Sex-discrete role of depressive symptomatology on 10-year first and recurrent cardiovascular disease incidence: results from ATTICA and GREECS prospective studies

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Abstract

Objective: The sex-specific effect of depressive symptomatology on 10-year first and recurrent cardiovascular disease (CVD) events was evaluated.

Methods: The Greek samples from ATTICA (2002-2012, n = 845 free-of-CVD subjects) and GREECS (2004-2014, n = 2,172 subjects with acute coronary syndrome [ACS]) prospective epidemiological studies with baseline psychological assessments were used for the first and the recurrent event, respectively. Depressive symptomatology was assessed at baseline, through Zung Self-Rating Depression Scale in the ATTICA study, and through the Center for Epidemiological Studies-Depression scale in the GREECS study.

Results: ACS as well as free-of-CVD women scored significantly higher for depressive symptomatology. Men scored higher than women against first (19.7% vs. 11.7%) and subsequent CVD events (38.8% vs. 32.9%). In participants with depressive symptoms man-to-woman first and recurrent CVD event rate ratio was below 1, confirming that depressive women were more likely to have a CVD event than depressive men. Multiadjusted analysis revealed that depressive symptomatology had an independent aggravating effect on the first (hazard ratio (HR) = 2.72, 95% confidence interval (95% CI) 1.50, 9.12) and recurrent (HR = 1.31, 95% CI 1.01, 1.69) CVD events only in women. Mediation analysis in women revealed that 35% (23%, 44%) of excess first-CVD-event risk of depressive symptoms was attributed to conventional risk factors. The respective number for recurrent CVD events was 46% (23%, 53%); different patterns of ranking regarding the mediating effect corresponding to each adjustment factor were observed.

Conclusions: The present work augments prior evidence that psychological stressors possess important drivers of CVD onset and progression mainly in women, while it gives rise to research toward unidentified paths behind this claim.

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1. Introduction

More than 300 million people are currently living with depression, an increase of more than 18% between 2005 and 2015.\cite{1} Drawing on the most updated evidence, depression is a major driver of overall quality of life. This claim is even more supported in women with recent metrics, revealing 41 million years lost due to disability for depressed women, which is almost twice as high as the corresponding number in men.\cite{1} In May 2013, the Comprehensive Mental Health Action Plan 2013–2020 was adopted by the World Health Assembly. This represents a formal recognition that depression requires prevention, detection, and management in its own right.\cite{1}

The interplay between the brain and the heart remains a field of considerable research. Severe depression is to promote CVD onset, while an impending cardiac episode usually results in subclinical psychological disorders.\cite{2,3} Currently, CVD and depression are on the top of disability rank in high-income countries, expected to become so for all income levels by 2030.\cite{1} Such claims spur the need for confirmation and extension of the obtained knowledge to vulnerable subgroups. Under this context, the interaction among sex-psychological stressors is highly discussed in cardiac health-emergency units of 6 General Hospitals in Greece, were enrolled

nosis [AMI or unstable angina], hospitalized in cardiology clinics/ hospitals from 2001-2002, in the greater metropolitan Athens area, 3,042 apparently healthy volunteers agreed to participate [75% participation rate]. Among the enrolled patients, 1,649 [76%] were men [65 ± 13 years] and 523 [24%] were women [62 ± 11 years].

2. Material and methods

2.1. Sampling

ATTICA is a prospective, observational cohort study.\cite{6} During 2001–2002, in the greater metropolitan Athens area, 3,042 apparently healthy volunteers agreed to participate [75% participation rate]. Among the enrolled patients, 1,514 [50%] were men [46 ± 13 years] and 1,528 [50%] were women [49 ± 14 years]. All participants were free of CVD and other chronic diseases as per the protocol.

GREECS is a prospective, observational cohort study.\cite{7} During 2003–2004, 2,172 consecutive patients with discharge ACS diagnosis [AMI or unstable angina], hospitalized in cardiology clinics/ emergency units of 6 General Hospitals in Greece, were enrolled

2.2. Baseline measurements

2.2.1. Psychological characteristics

In the ATTICA study, 853 free-of-CVD participants underwent psychological evaluations through validated, self-reporting questionnaires. Depressive symptomatology was assessed using ZDRS (range 20–80). The validated-for-Greek population ZDRS cut-off score of 45 was used to dichotomize the sample to participants with (ZDRS ≥ 45) and without (ZDRS < 45) depressive symptomatology. Anxiety symptomatology was assessed through the STA (range 20–80). Subsequently, 2,172 patients with ACS from the GREECS study were assessed for depressive symptomatology through the CES-D scale (range 0–60), validated for the Greek population. Because of nonavailable national thresholds for the reference population, patients were divided into three equal-sized categories (tertiles): (a) 1st tertile (CES-D < 7), normal (b) 2nd tertile (7 < CES-D < 20), mild-to-moderate symptoms, and (c) 3rd tertile (CES-D ≥ 20) severe symptoms. The 2nd and 3rd tertiles were merged and examined against the 1st.

