Prospective Associations between Depressive Symptoms and the Metabolic Syndrome:

The Spirited Life Study of Methodist Pastors in North Carolina

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Abstract

Background: Metabolic syndrome (Met-S) has a robust concurrent association with depression. A small, methodologically limited literature suggests that Met-S and depression are reciprocally related over time, an association that could contribute to their overlapping influences on morbidity and mortality in cardiovascular disease, diabetes, and cancer. Purpose: Using a refined approach to the measurement of Met-S as a continuous latent variable comprising continuous components, this study tested the prospective associations between Met-S and depression. Methods: This study of 1,114 clergy included four annual assessments of depressive symptoms and Met-S components. Standard methods were used to measure Met-S risk factors, and the PHQ-8 was used to assess depressive symptoms. We used confirmatory factor analysis to verify the structure of Met-S and depression and structural equation modeling to quantify the prospective relationships. Results: The statistical models confirmed the validity of quantifying Met-S as a continuous latent variable, replicated previous evidence of a concurrent association, and indicated a significant prospective association of initial depressive symptoms with subsequent Met-S. Initial Met-S was at most only weakly associated with subsequent depressive symptoms, and the former prospective effect was significantly larger. Associations of depressive symptoms and Met-S were significant for both men and women, but somewhat stronger among men. Conclusions: Results support representation of Met-S as a continuous latent variable. The association of initial depressive symptoms with later Met-S suggests that interventions addressing these correlated risk factors may prove useful in preventive efforts.

KEYWORDS
Metabolic syndrome; Depression; Prospective studies

ABBREVIATIONS
Met-S: Metabolic Syndrome; UMC: United Methodist Church; PHQ-8: Patient Health Questionnaire (8); SEM: Structural Equation Modeling; CFA: Confirmatory Factor Analysis; CFI: Comparative Fit Index; RMSEA: root mean square error approximation; FIML: Full information maximum likelihood

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Introduction

The metabolic syndrome (Met-S) is a medically worrisome clustering of physiologic risk factors, specifically abdominal obesity, insulin resistance, dyslipidemia, and elevated blood pressure.(1) Common in industrialized nations and increasingly prevalent in non-industrialized countries,(2) Met-S is associated with an increased risk of serious illness and death, including morbidity and mortality associated with coronary heart disease,(3) stroke,(4) diabetes,(5) and some forms of cancer.(6) Recent research has examined the association between Met-S and depression,(7) as it could be a mechanism contributing to the association of depression with subsequent coronary heart disease,(8) stroke,(9) diabetes,(10) and cancer.(11)

Most studies of depression and Met-S are cross-sectional in design, and find a significant concurrent association.(7) The smaller number of prospective studies of initial depression and incident Met-S also find a significant association, consistent with the view that depression contributes to the development of this constellation of cardio-metabolic risk factors.(7) However, in some prospective studies, Met-S also predicts the later development of depressive symptoms and disorders,(7) suggesting a possible reciprocal association over time in which depression functions both as a contributing cause and a consequence of Met-S, similar to the bidirectional association between depression and Type 2 diabetes.(10, 12)

Associations between depression and Met-S could reflect physiological or behavioral mechanisms. For example, the prospective association of depression with subsequent Met-S could involve effects of physiological correlates of stress and dysphoric emotion on metabolic processes associated with central adiposity and insulin regulation (13), and the association of Met-S with later depression could involve the effects of inflammatory correlates of these elevated cardio-metabolic risk factors on negative mood and related depressive symptoms.(14) Initial depression could also contribute to later Met-S through its effects on reduced levels of

physical activity or dysfunctional eating, and initial Met-S could contribute to later depressive symptoms and disorders through similar behavioral and psychological mechanisms. (15)

The possible reciprocal association between depression and Met-S can be evaluated indirectly through comparisons of prospective pathways in separate studies, especially when the aggregated results of several studies can be compared.(7) However, given the complexities of comparing studies with different methods and designs, the two paths are best tested within the same study. To date only two studies have included the minimally necessary assessments of both depression and Met-S at two points in time that permit this comparison. A study of lifetime history of depression and major depressive disorder diagnoses found that initial depression predicted incident Met-S, but initial Met-S did not predict later depression.(16) In contrast, a study assessing Met-S in childhood and adulthood that also assessed depressive symptoms at two time points in adulthood found that childhood Met-S predicted depression in adulthood, and that initial depression in adulthood predicted subsequent Met-S.(17) Although consistent with a bi-directional association, the unbalanced timing of assessments across childhood and adulthood complicates the interpretation of these findings, as do the inconsistent results across studies.

The present study tested the prospective associations between depression and Met-S using a four-wave panel design, in which depressive symptoms and components of Met-S were assessed in each annual wave. The Spirited Life Study(18) enrolled 1,114 United Methodist ministers in North Carolina, and tested the effects of a combination of lifestyle interventions on Met-S and depressive symptoms. The effect of the intervention was controlled in the analyses reported here. Ministers represent an appropriate population for testing the associations between depression and Met-S, as, both nationally and in the specific population studied here, they experience high levels of stress and depression(19) and high rates of obesity.(20)

