

Association of depression and anxiety status with 10-year cardiovascular disease incidence among apparently healthy Greek adults: the ATTICA Study

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Abstract

Background: Chronic stress, frequently manifests with anxiety and/or depressive symptomatology and may have detrimental cardio-metabolic effects over time. As such, recognizing the potential links between stress-related psychological disorders and cardiovascular disease (CVD) is becoming increasingly important in cardiovascular epidemiology research. The primary aim of this study was to prospectively explore potential associations between clinically relevant depressive symptomatology and anxiety levels and the 10-year CVD incidence among apparently healthy Greek adults.

Design: A population-based, health and nutrition prospective survey.

Methods: In the context of the ATTICA study (2002-2012), 853 adult participants without previous CVD history [453 men (45±13 years) and 400 women (44±18 years)] underwent psychological evaluations through validated, self-reporting depression and anxiety questionnaires.

Results: After adjustment for multiple established CVD risk factors, both reported depression and anxiety levels were positively and independently associated with the 10-year CVD incidence, with depression markedly increasing the CVD risk by approximately 4-fold [adjusted odds ratio and 95% confidence interval: 3.6 (1.3, 11) for depression status; 1.03 (1.0, 1.1) for anxiety levels].

Conclusions: Our findings indicate that standardized psychological assessments focusing on depression and anxiety should be considered as an additional and distinct aspect in the context of CVD preventive strategies that are designed and implemented by health authorities at the general population level.

Key words: ATTICA study, depression, anxiety, cardiovascular disease, CVD risk factors.

Introduction

Despite recent decreases in cardiovascular disease (CVD) mortality rates in several European countries, CVD remains the leading cause of death in Europe (almost 50% of all deaths; responsible for over 4 million deaths per year) [1–2]. As such, cardiovascular epidemiology research has further focused on identifying potentially modifiable CVD risk factors, which may be early diagnosed and managed in the context of CVD preventive strategies at the general population level.

Stress is defined as a state of threatened body homeostasis which rapidly mobilizes adaptive physiologic and behavioral responses via the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS), in order to preserve the challenged equilibrium while this acute stress response serves the adaptation of the individual [3]. However, chronic stress is frequently manifested with anxiety and/or depressive symptomatology, with melancholic depression constituting the prototypic example of chronic stress system (HPA and SNS) hyperactivation which can be manifested with a spectrum of severe somatic sequelae, including symptomatic atherosclerotic disease [4]. Overall, depression is considered not only to substantially impair the ability to function, but when untreated may also curtail life expectancy by 15-20 years even after excluding suicides [4]. Thus, chronic stress may have detrimental cardio-metabolic effects over time, leading to metabolic syndrome manifestations and CVD [5]. Indeed, growing evidence links the development, severity and progression of CVD with a spectrum of chronic stress-related conditions, ranging from depression to posttraumatic stress disorder and anxiety [6–7], in addition to other established pathogenetic factors (i.e., the classical CVD risk factors, including smoking and unhealthy lifestyles). Meta-analyses data have indicated that depression is associated with incident coronary heart disease (CHD) and an increased risk of stroke morbidity and mortality [8–9]. Similarly, although the evidence is not extensive, there

are data from both meta-analysis and large prospective national registry studies which suggest that anxiety is also associated with incident CHD [10–12]. Results obtained from patients with previous cardiac medical history point to similar associations [13–14].

With the aforementioned evidence, herein we sought to explore the potential associations between clinically relevant depressive symptomatology and anxiety levels and the 10-year incidence of CVD among Greek adults from the general population without previous CVD history.

Methods

Study sample

The ATTICA study is a population-based, prospective survey conducted in Attica of Greece. Recruitment of the participants was conducted during 2001-2002 through a multi-stage, random sampling protocol. The detailed ATTICA study design and methodology has been previously described in the methodology paper [15]. Briefly, adults without CVD history were recruited, whilst validated self-reporting depression and anxiety questionnaires were administered to a subsample of 853 participants [453 men (45±13 years); 400 women (44±18 years)]. This study subsample was representative of the general and the total study population regarding its age and gender distribution. The ATTICA study protocol was approved by our Institutional Ethics Committee and the study was conducted according to the World Medical Association Declaration of Helsinki, with all study participants providing written informed consent.

