Metabolic syndrome and risk of death from cancers of the digestive system

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Abstract

We tested the hypothesis that risk of early mortality from cancers of the digestive system will be greater in men with, compared with men without, the metabolic syndrome (MetS). Participants were 33 230 men who were seen at the Cooper Clinic in Dallas, TX, and followed for 14.4 (SD = 7.0) years. *Metabolic syndrome* was defined as having at least 3 of the following risk factors: abdominal obesity, fasting hypertriglyceridemia, low high-density lipoprotein cholesterol, high blood pressure, or high fasting glucose level or diabetes. Metabolic syndrome was associated with higher mortality (hazard ratio [HR] = 1.90 [95% confidence interval = 1.42-2.55]), and there was a graded positive association for the addition of more syndrome components ($P < .01$). Adjustment for cardiorespiratory fitness attenuated the risk estimates by 20% to 30%, but they remained significant after this adjustment. Evaluation of the independent contribution of each of the syndrome components revealed that both abdominal obesity (HR = 1.89 [1.36-2.62]) and high glucose (HR = 1.38 [1.02-1.87]) were independently associated with cancer mortality. Our results support the hypothesis that metabolic syndrome is positively associated with mortality from cancers of the digestive system. Interventions that reduce abnormalities associated with the syndrome could reduce risk of premature death from these cancers.
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1. Introduction

Cancers of the digestive system will result in more than 270 000 deaths in the United States in 2007, and this represents nearly 25% of all deaths from cancer in this period [1]. Cancers of the digestive system include those of the alimentary canal below the neck (eg, esophagus, stomach, small and large intestines) and key digestive organs (ie, pancreas, liver, gallbladder). Whereas the 5-year survival rates are nearly 90% or greater for breast and prostate cancer, the survival rate for digestive cancers as a group is only 45% [2]. Therefore, identification of modifiable risk factors for these more lethal cancers may provide important opportunities for reducing overall cancer mortality.

The *metabolic syndrome* (*MetS*) is a condition that has been defined as a clustering of at least 3 of 5 cardiovascular and diabetes risk factors, including: abdominal obesity, elevated fasting blood glucose, elevated blood pressure, hypertriglyceridemia, and low levels of high density lipoprotein (HDL) [3]. The prevalence of MetS in the United States is approximately 24% for all adults but is greater than 40% for those older than 60 years [4], the age group in which the majority of cancers develop. The prevalence of MetS for those with diabetes is greater than 60% [5].

Metabolic syndrome represents the development of central adiposity and abnormalities in carbohydrate and lipid metabolism as a consequence of genetic predisposition coupled with sedentary lifestyles and poor dietary habits [3,6]. Hallmark features associated with MetS are hyperinsulinemia and low-level, chronic inflammation [6], both of which are believed to play an important role in the

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development and growth of invasive cancers [7]. Indeed, recent investigations have indicated a positive association between clusters of the MetS components and adenomatous polyps [8], and incident [9-11] and fatal colon cancer outcomes [12,13]. In addition, positive associations between pancreatic cancer and elements of the syndrome, including abdominal obesity [14,15], hyperinsulinemia [16], and elevated glucose [16,17], also have been reported.

There is substantial evidence that clusters of the MetS components are positively associated with risk for early mortality [18,19], cardiovascular disease [18,20-22], and diabetes [21,23]. However, fewer studies have estimated the risk associated with cancer outcomes using standardized definitions of MetS that are now frequently used in clinical practice. For this reason, our current understanding of the degree to which MetS is associated with the risk of cancer outcomes remains incomplete.

Accordingly, the purpose of this investigation was to (1) test the hypothesis that risk of early mortality from cancers of the digestive system will be greater in those with, compared with those without, MetS and (2) to estimate the risk associated with a higher number of MetS components on mortality from these cancers. Results from this study provide important translational insight into risk for cancer mortality relative to commonly measured clinical metabolic risk factors.