In testing the association between depression and Met-S, in addition to the use of the parallel repeated assessments that permitted estimation of both prospective paths and direct comparison of their relative magnitude, we addressed three methodological issues present in prior research. First, Met-S is most often quantified as a categorical variable, despite the fact that the diagnosis imposes on continuous components criteria that vary across multiple Met-S classification systems.(21) Use of multiple classification systems complicates comparisons across studies. (1) Importantly, imposing dichotomous criteria on continuous variables is also problematic because it can weaken estimates of substantive associations,(22, 23) a practice that has been questioned in Met-S research.(21) Measurement research has demonstrated that Met-S can be represented appropriately as a continuous latent variable comprising abdominal obesity, insulin resistance, dyslipidemia, and elevated blood pressure components.(24, 25) Second, some evidence indicates gender differences in the structure of Met-S, suggesting that this latent variable should be estimated separately for men and women.(26, 27) Third, as in the case of Met-S, taxometric research suggests that depression is often more accurately seen as a continuous variable, as opposed to the categorical variable of diagnosed depressive disorder.(28) Even when taxometric analyses suggest the presence of a distinct category of depressive disorder, the optimal cutpoint for symptom severity in those analyses is below that associated with diagnostic criteria for mood disorders and there is meaningful variance in severity of depressive symptoms that is not captured by the diagnostic categorical approach to representing depression.(29) Hence, representing both Met-S and depression as continuous

latent variables rather than dichotomous categories may provide a more sensitive test of their concurrent and prospective associations. To facilitate description of the present sample and comparison with other studies, we used standard categorical approaches to quantify the prevalence of Met-S and depression. However, given the advantages of examining associations between continuous variables, we utilized continuous latent variable scores representing depressive symptoms and Met-S in the primary analyses.

Methods

Sample

In our study, participants were 1,114 Methodist clergy from North Carolina enrolled in a randomized controlled trial held from October 2010-December 2014 (see supplement).(18) There were no health inclusion criteria for this study; exclusion criteria were retired clergy and clergy on leave. We collected cardiometabolic and survey data for participants at baseline and at their corresponding 12-, 24- and 36-month follow-up. Our response rates to the survey and participation rates in the health screenings were high; 100% of those invited completed the health screening and 100% completed the survey in 2010, 95.2%/93.9% in 2011 for the health screen and survey, respectively, 84.8%/87.1% in 2012, and 78.0%/87.2% in 2013. As shown in Table 1, participants had high levels of education (82.1% of males and 83.3% of females possessing a graduate degree); had average ages of 52.4 for males and 50.8 for females; were predominantly white (89.5% males and 87.4% females) and married (95.8% males and 72.8% females). This group had high rates of obesity; at baseline, 50.7% and 44.8% of males and females, respectively, were classified as obese, and 37.4% and 26.1% as overweight.

Measures

Met-S. Cardiometabolic data collection assessing components of Met-S was performed by trained staff. For categorical classification, Met-S indicators were derived for each participant at each measurement time point using the International Diabetes Federation definition (IDF), which we summarize in Table 2.(30, 31) While the IDF criterion for insulin resistance uses fasting blood glucose, we measured glycated hemoglobin (HbA1c), and in the categorical Met-S criteria used the generally accepted standard of HbA1c levels ≥ 6.0% (42mmol/mol) to indicate people at risk for diabetes.(30, 32) For categorical classification, Met-S was defined as meeting the central obesity criterion plus meeting 2 or more of the 4 additional criteria (see supplement for additional details).

Depressive Symptoms. The online survey included measures of depressive symptoms. Depressive symptoms were measured using the Patient Health Questionnaire-8 (PHQ-8),(33) which consists of eight items on the frequency of depression symptoms during the past two weeks (the original PHQ includes an additional question on suicidality, which because of institutional review board restrictions, could not be included). The inventory has well-established reliability and validity, with a range from 0-24. Based on previous validation studies, for categorical descriptions we report scores ≥10 to indicate moderate or severe depression, which we refer to as “depressive symptoms.” In the CFA and SEM models, we grouped the PHQ items into three sets of combined manifest indicators for depression to reduce nuisance correlation at the item level, which can improve model efficiency. This is an approach that is common when the goal of the analysis is to measure the relationship between latent variables.

Using principal component analysis, we identified a three factor grouping model for the individual items contained in the PHQ-8. Each factor is an additive scale of responses to the individual questions on the PHQ-8. Set 1 (3 items) included cognitive-affective symptoms (i.e., little interest or pleasure in doing things; feeling down, depressed or hopeless; feeling bad about yourself, feeling that you are a failure, or feeling that you have let yourself or your family down). Set 2 (3 items) included somatic symptoms (i.e., trouble falling asleep, staying asleep, or sleeping too much; feeling tired or having little energy; poor appetite or overeating). Set 3 (2 items) included concentration and movement symptoms (i.e., trouble concentrating on things such as reading the newspaper or watching television; moving or speaking so slowly that other people could have noticed, or being so fidgety or restless that you have been moving around a lot more than usual).

Statistical Analyses

Rescaling

When systolic and diastolic blood pressure are both included in confirmatory factor analysis (CFA) and structural equation models (SEM), they tend to load together to the exclusion of other variables,(24, 34) given their high correlation. This is also true for HDL and triglycerides.(24, 34) Therefore, systolic and diastolic blood pressure were combined into a single measure of mean arterial pressure (MAP) using the following standard formula for resting values,

$$MAP = \frac{\left(2xP_{diastolic} + P_{systolic}\right)}{3}$$

For the dyslipidemia component, we used the ratio of triglycerides to HDL. Because HDL and triglyceride levels are highly correlated, including this ratio improves model efficiency.(24)

The models we used assume the measured variables reflect a multivariate normal distribution. When individual manifest variables are univariate normal, then the combined variables are usually multivariate normal. Two of the variables, HbA1c and the triglyceride to HDL ratio were skewed. They were log-transformed to normalize their distributions. To avoid problems with convergence, (35) each manifest variable was rescaled as a percentage of the maximum score in the study population for that particular measure according to the following formula:

$$X_{i,j}^{rescaled} = \frac{\left(X_{i,j} - X_{j[min]}\right)}{\left(X_{j[max]} - X_{j[min]}\right)} \quad ,$$

where i indexes case number and j indexes the manifest variables.