2.2.2. Sociodemographic, anthropometric, and lifestyle characteristics

Participants’ age, sex, educational/financial status, body mass index,\cite{8} level of adherence to Mediterranean diet, physical activity status, and smoking habits were assessed in both studies (for details).\cite{6} Only in the ATTICA study, waist and hip circumferences (cm) were measured and waist-to-hip ratio was calculated (waist circumference divided by hip circumference). Self-reported daily sleep duration was assessed only on the basis of ATTICA. Finally, in the GREECS study, all patients were asked about adherence to medication prescribed for hypertension, diabetes, dyslipidemia, nephropathy, and pre-existing CVD.

2.2.3. Clinical and biochemical characteristics

Baseline assessment of clinical characteristics [hypertension, hypercholesterolemia, and diabetes mellitus] was done according to established physical examination procedures and pharmaceutical treatment.\cite{9} In the ATTICA study, baseline biochemical measurements included, among others, lipid markers (high-density lipoprotein [mg/dL], low-density lipoprotein [mg/dL], triglycerides [mg/dL]), and inflammatory markers (C-reactive protein [mg/L] and interleukin-6 [mg/dL]).

2.3. Follow-up

Ten-year follow-up of the ATTICA study was performed in 2012. Regarding CVD evaluation, data without any missing information were obtained from 2,020 participants. Focusing on the 853 participants who underwent psychological evaluations, 8 were lost in follow-up; hence, 845 were included in the present analyses.

Ten-year follow-up of the GREECS study was performed in 2014; of the 2,172 enrolled patients with ACS, 1,918 were found at follow-up.

2.4. Endpoints

The endpoint examined here was the development of fatal or nonfatal CVD event within the decade: first event, for ATTICA participants and recurrent event, for GREECS patients. CVD event was defined as AMI, or angina, or other identified forms of ischemia (WHO-ICD codes 410-414.9, 427.2, and 427.6) or heart failure of
different types and chronic arrhythmias (WHO-ICD codes 400-404.9, 427.0-427.5, 427.9) or stroke (WHO-ICD code 430-438).

2.5. Ethical approval

The ATTICA and GREECS studies were approved by the Bioethics Committee of Athens Medical School study and the Medical Research Ethics Committee of the participating Institutions, respectively. Both studies were carried out in accordance with the Declaration of Helsinki (1989) of World Medical Association. All participants were informed about the study aims and procedures and signed an informed consent.

2.6. Statistical analysis

Continuous variables are presented as mean values ± standard deviation. Categorical variables are presented as absolute (n) and relative frequencies (%). Associations between normally distributed variables and sex were evaluated through Student’s t-test for independent samples. Whether these variables were normally distributed was tested through P–P plot and equality of variances through Levene’s test. For abnormally distributed variables, Mann-Whitney test was used. Associations between categorical variables and sex were tested through chi-square test. HRs and corresponding 95% CIs for depressive symptomatology in relation to the CVD event were evaluated through multivariate Cox regression analysis in the total sample as well as separately for men and women. Then, focusing on women subgroup, mediation analysis was performed; Cox regression analysis was reapplied through adding mediators, either separately or in combination of two or more. PERM was estimated with pooled HRs following the methodology suggested elsewhere.7 According to a posteriori statistical power analysis, it was revealed that the recruited sample in the ATTICA study was adequate to achieve power equal or higher to 70% for testing two-sided hypothesis of HR equal to 0.80 at 5% significance level, whereas the relevant statistical power achieved in the GREECS study was 0.95%. STATA software, version 14 (MP & Associates, Sparta, Greece), was used for all statistical analyses.

3. Results

CVD event rate in the ATTICA study was 15.7% (n = 317) [19.7% (n = 198) in men and 11.7% (n = 119) in women, p < 0.001]. Focusing on the ATTICA sample used here (n = 845 participants with baseline psychological evaluations), 43 cases were recorded; of these cases, 72% were men and 28% were women (p = 0.004). Regarding patients with ACS in the GREECS study, the subsequent CVD event rate was 37.3% (n = 811) (38.8% in men and 32.9% in women, p = 0.016). Table 1 illustrates baseline sociodemographic, lifestyle, and clinical characteristics of men and women participants. Both free-of-CVD women and women with ACS presented higher ZDRS and CES-D score, respectively, than men.

