Global Coronary Heart Disease Risk Assessment of Individuals With the Metabolic Syndrome in the U.S.

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OBJECTIVE — Although metabolic syndrome is related to an increased risk of coronary heart disease (CHD) events, individuals with metabolic syndrome encompass a wide range of CHD risk levels. This study describes the distribution of 10-year CHD risk among U.S. adults with metabolic syndrome.

RESEARCH DESIGN AND METHODS — Metabolic syndrome was defined by the modified National Cholesterol Education Program (NCEP)/Third Adult Treatment Panel (ATP III) definition among 4,293 U.S. adults aged 20–79 years in the National Health and Nutrition Examination Survey 2003–2004. Low-, moderate-, moderately high–, and high-risk statuses were defined as <6, 6 to <10, 10–20, and >20% probability of CHD in 10 years (based on NCEP/ATP III Framingham risk score algorithms), respectively; those with diabetes or preexisting cardiovascular disease were assigned to high-risk status.

RESULTS — The weighted prevalence of metabolic syndrome by NCEP criteria in our study was 29.0% overall (30.0% in men and 27.9% in women, $P = 0.28$): 38.5% (30.7% men and 46.9% women) were classified as low risk, 8.5% (7.9% men and 9.1% women) were classified as moderate risk, 15.8% (23.4% men and 7.6% women) were classified as moderately high risk, and 37.3% (38.0% men and 36.5% women) were classified as high risk. The proportion at high risk increased with age but was similar among Hispanics, non-Hispanic whites, and non-Hispanic blacks.

CONCLUSIONS — Although many subjects with metabolic syndrome have a low calculated risk for CHD, about half have a moderately high or high risk, reinforcing the need for global risk assessment in individuals with metabolic syndrome to appropriately target intensity of treatment for underlying CHD risk factors.

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The metabolic syndrome is a cluster of risk factors often linked to insulin resistance that has been shown to increase the risk for development of cardiovascular disease (CVD). Individuals with metabolic syndrome have an increased risk of coronary heart disease (CHD) and CVD mortality (1,2). Global risk assessment using Framingham risk prediction algorithms is often the initial evaluation of CHD risk in subjects with multiple risk factors, including those with metabolic syndrome (3). Although it is often assumed that individuals with metabolic syndrome have a high risk of CVD, many have only borderline elevations in risk factors and thus may actually have either a low or intermediate risk of CVD (4). Therefore, assessment of global risk of CHD in individuals with metabolic syndrome may be helpful to most appropriately target the intensity of cardiometabolic risk factor interventions for prevention of diabetes or cardiovascular disease.

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The aim of this article was to calculate the global risk of CHD in adults with metabolic syndrome in the U.S. to better characterize the diversity in their risk of CHD using the data from the National Health and Nutrition Examination Survey (NHANES) 2003–2004. In addition, we will examine the global risk of CHD in individuals with metabolic syndrome across sex, ethnicity, and age-groups and examine goal attainment and distance to recommended levels for key CHD risk factors.

RESEARCH DESIGN AND METHODS

— Among 4,293 adults aged 20–79 years in the NHANES 2003–2004, 3,034 had complete risk factor data allowing calculation of 10-year risk of a "hard " CHD event (nonfatal myocardial infarction or CHD death) according to National Cholesterol Education Program (NCEP)/Third Adult Treatment Panel (ATP III) Framingham risk score criteria (5). We defined metabolic syndrome by the modified NCEP definition if ≥3 of the following were present: *1*) waist circumference ≥102 cm for men or ≥88 cm for women, *2*) triglyceride level ≥1.69 mmol/l (150 mg/dl) if fasting, *3*) HDL cholesterol level ≤1.04 mmol/l (40 mg/dl) if male or ≤1.29 mmol/l (50 mg/dl) if female, *4*) blood pressure ≥130/85 mmHg or receiving antihypertensive treatment, and *5*) fasting glucose level ≥5.6 mmol/l (100 mg/dl) or receiving drug treatment for elevated glucose. Participants were classified as not having metabolic syndrome after confirming the absence of at least three metabolic syndrome risk factors. We also conducted similar analyses among individuals identified with metabolic syndrome by the International Diabetes Federation criteria requiring increased waist circumference as defined above plus ≥2 of the other criteria (based on the same cut points as shown above, except for a lower waist circumference cut point for Hispanics of ≥80 cm for women and ≥90 cm for men as recommended by the International Diabetes Federation for individuals of Central or South American ancestry) (6). Diabetes was defined as having a fasting

