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## Relations between Depressive Symptoms, Anxiety, and T Wave Abnormalities in Subjects without Clinically-apparent Cardiovascular Disease (from the Multi-Ethnic Study of Atherosclerosis [MESA])

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### Abstract

We hypothesized that depression and anxiety were associated with electrocardiographic (ECG) repolarization abnormalities in the Multi-Ethnic Study of Atherosclerosis (MESA), a cohort free of symptomatic cardiovascular disease. Depressive symptoms were assessed by the Center for Epidemiologic Studies-Depression scale, and trait anxiety symptoms by the Spielberger trait anxiety scale; both were categorized according to uppermost quartile. T wave inversions in ECG leads other than V1-V3 were obtained from resting electrocardiograms at the baseline exam. Participants with major intraventricular conduction abnormalities, or taking anti-arrhythmics, antidepressants, and/or anti-psychotics were excluded. Logistic regression models were estimated with multivariable adjustment for traditional cardiovascular disease risk factors. Among 5,906 participants, elevated depressive symptoms were associated with increased odds of T wave inversions after multivariable adjustment (odds ratio 2.02, 95% CI 1.33-3.06,  $p=0.001$ ) whereas greater trait anxiety was associated with a reduced odds of T wave inversions (odds ratio 0.47, 95% CI 0.29-0.77,  $p=0.003$ ). The divergent associations of depressive symptoms and trait anxiety with ECG T wave inversions were similar in men and women, and these associations were present across the racial/ethnic subgroups (non-Hispanic white, African-American, Hispanic, Chinese). In conclusion, symptoms of depression and anxiety were independently, yet oppositely associated

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with ECG T wave inversions. Negative emotions may have differential impact on cardiovascular mortality through unique relations with cardiac repolarization.

## Keywords

depression; anxiety; electrocardiogram; repolarization

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## Introduction

Cardiac repolarization measures by 12-lead electrocardiogram (ECG) have been recognized in population-based samples to be associated with cardiovascular mortality.<sup>1-4</sup> A study of 10,899 Finnish middle-aged men and women without known heart disease found T wave inversions in ECG leads other than V1-V3 were associated with cardiac (relative risk 2.65, 95% CI 1.86-3.78) and arrhythmic death (relative risk 3.16, 95% CI 1.86-5.36) over an average follow-up of 30 years.<sup>4</sup> Based on its prognostic utility, we examined the same indicator of abnormal repolarization to assess for its independent associations with depressive and anxiety symptoms in The Multi-Ethnic Study of Atherosclerosis (MESA). We hypothesized that depressive and anxiety symptoms would both be associated, albeit potentially differentially, with T wave abnormalities by ECG. We sought to identify a physiological measure that was related both with particular psychological symptoms and with cardiovascular mortality, such that it might provide insight into the mechanisms by which depression and anxiety are differentially related with cardiac mortality.

## Methods

MESA is a multicenter, longitudinal cohort study of the prevalence, correlates, and progression of subclinical cardiovascular disease.<sup>5</sup> MESA recruited 6,814 men and women 45 to 84 years old, self-identified as white, black, Hispanic, or Chinese and free of clinically apparent cardiovascular disease between July 2000 and August 2002 from six communities: Baltimore City and Baltimore County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; northern Manhattan and Bronx, New York; and St. Paul, Minnesota. Informed consent was obtained from the participants and the study was approved by Institutional Review Boards of each participating center. To minimize potential secondary repolarization effects from organic heart disease, we excluded participants whose ECG had QRS duration  $\geq 120$  msec. Also, we excluded participants who reported taking anti-arrhythmic medications, anti-psychotic medications, and/or antidepressant medications.

