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Association of Positive Well-Being with Reduced Cardiac Repolarization Abnormalities in the First National Health and Nutrition Examination Survey

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Abstract

Background—The mechanisms by which psychological factors may influence possibly arrhythmia risk are not known. We hypothesized that psychological wellness, measured by the General Well-Being Schedule (GBWS), is associated with less repolarization heterogeneity as measured by T-axis. We also explored whether T-axis was a mediator in the relationship of GWBS with adverse cardiac outcomes.

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Disclosures

None

Conflict of interest

There was no conflict of interest

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Methods—We studied 5,533 adults aged 25–74 years without a history of CVD from NHANES I (National Health and Nutrition Examination Survey) (1971–75). Frontal T-axis was obtained through 12-lead ECG and characterized as normal (15° to 75°), borderline (-15° to 15° or 75° to 105°) or abnormal ($> 105^\circ$ or $< -15^\circ$).

Results—The mean $\pm$ SD age was 43.1 ± 11.5 years and 55% were women. A 1-SD increase in GWBS score associated with a 23% reduced odds of abnormal T-axis ($p < 0.001$) and 11% lower hazard of composite CHD hospitalization and death ($p = 0.02$). When adjusting for sociodemographic factors, health behaviors, and CHD risk factors, the association was minimally changed and remained statistically significant. Additional adjustment for T-axis did not change the relationship with outcomes.

Conclusion—General well-being is independently associated with less abnormal frontal T-axis and CHD events in otherwise healthy individuals.

Keywords

Psychological well-being; cardiac repolarization; coronary heart disease

1. INTRODUCTION

Cardiovascular disease is the most prevalent cause of death worldwide;¹ in many cases, such deaths are mediated by ventricular arrhythmias.² Psychological factors are increasingly recognized as important determinants of cardiovascular disease, and also very relevant to public health; according to the World Health Organization, depression is the leading cause of disability world-wide.³ Because of this, the brain-heart relationship is an area of increasing interest and relevance.⁴ Studies have supported both a reduced heart disease risk in those with positive affect,⁵ and also increased cardiovascular risk with negative affect.⁶ One largely unexplored mechanism through which brain factors directly influence the heart, and in particular ventricular arrhythmias, is through effects on cardiac repolarization.⁷ In addition, such effects may also influence coronary artery disease pathogenesis.⁸

Abnormal frontal T-axis is an electrocardiographic (ECG) marker of repolarization heterogeneity, which may predispose to ventricular arrhythmias. Abnormal T-axis is also associated with fatal and nonfatal cardiac events.^{9,10} If an association between psychological status and frontal Taxis is found, this may help provide a better understanding of the heart's influence on the brain, and in particular its risk of arrhythmia.¹¹ Such data would also underscore the need for clinicians to consider neuropsychological factors that may influence a patient's risk when assessing unexplained arrhythmias or ECG abnormalities.

In a sample of 5,533 adults in the First National Health and Nutrition Examination Survey (NHANES), we sought to examine the relationship between psychological measures of well-being, measured by the general well-being schedule (GWBS), and primary repolarization heterogeneity, measured by T-axis.¹² Also, in light of previous findings that a low GWBS score is associated with increased cardiovascular disease risk,¹³ we assessed the influence of T-axis on the effect of GWBS in predicting adverse heart disease outcomes as an exploratory analysis of the potential mediating effects of T-axis on heart disease risk.⁹