Baseline assessments

Demographic data were collected including information on age, gender and socioeconomic status. For the purposes of the present work, participants with 0-12 years of

education were classified as “Low/Middle educated”, while those with >12 years as “Highly educated”. Moreover, mean annual incomes during the past three years up to 10,000 Euro were classified as “Poor/Low”, while $\geq 10,000$ Euro as “High/Very high”. Participants who reported smoking at least one cigarette per day at baseline or in the past, were defined as current or former smokers. Obesity was defined as Body Mass Index (BMI) >29.9 kg/m²; hypertension as average blood pressure levels $\geq 140/90$ mmHg, or being on antihypertensive treatment; hypercholesterolemia as total serum cholesterol levels >200 mg/dl, or being on lipid-lowering treatment; and diabetes mellitus as fasting glucose levels ≥ 126 mg/dl, or on anti-diabetic treatment. High sensitivity C-reactive protein (CRP) was assayed by particle-enhanced immunonephelometry (*N Latex, Dade-Behring Marburg GmbH, Marburg, Germany*).

Nutritional habits were evaluated by the EPIC-Greek questionnaire [16], while adherence to the Mediterranean dietary pattern was further assessed using a specific dietary index, *i.e.*, the MedDietScore, as we have previously described (MedDietScore range: 0-55; higher score values indicate better adherence to the Mediterranean diet) [17]. Ethanol intake was recorded in g/day. The short form of the International Physical Activity Questionnaire (IPAQ) was used to assess physical activity status, with participants being classified into two categories, *i.e.* low and moderate/high physical activity status, as previously described [18].

Depressive symptomatology was assessed using the validated Greek translation of the Zung Self-Rating Depression Scale (ZDRS) [19]. The time window was the preceding 4-week period before the administration. The ZDRS’ total score range is 20-80; with higher score values indicating more severe depressive symptoms. Based on the validated ZDRS cut-off score for the Greek population, we applied a cut-off score of 45 to dichotomize the study cohort to participants with and without clinically relevant depressive symptomatology [19].

Anxiety symptomatology was assessed using the validated Greek translation of the State Anxiety sub-scale of the Spielberger State-Trait Anxiety Inventory (STAI) [20]. The total score of the applied 20-item STAI ranges from 20 to 80 with higher score values being indicative of more severe anxiety symptoms. In the context of this study, the STAI score was used as a continuous variable, since cut-off scores for the adult Greek population require further validation [20].

10-year cardiovascular disease incidence assessment

The ATTICA study 10-year follow-up was performed during 2011-2012 [21]. The definition of the investigated CVD outcomes was based on the International Coding Disease (ICD) - 10th or 9th version (to ensure continuity ICD-9 coding was also kept, without noted discordant cases between the two coding systems). Information about the CVD health status of each study participant included development of: (a) myocardial infarction, angina pectoris, other identified forms of ischemia [ICD-9 coding (or 10th edition)] [410-414.9, 427.2,427.6 (I20-I25)]; coronary revascularization (414.01) (*i.e.*, coronary artery bypass surgery and percutaneous coronary intervention); (b) heart failure of different types [400.0-404.9, 427.0-427.5, 427.9, 428.-(I50.2-)], and chronic arrhythmias (I49.-); (c) development of stroke [430-438 (I63.-)]. Regarding CVD ascertainment medical records and hospital data were obtained. The adjudication was made by trained study physicians and followed the International Statistical Classification of Diseases and Related Health Problems 10th Revision (<http://apps.who.int/classifications/icd10/browse/2010/en>). Eight study participants were lost to follow-up, thus 10-year assessments were available for a total of 845 study participants.

Statistical analysis

Unadjusted associations between various demographic, anthropometric, and clinical characteristics at baseline and 10-year CVD incidence were performed using Student's t-test, Mann-Whitney U test and Pearson chi-square test where appropriate. Normality assumption was assessed via P-P plots. Nested multiple logistic regression models were developed in order to evaluate the association between the 10-year CVD incidence (dependent outcome) and the status of depression or anxiety at baseline (exposure variables), after adjusting for various participant characteristics (*i.e.*, gender, age, smoking habits, physical activity, adherence to Mediterranean dietary pattern, and the CVD risk factors score which was defined as the sum of several established CVD risk factors). The follow-up was till the first CVD event. Model 1 was the age-gender adjusted model and Model 2 was the full model evaluating the effect of depression on CVD. Models 3 and 4 were the corresponding models for anxiety levels. The Hosmer-Lemeshow statistic was applied to assess the models' fit. In order to explore the potential synergistic role between other factors and depressive/anxiety symptomatology on CVD development, unadjusted associations were also performed between depression/anxiety and several patients' characteristics using Pearson chi-square test, Mann-Whitney test and Spearman rho correlations where appropriate. All reported p-values were based on two-sided tests. SPSS 20 software (SPSS Inc., Chicago, IL, USA) was used for all statistical calculations.

