn by IDF-Only	1.57 (1.39, 1.78)	1.43 (1.26, 1.63)	1.44 (1.25, 1.65)	1.43 (1.24, 1.64)
MetSyn by Both	1.76 (1.64, 1.88)	1.90 (1.77, 2.04)	1.80 (1.67, 1.94)	1.74 (1.61, 1.88)
MetSyn by ATP-Only	2.22 (1.88, 2.63)	1.89 (1.59, 2.25)	1.71 (1.42, 2.06)	1.68 (1.39, 2.03)
Non-Diabetic Participants (n=18,156)				
No MetSyn	Referent	Referent	Referent	Referent
MetSyn by IDF-Only	1.39 (1.21, 1.61)	1.27 (1.10, 1.48)	1.28 (1.09, 1.51)	1.28 (1.09, 1.51)
MetSyn by Both	1.41 (1.30, 1.53)	1.53 (1.40, 1.66)	1.47 (1.35, 1.61)	1.44 (1.32, 1.59)
MetSyn by ATP-Only	1.84 (1.50, 2.27)	1.57 (1.27, 1.95)	1.38 (1.09, 1.74)	1.35 (1.06, 1.71)

ATP, Adult Treatment Panel; CI, Confidence Interval; IDF, International Diabetes Federation; MetSyn, Metabolic Syndrome; OR, Odds Ratio.

*Prevalent cardiovascular disease defined as a self-reported history of any of the following: myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, stroke, transient ischemic attack, carotid endarterectomy, carotid stenting, or surgery for peripheral arterial disease or abdominal aortic aneurysm.

†Model 1: crude odds ratio for metabolic syndrome category

‡Model 2: model 1 plus age, race, gender, and geography

§Model 3: model 2 plus education and income

□Model 4: model 3 plus smoking status, alcohol use, physical activity

Table 3

Proportion of Participants and Odds of Having a 10-Year Framingham Risk Score for CHD Death or Myocardial Infarction >20% by Metabolic Syndrome Classification in those Free of CHD* in the REasons for Geographic And Racial Differences in Stroke (REGARDS) Study.

	Number free of Baseline CHD	FRS >20%		
		N	%	OR (95% CI)§
All Participants				
Using Diabetes as a CAD Risk Factor †				
No MetSyn	9,665	571	6	Referent
MetSyn by IDF-Only	1,163	151	13	2.29 (1.81, 2.88)
MetSyn by Both	6,347	1,301	21	7.34 (6.39, 8.44)
MetSyn by ATP-Only	495	167	34	7.48 (5.75, 9.73)
Using Diabetes as a CAD Risk Equivalent ‡				
No MetSyn	9,665	918	9	Referent
MetSyn by IDF-Only	1,163	326	28	4.64 (3.84, 5.59)
MetSyn by Both	6,347	2,868	45	15.37 (13.66, 17.30)
MetSyn by ATP-Only	495	224	45	11.58 (8.74, 15.34)
Non-Diabetic Participants				
No MeSyn	9,240	493	5	Referent
MetSyn by IDF-Only	935	98	10	2.17 (1.63, 2.89)
MetSyn by Both	3,976	497	13	4.79 (4.01, 5.72)
MetSyn by ATP-Only	358	87	24	5.40 (3.83, 7.62)

ATP, Adult Treatment Panel; CAD, Coronary Artery Disease; CHD, Coronary Heart Disease; CI, Confidence Interval; FRS, Framingham Risk Score; IDF, International Diabetes Federation; MetSyn, Metabolic Syndrome; OR, Odds Ratio.

* Individuals were considered to be free of CHD if they did not have a self-reported history of CHD (myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft surgery) or evidence of myocardial infarction on their enrollment electrocardiogram.

† For this analysis, we calculated 10-Year Framingham Risk Scores for CHD death or myocardial infarction using diabetes as a risk factor for CAD as published by Wilson et al.[32]

‡ For this analysis, we considered diabetes to be a CAD risk equivalent as recommended by ATP III[4], and assumed that all diabetics had a 10-Year Framingham Risk for CHD death or myocardial infarction of >20%.

§ Adjusted for age, gender, race, geography, education, income, smoking status, alcohol use, and physical activity.