This transformation did not alter the distribution of the variable, but made the mean level of the variables more interpretable, as they were each expressed as a percent of the maximum value. For participants who indicated they were receiving treatment for lipid abnormalities, we set their triglyceride/HDL score equal to 1, similarly for those on blood pressure medication their MAP score was set to 1. For those with treated diabetes, we set their insulin resistance score equal to 1.

Measurement Modeling

A CFA was conducted to confirm the adequacy of the relations between the measured continuous indicators and underlying continuous latent variables for depression and Met-S. The CFA was conducted on the three depression item sets for the depressive symptoms latent variable, and on the four continuous MET-S components of MAP, waist circumference

(abdominal obesity), triglyceride to HDL ratio (dyslipidemia), and HbA1c (insulin resistance). The CFA model was estimated by full information maximum likelihood (FIML) using the *lavaan* package in R.(36) Using FIML allows us to take a model-based approach to account for missing data. We used the fixed-factor method to set the scale of the CFA by setting the latent variable variances at the first time point to 1. As indices of the models' statistical fit, we used standard criteria of the comparative fit index (CFI) > 0.90 and root mean square error of approximation (RMSEA) < 0.05.

As past research has produced mixed results on whether the structure of Met-S differs between genders, we gender-grouped these models and tested whether equating parameters between genders was justified. In order to test the adequacy of the measurement model, we tested whether the loadings followed the same pattern of association over the four waves of the study (configural invariance); whether it was valid to equate the factor loadings at each time point (weak invariance); whether the means of the indicator variables were equal over time (strong invariance); and whether the covariance between the latent constructs were different over time. As our primary interest is in the cross-time association of Met-S and depression, we allowed the latent means to vary over time. Model equivalence was tested as a change in CFI of less than 0.01.(37) We then tested the validity of equating the factor loadings between men and women. χ^2 tests with $p<0.001$ were used to compare models with and without gender constraints.

Associations of Met-S and Depressive Symptoms.

Once we established the adequacy of the CFA, we turned to SEM to explore the cross-time associations between the continuous latent depression and Met-S constructs. To begin, we removed the cross-time covariance relationships among the constructs and replaced them with directional associations. The primary hypothesis we tested was whether there was evidence to support the existence of cross-lagged, reciprocal associations between depression and Met-S. Not only did we compare the magnitude of these cross-lagged associations, but we also explored whether they differed between males and females. χ^2 tests were used to compare constrained vs. unconstrained models with the threshold for statistical difference set at $p<0.001$.

Control Variables

We controlled race as a dichotomous variable (1 = Black, 0 = otherwise) and age as a continuous variable. The design of this study included a health intervention that was staggered across the three cohorts in the study. Because the intervention could potentially alter the associations between the health indicators and Met-S/Depression, indicator variables were created for cohort 2 and cohort 3, with membership in cohort 1 as the reference category. Inclusion of the cohort indicators controlled for any possible differences induced by the intervention.

Results

Prevalence of Met-S and Depression

Table 1 presents the baseline metabolic status and indicators for depressive symptoms for men and women. On average, males had 2.45 elevated categorical Met-S criteria (Standard Deviation (SD)=1.48) and females, 2.57 (SD=1.33). 55.6% of males and 36.7% of females were

classified as having Met-S by the categorical criteria. Because Met-S was defined using the IDF definition, which requires individuals to meet the obesity criterion, and the males in our population had higher rates of obesity, the proportion of the population with Met-S was higher among males than females. In terms of depressive symptoms, 11.8% of males and 10.4% of females had PHQ-8 scores greater than or equal to 10, and 37.4% and 38.4% had scores greater than or equal to 5 (classified as mild depressive symptoms).

Met-S and Depression Measurement Models

In terms of the fit of the CFA models, pooled for males and females, these models establish configural invariance (χ^2 = 462.87, df=278, RMSEA=0.024[0.020 0.027], CFI=0.995), weak and strong invariance as well as stability in the latent covariances between and across waves (ΔCFI = 0.001, 0.005, and 0.000, respectively). Thus, results confirm prior evidence that Met-S is well-represented by a continuous latent variable comprising continuous measured components. (24, 25) The final test did not support constraining the factor loadings between gender ($\Delta\chi^2$ =429.24, Δdf=321, p<0.001), consistent with prior evidence of gender differences in the structure of Met-S.(26, 27) Specifically, as seen in Table 3, although all four measured components were strongly associated with the continuous latent Met-S variable for both males and females, the loadings for the blood pressure and dyslipidemia components were somewhat stronger for females than males. Loadings for abdominal obesity (i.e, waist circumference) and insulin resistance (i.e., HbA1c) on the Met-S latent variable were nearly identical for males and females, as were loadings of the PHQ-8 item sets on the latent depressive symptom variable.

