MAYO CLINIC

ORIGINAL ARTICLE

Cardiorespiratory Fitness Is Inversely Associated With Clustering of Metabolic Syndrome Risk Factors: The Ball State Adult Fitness Program Longitudinal Lifestyle Study

Elizabeth Kelley, MS; Mary T. Imboden, MS; Matthew P. Harber, PhD; Holmes Finch, PhD, PStat; Leonard A. Kaminsky, PhD; and Mitchell H. Whaley, PhD

Abstract

Objective: The focus of this study was the association between the metabolic syndrome (MetSyn) and cardiorespiratory fitness (CRF) defined as maximal oxygen uptake (VO_{2max}). Although previous research has shown a relationship between MetSyn and CRF, most studies are based on *less objective* measures of CRF and different cardiometabolic risk factor *thresholds* from earlier guidelines.

Participants and Methods: The metabolic markers included in the present study were central obesity, elevated plasma triglycerides, elevated fasting high-density lipoprotein cholesterol, impaired fasting plasma glucose, hypertension, or pharmacologic treatment for diagnosed hypertension, hypertriglyceridemia, low high-density lipoprotein cholesterol, or diabetes. A cohort of 3636 adults (1629 women, 2007 men; mean ± SD age, 44.7±12.3 years) completed CRF and metabolic risk factor assessment between January 1, 1971, and November 1, 2016. The CRF was defined as a measured VO_{2max} from a cardiopulmonary exercise test on a treadmill, with a respiratory exchange ratio value of 1.0 or more.

Results: Prevalence of MetSyn (≥3 factors) was 26% (n=953) in the cohort, with men having a greater likelihood for MetSyn compared with women ($P<.001$). The difference in VO_{2max} between those individuals with MetSyn and those without was approximately 2.3 (2.0-2.5) metabolic equivalents. Logistic regression analyses showed a significant inverse and graded association between quartiles of CRF and MetSyn for the group overall ($P<.001$), with odds ratios (95% CI) using the lowest fitness group as the referent group of 0.67 (0.55-0.81), 0.41 (0.34-0.51), and 0.10 (0.07-0.14) for VO_{2max} ($P<.001$). The sex-specific odds ratios were 0.25 (0.18-0.34), 0.05 (0.02-0.10), and 0.02 (0.01-0.09) for women and 0.43 (0.31-0.59), 0.19 (0.14-0.27), and 0.03 (0.02-0.05) for men ($P<.001$).

Conclusion: These results with current risk factor thresholds and a large number of women demonstrate that low VO_{2max} is associated with MetSyn.

 ■ Mayo Clin Proc Inn Qual Out 2018;2(2):155-164

The metabolic syndrome (MetSyn) is a high-risk phenotype characterized by the combination of cardiometabolic risk factors, including obesity, dyslipidemia, hypertension, impaired fasting glucose, proinflammatory state, and a prothrombotic state.[1] First described by Reaven,[2] MetSyn is believed to be a common physiologic predecessor for chronic diseases including cardiovascular disease,[3-5] type 2 diabetes mellitus,[6] and premature mortality.[4,7] Defining criteria for MetSyn have been established by multiple agencies over time,[1,8-11] but the most frequently used are those published by the National Cholesterol Education Program (NCEP)/Adult Treatment Panel[12] and the International Diabetes Foundation.[9,11] The prevalence of MetSyn has varied as a function of the defining criteria,[13] but it has been reported to exist in one-fourth to one-third of adults in the United States.[13-16] Moreover, the prevalence appears to be on the rise,[14-16] particularly in women,[14-16] and with advancing age, with the greatest prevalence seen in adults 60 years

From the Clinical Exercise Physiology Program, Human Performance Laboratory (E.K., M.T.I., M.P.H.), Department of Educational Psychology (H.F.), Fisher Institute of Health and Well-Being (L.A.K.), and College of Health (M.H.W.), Ball State University, Muncie, IN.

or older.[14] When combining the adverse consequences associated with MetSyn with its continuing rise in prevalence, it seems clear that MetSyn will continue to represent a serious public health issue well into the future.

Low cardiorespiratory fitness (CRF) has been associated with the presence of metabolic risk factor clustering and MetSyn in numerous published studies.[17-31] However, the defining criteria for MetSyn, the assessment of CRF, and the specific cohort characteristics have varied considerably among these studies. Variations in any one or all the above parameters could influence the overall study findings and the generalizability of the results. Early reports used higher thresholds for impaired fasting blood glucose (≥110 mg/dL [to convert to mmol/L, multiply by 0.0555]),[18,21,23,26-28,31] hypertension (blood pressure ≥140/90 mm Hg),[18,27,31] and/or varying measures/thresholds for abdominal obesity,[17,18,27,31] which were more consistent with the defining criteria for MetSyn at the time. Other studies used population- and/or country-specific definitions for abdominal obesity.[17,24,28,30] Only 3 recent reports incorporated the current MetSyn risk factor criteria for each of the 5 common markers—including drug treatment for hypertension, dyslipidemia, and/or elevated fasting glucose as a qualifying factor.[25,29,30] Of these, 2 of the studies included only older[30] or only younger[29] adults, and only 1 study included women.[30]