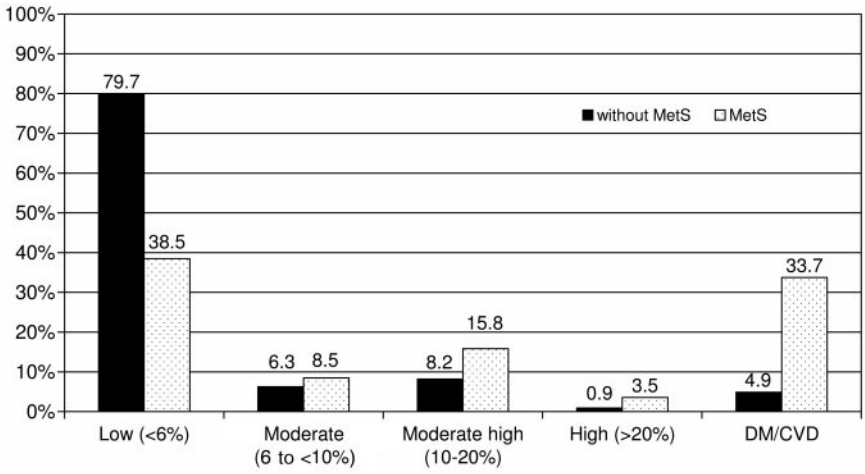

Figure 1—*Proportion of individuals with and without metabolic syndrome (MetS) classified by 10-year CHD risk group: low- (<6%), moderate- (6 to <10%), moderately high– (10–20%), and high- (>20% or diabetes [DM]/CVD) risk groups.* $P < 0.001$ *comparing distribution of risk groups between those with versus without metabolic syndrome.*

glucose level ≥6.99 mmol/l (126 mg/dl) after a 12-h fast, a nonfasting glucose level of ≥11.1 mmol/l (200 mg/dl), use of oral hypoglycemic agents or insulin, or self-reported diagnosis of diabetes. We examined the proportion of individuals with and without metabolic syndrome among each risk group that had a low (<6%), moderate (6 to <10%), moderately high (10–20%), or high (>20%) 10-year probability for CHD on the basis of the Framingham risk algorithm (5) and classified according to the American Heart Association (AHA)/National Heart, Lung, and Blood Institute (NHLBI) scientific statement on metabolic syndrome (3), which defines moderately high risk as a 10–20% and high risk as a >20% 10-year probability of CHD. Whereas this statement also defined moderate risk as <10% with ≥2 risk factors present, "intermediate" risk has been suggested previously to be a CHD risk of 0.6–2.0% per year (7), so we have therefore defined moderate risk as 6 to 10% and low risk as <6% risk in 10 years for the purposes of this article. Individuals with preexisting diabetes (as defined above) or self-reported CVD (including heart attack, heart failure, or stroke) were assigned to the high-risk group. We stratified our analyses by age-group, sex, and ethnicity.

We also examined the percentage of subjects with metabolic syndrome with measurements that were not at the recommended levels for HDL cholesterol, triglycerides, systolic blood pressure, diastolic blood pressure, fasting glucose, and LDL cholesterol. Mean distances from recommended levels for each of these risk factors were calculated among all those not at goal. Distance from goal was calculated as the difference between the actual levels and recommended goal. Goals for blood pressure were <140/90 mmHg or <130/80 mmHg if diabetes or chronic kidney disease was present. The LDL cholesterol goal for those with a low risk was <160 mg/dl, for those with a moderate to moderately high risk (6–20%) it was <130 mg/dl, and for those with a high risk (>20%, diabetes, or CVD) it was <100 mg/dl. Goals for fasting glucose were <100 mg/dl, for HDL cholesterol were ≥40 mg/dl (men) and ≥50 mg/dl (women), and for triglycerides were <150 mg/dl, on the basis of revised AHA/NHLBI metabolic syndrome recommendations (5).