Tests of Associations of MetS and Depression

With the cross-time covariances removed and directional relationships added, the initial SEM had an adequate fit (CFI=0.962; RMSEA=0.059). The results supported the contention that the primary associations of interest did not vary across the multiple waves. Constraining the autoregressive, within-time covariances, and cross-lagged parameters to be equal over time was statistically valid ($\Delta\chi^2$ = 24.46, Δdf=8, p=0.001; $\Delta\chi^2$ = 9.80, Δdf=6, p=0.134; $\Delta\chi^2$ = 12.38, Δdf=8, p=0.135). Hence, in Table 3 and Figure 1 we report the associations between continuous latent variables representing depressive symptoms and Met-S collapsed across the multiple assessment waves. Additionally, constraining the autoregressive coefficients between genders did not significantly alter model fit ($\Delta\chi^2$ = 3.92, Δdf=2, p=0.141). Constraining one of the cross-lagged parameters between genders did not significantly alter model fit ($\Delta\chi^2$ = 0.11, Δdf=1, p=0.744 constraining depression to MetS; $\Delta\chi^2$ = 0.39, Δdf= 1, p=0.553 constraining MetS to depression, see supplement). Constraining both cross-lagged paths significantly altered model fit, ($\Delta\chi^2$ = 56.63, Δdf=2, p=<0.001), so we only constrained one path. Choosing which cross-lagged pathway to constrain was an arbitrary decision from a model fit perspective. We constrained the pathway from depression to MetS because it added the least amount of extra fit to the model. The models did not support constraining the latent covariances between genders ($\Delta\chi^2$ = 77.32, Δdf=2, p=<0.001), indicating that associations between depression and MetS differed significantly between males and females.

The parameter estimates from the final SEM, with the appropriate controls and constraints added, are reported in Table 3. The concurrent and prospective relationships are also presented graphically in Figure 1. The concurrent association between depression and Met-S was significant overall, did not vary significantly across the four waves, and was significant for both males and females, but was larger among males ($\sigma_{\text{Met-S,Depression}}$=0.115 [0.046 0.184] for

females and 0.191 [0.0871 0.295] for males). Also, as seen in Table 3, the association of initial depression with subsequent Met-S was also significant for both males and females, but again was somewhat larger among males (standardized β_{female}=0.076 [0.033 0.119]; β_{male}=0.100 [0.026 0.174]). The association of initial Met-S with subsequent depression approached, but did not reach, statistical significance (standardized β=0.021 [0.00 0.043], p=0.068).

To put these results in context, in terms of the overall effect of increased depression on subsequent Met-S, a one SD increase in the value of depression at the initial time point was associated with a 0.182 SD increase in Met-S for females and a 0.271 SD increase for males one year later (total effect=0.076+0.893*0.115 for females; 0.100+0.893*0.191 for males). Because the latent variables are on a standardized scale, a standard deviation can be interpreted like a z-score. 42% of this relationship in women and 37% in men was due to the direct, prospective relationship between depression and Met-S (0.076/0.182 for females; 0.100/0.245 for males). For the overall effect of increased Met-S on subsequent depression, a one SD increase in the value of Met-S initially was associated with a 0.114 SD increase in depression for women and a 0.176 SD increase in depression for men one year later (0.021+0.809*0.115 for females; 0.021+0.809*0.191 for males). 18% of this relationship in women and 12% of this relationship in men was due to the direct, prospective relationship between MetS and depression (0.021/0.114 for females; 0.021/0.176 for males)).

Discussion

A substantial body of research documents a concurrent association between depression and Met-S, and a smaller but methodologically limited literature suggests that these risk factors for multiple sources of morbidity and mortality may be reciprocally related over time.(7) The present study examined these associations across four annual assessments of Met-S and depressive symptoms in a sample of UMC pastors in North Carolina, using continuous latent variables to represent Met-S and depressive symptoms. The concurrent association between Met-S and depression found in prior studies was replicated, as was the prospective positive association of initial depressive symptoms with subsequent Met-S. The association of initial Met-S with subsequent depression only approached significance. Thus, there was at best very weak evidence to support prior suggestions that these risk factors are reciprocally related over time. Instead, initial depressive symptoms predicted subsequent Met-S, and this association was significantly larger than the association of initial Met-S with later depressive symptoms.

The magnitude of these associations cannot have been limited by measurement concerns in prior studies. The practice of dichotomizing the Met-S through standard criteria, and in some cases dichotomizing depression through clinical diagnoses or cut-off scores for continuous measures, likely had the effect of reducing estimates of the magnitude of these associations in prior studies.(22, 23) As in prior research,(24, 25) the continuous latent variable measurement model fit the data well for Met-S in the present study. Further, the present models for these latent variables included gender differences, which also could have obscured estimates of association in prior studies. The large sample size also likely improved the precision of the estimates of the magnitude of association in the current study, relative to previous smaller studies.

Prior studies specifically testing the reciprocal association between Met-S and depression had methodological limitations and produced differing results. The four parallel annual assessments of both Met-S and depressive symptoms in the present study provided a strong test of the reciprocal association and an internal replication over the multiple annual assessments, using well-validated approaches to measuring both risk factors. Hence, in the most compelling methodological design to date, the prospective associations differed significantly in magnitude, and only the association of initial depression with subsequent MetS reached statistical significance.

The present results also provided evidence of gender differences in several respects. Consistent with prior evidence (26, 27), the associations of individual indicators with overall Met-S differed for males and females somewhat. Further, the associations between depressive symptoms and Met-S were significant for both males and females, but were significantly stronger among males. These gender differences could reflect parallel differences in the behavioral or physiological mechanisms linking depression and Met-S described previously, but could also reflect gender differences in rates of depression and obesity in this population.

Limitations and Qualifications

There are several important potential limitations of these findings. Perhaps most obviously, given the unique sample of ministers, caution is warranted in generalizing the results. However, it is important to note again that this population experiences considerable levels of stress and depression,(19) as well as a relatively high prevalence of obesity.(20) The prevalence of significant elevation of depressive symptoms, elevated Met-S components, and elevated rates of qualification for Met-S in the current sample are consistent with this view. Nonetheless, replication of the present results with more representative samples would help strengthen the generalizability of these results.