In light of the recent public health recommendation to include assessment of CRF in medical examinations[32] and the advocacy for inclusion of cardiopulmonary exercise testing (CPX),[33,34] more information from studies in which CRF was directly measured may aid clinicians in the evaluation and treatment of multiple chronic diseases (eg, cardiovascular disease and heart failure). Most of the published studies on MetSyn incorporated a CRF level estimated from a maximal exercise test,[17,19,21-23,26-31] which has been associated with an estimation error of between 1 and 2 metabolic equivalents. Only 5 of the published studies on MetSyn used CPX-derived maximal oxygen uptake (VO_{2max})[23,27-30] to define CRF. Two of these studies used leg cycling as the mode of exercise, which is associated with 10% to 20% lower measured oxygen uptake as compared with treadmill testing.[23,27,35] Four of the 5 studies incorporated solely older[23,30] or younger[28,29] adults, which would not be as generalizable across a wide age spectrum. Furthermore, only 2 of the studies in which CRF was defined using measured VO_{2max} included women, and these 2 cohorts collectively represented approximately 1171 older women.[23,30] When combining the limited number of participants within these studies with the sex and/or age delimitations, the VO_{2max} thresholds associated with increased risk for MetSyn in middle-aged adults are less clear. Therefore, additional information from studies that include (1) contemporary risk factor thresholds, (2) a large sample and broad age range of men and women, and (3) VO_{2max} determined with CPX is needed to refine the understanding of the association between CRF and MetSyn.

The purpose of the present investigation was to assess the association between directly measured CRF (VO_{2max}) and metabolic risk factor clustering in a broad age range of men and women using current MetSyn risk factor criteria.

PARTICIPANTS AND METHODS

Study Population and Design

Participants completed laboratory assessments through the Ball State Adult Fitness Program Longitudinal Lifestyle STudy (BALL ST), which is an ongoing population-based program initiated in 1970 to promote healthy lifestyles and physical fitness. This retrospective cross-sectional analysis included 3636 self-referred adult males and females (aged 19-95 years) who completed a physical examination including maximal exercise testing with respiratory gas analysis (CPX) within the BALL ST between the years January 1, 1971, and November 1, 2016. Deidentified data were exported from the BALL ST longitudinal database. Inclusion criteria consisted of being 18 years or older, having complete data for all MetSyn risk markers (see below), and attainment of greater than or equal to 1.0 respiratory exchange ratio during the maximal exercise test. For individuals with multiple test records, the first test with complete data for all relevant MetSyn risk markers was used. All data were deidentified, and participants provided written informed consent for their

Mayo Clin Proc Inn Qual Out ■ June 2018;2(2):155-164 ■ https://doi.org/10.1016/j.mayocpiqo.2018.03.001
www.mcpiqojournal.org

TABLE 1. Defining Characteristics of the BALL ST Cohort[a,b,c]

Characteristic	Men (n=2007)	Women (n=1629)	Total (n=3636)
Age (y)[d]	45.0±11.9	44.2±12.7	44.7±12.3
Current smoking (%)[d]	13.9	8.8	11.6
BMI (kg/m^2)[d]	27.7±5.0	27.0±6.3	27.4±5.6
Waist circumference (cm)[d]	96.1±13.3	82.8±14.4	90.1±15.3
Resting SBP (mm Hg)[d]	126±15	118±15	122±15
Resting DBP (mm Hg)[d]	81±10	75±10	79±10
Total cholesterol (mg/dL)[d]	208.4±45.5	200.4±40.6	204.8±43.4
LDL-C (mg/dL)[d]	130.7±37.9	118.3±35.2	124.9±37.2
HDL-C (mg/dL)[d]	45.7±12.4	58.0±15.2	51.4±15.1
Triglycerides (mg/dL)[d]	146.8±120.6	116.3±73.0	134.8±103.2
Fasting glucose (mg/dL)	98.6±22.9	93.8±19.0	96.5±21.4
Physically active (%)[d]	32.5	23.1	28.2
Resting HR (beats/min)[d]	67±11.5	70±10.0	68±11.0
Maximal HR (beats/min)	176±17.6	175±16.4	175±17.0
VO_{2max} (mL/kg/min)[d]	36.2±10.3	27.5±8.0	32.2±10.3
FRIEND percentile[d]	44±27.0	48±26.0	45±27.0

[a]BMI = body mass index; BALL ST= Ball State Adult Fitness Longitudinal Lifestyle Study; DBP = diastolic blood pressure; FRIEND = Fitness Registry and the Importance of Exercise National Database; HDL-C = high-density lipoprotein cholesterol; HR = heart rate; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure; VO_{2max} = maximal oxygen uptake.

[b]Values presented as mean ± SD unless otherwise specified. Current cigarette smoking and habitual physical activity as described within Whaley et al.[36] FRIEND percentile referenced from Kaminsky et al.[34]

[c]SI conversion units: To convert total cholesterol, LDL-C, and HDL-C values to mmol/L, multiply by 0.0259; to convert triglyceride values to mmol/L, multiply by 0.0113; to convert glucose values to mmol/L, multiply by 0.0555

[d]Significant difference between males and females ($P<.001$).

information to be used for research. Ball State University (BSU) Institutional Review Board approved all data collection procedures and determined the study "exempt" because of the use of deidentified data.