LDL cholesterol was calculated using the Friedewald equation (LDL cholesterol = total cholesterol − HDL cholesterol − ⅕ triglycerides) if triglycerides were <400 mg/dl. HDL cholesterol levels were measured by a precipitation method using a heparin-manganese chloride mixture on a Hitachi 704 analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN). Total cholesterol and triglycerides were measured enzymatically after hydrolyzation to glycerol on a Hitachi 704 analyzer. Glycohemoglobin was measured using a glycohemoglobin analyzer. Blood pressure was measured using a mercury sphygmomanometer and taking the average of four readings. Detailed specimen and data collection are discussed in the *NHANES Laboratory/Medical Technologists Procedures Manual* (8).

Cross-tabulation procedures with SUDAAN software were used for population-weighted percentages. The χ^2 test of proportions and ANOVA tests for comparing means were used to compare the extent of positive risk factors for each parameter by sex and ethnicity. SAS statistical software (version 9.1.3; SAS Institute, Cary, NC) as well as SUDAAN statistical software (version 9.0.1; Research Triangle Institute, Research Triangle Park, NC) were used for analysis and computation of weighted estimates for projection to the U.S. population in 2003–2004.

RESULTS

10-year global risk of individuals with metabolic syndrome

The 2003–2004 NHANES weighted prevalence of metabolic syndrome as defined by the AHA/NHLBI modified NCEP/ATP III definition was 29.0% (the unweighted prevalence was 32.0%, based on 971 of 3,034 subjects being classified with metabolic syndrome). Among those with metabolic syndrome, 38.5% had a calculated 10-year risk for CHD of <6% (low), 8.5% had a 10-year CHD risk of 6 to <10% (moderate), 15.8% had a 10-year CHD risk of 10–20% (moderately high), and 3.5% had a 10-year CHD risk of >20% (high). The remaining 33.7% of subjects with metabolic syndrome had diabetes and/or CVD, which would put them in the highest risk category. This contrasts with those without metabolic syndrome, of whom a significantly higher proportion had a low risk (79.7%) and lower proportions had a moderate (6.3%), moderately high (8.2%), or high risk (0.9%) or had diabetes and/or CVD (4.9%) ($P < 0.001$) (Fig. 1). Logistic regression shows that the odds of being categorized as having a high risk in those subjects with metabolic syndrome is 9.68 (95% CI 7.53–12.45), unadjusted, and after age adjustment, although this risk is attenuated, it remains highly significant: odds 6.05 (4.61–7.93).

Although a similar proportion of male versus female subjects with metabolic syndrome were categorized as having a high CHD risk (>20% 10-year risk of CHD, diabetes, and/or CVD) (38.0 vs. 36.5%), 23.4% of men but only 7.6% of women were classified as having a moderately high risk ($P < 0.001$ between men and women across risk categories). There were, however, no significant differences in CHD risk distribution when different ethnic groups were compared (Fig. 2),