Results

During the 10-year study follow-up, 43 cases (5.1%) had developed either fatal or non-fatal CVD; of these cases 72% ($n=31$) were men and 28% ($n=12$) were women (p for gender difference 0.004) (Table 1). Clinically relevant depressive symptoms at baseline were reported by 86 participants (72% women, p for gender difference <0.001), whilst the median

anxiety score was 40, ranging from 20 to 77 [the corresponding median score for women was 41 (range: 20-77) and for men 40 (range: 20-76), $p=0.07$].

Baseline associations for Depression and Anxiety status

Depression and anxiety were positively associated at baseline ($p<0.001$). The median anxiety score between depressive patients was 54 (range: 26-76), while for the non-depressed it was 16 units lower (range: 20-77). Furthermore, depressive symptomatology ($ZDRS \geq 45$) was more frequent among older patients ($p=0.04$) and negatively associated with educational and financial status ($p=0.02$ and $p<0.001$, respectively). In addition, higher anxiety scores were recorded among participants with low/middle educational status or poor/low financial status ($p<0.001$ in both cases), whilst patients with moderate/high physical activity were found to have lower anxiety levels ($p=0.001$). Depression was associated with the MedDietScore ($p<0.001$) with the participants reporting depressed mood being closer to the Mediterranean dietary pattern while anxiety showed no association. Moreover, no associations were found between depression or anxiety and baseline obesity, smoking habits, alcohol consumption, hypertension, hypercholesterolemia, diabetes mellitus, family history of CVD and CRP levels (data not shown).

Effect of Depression and Anxiety on 10-year CVD incidence

In total, 14% of the study participants with depressive symptomatology developed CVD during the follow-up period, compared to 7.6% for the non-depressed. Anxiety median score was 4 units higher among those who developed CVD during the 10-year follow-up.

In the age-gender adjusted model (Model 1; Table 2) depression was associated with almost a 4-fold higher 10-year CVD incidence ($p=0.01$), whilst these results remained relatively unaffected ($p=0.02$) after further adjustment for smoking habits, physical activity,

adherence to Mediterranean diet, CRP levels and CVD risk factors score (*i.e.*, the sum of the following established CVD risk factors at baseline: Hypertension, Hypercholesterolemia, Diabetes Mellitus, Obesity and Family History) (Model 2; Table 2).

Additionally, CVD patients did not score significantly higher in the anxiety scale at baseline ($p=0.12$) after adjusting for age and gender (Model 3; Table 2), while in the full model (Model 4; Table 2) this association was strengthened ($p=0.08$).

Discussion

CVD pathogenesis is multi-factorial and associated with both genetic and modifiable risk factors (*e.g.*, nutritional, lifestyle and psychosocial factors) [22–23]. Our study presents new, prospective, long-term data that identify depression as a strong and independent risk factor for CVD development in apparently healthy Greek adults from the general population during the ATTICA study 10-year follow-up. This effect persisted even after taking into account the influence of other well-established risk factors, whether behavioral/lifestyle (*i.e.*, smoking, diet, and exercise), genetic (*i.e.*, CVD family history), or related to metabolic syndrome (*i.e.*, obesity, diabetes, hypercholesterolemia and hypertension). Moreover, even after adjusting for circulating CRP levels, depression was still associated with the noted 10-year CVD incidence, indicating that this correlation may involve further mechanisms beyond chronic sub-clinical inflammation, as expressed by circulating CRP. Similarly, increased baseline anxiety levels, another frequent expression of chronic stress, was also associated with increased 10-year CVD incidence, although at a marginally significant level. Notably, the adjustment of these findings for behavioral/lifestyle variables (*i.e.*, smoking, diet and exercise) allows the hypothesis that the mechanisms mediating the associations we documented between these stress-related disorders and CVD may also extend beyond the adaptation of unhealthy lifestyle habits [3, 5]. Overall, the aforementioned findings agree

with most of the existing literature, supporting positive associations between depression, anxiety and CVD [6, 8–12, 24–26]. To date, such prospective, long-term data are limited for the Greek adult general population, which may be considered, at least to a certain extent, representative of the Southern/Mediterranean European nations.