Clinical Measurements

All participants were instructed to refrain from exercise, caffeine, and alcohol for 12 hours before testing and arrive on the initial day of testing in a fasting state. They were also instructed to continue their regular medication routines. Participants completed a health history questionnaire, which provided self-reported information about medical history, lifestyle habits (eg, smoking, physical activity, and diet), and medications.[36] Each participant then completed a series of assessments including anthropometric measurements (height, weight, and waist and hip circumferences), body composition, resting heart rate and blood pressure, blood chemistry, and resting 12-lead electrocardiography. Standardized laboratory techniques were used for all resting assessments and have been described in detail elsewhere.[36-38]

Metabolic Markers

Metabolic syndrome markers and their thresholds were defined according to the NCEP.[1,8] Markers and thresholds included central obesity (waist circumference ≥102 cm for men or ≥88 cm for women), elevated fasting plasma triglycerides (≥150 mg/dL; to convert to mmol/L, multiply by 0.0113), low high-density lipoprotein cholesterol (HDL-C; <40 mg/dL for men or <50 mg/dL for women; to convert to mmol/L, multiply by 0.0259), elevated fasting plasma glucose (≥100 mg/dL), hypertension (blood pressure ≥130 mm Hg systolic or 85 mm Hg diastolic), or pharmacologic treatment for diagnosed hypertension, hypertriglyceridemia, low HDL-C, or diabetes. Waist girth was taken in the horizontal plane at the smallest circumference in the abdominal region, generally 2 to 4 in above the umbilicus. Plasma lipids were measured after a 12-hour fast, and resting blood pressure values were measured in the seated position after a 5-minute rest period. A minimum of 2 blood pressure measurements were recorded, with additional measurement taken if the initial 2 differed by more than 6/4 mm Hg for systolic

TABLE 2. Prevalence of Metabolic Syndrome Risk Factors[a]

Risk factor	Men (n=2007)	Women (n=1629)	Combined (N=3636)
Waist circumference[b]	28.1% (564)	31.7% (516)	29.7% (1080)
Impaired fasting glucose[c]	37.2% (746)	23.6% (385)	36.1% (1311)
Hypertension[d]	52.3% (1049)	32.9% (536)	43.6% (1585)
HDL-C[e]	29.2% (586)	28.5% (464)	28.9% (1050)
Triglycerides[f]	34.2% (686)	21.2% (345)	28.4% (1031)

[a]HDL-C = high-density lipoprotein cholesterol.
[b]≥102 cm for men; ≥88 cm for women.
[c]≥100 mg/dL (to convert to mmol/L, multiply by 0.0555) or drug treatment for impaired fasting glucose.
[d]≥130 systolic or 85 diastolic mm Hg; or drug treatment for hypertension.
[e]<40 mg/dL for men; <50 mg/dL for women, (to convert to mmol/L, multiply by 0.0259), or drug treatment for low HDL-C.
[f]≥150 mg/dL (to convert to mmol/L, multiply by 0.0113) or drug treatment for high serum triglycerides.

or diastolic, respectively. Participants reporting medication use for treatment of hypertriglyceridemia or low HDL-C were classified as positive for these metabolic markers.[8,11] The presence of the metabolic syndrome was defined as meeting the criteria for 3 or more of the metabolic markers.[8]

Exercise Testing and CRF

All participants completed a maximal CPX on a treadmill as part of their physical examination. Exercise test protocols varied and included Bruce,[39] Ball State University Bruce Ramp,[40] modified Balke,[41] or other nonspecified protocols. In most cases, selection of test protocol was individualized on the basis of participant characteristics, with a goal to achieve maximal effort within 8 to 12 minutes. Exercise heart rate was measured using electrocardiography (single-lead or 12-lead, depending on date) and recorded each minute at peak exercise and during recovery from the exercise test. Exercise blood pressures were monitored manually during exercise and recovery. Gas exchange data were collected using open circuit spirometry with methods described previously.[36] Standardized procedures for metabolic cart calibration were followed for all tests, and tests were supervised by clinical exercise physiologists, with additional medical supervision when appropriate.[42] Participants were verbally encouraged to exercise to volitional fatigue. Cardiorespiratory fitness was indicated by VO_{2max}, defined as the average of 2 or 3 consecutive VO_2 values within 2 mL per kg/minute, occurring in the last 2 minutes of the CPX.

TABLE 3. Clustering of Metabolic Syndrome Risk Factors

No. of risk factors meeting threshold	Men (n=2007)	Women (n=1629)	Combined (N=3636)
0	20.0% (403)	32.9% (537)	25.9% (940)
1	26.4% (529)	29.0% (479)	27.7% (1008)
2	23.3% (467)	16.5% (268)	20.2% (735)
3[a]	17.0% (341)	12.0% (195)	14.7% (536)
4[a]	9.5% (190)	6.4% (104)	8.1% (294)
5[a]	3.8% (77)	2.8% (46)	3.4% (123)

[a]Those with ≥3 of the risk factors were coded for analyses as having the metabolic syndrome.

Statistical Analyses

Descriptive statistics were computed for all study variables and are presented in Table 1. For analyses purposes, cigarette smoking was characterized as current smoker, former smoker, or never smoked, and physical activity was characterized as regularly active in endurance exercise (≥3 sessions per week of running, walking, swimming, and/or cycling) or not. Differences in participant characteristics and metabolic markers between those with and without the MetSyn were tested for statistical significance with Student *t* test or the χ^2 test where indicated.