Participants underwent an extensive baseline evaluation (Exam 1), including a standardized questionnaire, measurements of height, weight, body mass index, anthropometric data, and blood pressure, and blood samples for total and high-density lipoprotein cholesterol, triglycerides, and glucose levels after a 12-hour fast.<sup>5</sup> Information on demographics, current smoking, education level, current alcohol use, physical activity and medical history were obtained using standardized questionnaires. Education level was defined by the highest level of schooling achieved. Physical activity was defined as the total of all light, moderate, and vigorous activities multiplied by individual metabolic equivalent values (METs) for these activities. Diabetes was defined as a fasting serum glucose  $\geq 126$  mg/dL or use of

hypoglycemic drugs or insulin. Serum creatinine was measured and estimated glomerular filtration rate (eGFR) was calculated by the Modification of Diet in Renal Disease equation.<sup>6</sup> Urine albumin and creatinine were measured at the Clinical Chemistry Laboratory at Fletcher Allen Health Care (Burlington, Vermont).<sup>7</sup> Urine albumin-to-creatinine ratios were classified according to presence of albuminuria ( $\geq 30$  mg albumin/g creatinine). High sensitivity C-reactive protein was measured using a BNII nephelometer (Dade-Behring, Deerfield, Illinois). Cardiac magnetic resonance imaging (MRI) was performed with 1.5-T magnets with determination of left ventricular mass as described previously.<sup>8</sup> Left ventricular mass index (LVMI) was calculated by using the formula  $LVMI = \text{left ventricular mass} / \text{body surface area (g/m}^2\text{)}$ .

Depressive symptoms were assessed at Exam 1 using the CES-D (Center for Epidemiologic Studies-Depression).<sup>9</sup> The CES-D is a 20-item survey that measures mood, somatic symptoms, social interactions, and motor functioning. Each item uses a 4-point Likert scale for responses. The sum total over the 20 items can range from 0 to 60, with higher scores indicating more severe symptoms of depression. The survey asks about the frequency in the past week that one has felt or behaved a certain way. Sample items include 'I felt depressed'; 'my sleep was restless'; 'I lost interest in my usual activities'. The CES-D does not include items for increased appetite or sleep, guilt, or suicidal thoughts. Anxiety was assessed at Exam 1 with the Trait-subscale of the State-Trait Anxiety Inventory.<sup>10</sup> This is a 20-item scale that requires respondents to indicate how frequently they experience a variety of anxiety symptoms, also using a 4-point Likert scale. Based on the skewed distributions of both the CES-D scores and Trait Anxiety scores in the MESA sample (Supplemental Figure 1), we categorized elevated depressive symptoms and anxiety according to the upper quartile for each score. This resulted in a cut-point score of 10 for the CES-D scale and 19 for the Trait Anxiety scale. The cut-point of 10 for CES-D score has previously been used to define elevated depressive symptoms and has been associated with increased risk of ischemic heart disease events in a cohort without known cardiovascular disease.<sup>11,12</sup>

Standard 12-lead ECGs were digitally acquired at Exam 1 using a Marquette MAC-PC electrocardiograph (Marquette Electronics, Milwaukee, Wisconsin) at 10 mm/mV calibration and speed of 25 mm/sec. All ECGs were centrally read at the EPICARE reading center, Wake Forest School of Medicine (Winston Salem, North Carolina), and visually inspected for technical errors and inadequate quality. The dependent variable for our analyses was presence of T wave inversions in leads other than V1-V3, according to the analysis by Aro et al.<sup>4</sup> Specifically, this included any negative T wave amplitude 0.1 mV or more in precordial leads V4, V5, or V6, or limb leads I, II, or aVF. T wave inversions in leads V1-V3 were not included in the dependent variable given their lack of prognostic significance.<sup>4</sup>

Demographic and coronary disease risk factors for MESA participants included and excluded from the current analysis were compared using chi-square tests, analysis of variance, or non-parametric tests as appropriate. Among MESA participants included in our analysis, we compared these same characteristics across categories defined by the uppermost quartile of CES-D depressive symptom score and trait anxiety score. Logistic regression models were used to estimate the odds ratios for T wave inversions with elevated depressive