The World Health Organization (WHO) recognizes depression as a major contributor to the overall global burden of disease and as the leading cause of disability worldwide [27]. Moreover, data from large population-based European studies [including the European Study of the Epidemiology of Mental Disorders (ESEMeD)] indicate that anxiety disorders constitute the most prevalent mental health problem (33.7% of the population are affected by an anxiety disorder during their lifetime), whilst are also associated with a high burden of disease [28]. Thus, it is not surprising that these two stress-related, mental health disorders are becoming increasingly significant in cardiovascular epidemiology research. Of note, in a meta-analysis of 10 large prospective cohort studies ($n=68,222$), a dose-response association between psychological distress across the full range of severity and increased CVD mortality risk was detected [29]. However, it should be also highlighted that effective treatment of depression (by various modalities, including pharmacotherapy) is an end in itself, and does not guarantee subsequent CVD risk modification.

Interestingly, the WHO Regional Office for Europe has also reported that the economic crisis and recession in Europe is expected to further heighten such mental health disorders, due to poverty, deprivation, inequality and other socio-economic determinants of health [30]. As such, it is important to note that our analyses on potential synergistic factors in the relationship between the reported anxiety/depression levels and CVD, suggest that the socio-economic status is a potential mediating factor. Indeed, both low educational and financial status within our study population were strongly correlated with depression and anxiety levels at baseline, in accordance with previous research findings (particularly

depression), suggesting that an interplay between certain psychological factors and the socio-economic status may partly explain the complexity of associations in CHD pathophysiology [31–35]. However, we must also note that power limitations within our study do not allow further investigation of these potential synergistic effects. Furthermore, potential synergy of depression and anxiety on CVD incidence could not be also assessed due to multi-collinearity issues. Overall, it should also be noted that our data on the psychological profile (depression and anxiety levels) of the study participants were obtained from self-reporting, validated scales, and not from diagnostic interviews for depressive and/or anxiety disorders, and this can also be considered as a limitation of the present work. Moreover, only the Greek translation of the Spielberger state anxiety sub-scale was evaluated and, thus, no data on trait anxiety levels were obtained. In addition, chronic stress, itself, was not the direct subject of the present analyses, which were instead based on assessing self-reported levels of two common mental health disorders (i.e., depression and anxiety) that are frequently expressed as negative behavioral consequences of chronic stress exposure with potential relationship to CVD. In this context and also due to the long follow-up study period, other confounding factors may also have escaped our attention and thereby have not been included in the present analyses.

Finally, although power limitations did not allow the conduction of a stratified by gender analysis, our documented associations between depression or anxiety and gender were in favor of men in both cases, whilst an increment in the prevalence of depression was noted with increasing age. Based on the existing evidence, women typically have a two-fold increased risk of major depression compared to men, whilst depression prevalence rates generally decrease with age [36]. However, the available data come mostly from studies conducted in Western, high-income countries, while the sparse data from low/middle-income countries suggest that this age/depression pattern might be reversed compared to the former

countries, with depression increasing with age [36], as noted in the present work. Similarly, the prevalence of anxiety disorders in women is consistently almost twice higher than in men, potentially due to psychosocial contributors (*e.g.*, sexual abuse and chronic stressors), as well as genetic and neurobiological factors [28]. Of note, although data from general population studies indicate that depression and/or anxiety disorders frequently co-exist with alcohol use disorders [37–38], no such associations were identified in the present work.

Concluding Remarks

One of the key challenges in cardiovascular epidemiology is rapidly responding to dynamic societal and policy changes in order to characterize their impact on CVD and identify feasible solutions [39]. Depression and anxiety disorders pose such a challenge for current CVD research, since both: (i) are frequent across different countries/cultures; (ii) are usually long-lasting or recurrent; (iii) are significantly under-diagnosed and/or under-treated; (iv) can be effectively treated if properly/promptly diagnosed and (v) are dynamically affected by socio-economic factors [27–28, 36].

In the present study, depression was strongly and independently associated with the 10-year CVD incidence, while the corresponding association for anxiety was less obvious. Our findings support the notion that standardized psychological assessments focusing on depression and anxiety should be considered as an additional and distinct aspect in the context of CVD preventive strategies that are designed and implemented by health authorities at the general population level. In this context, incorporating both mental health parameters and socio-economic health determinants in public health strategies/interventions targeting CVD risk, may further facilitate the improved life expectancy trends noted in the second half of the last century (substantially decreased trends in CVD mortality) as the result mainly from advances in CVD treatment and control of established CVD risk factors (*e.g.*, high blood

pressure, high cholesterol and smoking) [40–41]. This approach could potentially broaden the existing frameworks for CVD preventive public health actions by addressing additional health determinants (e.g., improved education, poverty reduction, strengthening community actions and creating supportive environments and social support networks), whilst respecting the traditional levels of the health impact pyramid (i.e., population-wide interventions, followed by primary, secondary and tertiary care, in ascending order) [41].