Also, the primary prospective result between initial depressive symptoms and subsequent Met-S suggests a modest effect size. Hence, some caution is warranted in conclusions about the overall importance or clinical implications of this association. The significant difference in the magnitude of the two prospective associations is consistent with the interpretation that it is more likely that depression influences Met-S than the opposite causal direction. However, despite the prospective design, such causal conclusions are tentative at best in observational studies, and are more appropriately tested in experimental studies. It is also important to note again that participants were enrolled at different times across cohorts in a lifestyle risk-reduction intervention. Although statistical control of the intervention cohort variable precludes the possibility that the association of initial depression with subsequent Met-S is somehow due to the intervention, replications with non-intervention samples is also important. Finally, the IDF criteria we utilized to describe the prevalence of Met-S and its components is one of several available.(1) Although this relatively recent system was developed to increase the range of application across various populations, the prevalence of Met-S and its components in the present sample should be interpreted with appropriate caution. It should be noted again, however, that we did not use the categorical definition of Met-S in our primary analyses. Rather, the continuous latent variable approach that has been recommended generally (21) was supported in our measurement modeling, and it is this more refined measurement approach that provided the basis for the present results regarding the association of depression with Met-S.

Conclusions and Implications

The present results support prior suggestions that Met-S and depression may have overlapping effects on morbidity and mortality. However, the relative magnitude of the prospective associations provides greater support for the possibility that depression may influence health through intervening effects on Met-S, than for the opposite pattern. Further, interventions focused on depression may have larger effects on Met-S, compared to the effects of interventions for Met-S on depression. However, treatments that have beneficial effects on both factors warrant consideration, such as physical activity interventions. Low physical activity is a risk factor for both depression and Met-S, and randomized controlled trials suggest exercise interventions can reduce the severity of depressive symptoms, components of Met-S, and Met-S itself.(38, 39) Given recent evidence of effectiveness in the management of co-morbid depression and conditions related to Met-S, such as diabetes,(40) collaborative care interventions in which multidisciplinary teams provide coordinated management may also be appropriate for comorbid Met-S and depression.

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Table 1
Sample demographics and weight status at baseline

	Males (n=771)	Females (n=335)
Demographic Variables		
Age in years, mean (range)	53 (25-83)	53.7 (27-78)
Race		
White (%)	89.5	87.5
Black (%)	5.19	8.36
Other (%)	5.32	4.18
Education		
< 15 years (%)	8.82	6.87
4-year college (%)	8.95	9.55
Masters or Professional (%)	68.4	76.1
Doctorate (%)	13.7	7.16
Currently Married (%)	95.8	72.8
Rural or Small Town Residence (%)	34.4	29.0
BMI Status [a]		
Obese (%)	50.7	44.8
Overweight (%)	37.4	26
Normal (%)	11.5	28.7
Met-S and Depression Measures:		
Systolic Blood Pressure mmHg, mean (SD)	127 (14.4)	119 (16.2)
Diastolic Blood Pressure mmHg, mean (SD)	79.2 (10.1)	75.5 (11)
Mean Arterial Blood Pressure (SD)	95.3 (10.6)	89.9 (12.1)
Waist Circumference cm, mean (SD)	108 (16.1)	95.2 (18.9)
Triglycerides, mean (SD)	155 (87.7)	125 (73.3)
High Density Lipoprotein, mean (SD)	41.3 (13.4)	57.7 (16)
Hemoglobin A1c %HbA1c, mean (SD)	5.7 (0.782)	5.64 (0.753)
Hemoglobin A1c mmol/mol, mean (SD)	38.7 (8.54)	38.2 (8.23)
Central Adiposity Criterion Elevated (%) [c]	79.9	76.1
Triglyceride Criterion Elevated (%) [e]	52.0	36.1
Dyslipidemia Criterion (%) [d]	62.3	44.2
Blood Pressure Criterion Elevated (%) [b]	59.3	40.9
Insulin Metabolism Criterion Elevated (%) [f]	21.5	16.7

Table 1 (continued)

	Males (n=771)	Females (n=335)
Number of Elevated Met-S Criteria, mean (SD) [g,h]	2.45 (1.48)	2.57 (1.33)
Metabolic Syndrome (%) [i,h]	55.6	36.7
Taking medication for high blood pressure (%)	30.5	25.4
Taking medication for lipid abnormality (%)	26.3	18.5
Taking medication for diabetes (%)	11.9	9.25
Taking medication for depression (%)	15.7	24.2
PHQ-8, mean (SD)	3.92 (3.96)	4.08 (3.92)
PHQ-8 >= 10 (%)	11.8	10.4

Notes: a-Obese ≥30 kg/m^2, Overweight 25-29.9 kg/m^2, Normal 18.5-24.9 kg/m^2, no one underweight in study. Defined according to the categories used the National Heart, Lung, and Blood Institute definition.
b - systolic BP ≥130 or diastolic ≥85 or receiving treatment for previously diagnosed hypertension
c - Waist circumference ≥94cm men, ≥80cm women
d - HDL < 40 mg/dL men; < 50 mg/dL women or receiving treatment for lipid abnormality
e- ≥ 150 mg/dL, or receiving treatment for lipid abnormality
f - A1C ≥ 6.0% (42mmol/mol), or receiving treatment for diabetes, note that the IDF uses a fasting plasma glucose criterion, however the International Expert Committee of the IDF has recommended A1C≥6.0% (42mmol/mol) as a meaningful cutoff for people who should be considered at elevated risk for developing diabetes mellitus and 6.5% (48mmol/mol) to be diagnosed as having diabetes mellitus. [30]
g - medication criteria included
h - women have lower rates of obesity, but more Met-S criteria, men have higher rates of obesity, leading to the opposite gender relationship between number of Met-S criteria present versus the percentage with Met-S
i - central obesity plus 2 or more of the remaining 4 criteria present