2. Methods

2.1. Study population

Participants were 33 230 men aged 20 to 88 years who were free of known cancer, who had a baseline preventive medical examination at the Cooper Clinic, Dallas, TX, between 1977 and 2003, and are enrolled in the Aerobics Center Longitudinal Study (ACLS). Study participants came to the clinic for periodic preventive health examinations and for counseling regarding diet, exercise, and other lifestyle factors associated with increased risk of chronic disease. Many participants were sent by their employers for the examination. Some were referred by their personal physicians. Others were self-referred. All participants in the current analysis had complete measures for each MetS component. Participants were followed from the date of their baseline examination until their date of death or until the time of censoring for the current analyses, December 31, 2003. Person-years of exposure were computed as the sum of follow-up time among decedents and survivors.

2.2. Baseline examination

Clinical examinations were performed after receiving written informed consent from each participant. These included fasting blood chemistry analyses, personal and family health history, anthropometry, resting blood pressure and electrocardiogram, and a maximal graded exercise test.

Examination methods and procedures followed a standard manual of operations and have been previously described [24,25]. Briefly, body mass index (BMI; weight [in kilograms]/height [in meters]^2) was computed from measured height and weight. Waist circumference was measured at the umbilicus. Resting blood pressure was recorded as the first and fifth Korotkof sounds by auscultatory methods. Serum samples were analyzed for triglycerides, HDL cholesterol, and glucose using standardized automated bioassays that met Centers for Disease Control and Prevention standards. Information on smoking habits (current smoker or not), alcohol intake (drinks per week), personal history of hypertension and diabetes, and family history of diseases (cancer, cardiovascular disease, hypertension, and diabetes) was obtained from a standardized questionnaire.

Cardiorespiratory fitness (CRF) was assessed at the baseline examination as the duration of a symptom-limited maximal treadmill exercise test using a modified Balke protocol [24,26]. The duration of the test on this protocol is highly correlated with directly measured maximal oxygen uptake in men ($r > 0.90$) [27], an accepted measure of CRF. We used our previously published age-specific distribution of treadmill duration from the overall ACLS population to define fitness as not fit (lowest 20%) and fit (upper 80%) to maintain consistency in the study methods and because we have found that not fit, defined in this way, is an independent predictor of mortality [25,28] and morbidity [29]. The respective cut points for the fitness classifications in the not fit and fit groups have been described in detail previously [29].

2.3. Metabolic syndrome definition

Participants were classified as having MetS using the criteria of the National Cholesterol Education Program Adult Treatment Panel III based on the presence of 3 or more of the following risk factors [6,30] : (1) abdominal obesity (waist girth >102 cm), (2) fasting hypertriglyceridemia (≥150 mg/dL), (3) low HDL cholesterol (<40 mg/dL), (4) high blood pressure (≥130/85 mm Hg), and (5) high fasting glucose (≥110 mg/dL). History of physician-diagnosed hypertension and diabetes also was used to identify individuals with an abnormal blood pressure and glucose level, respectively, as done in other epidemiologic studies [9,10] and in our previous report [30].

2.4. Assessment of outcomes

The National Death Index (NDI) was the primary data source for mortality surveillance, and vital status was determined for more than 95% of the cohort in this study period. The underlying cause of death was determined from the NDI report or by a nosologist's review of official death certificates obtained from the department of vital records in the decedent's state of residence. The NDI has been found to provide cancer mortality data that are of similar accuracy to those determined by an end points review committee, which

reviews both death certificates and relevant medical records to make its determination. Sesso and colleagues [31] compared cause of death determined by an end points committee to those from NDI in the Physicians Health Study for deaths occurring between 1982 and 1998. For NDI, the sensitivity for cancer mortality was 89% and the specificity was 100%. Causes of cancer death were identified using the *International Classification of Diseases, Ninth Revision* codes for deaths occurring before 1999 and the *10th Revision* codes (in parentheses) for deaths during 1999-2003. Our primary outcome for this analysis was death from digestive and gastrointestinal cancers, 150-159 (C15-C26); and our secondary mortality outcomes were colon, 153 (C18); rectum, 154 (C19-C21); pancreas, 157 (C25); esophagus, 150 (C15); stomach, 151 (C16); and liver, 155 (C22). Although the classification and rule changes between *10th Revision* and *Ninth Revision* have resulted in the shifting of deaths away from some underlying cause-of-death categories into others, the number of deaths due to cancer remained stable across revisions [32]. The study protocol was approved annually by the Institutional Review Board of the Cooper Institute.