Several methods were used to assess the association between CRF and MetSyn. First, CRF was used as a continuous scale variable in analyses (mL/kg per minute) and the age- and sex-adjusted difference in CRF was computed between those with and without MetSyn. Second, sex-stratified CRF quartiles were created and logistic regression models were computed using the lowest fitness quartile as the reference group. Finally, as a complementary approach to assessing the relationship between CRF and MetSyn, an individual's VO_{2max} was converted to an age- and sex-specific percentile score using the reference values from the Fitness Registry and the Importance of Exercise National Database (FRIEND).[34] For analysis, participants were stratified into lowest VO_{2max} (Q1 ≤25th percentile), Q2 was 26th to 50th percentile, Q3 was 51st to 75th percentile, and highest VO_{2max} (Q4 >75th percentile) of the FRIEND. Odds ratios were computed for the FRIEND quartiles using the lowest fitness category (Q1) as the reference group.

Mayo Clin Proc Inn Qual Out ■ June 2018;2(2):155-164 ■ https://doi.org/10.1016/j.mayocpiqo.2018.03.001
www.mcpiqojournal.org

TABLE 4. Defining Characteristics—MetSyn Compared With Apparently Healthy Individuals[a,b,c]

Characteristic	MetSyn (n=953)	No MetSyn (n=2683)
Age (y)[d]	48.3±11.8	43.4±12.2
Current smoking (%)	11.5	11.6
BMI (kg/m^2)[d]	32.3±5.0	25.6±6.3
Waist circumference (cm)[d]	104.5±13.6	85.0±12.3
Resting SBP (mm Hg)[d]	132±16	119±14
Resting DBP (mm Hg)[d]	85±10	77±10
Total cholesterol (mg/dL)[d]	213.2±48.4	201.9±41.1
LDL-C (mg/dL)[d]	129.7±38.2	123.2±36.7
HDL-C (mg/dL)[d]	45.7±12.4	58.0±15.2
Triglycerides (mg/dL)[d]	146.8±120.6	116.3±73.0
Fasting blood glucose (mg/dL)[d]	110.0±31.6	91.7±13.3
Physically active (%)[d]	15.2	33.2
Resting HR (beats/min)[d]	72±10.6	67±10.8
Maximal HR (beats/min)[d]	169±19.2	178±15.6
VO_{2max} (mL/kg/min)[d]	26.6±7.1	34.3±10.5
FRIEND percentile[d]	28±20.0	52±26.0

[a]BMI = body mass index; DBP = diastolic blood pressure; FRIEND = Fitness Registry and the Importance of Exercise National Database; HDL-C = high-density lipoprotein cholesterol; HR = heart rate; LDL-C = low-density lipoprotein cholesterol; MetSyn = metabolic syndrome; SBP = systolic blood pressure; VO_{2max} = maximal oxygen uptake.
[b]Values presented as mean ± SD unless otherwise specified. FRIEND percentile referenced from Kaminsky et al.[34]
[c]SI conversion units: To convert total cholesterol, LDL-C, and HDL-C values to mmol/L, multiply by 0.0259; to convert triglyceride values to mmol/L, multiply by 0.0113; to convert glucose values to mmol/L, multiply by 0.0555
[d]Significant difference between MetSyn and healthy ($P<.001$).

All analyses were performed using SPSS version 24 and SAS version 9.3. A P value of less than .01 was considered statistically significant.

RESULTS

The prevalence of each of the metabolic markers of the MetSyn is presented in Table 2. Hypertension was the most frequent risk factor, followed by impaired fasting blood glucose, and then the others. The proportion of the cohort with clustering of one or more metabolic markers is presented in Table 3. Within this cohort, the presence of MetSyn as defined by having 3 or more risk factors was 26% (953 of 3636). Men were more likely to have each of the associated risk factors and MetSyn than women (30% vs 21%) ($P<.001$). Those with MetSyn were also older, less physically active, and had lower maximal heart rate and VO_{2max} compared with those who were free of the syndrome ($P<.001$). Those within the cohort who had MetSyn had a VO_{2max} value of 7.8 (7.1-8.5) mL/kg per minute lower than did those without MetSyn. After adjusting for age and sex in the model, those with MetSyn had a CRF value of 7.2 (6.6-7.7) mL/kg per minute lower than did those without MetSyn (Table 4).

Results from the logistic regression based on the cohort analyses are presented in

TABLE 5. Prevalence and Cohort Logistic Regression Models for MetSyn[a,b]

Model	Lowest-fit quartile	Quartile 2	Quartile 3	Highest-fit quartile
N=MetSyn	484 (53.3%)	294 (32.4%)	148 (16.3%)	27 (3.0%)
OR	1.0	0.67 (0.55-0.81)	0.41 (0.34-0.51)	0.10 (0.07-0.14)
OR[c]	1.0	0.49 (0.40-0.60)	0.30 (0.34-0.38)	0.07 (0.05-0.10)
OR[d]	1.0	0.29 (0.23-0.37)	0.13 (0.10-0.17)	0.03 (0.02-0.04)

[a]MetSyn = metabolic syndrome; OR = odds ratio.
[b]Data for ORs are presented as ORs (CIs).
[c]Adjusted for age at test date.
[d]Adjusted for age at test date, sex, physical activity, and cigarette smoking.