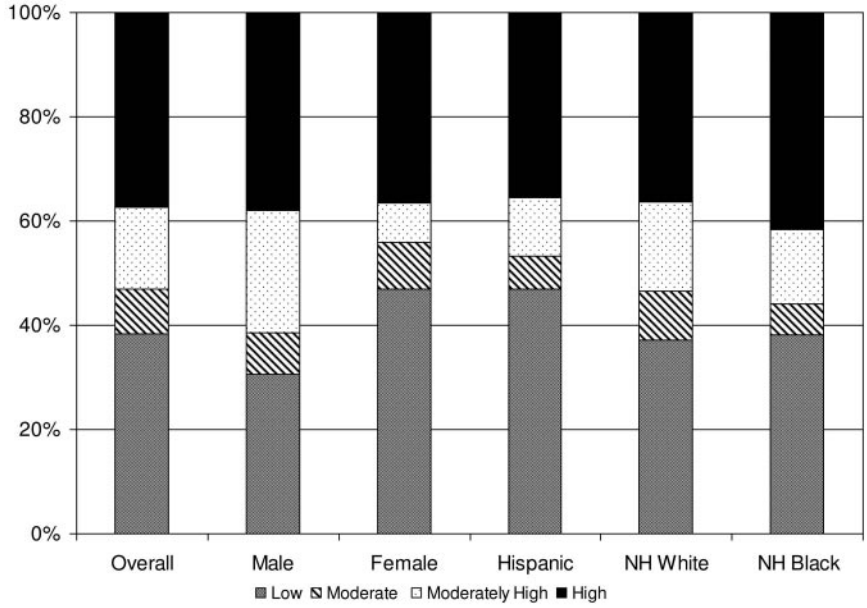

Figure 2—*Distribution of 10-year estimated risk for CHD: low- (<6%), moderate- (6 to <10%), moderately high– (10–20%), and high- (>20% or diabetes or CVD) risk individuals with metabolic syndrome stratified by sex and race.* P < *0.001 comparing distribution of risk groups between men and women. NH, non-Hispanic.*

with the proportions at high risk among Hispanics, non-Hispanic whites, and non-Hispanic blacks being 35.6, 36.3, and 41.6%, respectively ($P = 0.27$). Among individuals with metabolic syndrome, from logistic regression analyses both unadjusted and age adjusted, there were no significant differences in the likelihood of high-risk status by sex or ethnicity (results not shown). Across age-groups, the proportion of individuals with metabolic syndrome at high risk (>20% 10-year risk or diabetes/CVD) increased dramatically with age from 4.4% in those aged 20–29 years to 75.8% in those aged 70–79 years among men and 17.1% to 55.0%, respectively, among women ($P < 0.001$ when risk category distributions by age for both men and women were compared) (Fig. 3).

A very similar risk distribution was calculated for subjects with metabolic syndrome identified under the International Diabetes Federation criteria, for whom an overall weighted prevalence of 26.8% (unweighted prevalence 29.0%) for metabolic syndrome was obtained. Of these subjects, 39.6% had a low risk, 8.5% had a moderate risk, 15.5% had a moderately high risk, and 3.4% had a high risk, and 33.2% had diabetes or CVD when the International Federation criteria for metabolic syndrome were used. By sex, 37.1% of men and 35.9% of women, and by ethnicity, 34.3% of Hispanics, 35.6% of non-Hispanic whites, and 40.7% of non-Hispanic blacks ($P < 0.001$ across sex) were defined as having a high risk, including CVD or diabetes, comparable to the proportions obtained using the NCEP definition above.

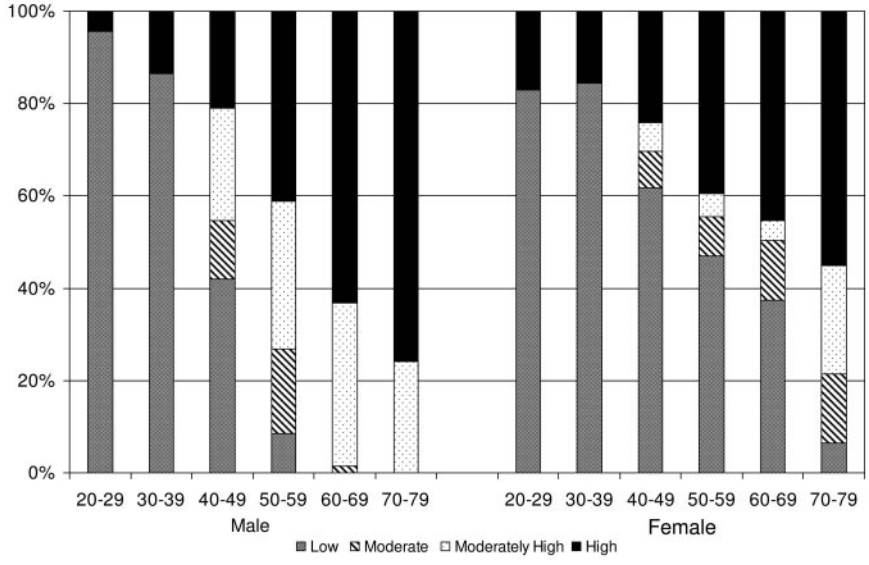

Figure 3—*Distribution of 10-year estimated risk for CHD by age-group stratified by sex: low (<6%), moderate (6 to <10%), moderately high (10–20%), and high (>20% or diabetes or CVD).* P < *0.001 comparing distribution of risk groups across age-groups for both men and women.*