2.5. Statistical analysis

Characteristics of the cohort at baseline were compared by MetS status using t tests and χ^2 tests. Kaplan-Meier survival curves were generated for MetS and according to the number of prevalent MetS risk factors. Cox proportional hazard modeling was used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs), as is the convention in portraying results from epidemiologic studies such as this [33]. Tests for trend of HRs across number of MetS components were obtained by modeling the categories as continuous, ordinal variables. Three types of Cox models were fit. First, we estimated the associations adjusting only for baseline age (years). Second, we adjusted for baseline age (years), examination year (calendar year), height (inches), current smoker (yes/no), alcohol intake (≥5 drinks per week or not), and family history of cancer (model 1). Third, we adjusted for the covariates in model 1 and further adjusted for CRF (treadmill test duration [minutes]; model 2). Cumulative hazard plots grouped by exposure suggested no appreciable violations of the proportional hazards assumption. Because of the known correlation between BMI and several of the MetS components, we elected not to include it as a covariate in our models; but we do describe the effect of BMI on risk in our joint analyses, described below. We estimated the joint effects of MetS exposure across categories of age (<50, ≥50 years), BMI (<25, 25-29.9, ≥30 kg/m^2), and CRF (fit, not fit) using a common referent group at low risk (eg, no MetS and <50 years). In addition, we tested for multiplicative interaction between MetS (yes, no) and age, BMI, and fitness (all in continuous form) by fitting each of these terms and their cross-product, along with the covariates in model 1. We also completed our primary

analyses after excluding deaths that occurred in the first 5 years of follow-up and after excluding men with prevalent cardiovascular disease at baseline. Similar patterns of association were observed in these analyses. Statistical analyses were performed using SAS (version 9.1; SAS Institute, Cary, NC) software. All *P* values were obtained from 2-sided hypothesis tests.

3. Results

At baseline, the prevalence of MetS was 27.9% (3+ components). The characteristics of participants with and without the syndrome are shown in Table 1. Compared with individuals without MetS, those with the syndrome were on average older, less fit, had higher BMIs, drank less alcohol,

Table 1
Baseline characteristics according to MetS status

	MetS[a]	
	No	Yes
n	23 962	9 268
Age (y)	44.0 ± 10.0	47.2 ± 9.8
Fitness (treadmill time [min])	19.5 ± 4.9	14.7 ± 4.4
Height (cm)	178.8 ± 6.5	179.3 ± 8.2
BMI (kg/m^2)	25.4 ± 2.9	29.6 ± 4.5
Current smoker (%)	15.9	20.4
≥5 Alcohol drinks per week (%)	36.9	30.7
Family history (%)		
Hypertension	16.4	22.6
Diabetes	6.4	10.6
Cardiovascular disease	27.8	32.8
Cancer	23.6	31.0
MetS components		
Abdominal obesity		
Waist circumference (cm)	90.5 ± 8.6	103.1 ± 12.0
Abdominal obesity (%)[b]	7.2	55.9
Blood pressure		
Systolic (mm Hg)	119 ± 13	128 ± 14
Diastolic (mm Hg)	79 ± 9	86 ± 10
High blood pressure (%)[c]	32.1	76.8
Blood lipids		
HDL (mmol/L)	1.3 ± 0.3	1.0 ± 0.2
Low HDL (%)[d]	19.7	70.3
Triglycerides (mmol/L)	1.2 ± 0.7	2.5 ± 2.0
High triglycerides (%)[e]	13.6	75.7
Fasting blood glucose		
Glucose level (mmol/L)	5.4 ± 0.7	6.1 ± 1.4
High glucose (%)[f]	33.6	76.9

Data shown as mean ± SD unless specified otherwise.

[a] *No* defined as 0 to 2 components, and *Yes* defined as the presence of ≥at least 3 of the 5 components.

[b] *Abdominal obesity* was defined as waist girth ≥102 cm [40 in] in men.

[c] *High blood pressure* was defined as systolic blood pressure ≥130 mm Hg, diastolic blood pressure of ≥85 mm Hg, or history of physician-diagnosed hypertension.

[d] *Low HDL-C* was defined as HDL <1.04 mmol/L (40 mg/dL) in men.

[e] *High triglycerides* was defined as triglycerides ≥1.69 mmol/L (150 mg/dL).