TABLE 6. Prevalence and Sex-Specific Cohort Logistic Regression Models for MetSyn[a,b]

Model	Lowest-it quartile	Quartile 2	Quartile 3	Highest-fit quartile
Women				
N=MetSyn	192 (47.2%)	97 (23.8%)	53 (13.0%)	3 (0.7%)
VO_{2max} (mL/kg/min)	≤21.5	21.6-26.1	26.2-31.7	≥31.8
OR	1.0	0.25 (0.18-0.34)	0.05 (0.02-0.10)	0.02 (0.01-0.09)
OR[c]	1.0	0.26 (0.19-0.36)	0.05 (0.03-0.12)	0.03 (0.01-0.13)
Men				
N=MetSyn	292 (58.3%)	197 (39.2%)	95 (18.9%)	24 (4.8%)
VO_{2max} (mL/kg/min)	≤28.7	28.8-35.1	35.2-42.6	≥42.7
OR	1.0	0.43 (0.31-0.59)	0.19 (0.14-0.27)	0.03 (0.02-0.05)
OR[c]	1.0	0.39 (0.27-0.55)	0.16 (0.11-0.24)	0.03 (0.02-0.05)

[a]MetSyn = metabolic syndrome; OR = odds ratio; VO2max = maximal oxygen uptake.
[b]Data for ORs are presented as ORs (CIs).
[c]Adjusted for age at test date, physical activity, and cigarette smoking status.

Tables 5 and 6. They show a statistically significant inverse and graded association between VO_{2max} and the prevalence of MetSyn for the group overall ($P<.001$) and for the men and women separately ($P<.001$). In the analysis that included all participants (n=3636), the association was statistically significant after adjusting for age and sex ($P<.001$), and the prevalence of MetSyn ranged from 53.3% in the lowest-fit quartile (Q1) to 3.0% in the most-fit quartile (Q4). The most-fit quartile was more than 20 times less likely to have MetSyn compared with their least-fit counterparts, and the association showed a graded response, with the middle 2 quartiles also significantly less likely to have the MetSyn than the least-fit quartile ($P<.01$). This relationship was also shown for men and women, respectively.

Those with MetSyn had a VO_{2max} percentile from the FRIEND of 28±20 percentile as opposed to those without the syndrome who averaged a VO_{2max} percentile of 52±26 ($P<.001$). The logistic regression results for the analysis that incorporated the FRIEND version of CRF for the women and men are presented in Table 7 and also show a significant inverse gradient for MetSyn and VO_{2max} ($P<.01$). The results remain significant after adjusting for age in the logistic regression models.

DISCUSSION

The major finding of this study was the significant inverse association between VO_{2max} and MetSyn, with the most physically fit individuals (upper quartile) being more than 20 times less likely to have MetSyn compared with the least-fit individuals. The difference in VO_{2max} between those individuals with MetSyn and those without was approximately 2.5 metabolic equivalents. The association between VO_{2max} and MetSyn was also graded across the range of fitness scores within our cohort, with the 2 middle groups having intermediate prevalence rates (Tables 5 and 6). This relationship remained significant and was strengthened by adjusting for age and sex in the models. This large cohort of men and women had a broad range of scores for age, VO_{2max}, and the risk factors for MetSyn.

TABLE 7. Prevalence and Logistic Regression Models for MetSyn Using the FRIEND Percentiles[a,b]

Model	Lowest-fit FRIEND ≤25th percentile	Quartile 2 26th-50th percentile	Quartile 3 51st-75th percentile	Highest-fit FRIEND ≥76th percentile
Women with MetSyn	179 (43.2%)	95 (20.6%)	53 (12.6%)	18 (5.4%)
Odds ratio	1.0	0.36 (0.26-0.49)	0.19 (0.13-0.30)	0.07 (0.04-0.13)
Men with MetSyn	357 (54.6%)	169 (29.4%)	64 (14.4%)	18 (5.4%)
Odds ratio	1.0	0.31 (0.24-0.40)	0.13 (0.09-0.18)	0.06 (0.04-0.09)

[a]FRIEND = Fitness Registry and the Importance of Exercise National Database; MetSyn = metabolic syndrome.
[b]FRIEND percentile referenced from Kaminsky et al.[34]

Mayo Clin Proc Inn Qual Out ■ June 2018;2(2):155-164 ■ https://doi.org/10.1016/j.mayocpiqo.2018.03.001
www.mcpiqojournal.org

Although these findings are generally consistent with previous studies,[17-21,23,25-31] our results are based on *current* risk factor thresholds for MetSyn,[1,8] represent the largest cohort with directly measured VO_{2max} of the available studies, and incorporate the FRIEND percentiles into our analysis.[34] Our results demonstrate that a lower VO_{2max} (or lower VO_{2max} percentile from FRIEND) is associated with a greater prevalence of MetSyn in both men and women, and based on the analyses deployed, our results are graded in nature.

Only a handful of studies of CRF and MetSyn[20,25,29] have used the current risk factor thresholds defined by the NCEP/Adult Treatment Panel,[1,8] which is most likely due to the modifications in the risk factor thresholds over time. Nonetheless, these modifications increase the number of individuals classified as having MetSyn. Considering only those studies that used the current risk factor thresholds, Ekblom et al[20] studied approximately 686 men and women and quantified CRF using a submaximal cycling test. They did not measure VO_{2max} in their study, but using the current thresholds did report that the sex-adjusted high-fit group was less likely to have MetSyn. Misigoj-Durakovic et al[29] studied 577 younger men (mean age, 30 years) and used a maximal treadmill test with measured VO_{2max}. These authors reported higher odds ratios for the upper 3 CRF quartiles (0.42, 0.38, and 0.10) when using the least-fit quartile as the reference group compared with the present study (0.37, 0.16, and 0.02 for men). Their study was in younger men, so direct comparisons of results are not prudent, but our findings suggest a stronger graded relationship in men and add women to these findings. Finally, Ingle et al[25] studied a much larger sample of men (~9666) compared with the present study but used a submaximal treadmill test to assess CRF and reported only 2 categories of men, *unfit* vs *fit*. Although their higher *fit* men were less likely to have clustering of the risk factors, their odds ratio of 0.51 for the *fit* men is not directly comparable to that in the present study. Our results, using the criterion standard (eg, measured VO_{2max}), represent a stronger study design compared with these reports.