symptoms and elevated anxiety, separately, with simultaneous inclusion of both symptom types. Two levels of adjustment were performed. First, we adjusted for age, gender, and race-ethnicity (White, African-American, Hispanic, Chinese). Next, odds ratios were calculated after further adjustment for center, body mass index, hypertension, diabetes mellitus, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels, heart rate on the resting ECG, systolic and diastolic blood pressure, cigarette smoking (never, former, or current), self-reported moderate and vigorous physical activity by quartile, estimated glomerular filtration rate, albuminuria, left ventricular hypertrophy according to Cornell ECG criteria,<sup>13</sup> log-transformed highly-sensitive plasma C-reactive protein levels, benzodiazepine, and beta blocker use. Variance inflation factors were examined to evaluate the presence of multicollinearity. The consistency of the results were evaluated in subgroups defined by gender and race/ethnicity. Based on a prior analysis that observed a relationship between left ventricular cavity size and T wave amplitude,<sup>14</sup> in a sensitivity analysis we estimated models that included left ventricular mass index measured by cardiac MRI as an additional covariable. All analyses were conducted using SPSS Version 22 (IBM Corp., Armonk, NY).

## Results

After excluding participants with QRS duration  $\geq 120$  msec and those taking anti-arrhythmic, antidepressant, and/or anti-psychotic medication, our sample consisted of 5,906 participants. Participants included in the analysis were younger (average age 62 years versus 63.2 years), less likely to be non-Hispanic white (35.6% versus 56.9%) and more likely Chinese-American, Hispanic, or African-American than participants who were excluded (Supplementary Table 1). Included participants had fewer coronary disease risk factors such as hypertension (44.2% versus 49.3%) and current smoking (12.9% versus 14.3%), and lower prevalence of reduced glomerular filtration rate  $< 60$  ml/min/1.73 m<sup>2</sup> (9.1% versus 12.3%). Depressive and anxiety symptom scores were lower in the included sample.

Depressive symptom scores and anxiety scores were moderately correlated with each other (Spearman correlation=0.48,  $p<0.01$ ). Compared to participants with depressive symptoms score  $< 10$ , those with elevated depressive symptoms were younger, more likely to be female, more frequently Hispanic, and more likely to report current smoking (Table 1). Average body mass index and heart rate were higher in those with elevated depressive symptoms, and prevalence of hypertension, diabetes, and albuminuria were higher. Both HDL cholesterol and C-reactive protein were higher among participants with elevated depressive symptoms. Similar patterns were observed comparing participants with trait anxiety score  $< 19$  to those with elevated symptoms. However, the prevalence of albuminuria and average C-reactive protein levels were not significantly different between participants with and without elevated anxiety symptoms.

Figure 1 presents the percentage of participants with T wave inversions, according to category of anxiety and depressive symptoms. The prevalence of T wave inversions was *lower* among those with (1.9%) compared to those without (2.9%) elevated anxiety symptoms. However, the prevalence of T wave inversions was *higher* among those with elevated depressive symptoms (3.4%) compared to those without (2.4%). When participants

were categorized both according to depressive and anxiety symptoms, the highest prevalence of T wave inversions was among participants who reported elevated depressive symptoms but who did not report elevated anxiety symptoms. Conversely, the lowest prevalence of T wave inversions was in participants who reported elevated anxiety but who did not report elevated depressive symptoms.

In logistic regression models that simultaneously included both depressive and anxiety symptoms (Table 2), elevated depressive symptoms were associated with increased odds of T wave inversions (odds ratio 1.91, 95% CI 1.30-2.80 in age/sex/race adjusted models), while elevated anxiety score was associated with reduced odds of T wave inversions (OR 0.56, 95% CI 0.35-0.88). Results were similar after full multivariable adjustment. Variance inflation factors were 1.30, indicating low multi-collinearity between depressive and anxiety symptoms. In gender-stratified analyses, the odds ratios for elevated depressive and anxiety symptoms were consistent for men and women. In subgroups defined by race-ethnicity (Table 3), the magnitude of the association between elevated depressive symptoms and T wave inversions was similar, with odds ratios ranging from 1.80 to 2.80 in multivariable models, although 95% confidence intervals crossed unity except in African-Americans. In addition, trends remained toward reduced odds of T wave inversions associated with anxiety, although this was statistically significant only for African-Americans. In sensitivity analyses that included left ventricular mass index by cardiac MRI as an additional covariate (n=4295), the odds ratios for T wave inversions were similar to our base case analyses, 2.50 (95% CI 1.47-4.26, p=0.001) for elevated depressive symptoms and 0.38 (95% CI 0.19-0.74, p=0.004) for elevated anxiety.