2. METHODS

2.1 Study Population and Baseline Examination

We examined a subsample of the 31,973 persons aged 1–74 in the NHANES I, who were enrolled from 1971 through 1975; of those participants, 6,913 received a detailed physical examination, and within this group, and 6,316 provided ECG data specifically.¹⁴ We excluded subjects with a history of cardiovascular disease (CVD), including stroke, heart attack, or heart failure. We also excluded participants whose ECG had QRS duration >120 milliseconds because underlying cardiac conduction disease is an important potential effect modifier of the neurocardiac relationship. Participants for NHANES were sampled using a complex survey design.¹⁵ They were interviewed in their homes and examined in mobile examination centers. Information on demographics, current or past smoking, physical activity, medication use, and medical history were obtained via self-report. In addition diabetes was defined as glucose ≥ 126 or hemoglobin A1c of $\geq 6.5\%$. Total cholesterol was measured using commonly available reagents (cat. no 816302 from Boehringer Mannheim). Blood pressure was measured manually by a physician using standard techniques and was calculated as the average of 3 resting measurements.¹⁶ Sedentary behavior was assessed via self-report when participants reported being “quite inactive.” Poverty was defined as poverty index <1 based on subject’s income. BMI was measured during the physical examination. Heavy alcohol use was identified when participants reported normally drinking > 3 drinks per 24 hours.

2.2 Assessment of Well-being

The General Well-Being Schedule (GWBS) was developed to measure self-representations of subjective well-being and distress.¹² It contains 33 items and 6 subscales: freedom from health worry, energy level, satisfying interesting life, cheerful (vs. depressed) mood, emotional-behavioral control, and relaxed (vs. tense-anxious) mood. GWBS has an internal consistency coefficient of 0.912 for males and 0.945 for females. As opposed to other scales in which negative symptoms are exclusively queried, the GWBS assesses both wellness (i.e. satisfaction with life) as well as negative mood. The score ranges from 0 to 110, and a high GWBS score reflects a high self-representation of well-being.

2.3 Outcomes Data

Outcomes were assessed via the NHANES I Epidemiologic Follow-up Study (NHEFS), in which 4 serial follow-up surveys (1982–84, 1986, 1987, and 1992) were completed. This included interviews with subjects and proxies. Source documents such as hospital records were also traced.¹⁷ Trained medical coders reviewed the cases and classified the primary diagnoses based on the International Classification of Diseases, Revision 9 (ICD-9). Relevant events included those coded as coronary heart disease (ICD-9 codes 410–414). Fatal events were also assessed in a similar manner, and also included data from the National Death Index. The primary outcome was composite (fatal or non-fatal) CHD. The follow-up period was limited to a standard 10 years period¹⁸ for this study to allow for complete follow-up because of potential changes in health status over time that may result in regression dilution bias.¹⁹

2.4 ECG Analysis

A comprehensive ECG analysis was collected as part of the baseline examination. Twelve-lead ECG's were collected using Beckman Digicorders, which performed a digital-to-analog conversion at a sample rate of 500 samples per second. Visual inspection of the ECG was performed in real time, and recording was repeated if necessary. Digital measurement of intervals and vectors was performed using a program named ECAN developed by Phone-A-Gram systems. Frontal T-Axis was computed by the NHANES investigators using T-wave amplitudes in limb leads and classified as normal (15° to 75°), borderline (-15° to 15° or 75° to 105°), or abnormal (-180° to -15° or 105° to 180°).²⁰ Vector metrics such as frontal T-axis are considered relatively stable over time, with intraclass correlation coefficients of 0.9 or higher for a related vector metric (spatial QRS-T angle).²¹

2.5 Data Analysis

Baseline characteristics were compared between subjects with GWB score above and below the median, as well as between those with normal T-axis vs. abnormal T-axis. Student's T-tests and chi-square statistics were used to compare groups for continuous and categorical variables, respectively.

For the primary analysis, GWBS was examined as a continuous variable, and higher scores described more well-being. A modified GWBS score, in which the questions regarding freedom from healthy worry were removed, was also included in secondary analyses. To examine the association of GWBS with borderline and abnormal T-axis, a multinomial logistic regression model was used, and normal T-axis was the reference value. In addition to overall, each subscale of the GWBS was also evaluated separately to assess whether the findings were driven by any particular subscale. To allow for comparison between subscales, they were all normalized to a mean of 0 and standard deviation of 1 for analysis. Separate results were generated for both borderline and abnormal T-axis outcomes, with normal T-axis as the reference value. To measure for confounding or mediating effects due to modifiable risk factors, multivariable modeling was performed in staged sequential models with sociodemographic factors (age, sex, race, education, and income) in the first model; health behaviors (heavy alcohol use, smoking, and sedentary behavior) were added in the second model; traditional physical health factors (diabetes, hypertension, body mass index, and total cholesterol) were then added in the final model. All such factors were considered important because of their known relationships with CHD and therefore T-axis as well.¹⁸ The primary analyses were evaluated for age and sex interaction as well.