Our study results are novel for the inclusion of measured VO_{2max} as the measure of CRF in a cohort of men and women with a broad age range. Most published studies[17,19,21-23,26-31] incorporated a maximal exercise test for assessment of CRF, but of these, only 5 used directly measured VO_{2max} as the measure of CRF.[23,27-30] Lakka et al[27] and Hassinen et al[23] reported results where VO_{2max} was quantified using a cycle ergometer test, whereas Lee et al,[28] Misigoj-Durakovic et al,[29] and Sandbakk et al[30] deployed a maximal treadmill test. Although all the studies reported a significant inverse association between VO_{2max} and the prevalence of MetSyn, the studies most comparable to the present one are those measuring VO_{2max} using a motorized *treadmill* protocol. Lee et al[28] assessed 909 young men (age, 24±2 years) who had a much higher CRF, and the risk factor thresholds for waist circumference and fasting blood glucose were not the same as in the present study. Nonetheless, they reported that the middle and high fitness tertiles had a significantly lower risk for MetSyn. Sandbakk et al[30] studied older men and women (aged 70-77 years) and reported that high CRF was associated with a lower risk for MetSyn. However, their risk thresholds for waist girth were lower than in the present study and the present study included a much wider range of age and CRF. Finally, Misigoj-Durakovic et al[29] assessed a smaller group of younger men (577; age, 19-47 years) and as stated above, their results for the highest fitness group of men were similar to those of the present study. Based on these available studies that defined CRF measured with CPX and treadmill exercise, our results represent the association with a much broader age range of both men and women.

Although multiple studies included women[19-24,30,31] and show the inverse association between a measure of CRF and MetSyn, the present study represents the largest group of women that used a measured VO_{2max} to define CRF. Four of the studies that included women were from the same cohort[19,21,22,31] and defined CRF with a maximal exercise test without CPX. Although they reported an inverse association between CRF and MetSyn for women, they reported much lower overall prevalence rates for MetSyn compared with the present study (6.5% and 4.2% vs 21%). Differences in prevalence rates are partly due to a difference in the risk factor thresholds

used compared with the present study (fasting blood glucose, ≥110 mg/dL vs ≥100 mg/dL), but could also be due to other factors such as sampling differences. The number of women with each metabolic risk factor was significantly lower in the study by Farrell et al[21] compared with the present study, and the other study is from the same cohort.

There are 2 studies that incorporated VO_{2max} as the measure of CRF in women.[23,30] Although these studies used slightly different risk factor thresholds and represented much older women (Sandbakk et al[30]: age, 70-77 years; Hassinen et al[23]: age, 65±5 years), they do represent studies with a measured VO_{2max}. Both these studies used tertiles of VO_{2max} in their analyses, and the lowest-fit women were significantly more likely to have MetSyn compared with the highest-fit women in their respective analyses. The present study represents a significantly larger sample of women and also represents a much wider age *range* compared with these previous studies that defined CRF with VO_{2max}. Therefore, our results extend the findings of these previous reports to a much broader age range of women.

This is the first study to incorporate the FRIEND database values for CRF into analyses[34] (Table 7). Each participant in the present study had their VO_{2max} converted into a sex- and age-adjusted FRIEND percentile, and then this value was used in the logistic regression model as opposed to their actual VO_{2max} value. Both men and women showed significant drops in MetSyn across the CRF continuum. The largest declines were from the lowest-fit groups for men and women (≤25th percentile) to the adjacent category (Q2), but the relationship was graded, meaning that moving from Q2 to Q3 and ultimately to the highest-fit group represented a statistically significant decline in risk for MetSyn within our study. These results support our original findings by incorporating a national CRF database into the analytic model. The FRIEND for CRF accounts for the naturally occurring differences in VO_{2max} that occur between sexes and across the age continuum and provides a national database for comparison across studies.

The protective effects of higher VO_{2max} that are shown in the present study represent values that are attainable by most of the general public. Cardiorespiratory fitness values of approximately 22.0 and 29.0 mL/kg per minute for women and men, respectively, which represents the threshold between the lowest VO_{2max} quartile and the second quartile, are reasonably attainable through regular aerobic exercise training. Further reduction in MetSyn was seen in those individuals who were in the 2 upper fitness quartiles. Age did not affect the logistic results for the women in a meaningful way and only modestly affected the results for men. Additional support for the modest effect of age on our results comes from the FRIEND, which categorizes VO_{2max} into sex-age categories. Values for measured VO_{2max} below the 25th percentile (sex- and age-adjusted) in the FRIEND are clearly risky for the presence of MetSyn. Therefore, we suspect that the differences in fitness associated with aging did not impact our results much. Obviously, multiple factors are related to our measure of CRF, but sedentary lifestyle is a major part of the relationship. Most of the adults in the present analysis were sedentary at the time of exercise testing. Further protection from MetSyn would likely be accrued as one moves up the CRF continuum with regular exercise training.