[f] *High glucose* was defined as glucose ≥6.1 mmol/L (110 mg/dL) or history of physician-diagnosed diabetes.
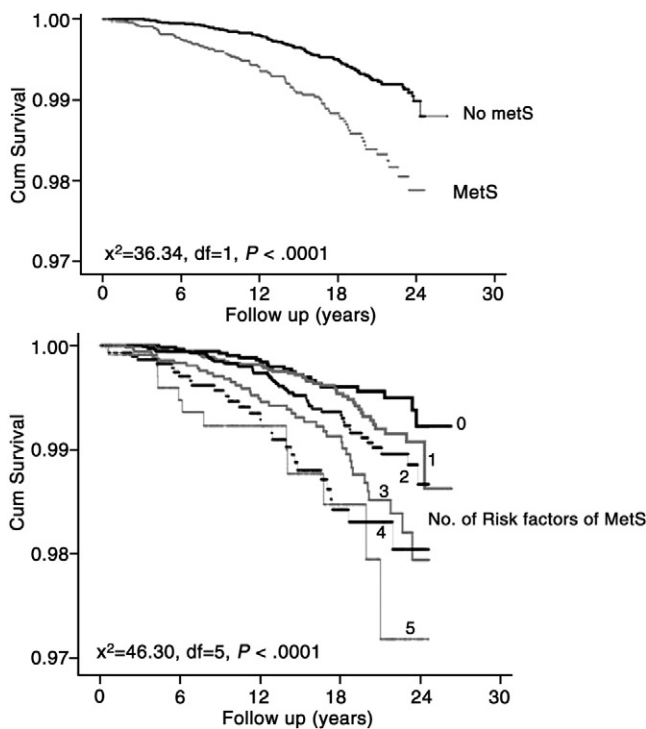
Fig. 1. Kaplan-Meier plots of survival for cancers of the digestive system in men, the ACLS (1977-2003).

and had more family history of disease, including cancer. Men with MetS were also taller and more likely to have smoked at study baseline. The mean values of each of the MetS components and the prevalence of meeting the criteria for each are provided at the bottom of Table 1.

Over an average of 14.4 (SD = 7.0) years of follow-up, 478 512 person-years of exposure accrued; and 188 digestive and gastrointestinal cancer deaths were identified. The distribution of the deaths for specific cancer types was as follows: esophageal (n = 24), stomach (n = 22), small

intestine (n = 2), colon (n = 47), rectum/anus (n = 10), liver (n = 18), gall bladder (n = 7), pancreas (n = 56), and other (n = 2).

Kaplan-Meier plots for overall MetS (0-2 vs 3+ components) and according to the number of prevalent syndrome components are displayed in Fig. 1. The presence of MetS was associated with earlier mortality, as was an increase in the incremental number of syndrome components (Fig. 1, $P < .01$).

In multivariable models, the presence of MetS (0-2 vs 3+ components) was associated with about 2-fold higher mortality from digestive cancers (HR = 1.90 [1.42-2.55]); and there was a graded increase in risk associated with a greater number of prevalent MetS components (P trend $< .01$, Table 2). Compared with men with 0 component, those with 3 or more components were at more than twice the risk (HR = 2.31 [1.42-3.76]), whereas men with all 5 components were at a 3-fold higher risk (HR = 3.07 [1.49-6.30]) for cancer death. Interestingly, further adjustment of model 1 for fitness weakened these associations by 20% to 30%; but MetS remained significantly associated with cancer mortality. Additional adjustment for prevalent cardiovascular disease at baseline (myocardial infarction or stroke) did not alter the magnitude of the associations observed (data not shown).

We also evaluated risk for overall mortality from cancers of the digestive system associated with the individual MetS components (Table 3). We found positive associations with abdominal obesity (HR = 2.15 [1.58-2.92]), high triglycerides (HR = 1.41 [1.05-1.90]), low HDL (HR = 1.45 [1.08-1.93]), and high glucose (HR = 1.54 [1.15-2.07]), but not high blood pressure (HR = 1.17 [0.87-1.57]), after adjustment for covariates in model 1 (Table 3). Adjustment for additional MetS components revealed that only abdominal obesity (HR = 1.89 [1.36-2.62]) and high glucose levels (HR = 1.38 [1.02-1.87]) remained independently associated with mortality. Further adjustment for CRF with other covariates and additional MetS components attenuated the association with abdominal obesity somewhat (HR = 1.56