Table 2
Factors used in this study for categorically-defined Met-S

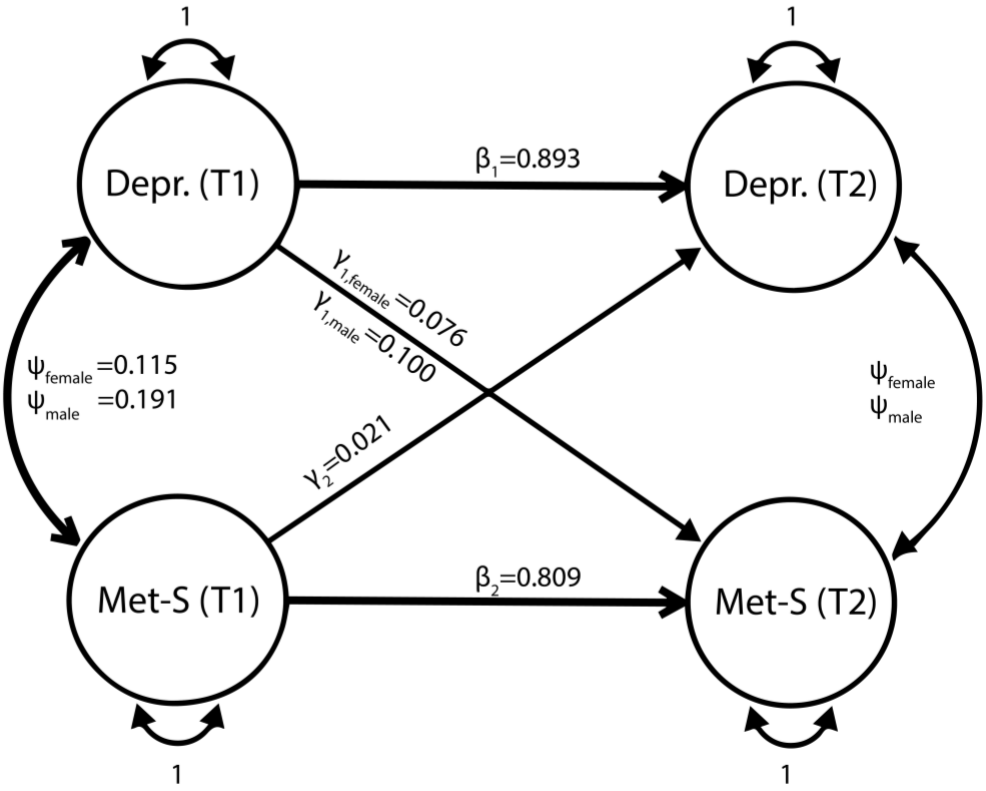
Met-S is indicated if the participant met the criterion for central obesity plus 2 or more of the 4 remaining criteria.	Threshold
Central Obesity Criterion	≥94cm for men and ≥80cm for women
Triglyceride Criterion	≥150mg/dl (1.7 mmol/L) or current treatment of a cholesterol abnormality
HDL Criterion	< 40mg/dl (1.03 mmol/L) in males and < 50mg/dl (1.29 mmol/L) in females or treatment of a cholesterol abnormality
Blood Pressure Criterion	systolic blood pressure ≥130mmHg or diastolic blood pressure ≥85 mmHg or current treatment of hypertension
Glucose Exposure Criterion [a]	≥ 6.0% (42mmol/mol) HbA1c

Note: a -The International Diabetes Federation defines diabetic risk in terms of fasting plasma glucose of greater than or equal to 5.6 mmol/l. However, we measured diabetic risk using HbA1c rather than fasting plasma glucose levels; because HbA1c is not sensitive to recent food intake it provides a longer-term measure of degree of glucose exposure and is more closely related to the risk of health complications than single measures of glucose levels.(30, 32)

Table 3
Parameter estimates from structural equation model that examines the prospective relationship between metabolic syndrome and depression