Cox proportional hazards models were then used to examine the associations between GWBS, T-axis, and CHD outcomes. Because T-axis and GWBS were collected at the same time, formal mediation models were not performed because of possible bias.²² GBWS was examined in univariate and multivariate models, and T-axis was included in the final model. Additionally, the interaction of GWBS with T-axis was examined. The proportional hazards assumption was tested using Schoenfeld residuals and visual inspection of the log-log plots.

3. RESULTS

Of the 6,316 individuals who received an ECG, a total of 5,969 remained after excluding those with known CVD; we then excluded 436 with wide QRS (≥ 120 ms), leaving 5,533 individuals for analysis. The sociodemographic and health characteristics of our sample are described in table 1, where subjects were divided into groups based on a GWBS score above (≥ 80) or below (< 80) the median. Most notably, those with higher GWBS were less likely to be female, black, a smoker, diabetic, sedentary, low education, a heavy drinker, and with an income below the poverty line. Supplemental table 1 shows baseline differences by T-axis categories, and describes a globally higher risk factor profile in those with borderline or abnormal T-axis.

Table 2 shows the results of the multinomial logistic regression models for borderline and abnormal T-axis. A significant association was found between GWBS and reduced odds of abnormal T-axis in all models, such that a 1-SD increase in GWBS associated with an odds ratio of 0.77 (95% confidence interval (CI), 0.65–0.91) for abnormal T-axis. This relationship was consistent in all models, regardless of adjustment for sociodemographic and traditional risk factors. The relationship between GWBS and borderline T-axis was less consistent, and was statistically significant for model 2 only (adjusting for sociodemographic factors); after adjusting for lifestyle factors in models 2 and 3, the association was attenuated and no longer statistically significant. When analyzing the subscales in separate models (supplemental tables 2 and 3), cheerful mood, freedom from health worry, and higher energy level were significantly associated with reduced odds of abnormal T-axis in fully adjusted models, while relaxed mood, satisfying interesting life, and emotional-behavioral control were not associated with T-axis. No interaction with age or sex were found.

After 10 years of follow-up, 410 individuals had coronary heart disease hospitalization or death. For both GWBS and T-axis the proportional hazards assumptions were met, with Schoenfeld $p > 0.05$ and parallel log-log plots for each group. Table 3 shows the association of GWBS with incident CHD. A 1-SD higher GWBS score at baseline was associated with an 11% lower risk of CHD [hazards ratio (HR), 0.89; 95% CI, 0.75–0.99]. Adjustment for sociodemographics, however, reduced the HR (model 1); with additional adjustment for T-axis, the HR did not significantly change (model 2); when adjusting for behavioral factors, traditional CHD risk factors, and borderline/abnormal T-axis, the fully adjusted HR was 0.87 (95% CI, 0.79–0.96) in model 5. Notably, in model 5, borderline and abnormal T-axis were independently associated with a 1.46 (95% CI, 1.15–1.86) and 1.82 (95% CI, 1.19–2.79) HR for incident CHD, respectively. No statistical interactions were found between GWBS (overall and subscales) and borderline or abnormal T-axis. All GWBS subscales except for emotional-behavioral control were associated with reduced risk of CHD outcomes in fully adjusted models (supplemental table 4).

Additional analyses in which freedom from health worry was subtracted from the GWBS score was performed, and results were grossly similar for both T-axis and CHD outcomes (supplemental tables 5 and 6).