Table 2
Associations between MetS, the number of metabolic components, and mortality for cancers of the digestive system: the ACLS (1977-2003)

	n	Deaths	Age-adjusted model HR (95% CI)	Multivariable model 1[b] HR (95% CI)	Multivariable model 2[c] HR (95% CI)
MetS[a]					
No	23 962	106	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Yes	9268	82	1.94 (1.45-2.59)	1.90 (1.42-2.55)	1.52 (1.11-2.09)
No. of MetS components					
0	6484	21	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
1	9489	41	1.19 (0.70-2.01)	1.18 (0.70-2.00)	1.11 (0.65-1.88)
2	7989	44	1.40 (0.83-2.37)	1.40 (0.83-2.36)	1.22 (0.72-2.07)
3	5214	41	2.11 (1.24-3.59)	2.07 (1.22-3.52)	1.62 (0.94-2.81)
4	2952	29	2.56 (1.45-4.51)	2.50 (1.42-4.41)	1.82 (1.00-3.31)
5	1102	12	3.12 (1.52-6.37)	3.07 (1.49-6.30)	2.05 (0.96-4.38)
P for linear tend			<.0001	<.0001	.007

[a] *No* defined as 0 to 2 components, and *Yes* defined as the presence of ≥3 of the 5 MetS components.
[b] Adjusted for age, examination year, height, current smoking, alcohol intake, and family history of cancer.
[c] Adjusted for age, examination year, height, current smoking, alcohol intake, family history of cancer, and treadmill test duration.

Table 3
Independent effects of MetS components on risk for mortality from cancers of the digestive system: the ACLS (1977-2003)

	n	Deaths	Age-adjusted HR (95% CI)	Model 1 HR (95% CI)[a]	Model 2 HR (95% CI)[b]
Abdominal obesity	6915	63	2.16 (1.59-2.92)	2.15 (1.58-2.92)	1.89 (1.36-2.62)
High blood pressure	14 808	97	1.17 (0.87-1.56)	1.17 (0.87-1.57)	1.00 (0.74-1.35)
High triglycerides	10 284	73	1.43 (1.07-1.92)	1.41 (1.05-1.90)	1.08 (0.77-1.50)
Low HDL-C	11 245	84	1.50 (1.12-1.99)	1.45 (1.08-1.93)	1.24 (0.90-1.71)
High glucose	15 175	111	1.49 (1.11-2.01)	1.54 (1.15-2.07)	1.38 (1.02-1.87)

[a] Adjusted for age, examination year, height, current smoking, alcohol intake, and family history of cancer.
[b] Adjusted for age, examination year, height, current smoking, alcohol intake, family history of cancer, and each of the other MetS components.

[1.09-2.21]), but not the association with high glucose (HR = 1.36 [1.00-1.83]).

We next described the associations between MetS and site-specific cancer mortality for which there were 15 or more deaths. Metabolic syndrome was significantly associated with higher risk for colon, colorectal, esophageal, and liver cancer deaths, but not pancreatic or stomach cancer (Table 4). Further adjustment of model 1 covariates for fitness attenuated the associations by about 10% to 20%; and after this adjustment, only colorectal and esophageal cancer remained significantly associated with the presence of MetS.

Finally, we described the joint associations between the presence of MetS and other risk factors for digestive cancer mortality. For this analysis, the referent group consisted of men who did not have MetS and were at lowest risk for the other factor (Table 5). Among men without MetS, age was associated with increased risk (HR = 3.48 [2.37-5.13], <50 vs ≥50 years); as was obesity (HR = 2.02 [0.95-4.27], <25 vs ≥30 kg/m^2) and low fitness levels (HR = 2.03 [1.18-3.47], vs fit). Older men (≥50 years) were at greater risk if they had MetS (HR = 7.55 [5.14-11.08]). Interestingly, among normal-weight men (BMI <25), MetS was not associated with increased risk (HR = 0.93 [0.40-2.18]); but it did increase risk among overweight (BMI 25-29 kg/m^2: HR = 1.95 [1.28-2.95]) men and further still among obese men (BMI ≥30 kg/m^2: HR = 2.92 [1.88-4.52]) as compared with men who were of normal weight and without MetS (Table 5). Compared with men who were fit and without MetS, mortality risk was higher among those with MetS who were more fit (HR = 1.78 [1.26-2.51]) and in those who were unfit

(HR = 2.81 [1.86-4.26]). No tests for multiplicative interactions among our joint effects reached statistical significance (all *P*s > .05).