	Females		95% Confidence				**Males**		95% Confidence			
	Est.	*SE*	Interval		*z*	*P(>|z|)*	*Est.*	*SE*	Interval		*z*	*P(>|z|)*
Standardized Factor Loadings on Latent Variables (fixed between waves)												
Met-S												
Average BP	0.046	0.005	[0.036	0.056]	8.52	<0.001	0.036	0.008	[0.020	0.052]	4.27	<0.001
Log(Triglycerides/HDL)	0.042	0.005	[0.032	0.052]	8.37	<0.001	0.036	0.007	[0.022	0.050]	5.16	<0.001
Waist Circumference	0.032	0.003	[0.026	0.038]	9.87	<0.001	0.031	0.005	[0.021	0.041]	6.42	<0.001
Log(HbA1c)	0.011	0.003	[0.005	0.017]	3.28	0.001	0.012	0.004	[0.004	0.020]	2.86	0.004
Depression												
Depression 1	0.252	0.007	[0.238	0.266]	35.65	<0.001	0.291	0.009	[0.273	0.309]	32.66	<0.001
Depression 2	0.231	0.006	[0.219	0.243]	35.48	<0.001	0.252	0.008	[0.236	0.268]	32.88	<0.001
Depression 3	0.249	0.008	[0.233	0.265]	31.31	<0.001	0.295	0.010	[0.275	0.315]	29.45	<0.001
Standardized Path Coefficients (fixed between waves)												
Lag Depression Predicting Met-S	0.076	0.022	[0.033	0.119]	3.39	0.001	0.100	0.038	[0.026	0.174]	2.67	0.008
Lag Met-S Predicting Depression	0.021	0.011	[-0.001	0.043]	1.82	0.068	0.021	0.011	[-0.001	0.043]	1.82	0.068
Auto-Regressive Met-S	0.893	0.034	[0.826	0.960]	25.97	<0.001	0.893	0.034	[0.826	0.960]	25.97	<0.001
Auto-Regressive Depression	0.809	0.017	[0.776	0.842]	46.79	<0.001	0.809	0.017	[0.776	0.842]	46.79	<0.001
Covariances (fixed between waves)												
Depression and Met-S	0.115	0.035	[0.046	0.184]	3.24	0.001	0.191	0.053	[0.087	0.295]	3.62	<0.001
Females (N)	342											
Males (N)	772											
Total (N)	1114											

Figure 1
Parameter estimates for the prospective associations between depression and metabolic syndrome.



Legend: The parameter estimates for the structural equation model predicting the prospective relationship between depression and Met-S in a sample of United Methodist clergy in North Carolina (N=1,114 [Female(N)=390; Male(N)=390] at baseline). The parameters were stable among all three waves; were standardized; and where only one coefficient is listed, it was constrained to be equal between males and females. The within-wave co-variation between Met-S and depression was 0.115 [0.046 0.184] for females and 0.191 [0.087 0.295] for males and it was constrained to be equal between time points. The auto-regressive (across wave) association between Met-S and depression is also significant at 0.893 [0.826 0.960] for females and 0.809 [0.776 0.842] for males. The prospective relationship between depression and Met-S is significant at 0.076 [0.033 0.119] for females and 0.100 for males [0.026 0.174]. The prospective relationship between Met-S and depression was smaller and more variable at 0.021 [-0.001 0.043] and constrained to be equal between genders.

eAppendix: Supplemental Detail on Sample Recruitment, Measurement and Statistical Models

Sample

The data for this study come from the Spirited Life Study, a randomized controlled trial held October 2010-December 2014. Eligible participants were clergy members in July 2010 of either the North Carolina (NC) or Western NC Annual Conferences of the United Methodist Church (UMC), the two NC governing bodies that employ approximately 1,800 UMC clergy. There were no health status inclusion criteria. Exclusion criteria were pastors on leave and most extension ministers (e.g., seminary professors, hospital chaplains). The study was reviewed and approved by the Arts and Sciences Institutional Review Board at Duke University, Durham NC, USA.

An extensive communication campaign in September-October 2010 informed all NC UMC clergy about the study. We invited the 1,745 eligible clergy to consent online. Consenting participants had to complete in-person cardiometabolic data collection and an online survey to enroll. A total of 1,114 (64%) clergy met these criteria. Using a multiple baseline design, participants were randomized to one of three intervention start dates: January 2011 (Cohort 1, "immediate-intervention cohort"); January 2012 (Cohort 2, "one-year waitlist intervention cohort"); and January 2013 (Cohort 3, "control cohort"). We collected cardiometabolic and survey data for all three cohorts at baseline (Fall 2010) and at their corresponding 12-, 18-, and 24-month follow-up. For the purposes of the current study, we used only data collected during the fall to hold seasonality constant and to provide equal spacing between time points. All participants who consented to participate in the randomized controlled trial were invited to participate in the survey component of this study. The survey was administered online and took approximately 45 minutes to complete. Participants were offered incentives ranging from $25-$100 if they completed both the online survey and the health screenings. The online survey was used to derive depression measures, information about treatment for hypertension, abnormal cholesterol and diabetes, and demographics.

Measurement Protocols

Participants were asked to fast for at least 9 hours prior to data collection. Finger sticks were used to collect blood samples for lipid tests and glycated hemoglobin (HbA1c). Lipid values were measured by the Cholestech LDX system. The lipids of interest for Met-S were high-density lipoprotein (HDL) and triglycerides. HbA1c was analyzed using the Afinion HbA1c test. After an initial five-minute resting period, blood pressure was assessed three times using an Omron HEM-907XL machine with the right arm, with a thirty second rest between measurements. During the rest and measurement periods, participants remained seated with feet flat on the floor and arm resting at heart level. The mean of the three values was used in data analysis. Waist circumference was defined as the abdominal girth halfway between the iliac crest and the lower costal margin and measured to the nearest 0.25 inch. Height to the nearest 0.25 inch using a Seca 213 stadiometer, and weight to the nearest 0.2 lb. on a high-quality, calibrated digital scale (Seca 876), with the participant removing heavy clothing and shoes prior to being weighed. Cardiometabolic data were recorded by assessor staff on paper and double data-entered. Consistency checks were performed on all data sets in order to create reliable final databases for analysis. The online survey included questions about whether the participant was undergoing active treatment for hypertension, cholesterol abnormalities, and diabetes.