There are several strengths and limitations to the present study. Strengths include a large apparently healthy cohort that was self-referred, measured VO_{2max}, and inclusion of the FRIEND in the analysis. To our knowledge, this study represents the largest cohort of adults that has shown this association with MetSyn using VO_{2max} as the measure of CRF. Limitations include that the cohort was approximately 95% percent white and that exercise testing and risk factor assessments took place over a large period of years with only slight modifications in some testing procedures. However, we believe these limitations to be marginal because the laboratory techniques used were similar and consistent with guidelines at the time of testing. What did change over time are the metabolic risk factor *values* that were considered abnormal, and we have used the most recent thresholds for each risk factor in our analyses. In addition, because there was a relatively low prevalence of MetSyn in the highest CRF groups for men and women, caution is warranted in the interpretation of the risk level for these groups. And finally, results from the present study are cross-sectional in nature, so

Mayo Clin Proc Inn Qual Out ■ June 2018;2(2):155-164 ■ https://doi.org/10.1016/j.mayocpiqo.2018.03.001
www.mcpiqojournal.org

we should be cautious in drawing conclusions about causation.

CONCLUSION

The present study confirms the association between CRF and MetSyn in men and women and extends it to include CRF as defined by measured VO_{2max}. The results of the present study are also strengthened by the FRIEND application, which standardizes VO_{2max} across sex and gender percentiles and are generalizable to the larger population. On the basis of our results, clinicians should first focus on the lowest-fit individuals and encourage them to adopt a more physically active lifestyle, which would improve their VO_{2max}. Because our results were graded in nature, individuals should be encouraged to adopt a regular exercise program that contributes to an improvement in VO_{2max} to upper quartiles.

Abbreviations and Acronyms: **BALL ST** = Ball State Adult Fitness Program Longitudinal Lifestyle Study; **CPX** = cardiopulmonary exercise; **CRF** = cardiorespiratory fitness; **FRIEND** = Fitness Registry and the Importance of Exercise National Database; **HDL-C** = high-density lipoprotein cholesterol; **MetSyn** = metabolic syndrome; **NCEP** = National Cholesterol Education Program; **VO_{2max}** = maximal oxygen uptake

Potential Competing Interests: The authors report no competing interests.

Correspondence: Address to Mitchell H. Whaley, PhD, College of Health, AT101, Ball State University, Muncie, IN 47306 (mwhaley@bsu.edu).

REFERENCES

1. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement; executive summary. *Crit Pathw Cardiol*. 2005;4(4):198-203.
2. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes*. 1988;37(12):1595-1607.
3. Reaven GM. Role of insulin resistance in human disease (syndrome X): an expanded definition. *Annu Rev Med*. 1993;44:121-131.
4. Gami AS, Witt BJ, Howard DE, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. *J Am Coll Cardiol*. 2007;49(4):403-414.
5. Ardern CI, Katzmarzyk PT, Janssen I, Church TS, Blair SN. Revised Adult Treatment Panel III guidelines and cardiovascular disease mortality in men attending a preventive medical clinic. *Circulation*. 2005;112(10):1478-1485.
6. Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. *Compr Physiol*. 2012;2(2):1143-1211.
7. Hu G, Qiao Q, Tuomilehto J, Balkau B, Borch-Johnsen K, Pyorala K; DECODE Study Group. Prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular mortality in nondiabetic European men and women. *Arch Intern Med*. 2004;164(10):1066-1076.
8. Alberti KG, Eckel RH, Grundy SM, et al; International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120(16):1640-1645.
9. Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group. The metabolic syndrome—a new worldwide definition. *Lancet*. 2005;366(9491):1059-1062.
10. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications, Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med*. 1998;15(7):539-553.
11. International Diabetes Foundation. The IDF consensus worldwide definition of the metabolic syndrome. wwwidforg/webdata/docs/IDF_Meta_def_finalpdf. 2006. Accessed June 7, 2017.
12. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106(25):3143-3421.
13. Cheung BM, Ong KL, Man YB, Wong LY, Lau CP, Lam KS. Prevalence of the metabolic syndrome in the United States National Health and Nutrition Examination Survey 1999-2002 according to different defining criteria. *J Clin Hypertens (Greenwich)*. 2006;8(8):562-570.
14. Aguilar M, Bhuket T, Torres S, Liu B, Wong RJ. Prevalence of the metabolic syndrome in the United States, 2003-2012. *JAMA*. 2015;313(19):1973-1974.
15. Ford ES, Giles WH, Mokdad AH. Increasing prevalence of the metabolic syndrome among U.S. adults. *Diabetes Care*. 2004;27(10):2444-2449.
16. Mozumdar A, Liguori G. Persistent increase of prevalence of metabolic syndrome among U.S. adults: NHANES III to NHANES 1999-2006. *Diabetes Care*. 2011;34(1):216-219.
17. Baur DM, Christophi CA, Kales SN. Metabolic syndrome is inversely related to cardiorespiratory fitness in male career firefighters. *J Strength Cond Res*. 2012;26(9):2331-2337.
18. Carroll S, Cooke CB, Butterly RJ. Metabolic clustering, physical activity and fitness in nonsmoking, middle-aged men. *Med Sci Sports Exerc*. 2000;32(12):2079-2086.
19. Earnest CP, Artero EG, Sui X, Lee DC, Church TS, Blair SN. Maximal estimated cardiorespiratory fitness, cardiometabolic risk factors, and metabolic syndrome in the Aerobics Center Longitudinal Study. *Mayo Clin Proc*. 2013;88(3):259-270.
20. Ekblom Ö, Ekblom-Bak E, Rosengren A, Hallsten M, Bergstrom G, Borjesson M. Cardiorespiratory fitness, sedentary behaviour and physical activity are independently associated with the metabolic syndrome: results from the SCAPIS pilot study. *PLoS One*. 2015;10(6):e0131586.
21. Farrell SW, Cheng YJ, Blair SN. Prevalence of the metabolic syndrome across cardiorespiratory fitness levels in women. *Obes Res*. 2004;12(5):824-830.
22. Finley CE, LaMonte MJ, Waslien CI, Barlow CE, Blair SN, Nichaman MZ. Cardiorespiratory fitness, macronutrient intake, and the metabolic syndrome: the Aerobics Center Longitudinal Study. *J Am Diet Assoc*. 2006;106(5):673-679.