## Discussion

In this sample of men and women without known cardiovascular disease, elevated depressive symptoms were associated with increased odds of ECG T wave inversions in leads other than V1-V3, and elevated trait anxiety symptoms were associated with decreased odds of T wave inversions. The divergent associations of depressive symptoms and anxiety with T wave inversions may seem surprising, given their moderate correlation, yet was generally preserved across gender and racial/ethnic subgroups and rigorous sensitivity models. We focused our analyses on primary repolarization abnormalities by excluding participants with prolonged QRS duration. In addition, we excluded participants who reported use of psychoactive medications such as antidepressants and antipsychotics.

Depression is a well-recognized risk factor for cardiovascular mortality among the general population.<sup>15</sup> Anxiety often co-occurs with depression, and has also been associated with cardiovascular mortality and cardiac events in samples of apparently healthy people.<sup>16-20</sup> However, large studies that simultaneously assessed depression and anxiety have found that these two conditions may have divergent relations with outcomes. In the population-based Health Study of Nord-Trøndelag County (HUNT-2) involving 61,349 men and women, anxiety symptoms measured by self-report questionnaire were associated with reduced cardiovascular mortality (hazard ratio 0.76, 95% CI 0.69-0.83) and depressive symptoms with increased cardiovascular mortality (hazard ratio 1.23, 95% CI 1.12-1.34) in multivariable models adjusting for both negative emotions.<sup>21</sup> Also, a study of 5,057 patients

referred for routine exercise testing found that self-reported anxiety symptoms were associated with lower mortality (hazard ratio 0.81, 95% CI 0.72-0.92) whereas depressive symptoms were associated with increased mortality (hazard ratio 1.14, 95% CI 1.01-1.30).<sup>22</sup> Cardiac repolarization is a potential avenue for investigation for the differential relations between depression, anxiety, and mortality outcomes that have been observed in previous observational studies.

There are a number of potential important limitations to our study. Of note, the overall proportion of subjects with T wave inversions in MESA (2.6%) was higher than in the prior study by Aro, et al. (0.7%),<sup>4</sup> although we would speculate that this is the result of the higher average age in MESA (62 years) compared with the latter study (44 years). Despite the attempts to adjust for numerous risk factors in our multivariable analyses, our results may suffer from residual confounding. We used self-reported depressive symptoms and trait anxiety for our indicators of each negative emotion, and these do not substitute for clinical diagnoses of depression or anxiety. Also, our study included only one-time assessments of depressive symptoms and anxiety, and we could not determine whether changes in either symptom affect T wave amplitude over time. Nonetheless, our analysis opens a potential line of investigation into the differences that have been observed in the relations between depressive symptoms, anxiety, and cardiac prognosis.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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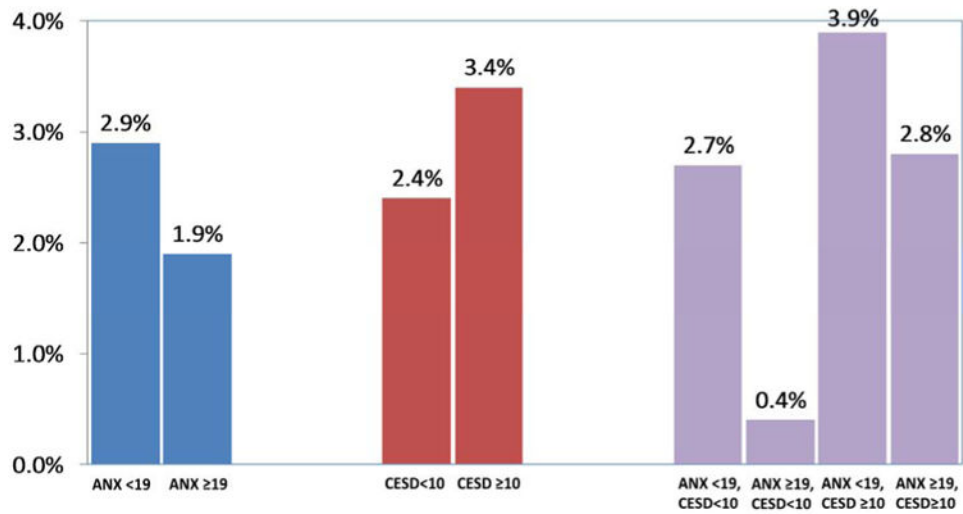
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### Highlights