CFA Analysis

In Figure e1, we provide a graphical representation of the CFA model used in this study. In Table e1, we report model fit statistics for the CFA models. The configural invariance model evidenced adequate fit (CFI=0.995; RMSEA =0.024). The weak invariance assumption was supported (ΔCFI=0.001), the strong invariance assumption was supported (ΔCFI=0.005), the assumption of stability in the latent covariances within waves and between waves was also supported (ΔCFI<0.001), and the analysis supported the

assumption that the means of the latent constructs also remained constant over time (ΔCFI=0.002). Table e1 also presents the outcome of constraining the loadings between gender. Models where the factor loadings were not constrained to be equal between men and women for both depression and Met-S to be unconstrained between genders was also supported ($\Delta\chi^2$ =429.24, p<0.0001).

SEM Models

In Table e1 we also present the complete model fit statistics for the SEM models with and without gender constraints added. The first model tests constraining the latent mean of depression at times 1 and 2. This model was investigated because several of the models were converging to a negative solution. This constraint was supported by the data and it allowed the model to converge to the positive solution. With this constraint in place all of the control variables were added. The model with controls formed the basis of comparison for subsequent models.

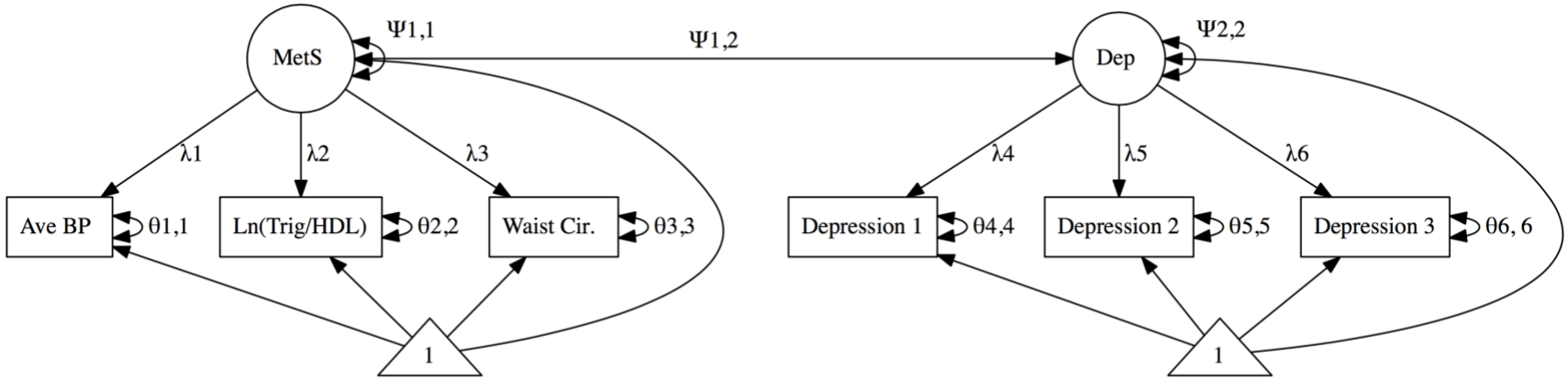
Table e1

χ^2 tests for gender differences in the coefficients for models of the prospective relationship between metabolic syndrome and depression

Model Tested	χ2	df	p	RMSEA	RMSEA 90% CI Lower	RMSEA 90% CI Upper	CFI	Δ CFI	Δχ2	p
Null Model	19889.68	409	<0.001	0.200	0.197	0.202	0.474			
CFA										
Configural invariance model	462.87	278	<0.001	0.024	0.020	0.027	0.995			
Weak invariance model	507.30	289	<0.001	0.025	0.022	0.029	0.994	0.001		
Strong invariance (indicator means stay constant over time)	720.12	310	<0.001	0.033	0.030	0.036	0.989	0.005		
Var/covar stabilities over time	732.67	319	<0.001	0.033	0.030	0.036	0.989	0.000		
Group factor loadings between gender	1161.91	640	<0.001	0.037	0.034	0.040	0.986	0.003	429.24	<0.001
SEM (models grouped by gender)										
Initial SEM	2028.21	656	<0.001	0.059	0.056	0.062	0.962			
Constrain latent mean of depression at times 1 and 2	2028.44	658	<0.001	0.059	0.056	0.062	0.962	0.000	0.23	0.891
Add control variables	2240.11	825	<0.001	0.054	0.051	0.056	0.962	0.000		
Autoregressive coefficients constrained to be equal across time	2264.57	833	<0.001	0.054	0.051	0.056	0.962	0.001	24.46	0.001
Within-time variances constrained to be equal across time	2274.37	839	<0.001	0.054	0.051	0.056	0.962	0.000	9.80	0.134
Cross lagged coefficients constrained to be equal across time	2286.75	847	<0.001	0.053	0.051	0.056	0.961	0.000	12.38	0.135
Test Gender Constraints[a]										
Constrain autoregressive coefficients between genders	2290.67	849	<0.001	0.053	0.051	0.056	0.961	0.000	3.92	0.141
Constrain only cross-lagged parameters on depression to MetS	2290.78	850	<0.001	0.054	0.052	0.057	0.960	0.001	0.11	0.744
Constrain only cross-lagged parameters on MetS to depression	2291.06	850	<0.001	0.053	0.051	0.056	0.961	0.001	0.39	0.533
Constrain both cross-lagged parameters same between genders	2347.30	851	<0.001	0.053	0.051	0.056	0.961	0.000	56.63	<0.001
Constrain only latent covariances same between genders	2367.99	851	<0.001	0.054	0.052	0.057	0.959	0.002	77.32	<0.001

Notes: a – The first model in this section is tested against the final model of the grouped SEM model. The subsequent models are tested against the first model listed in this section.

Figure e1
Representation of the CFA model



All loadings were time-invariant