23. Hassinen M, Lakka TA, Savonen K, et al. Cardiorespiratory fitness as a feature of metabolic syndrome in older men and women: the Dose-Responses to Exercise Training study (DR's EXTRA). *Diabetes Care*. 2008;31(6):1242-1247.
24. Hong S, Lee J, Park J, et al. Association between cardiorespiratory fitness and the prevalence of metabolic syndrome among Korean adults: a cross sectional study. *BMC Public Health*. 2014; 14:481.
25. Ingle L, Mellis M, Brodie D, Sandercock GR. Associations between cardiorespiratory fitness and the metabolic syndrome in British men. *Heart*. 2017;103(7):524-528.
26. Jurca R, Lamonte MJ, Church TS, et al. Associations of muscle strength and fitness with metabolic syndrome in men. *Med Sci Sports Exerc*. 2004;36(8):1301-1307.
27. Lakka TA, Laaksonen DE, Lakka HM, et al. Sedentary lifestyle, poor cardiorespiratory fitness, and the metabolic syndrome. *Med Sci Sports Exerc*. 2003;35(8):1279-1286.
28. Lee J, Kim SU, Kang HS. Low cardio/respiratory fitness as an independent predictor of metabolic syndrome in Korean young men. *Eur J Appl Physiol*. 2010;108(4):633-639.
29. Mišigoj-Duraković M, Sorić M, Matika D, Jukić I, Duraković Z. Which is more important for reducing the odds of metabolic syndrome in men: cardiorespiratory or muscular fitness? *Obesity (Silver Spring)*. 2016;24(1):238-244.
30. Sandbakk SB, Nauman J, Zisko N, et al. Sedentary time, cardiorespiratory fitness, and cardiovascular risk factor clustering in older adults—the Generation 100 Study. *Mayo Clin Proc*. 2016;91(11):1525-1534.
31. Whaley MH, Kampert JB, Kohl HW III, Blair SN. Physical fitness and clustering of risk factors associated with the metabolic syndrome. *Med Sci Sports Exerc*. 1999;31(2):287-293.
32. Ross R, Blair SN, Arena R, et al; American Heart Association Physical Activity Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Cardiovascular and Stroke Nursing; Council on Functional Genomics and Translational Biology; Stroke Council. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign; a scientific statement from the American Heart Association. *Circulation*. 2016;134(24):e653-e699.
33. Kaminsky LA, Arena R, Beckie TM, et al; American Heart Association Advocacy Coordinating Committee, Council on Clinical Cardiology, Council on Nutrition, Physical Activity and Metabolism. The importance of cardiorespiratory fitness in the United States: the need for a national registry; a policy statement from the American Heart Association. *Circulation*. 2013; 127(5):652-662.
34. Kaminsky LA, Arena R, Myers J. Reference standards for cardiorespiratory fitness measured with cardiopulmonary exercise testing: data from the Fitness Registry and the Importance of Exercise National Database. *Mayo Clin Proc*. 2015;90(11): 1515-1523.
35. Kaminsky LA, Imboden MT, Arena R, Myers J. Reference standards for cardiorespiratory fitness measured with cardiopulmonary exercise testing using cycle ergometry: data from the Fitness Registry and the Importance of Exercise National Database (FRIEND) registry. *Mayo Clin Proc*. 2017;92(2):228-233.
36. Whaley MH, Kaminsky LA, Dwyer GB, Getchell LH. Failure of predicted VO2peak to discriminate physical fitness in epidemiological studies. *Med Sci Sports Exerc*. 1995;27(1):85-91.
37. Whaley MH, Kaminksy LA, Getchell LH, Kelly MD, Treloar JH. Changes in total cholesterol following endurance training: a function of initial values. *J Cardiopulmon Rehabil*. 1992;12(1):42-50.
38. Whaley MH, Kaminsky LA, Dwyer GB, Getchell LH, Norton JA. Predictors of over- and underachievement of age-predicted maximal heart rate. *Med Sci Sports Exerc*. 1992;24(10): 1173-1179.
39. Bruce RA, Blackmon JR, Jones JW, Strait G. Exercising testing in adult normal subjects and cardiac patients. *Pediatrics*. 1963; 32(suppl):742-756.
40. Kaminsky LA, Whaley MH. Evaluation of a new standardized ramp protocol: the BSU/Bruce Ramp protocol. *J Cardiopulm Rehabil*. 1998;18(6):438-444.
41. Pollock ML, Foster C, Schmidt D, Hellman C, Linnerud AC, Ward A. Comparative analysis of physiologic responses to three different maximal graded exercise test protocols in healthy women. *Am Heart J*. 1982;103(3):363-373.
42. American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing and Prescription*. 9th ed. Baltimore, MD: Wolters Kluwer/Lippincott Williams & Wilkins; 2013.