4. DISCUSSION

To the best of our knowledge, this is the first study to evaluate the relationship between psychological well-being and reduced repolarization heterogeneity in middle-aged community-dwelling individuals without cardiovascular disease. We believe these findings show a novel mechanistic relationship between mood and baseline arrhythmia risk in otherwise healthy individuals, and advocate for a more holistic approach towards arrhythmia management and prevention. A 1-SD increase in GWBS was associated with an approximately 22% decreased odds of abnormal T-axis in fully adjusted models. Overall, these findings suggest an independent relationship of psychological factors cardiac repolarization. Although this relationship did not substantially explain the relationship between GWBS and CHD, further research is needed in a larger cohort to explore sudden cardiac death specifically.

This study uniquely examined general well-being scale in association with repolarization abnormalities as a proxy for sudden cardiac death risk, while other studies have exclusively focused on the relationship of negative mood with repolarization and/or SCD. Whang *et al.* found that elevated depressive symptoms were associated with an increased odds of having T wave inversions.²⁴ Empana *et al.* also found an association between clinical depression and sudden cardiac death in the community.²⁵ The nurse's health study reported an increased risk of sudden cardiac death in women with anxiety as well.²⁶ Our focus on well-being is an important clinical consideration because wellness is a more universal concept with less associated stigma than depression, for example. The GWBS includes questions related to aspects of excellent health, such as waking up fresh/rested, as well as those related to negative mood. This mixture of questions allows for a more comprehensive examination of overall mental well-being, and gives the GWBS an advantage over prior studies that only focused on negative mood.

Other studies from NHANES evaluating GWBS have been performed, but none have focused on cardiac repolarization. Yanek *et al.* focused on the overall relationship with CHD,¹³ and other studies looked at specific mood states within the GWBS.^{27,28} Stroke was also evaluated as an outcome.²⁹ These studies support the importance and relevance of the GWBS as a prognostic tool; nonetheless, our focus for this study was specifically on the mechanism of abnormal repolarization in the consideration of sudden cardiac death.

The links between psychological well-being and cardiac repolarization are not clear but may include neurocardiac and behavioral mechanisms, for example.⁸ Specific neurologic circuits may stem from the amygdala and medial prefrontal cortex to the heart, for example, and lead to repolarization abnormalities through autonomic effects.^{30,31} Emotional stress induces changes on the HPA and sympathoadrenomedullary axes,³² which in turn may have electrophysiological consequences.^{8,33} Increased sympathetic/parasympathetic ratio may be a key mechanism by which emotional factors increase the risk for cardiac arrhythmias.^{34–37} Mood states may have varying autonomic effects: for example, depression and anxiety have been noted to have very different relationships with cardiac repolarization in previous work; this may, in part, explain why some components of the GWBS associated with T-axis, while others did not.²⁴ The neurocardiac relationship may also be bidirectional due to the fact that

afferent neurologic signals also travel from the heart to the brain, suggesting that cardiac disease itself may have direct neurologic effects.³⁸ This underscores the need for randomized studies of wellness interventions on arrhythmia risk.

Our findings that abnormal T-axis did not explain the relationship between GWBS and CHD outcomes supports the hypothesis that T-axis, in part, reflects a neurocardiac phenomenon, rather than simply being a biomarker of subclinical CAD. Of note, we found that the adjusted relationship of abnormal T-axis with CHD was a hazard ratio of nearly 2, which is similar to other traditional risk factors, and contributes modestly to prediction of CHD risk. Sudden cardiac death would have been a more appropriate outcome of choice to assess for this, but unfortunately only death certificate data were available, and the timing of the cardiac deaths (sudden vs. non-sudden) were not available. Additionally, such a study would have likely required a larger sample, considering that SCD is relatively rare compared to composite non-fatal and fatal CHD.

There are a number of potential important limitations to our study. We used self-reported measures of well-being and do not have data for major depressive disorder, which would have allowed us to assess whether wellness and depression independently contributed to cardiac repolarization and incident CHD. Our analysis linking GWBS with frontal T-axis is cross-sectional and therefore directionality cannot be determined. We also cannot rule out residual confounding due to unmeasured risk factors; nonetheless, several types of information were available, including health factors, behaviors, and demographic information. Sudden cardiac death was not phenotyped as a possible outcome, and therefore its relationship with GWBS could not be evaluated. The cohort was assessed many years ago, and many elements, such as clinical practice patterns, have changed; nonetheless, we do not expect fundamental neurocardiac relationships such as the ones explored in this study to change over time.