Authorship: KI and KN contributed to the conception and design of the work, to the acquisition, analysis and interpretation of data and drafted the manuscript. TC contributed to the conception and design of the work and critically revised the manuscript. PD, GE, CC, RHS, YM, SC, PaC and PiC critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Conflict of interest: None to declare.

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Table 1. Baseline demographic, anthropometric and bio-clinical characteristics of the study participants by the 10-year cardiovascular disease (CVD) incidence ($n=845$).

| Baseline Characteristics | CVD ^a events (10-year follow-up) | | | p |
|--|--|-------------------|------------------|--------|
| | Total sample | No ($n=802$) | Yes ($n=43$) | |
| ZDRS ^b (% ≥ 45) | 52 (10%) | 45 (9.5%) | 7 (17%) | 0.140 |
| STAI scale ^c (range: 20-80) | 41 \pm 12 | 41 \pm 12 | 44 \pm 13 | 0.086 |
| Gender (% male) | 289 (51%) | 258 (49%) | 31 (72%) | 0.004 |
| Age (years) | 43 \pm 12 | 38 \pm 11 | 48 \pm 11 | <0.001 |
| Current or former smoker (% Yes) | 328 (58%) | 299 (57%) | 29 (67%) | 0.172 |
| Physical activity (% Moderate/High) | 215 (38%) | 198 (38%) | 17 (40%) | 0.798 |
| MedDietScore (range: 0-55) | 27 (2, 55) | 27 (2, 55) | 25 (10, 29) | <0.001 |
| Obesity (% Yes) | 77 (14%) | 67 (13%) | 10 (23%) | 0.053 |
| Hypertension (% Yes) | 143 (26%) | 124 (24%) | 19 (44%) | 0.004 |
| Diabetes mellitus (% Yes) | 17 (3.0%) | 12 (2.3%) | 5 (12%) | 0.006 |
| Hypercholesterolemia (% Yes) | 164 (29%) | 144 (27%) | 20 (47%) | 0.008 |
| Family History of CVD ^c (% Yes) | 103 (43%) | 85 (39%) | 18 (75%) | 0.001 |
| C-reactive protein (mg/L) | 0.93 (0.01, 14.8) | 0.95 (0.01, 13.1) | 1.5 (0.02, 14.8) | 0.132 |

Results are presented as frequencies and relative frequencies within CVD [n (%)], mean \pm SD, median (min, max). ^a Cardiovascular disease; ^b Zung Self-Rating Depression Scale; ^c Spielberger State Anxiety Inventory.

Table 2. Results from nested logistic regression models evaluating the association between Depression and Anxiety (main effects, exposure variables) and the 10-year risk of cardiovascular disease (CVD) (dependent outcome), after adjusting for various socio-demographic, behavioral and bio-clinical characteristics assessed at baseline.

| | Model 1 | Model 2 | Model 3 | Model 4 |
|--|------------------|---------------------|---------------------|---------------------|
| ZDRS score ^a (≥ 45 vs. < 45) | 3.8 (1.4-10) | 3.6 (1.3-11) | | |
| STAI score ^b (per 1 unit) | | | 1.02 (0.99-1.05) | 1.03 (1.0-1.1) |
| Gender (males vs. females) | 2.7 (1.2-5.8) | 2.1 (0.92-4.8) | 2.3 (1.1-4.8) | 1.8 (0.82-4.0) |
| Age (per 10 years) | 2.4 (1.7-3.5) | 2.2 (1.5-3.2) | 2.3 (1.6-3.3) | 2.1 (1.4-3.1) |
| Current or former smoker (Y/N) | | 1.2 (0.56-2.5) | | 1.2 (0.55-2.4) |
| Physical activity (Moderate/High vs. Low) | | 1.4 (0.69-2.9) | | 1.6 (0.76-3.2) |
| MedDietScore (per 1 unit) | | 0.98 (0.93-1.04) | | 0.98 (0.92-1.05) |
| CVD risk factors score ^c (per 1 unit) | | 1.7 (1.2-2.3) | | 1.6 (1.2-2.3) |
| C-reactive protein (per 1 mg/L) | | 1.1 (0.96-1.2) | | 1.1 (0.97-1.2) |

Results are presented as odds ratio (OR) and 95% confidence interval (CI). ^a Zung Self-Rating Depression Scale; ^b Spielberger State Anxiety Inventory; ^c The sum of the following CVD risk factors at baseline: Hypertension, Hypercholesterolemia, Diabetes Mellitus, Obesity, and Family History of CVD.