1. We examined the relation of abnormal repolarization to depressive and anxiety symptoms.
2. Elevated depressive symptoms were associated with increased odds of T wave inversions.
3. Greater trait anxiety was associated with a reduced odds of T wave inversions.
4. Negative emotions may have unique relations with cardiac repolarization.



**Figure 1.** Prevalence of electrocardiographic T wave inversions according to elevated depressive and anxiety symptoms, defined by upper quartile of CES-D (Center for Epidemiologic Studies-Depression) or ANX (Spielberger trait anxiety) score.

**Table 1**  
 Characteristics of categories of participants based on cutoff values for CES-D and ANX scores.

Variable	CES-D <10 (n=4309)	CES-D 10 (n=1597)	P value	ANX <19 (n=4432)	ANX 19 (n=1474)	P value
Age (years)	62.2 (10.1)	61.4 (10.4)	<0.01	62.2 (10.1)	61.3 (10.3)	<0.01
Female	48.6%	62.9%	<0.01	49.6%	61.0%	<0.01
Race-ethnicity			<0.01			<0.01
Non-Hispanic white	37.6%	30.4%		35.4%	36.5%	
Chinese-American	13.6%	11.0%		12.3%	14.7%	
African-American	29.1%	27.4%		30.1%	24.4%	
Hispanic	19.7%	31.2%		22.3%	24.4%	
Body mass index (kg/m <sup>2</sup> )	28.0 (5.3)	28.8 (5.9)	<0.01	28.2 (5.3)	28.4 (5.8)	0.33
Hypertension	43.2%	46.8%	0.01	43.3%	47.0%	0.01
Systolic blood pressure (mmHg)	126.6 (21.3)	126.5 (22.2)	0.86	126.6 (21.3)	126.5 (22.2)	0.86
Diastolic blood pressure (mmHg)	72.2 (10.2)	71.6 (10.4)	0.03	72.2 (10.2)	71.6 (10.6)	0.04
LVH by ECG	3.3%	4.1%	0.13	3.4%	3.8%	0.51
Heart rate (BPM)	62.7 (9.4)	63.9 (9.8)	<0.01	62.9 (9.5)	63.5 (9.7)	0.03
Diabetes mellitus	10.4%	12.7%	0.03	10.8%	11.7%	0.32
LDL cholesterol (mg/dL)	111.0 (24.6)	111.8 (25.7)	0.31	111.5 (24.8)	110.6 (25.3)	0.27
HDL cholesterol (mg/dL)	50.1 (15.2)	51.3 (15.1)	0.01	50.0 (15.1)	51.9 (15.5)	<0.01
Current smoker	12.0%	15.2%	<0.01	12.5%	14.0%	<0.01
Mod/Vig Phys Activity (MET-min/wk)	4073 (2010, 7500)	4106 (1907, 7984)	0.84	4140 (2010, 7659)	3952 (1931, 7524)	0.30
Albuminuria	8.7%	11.3%	0.01	9.1%	9.4%	0.33
eGFR < 60 ml/min/1.73 m <sup>2</sup>	9.3%	8.6%	0.39	9.4%	8.4%	0.30
Log (C-reactive protein, mg/L)	0.59 (-0.22, 1.39)	0.73 (-0.14, 1.54)	<0.01	0.62 (-0.20, 1.43)	0.67 (-0.17, 1.45)	0.38
CES-D score	3 (1, 6)	15 (12, 20)		4 (1, 7)	12 (7, 18)	
Anxiety score	14 (11, 16)	19 (17, 22)		14 (11, 16)	21 (20, 23)	

Values are mean (standard deviation) or percentages, except for physical activity, C-reactive protein, CES-D score, and anxiety score where values are median (25<sup>th</sup>, 75<sup>th</sup> percentiles). P values correspond to Pearson chi-square tests for categorical variables, analysis of variance for continuous variables, and Mann-Whitney non-parametric tests for physical activity and C-reactive protein.