5. CONCLUSION

In conclusion, in this sample of community-based men and women without known heart disease, we found that general well-being was independently associated with a lower odds of abnormal frontal T-axis, implying that psychological well-being may be cardioprotective. Additionally, it was associated with decreased risk of CHD hospitalizations and death, even after adjustment for traditional risk factors and T-axis. Although the mechanisms linking general wellbeing with the lower risk of CHD need further evaluation, overall, our findings support a neurocardiac link between psychological wellness, cardiac repolarization and outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Glossary

GBWS General Well-Being Schedule

NHANES I National Health and Nutrition Examination Survey

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Table 1

Baseline Characteristics of Participants Above or Below Median GWBS Score.

	GWBS ≥ 80	GWBS < 80	p
Sample size	2790	2743	
Socioemographics			
Age, years	47.5 (14.1)	46.6 (13.8)	0.2
Female	45%	55%	<0.001
Black Race	9%	14%	<0.001
Did not graduate HS	33%	45%	<0.001
Health Behaviors			
Sedentary behavior	7%	12%	<0.001
Heavy drinking	13%	16%	<0.01
Traditional Risk Factors			
Systolic Blood Pressure, mmHg	133 (21)	132 (23)	0.01
Total Cholesterol, mg/dL	221 (46)	222 (47)	0.62
Current Smoker	35%	41%	<0.001
Body Mass Index (kg/m ²)	25.3 (4.6)	25.9 (5.5)	<0.001
Diabetes Mellitus	3%	5%	<0.001
Income below poverty line	5%	9%	<0.001

Values are mean (standard deviation) or percentages. P values correspond to chi-square tests for categorical variables, and T-tests for continuous variables.

GWBS=General well-being schedule; HS=high school

Table 2

Multinomial Logistic Regression of the Association of One Standard Deviation Increase in GWBS Score (Continuous) with Borderline and Abnormal T-axis (vs. Normal T-axis)

	Borderline Frontal T-Axis	Abnormal Frontal T-Axis
Unadjusted	0.95 (0.65–0.91), p=0.19	0.77 (0.65–0.91), p<0.01
Model 1 ^a	0.92 (0.85–0.99), p=0.03	0.79 (0.66–0.94), p=0.01
Model 2 ^b	0.94 (0.86–1.02), p=0.11	0.78 (0.65–0.94), p=0.01
Model 3 ^c	0.94 (0.87–1.02), p=0.15	0.78 (0.64–0.94), p=0.01

^a adjusted for age, race, sex, income, and education;

^b model 1 + past/current smoking, alcohol use, and sedentary behavior;

^c model 2+ systolic blood pressure, total cholesterol, body mass index, and diabetes

TRF=traditional risk factors; GWBS=General well-being schedule

Table 3

Associations of One Standard Deviation Increase in General Well-Being Schedule Score at baseline with Incident Cardiovascular Hospitalization and Death

	Hazard ratio (95% CI), p value
Unadjusted	0.89 (0.82–0.99), p=0.02
Model 1 ^b	0.82 (0.75–0.90), p<0.001
Model 2 ^a	0.83 (0.75–0.91), p<0.001
Model 3 ^c	0.86 (0.79–0.95), p<0.01
Model 4 ^d	0.87 (0.79–0.96), p<0.01
Model 5 ^e	0.87 (0.79–0.96), p=0.01

^a adjusted for age, race, sex, income, and education;

^b adjusted for model 1 + borderline and abnormal T-axis;

^c model 1 + past/current smoking, alcohol use, and sedentary behavior;

^d model 2+ systolic blood pressure, total cholesterol, body mass index, and diabetes;

^e model 3 + borderline and abnormal T-axis