4. Discussion

In this prospective study with an average of 14.4 (SD = 7.0) years of follow-up, we found that the presence of MetS at baseline was associated with an approximately 2-fold higher risk for mortality from cancers of the digestive system among men (HR = 1.90 [1.42-2.55]). We also found that MetS was associated with increased mortality risk for a number of different cancers of the digestive system, including colorectal, esophageal, and liver cancer. Central obesity and elevated fasting glucose levels were independently associated with mortality' but risk was also increased with each additional component present, and men with all 5 components were at more than a 3-fold higher risk (HR = 3.07 [1.49-6.03]) compared with men with no components. Evaluation of the joint effects of other putative risk factors indicated that risk associated with MetS was particularly elevated for men who were older than 50 years, were overweight and obese, smoked, or had low fitness levels. These findings indicate that the presence of MetS is positively associated with mortality from cancers of the digestive system among overweight and obese men and suggest that interventions that favorably affect adiposity and other abnormalities associated with the syndrome may reduce risk of premature death from these cancers. Given

Table 4
Associations between MetS (0-2 vs 3+ components) and site-specific cancers of the digestive system in men: the ACLS (1977-2003)

Outcomes (anatomical site)	Deaths by MetS category (yes/no)[a]	Age-adjusted HR (95% CI)	Model 1 HR (95% CI)[b]	Model 2 HR (95% CI)[c]
Colon	20/27	1.72 (0.97-3.08)	1.73 (0.97-3.11)	1.50 (0.80-2.83)
Colorectal	27/30	2.15 (1.27-3.62)	2.14 (1.26-3.62)	1.71 (0.97-3.02)
Pancreas	21/35	1.54 (0.89-2.65)	1.52 (0.88-2.64)	1.38 (0.76-2.49)
Esophagus	13/11	3.15 (1.40-7.10)	3.02 (1.34-6.83)	3.23 (1.32-7.90)
Stomach	5/17	0.74 (0.27-2.01)	0.69 (0.25-1.90)	0.45 (0.16-1.30)
Liver	10/8	3.25 (1.27-8.29)	3.05 (1.19-7.84)	1.62 (0.59-4.41)

[a] *No* defined as 0 to 2 components, and *Yes* defined as the presence of ≥3 of the 5 MetS components.
[b] Adjusted for age, examination year, height, current smoking, alcohol intake, and family history of cancer.
[c] Adjusted for age, examination year, height, current smoking, alcohol intake, family history of cancer, and treadmill test duration.

Table 5
Joint associations between MetS (0-2 vs 3+ components), age, BMI, smoking, and fitness, and mortality from cancers of the digestive system in men: the ACLS (1977-2003)

	n	Deaths	MetS[a]	
			No	Yes
			HR (95% CI)	
Age (y)[c]				
<50	22,959	70	1.00	1.62 (0.97-2.68)
≥50	10,271	118	3.48 (2.37-5.13)	7.55 (5.14-11.08)
BMI (kg/m^2)[b]				
<25	12,458	57	1.00	0.93 (0.40-2.18)
25-29	15,580	88	1.11 (0.75-1.65)	1.95 (1.28-2.95)
≥30	5,192	43	2.02 (0.95-4.27)	2.92 (1.88-4.52)
Current smoking[e]				
No	27,530	150	1.00	1.88 (1.36-2.61)
Yes	5,700	38	1.26 (0.77-2.08)	2.50 (1.52-4.11)
CRF[d]				
Fit	28,625	141	1.00	1.78 (1.26-2.51)
Not fit	4,605	47	2.03 (1.18-3.47)	2.81 (1.86-4.26)

[a] *No* defined as 0 to 2 components, and *Yes* defined as the presence of ≥3 of the 5 MetS components.

[b] Adjusted for age, examination year, height, current smoking, alcohol intake, and family history of disease.

[c] Adjusted for examination year, height, current smoking, alcohol intake, and family history of disease.

[d] Adjusted for age, examination year, height, current smoking, alcohol intake, and family history of disease.