Prevalence of metabolic syndrome risk factors

Among individuals with metabolic syndrome (classified by the NCEP ATP III definition), the most common risk factor components were increased waist circumference (93.4% of subjects with metabolic syndrome) followed by elevated triglycerides (64.6% of subjects with metabolic syndrome). Elevated LDL cholesterol, although among the least common of the associated risk factors, was still present in 40.2% of subjects with metabolic syndrome. When subjects with metabolic syndrome and with diabetes were compared with those without diabetes, those with diabetes showed a trend toward a lower prevalence of abnormal HDL (50.1% vs. 62.8% in those subjects with metabolic syndrome without diabetes) and triglycerides (59.3% vs. 65.9%).

Mean levels, proportion not at goal, and distance from goal of selected risk factors in subjects with metabolic syndrome

Mean levels of CVD risk factors for subjects with and without metabolic syndrome are shown in Table 1. Of all individuals with metabolic syndrome, 34.4% had systolic blood pressure not at recommended levels, whereas 17.9% had diastolic blood pressure above the recommended levels. Of those not at goal for blood pressure, mean blood pressures were 151 mmHg for systolic and 91 mmHg for diastolic, with an average distance from goal of 16 mmHg for systolic and 5 mmHg for diastolic blood pressure. Of all individuals with metabolic syndrome, 40.2% had LDL cholesterol that was not controlled to recommended lev-

Table 1—*Mean and distance to goal or recommended levels of cardiovascular risk factors in persons with and without metabolic syndrome*

	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Triglycerides (mg/dl)	Waist circumference (cm)	HDL cholesterol (mg/dl)	Fasting glucose (mg/dl)	LDL cholesterol (mg/dl)
Overall mean (median)							
Metabolic syndrome	131 (132)*	75 (73)*	204 (171)*	M: 114 (110)* F: 106 (104)*	M: 40 (39)* F: 48 (46)*	108 (103)*	124 (122)*
Non-metabolic syndrome	117 (116)	70 (69)	101 (89)	M: 94 (94) F: 88 (87)	M: 52 (51) F: 64 (63)	88 (88)	117 (116)
Proportion not at goal or recommended levels							
Metabolic syndrome	34.4*	17.9*	64.6*	M: 90.1* F: 96.9*	M: 53.4* F: 68.1*	56.3*	40.2*
Non-metabolic syndrome	7.4	3.8	11.5	M: 19.9 F: 42.6	M: 10.2 F: 17.8	7.9	18.5
Mean (median) among subjects not at goal or recommended levels							
Metabolic syndrome	151 (149)	91 (91)	261 (205)	M: 116 (112)* F: 107 (105)*	M: 35 (36) F: 41 (42)†	123 (112)*	154 (150)
Non-metabolic syndrome	152 (149)	93 (92)	231 (201)	M: 111 (109) F: 101 (99)	M: 34 (33) F: 43 (44)	110 (104)	163 (161)
Mean (median) distance from goal among subjects not at goal or recommended levels							
Metabolic syndrome	16 (13)	5 (3)	111 (55)	M: 14 (10)* F: 19 (17)*	M: 5 (4) F: 9 (8)†	23 (12)*	37 (29)
Non–metabolic syndrome	14 (11)	5 (3)	81 (51)	M: 9 (7) F: 13 (11)	M: 6 (5) F: 7 (6)	10 (4)	29 (23)

For those with diabetes or chronic kidney disease goals or recommended levels for systolic/diastolic blood pressure are <140/90 or <130/80 mmHg, for triglycerides are <150 mg/dl, for waist circumference are <102 cm for men or <88 cm for women, for HDL cholesterol are ≥40 mg/dl for men and ≥50 mg/dl for women, for glucose are <100 mg/dl, and for LDL cholesterol are <100 mg/dl for CVD, diabetes, or high risk (>20% 10-year risk), <130 mg/dl for moderate risk (6–20% 10-year risk), and <160 mg/dl for low risk (<6% 10-year risk). *$P < 0.001$; †$P < 0.01$ compared with those without metabolic syndrome. M, male; F, female.

els, with a mean LDL cholesterol of 154 mg/dl (averaging 37 mg/dl from goal) in those not at goal. Overall, HDL cholesterol levels in 53.4% of men and 68.1% of women with metabolic syndrome were below recommended levels, and 56.3% were not at goal for fasting glucose, with these individuals averaging 23 mg/dl from goal. As expected, subjects without metabolic syndrome had significantly lower levels of all measures (significantly higher for HDL cholesterol), with significantly lower proportions not at goal or recommended levels (Table 1).