CES-D=Center for Epidemiologic Studies-Depression score; ANX=Spielberger trait anxiety score; LVH=left ventricular hypertrophy; ECG=electrocardiogram; LDL=low-density lipoprotein; HDL=high-density lipoprotein; MET=metabolic equivalents; eGFR=estimated glomerular filtration rate.

**Table 2**

Logistic regression models of T wave inversions, in all subjects combined and stratified by gender.

Grouping	Age/race +/- sex adjusted	P value	Multivariable	P value
<i>All (n=5906)</i>				
CES-D 10	1.91 (1.30, 2.80)	0.001	2.02 (1.33, 3.06)	0.001
ANX 19	0.56 (0.35, 0.88)	0.013	0.47 (0.29, 0.77)	0.003
<i>Men (n=2807)</i>				
CES-D 10	2.00 (1.15, 3.47)	0.014	2.00 (1.08, 3.69)	0.027
ANX 19	0.60 (0.30, 1.18)	0.135	0.43 (0.20, 0.93)	0.031
<i>Women (n=3099)</i>				
CES-D 10	1.79 (1.04, 3.06)	0.035	1.77 (0.98, 3.21)	0.059
ANX 19	0.55 (0.29, 1.04)	0.064	0.55 (0.28, 1.10)	0.093

\* All models adjust simultaneously both for CES-D and ANX score. In addition to age/race, multivariable models also adjusted for center, body mass index, hypertension, diabetes mellitus, low-density lipoprotein and high-density lipoprotein cholesterol levels, systolic and diastolic blood pressure, cigarette smoking (never, former, or current), self-reported moderate and vigorous physical activity in quartiles, estimated glomerular filtration rate <60, albuminuria, left ventricular hypertrophy by Cornell ECG criteria, log-transformed highly-sensitive plasma C-reactive protein levels, benzodiazepine, and beta blocker use. Additionally, models with men and women combined adjusted for gender. Due to missing data, sample sizes were reduced in multivariable models (n=5831 for all participants, n=2776 for men, n=3055 for women).

**Table 3**

Logistic regression models of T wave inversions, stratified by race-ethnicity.

Grouping	Age/sex adjusted	P value	Multivariable	P value
<i>White (n=2105)</i>				
CES-D 10	1.79 (0.65, 4.92)	0.259	1.80 (0.61, 5.26)	0.285
ANX 19	0.57 (0.19, 1.78)	0.336	0.52 (0.17, 1.67)	0.273
<i>Chinese-American (n=761)</i>				
CES-D 10	1.78 (0.50, 6.41)	0.377	2.80 (0.47, 16.54)	0.256
ANX 19	0.93 (0.24, 3.65)	0.913	0.79 (0.12, 5.21)	0.809
<i>African-American (n=1693)</i>				
CES-D 10	2.09 (1.23, 3.56)	0.006	1.95 (1.09, 3.51)	0.025
ANX 19	0.44 (0.22, 0.88)	0.021	0.37 (0.17, 0.80)	0.011
<i>Hispanic (n=1347)</i>				
CES-D 10	1.60 (0.72, 3.57)	0.250	2.03 (0.80, 5.13)	0.134
ANX 19	0.78 (0.31, 1.94)	0.593	0.62 (0.21, 1.78)	0.373

\* All models adjust simultaneously both for CES-D and ANX score. In addition to age/gender, multivariable models also adjusted for center, body mass index, hypertension, diabetes mellitus, low-density lipoprotein and high-density lipoprotein cholesterol levels, systolic and diastolic blood pressure, cigarette smoking (never, former, or current), self-reported moderate and vigorous physical activity in quartiles, estimated glomerular filtration rate <60, albuminuria, left ventricular hypertrophy by Cornell ECG criteria, log-transformed highly-sensitive plasma C-reactive protein levels, benzodiazepine, and beta blocker use.