[e] Adjusted for age, examination year, height, alcohol intake, and family history of disease.

that cancers of the digestive system account for nearly 25% of all cancer deaths, we believe that such interventions may represent an important opportunity for reducing overall cancer mortality.

Our findings are consistent with those from a number of recent studies that have reported positive associations between the presence of the MetS, or a clustering of its components, and adenomatous polyps [8], incident colon cancer [10,11], and mortality from colorectal cancer [12,13]. Fewer studies have explicitly examined associations between clustered risk factors and other kinds of digestive cancer. Notwithstanding, there is now evidence of positive associations between obesity and adenocarcinoma of the esophagus [34,35], pancreatic [14,15,36], and liver cancer [37]. In particular, abdominal obesity has been linked to risk for pancreatic cancer in at least 2 prospective studies [14,15]. In terms of metabolic risk factors, insulin and glucose levels have been positively associated with pancreatic cancer [16,17]; and the presence of diabetes is associated with hepatocellular carcinoma, a common form of liver cancer [37]. Our results for stomach cancer are inconsistent with that of Calle and colleagues [38], who reported a positive association between BMI and mortality from stomach cancer. The reason for this discrepancy is not immediately clear; but it may be that our cases of stomach cancer mortality were a mixture of proximal (cardia) and distal cancers, the latter of which is believed to be more strongly linked to *Helicobacter pylori* infection than obesity [39].

It is notable that we found associations between MetS and a number of cancers of the digestive system. Although each type of cancer may have a unique natural history (ie, susceptibility genes, metabolic pathways, and environmental risk factors), several different biological mechanisms have been proposed that may explain our findings. Colorectal cancer is among the most heavily investigated digestive cancer, and there are links between this outcome and central obesity [40-42] and insulin and the IGF-1 axis [43]. Similarly, pancreatic cancer also has been associated with these factors. Both esophageal and liver cancers, for which the incidence rates have increased in the last 20 years [37], also have been linked to obesity; and it has been suggested that the obesity epidemic could be partly responsible for the parallel increase in the incidence of these cancers. Although it has been proposed that obesity influences risk for adenocarcinoma of the esophagus by increasing risk for gastroesophageal reflux disease, which can cause tissue damage, Barrett esophagus, and ultimately invasive disease [34,44], recent reports have highlighted a potential role for abdominal obesity [44], as well as alternate mechanisms [45,46]. Hepatocellular carcinoma accounts for a large proportion of all liver cancers, and liver damage from infection is thought to be an early event in the development of these cancers. Increasingly, nonalcoholic fatty liver disease, which is linked to obesity, also appears to contribute to liver damage, cirrhosis, and invasive cancer [37,47]. Our results suggest that the clustered obesity and metabolic abnormalities associated with the syndrome are adversely associated with both esophageal and liver cancer (Table 4).

The present study extends our understanding of risks associated with mortality from cancer of the digestive system in at least 3 important ways. First, we found that the information obtained from routinely measured cardiovascular and diabetes metabolic risk factors (ie, MetS components) were associated prospectively with risk for cancer mortality. Thus, our results provide a direct translation of risk associated with clinically defined MetS to death from cancers of the digestive system. Although we recognize the controversies surrounding definitions for MetS and the intended use of these definitions [3,48,49], we believe our results provide additional insights for other clinical outcomes, beyond cardiovascular and diabetes, that are associated with these clustered risk factors. Second, we observed associations between MetS and several different cancers of the digestive system. Other recent reports have linked similar exposures to breast cancer [9] and, together with our findings, suggest the potential for a more generalized effect of these metabolic risk factors on cancer outcomes. Third, our unique ability to evaluate the influence of CRF on these associations, both in multivariate modeling and joint effects analyses, provides evidence for the hypothesis that lifestyle interventions that can increase fitness and improve metabolic risk factors may help reduce risk for early mortality from digestive cancers. Results from our multivariate models revealed that inclusion of CRF in the models attenuated risk associated with MetS.