CONCLUSIONS — Whereas individuals with metabolic syndrome have a greater risk of CHD events compared with those without metabolic syndrome (1,2), the heterogeneity in CHD risk among individuals with metabolic syndrome has not been fully described. The present study is unique in describing the overall risk distribution of all individuals with metabolic syndrome and shows that a sizeable proportion of individuals with metabolic syndrome actually have a low global risk of CHD. However, more than one-third of adults with metabolic syndrome are in the high-risk group (the majority classified as such because of preexisting diabetes or CVD, and fewer subjects with multiple risk factors providing an estimated 10-year risk of CHD of >20%). Previous estimates of global risk in persons with metabolic syndrome (4) were based on an earlier NHANES survey (1988–1994) and included individuals aged 30–74 years without known diabetes or CVD; therefore, the full-spectrum of risk was not fully appreciated in that report. Moreover, our study is unique in showing the distance of metabolic syndrome and non-metabolic syndrome risk factors from recommended or goal levels and has shown that one-third of subjects with metabolic syndrome are not at recommended blood pressure levels, 40% are not at recommended LDL cholesterol goals, and more than half have above-normal levels of triglycerides and glucose and below-normal levels of HDL cholesterol. Such information may be of use to clinicians in deciding how they should approach risk assessment in individuals with metabolic syndrome, as well as how aggressively to treat it.

There are several limitations to our study. First, although the NCEP/ATP III risk algorithm used in this study incorporated many criteria found in the Framingham coronary disease prediction

algorithm, it did not include triglycerides and obesity, which could potentially affect risk estimation in subjects with metabolic syndrome in the multiethnic U.S. population, even though these factors did not add to prediction of CHD in the original Framingham cohort of primarily Caucasian subjects. Although the Framingham risk equation has been validated in some ethnic populations in previous reports (9), it may or may not be fully applicable for multiethnic populations such as those in the most recent NHANES 2003–2004 survey. Our analysis did not show estimated CHD risk to differ by ethnicity among individuals with metabolic syndrome. Populations such as Hispanics have lower CHD rates (10), so it is also possible we may have overestimated risk in our subset of Hispanics. Conversely, despite blacks having poorer CVD outcomes, our analysis did not identify estimated CHD risk to be significantly greater among blacks with metabolic syndrome. Certain factors that may relate to poorer outcomes in blacks (e.g., left ventricular hypertrophy), which are part of neither the metabolic syndrome definition nor the Framingham risk algorithms used, may help explain this result. Second, the NCEP/ATP III algorithm does not take into account family history of premature CHD or new markers (e.g., C-reactive protein) or subclinical measures of CHD, which may be more common in subjects with metabolic syndrome, thereby potentially underestimating risk in certain individuals. For example, it has been shown that within a given calculated risk strata (e.g., 10–20% CHD risk), actual CHD event risk varied severalfold according to level of coronary calcium score (11). In addition, as information on CVD was based on self-report, it is possible that these numbers could be underestimated, which would result in a lower overall risk of CHD than may actually be the case. Finally, this study only addresses 10-year risk for CHD; lifetime CHD risk is substantially greater and may be a more relevant end point for the purposes of targeting therapy (12).

In summary, a wide spectrum of estimated risk of CHD exists in U.S. adults with metabolic syndrome; about one-third of those with metabolic syndrome have a high risk of CHD (either due to preexisting CHD, diabetes, or >20% calculated risk of CHD), and approximately one-half have a ≥10% risk for CHD. These proportions are significantly higher in individuals with versus without metabolic syndrome. Specifically, more than one-third of men with metabolic syndrome are of high-risk status. Finally, many individuals with metabolic syndrome have measurements that remain a significant distance from recommended or normal levels of lipids, blood pressure, and/or glucose. These findings highlight the importance of global risk assessment in individuals with metabolic syndrome to appropriately intensify treatment of their cardiometabolic risk factors.

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