For example, the presence of the MetS was associated with a 2-fold higher risk (HR = 1.90 [1.42-2.55]) before further adjustment for fitness; but after adjustment, risk was reduced by about 20% (HR = 1.52 [1.11-2.09]). This finding is generally consistent with our previous finding that a high level of fitness also attenuated risk for all-cause and cardiovascular mortality associated the MetS [19]. Although inclusion of fitness in the models did not completely attenuate the association in this study, the magnitude of the associations were reduced considerably, which suggests an important role for physical activity and fitness in the causal pathway between MetS and mortality from digestive cancers. LaMonte and colleagues [30] and others [50] have reported that high fitness levels reduce the risk of developing MetS in prospective studies, and there is a wealth of evidence indicating that increased physical activity levels can increase CRF (eg, Church et al [51]) and improve the metabolic profile of high-risk individuals [52]. Collectively, we believe that these findings suggest that interventions designed to increase cardiorespiratory and metabolic fitness may be an important avenue for reducing risk of early death from cancers of the digestive system.

The present study also has limitations that should be carefully considered. The sample size of the ACLS cohort is modest relative to other cohorts designed to evaluate cancer outcomes; and accordingly, the number of deaths due to digestive cancers limited the precision with which we could estimate risk for site specific cancers. Although we did observe statistically significant associations with a number of outcomes, caution should be used when interpreting our results, particularly for our site-specific results. In addition, available sample size did not allow us to estimate weaker associations with much precision; therefore, future studies are needed to evaluate the robustness of our finding of a 40% to 50% higher risk for pancreatic cancer among men with MetS. In terms of exposure assessment, we used a clinical assessment of the MetS components to classify men at study enrollment; but in the present analysis, we were unable to evaluate the impact of changes in these risk factors over time on our outcomes. It is possible that many men with the MetS were treated for the presence of a particular syndrome component (eg, hypertension, high blood glucose) at some point in the follow-up interval. In addition, others may have experienced increases in these components. Such misclassification of exposure would likely lead to underestimating the magnitude of the association observed in the present study. In terms of confounder adjustment, we were able to adjust for many important factors (eg, age, smoking, alcohol intake); but we had little information on dietary behaviors or use of nonsteroidal anti-inflammatory drugs, factors that also could influence risk for our outcomes. Therefore, we cannot exclude the possibility that our lack of control for these covariates influenced our results. Finally, the ACLS cohort is predominantly white (>95%), well educated, and from middle– to upper–socioeconomic status households in the United States. For this reason, our results may not be generalizable to other ethnic and socioeconomic groups with substantially different demographic characteristics. Additional studies are needed to confirm and expand on the associations we report herein and to better understand the relationship between exposure timing and these outcomes.

The strengths of this report should also be considered. First, although the relative sociodemographic homogeneity of our cohort may limit the broad generalizablity of our results, this characteristic of our cohort is likely to increase the internal validity of the present study. Men in this study elected to obtain a preventive medical examination at the Cooper Clinic, which we believe to be a good indicator of the members of this cohort's access to health care. Thus, the potential for variation in access to cancer screening and treatment of cancer is likely small and therefore is less likely to have produced bias in our results. Second, our study had an average of roughly 14 years of follow-up; and exclusion of deaths from digestive cancers that occurred in the first 5 years of follow-up did not substantively alter our primary results, indicating that the potential for preclinical disease processes to influence levels of our metabolic exposures is low. The long follow-up available in this study provides assurance that we have maintained a reasonable temporal sequence between our exposures and outcomes and that the potential for preclinical disease processes to influence levels of our metabolic exposures is low. Finally, we had data on objectively measured CRF; and the addition of this information to our models substantially attenuated the association between MetS and gastrointestinal cancer mortality. Few other studies allow for adjustment of this exposure.

In conclusion, in this prospective study with an average of 14 years of follow-up, we found that the MetS and its components were positively associated with mortality from cancers of the digestive system. The presence of the syndrome was also positively associated with colorectal, esophageal, and liver cancer. Risk appeared to be particularly increased for men who were older, were heavier, smoked, or had low fitness levels. These findings suggest that interventions that reduce abnormalities associated with the syndrome may represent an important opportunity for reducing mortality from cancers of the digestive system. Because the MetS is quite prevalent in the US population, particularly among adults older than 60 years, and because these cancers account for about 25% of all cancer deaths, such interventions may provide an important mechanism for reducing overall cancer mortality. It will be important in future studies to determine when, along the progression to death from these cancers, factors associated with MetS produce their effect and the extent to which lifestyle and pharmacologic treatment of these metabolic abnormalities can reduce risk.

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