In Fig. 1, two epidemiological models for the first and the recurrent CVD event are illustrated. Apparently healthy participants with depressive symptomatology had 2.5 times higher CVD risk than their nondepressed counterparts (p = 0.01). Men-to-women CVD event rate ratio in the subgroup with depressive symptoms (n = 85) was slightly lower to 1 (0.80) when the respective ratio for the total ATTICA sample (n = 845) was consistently higher than 1 (2.30), pointing that depressive symptomatology attenuated the women privilege over CVD onset. Similarly, patients with ACS who had depressive symptomatology had 35%...
Depressive symptomatology and 10-year first and recurrent CVD event: a sex-based stratified analysis from ATTICA & GREECS studies

<table>
<thead>
<tr>
<th>Examined variable</th>
<th>Sex</th>
<th>10-year CVD event</th>
<th>Cases, % (n)</th>
<th>Men-to-women CVD incidence ratio</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>First</td>
<td>12 (5)</td>
<td>-</td>
<td>2.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recurrent</td>
<td>38 (414)</td>
<td>-</td>
<td>(0.95, 10.30)</td>
</tr>
<tr>
<td>Depressive symptomatology, (yes vs. no)*</td>
<td>Women</td>
<td>First</td>
<td>15 (9)</td>
<td>-</td>
<td>2.72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recurrent</td>
<td>42 (149)</td>
<td>-</td>
<td>(1.50, 9.12)</td>
</tr>
<tr>
<td>Total sample</td>
<td></td>
<td>First</td>
<td>14 (12)</td>
<td>0.80</td>
<td>2.52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recurrent</td>
<td>39 (563)</td>
<td>0.90</td>
<td>1.31</td>
</tr>
</tbody>
</table>

Fig. 1. Depressive symptomatology and 10-year first and recurrent CVD risk: a sex-based stratified analysis from ATTICA & GREECS studies. Abbreviations: CVD, Cardiovascular disease; HR, Hazard ratio; 95% CI, 95% Confidence interval. *Depressive symptomatology was defined as Zung Self-Rating Depression Scale (range 20-80) = 45-80 in ATTICA and Center for Epidemiological Studies-Depression scale (range 0-60) = 7-60 in GREECS. Hazard ratios (dots) and corresponding 95% CIs (horizontal lines) for depressive symptomatology (yes vs. no) were obtained from Cox-regression models adjusted for age, family CVD history, State Anxiety sub-scale of the Spielberger State-Trait Anxiety Inventory, MedDietScore, sleeping duration, physical activity, current smoking, financial status, educational status, diabetes, hypertension, waist-to-hip ratio, high- and low-density lipoproteins, triglycerides, C-reactive protein, and interleukin-6, with 10-year first CVD event as the dependent variable and age, family CVD history, MedDietScore, physical activity, current smoking, financial status, educational status, diabetes, hypertension, hypercholesterolemia, body mass index, discharge status, individual CVD history, and adherence to medication, with 10-year recurrent CVD event as the dependent variables.

higher risk of suffering from recurrent events within the decade ($p < 0.001$). Men-to-women recurrent CVD event rate ratio for participants with depressive symptomatology ($n = 1,433$) was quite close yet lower than 1 (0.90), with the respective ratio for the total sample indicating that men exhibited higher incidence than women (1.18). Interaction analysis revealed that sex interacted with depressive symptoms on the first and the recurrent CVD event ($p$-values for interaction $<0.10$). Despite the marginally significant interacting effect of gender on the association between depressive symptomatology and CVD incidence or recurrence, the obtained knowledge and evidence on this issue justifies the stratification of the sample. Stratified analysis revealed that depressive-symptomatology-aggravating effect was retained in both men and women, yet it remained significant only for women.

As the independent effect of depressive symptomatology on 10-year first and recurrent CVD events was retained only in women, mediation analysis for the association between these two disease states was performed for this subgroup.

Results for apparently healthy women are illustrated in Fig. 2. In particular, HR of the 10-year first CVD event for depressive symptomatology was decreased by 35% (23%, 44%) after adjusting for lifestyle, sociodemographic, clinical, and anthropometric factors as well as lipid and inflammatory markers. The factors mostly accounted for the excess depressive-symptomatology risk on CVD onset; close to the overall, were C-reactive protein (PERM = 38% 95% CI 31%, 51%), waist-to-hip ratio (PERM = 35% 95% CI 31%, 42%), and diabetes (PERM = 32% 95% CI 27%, 36%). Among lipid markers, the highest mediating effect was observed by high-density lipoprotein (PERM = 28% 95% CI 25%, 32%) and triglycerides (PERM = 26% 95% CI 22%, 33%). As for the nonclinical/biochemical factors, financial status (PERM = 23% 95% CI 15%, 31%) presented the biggest mediating effect followed by educational status, adherence to Mediterranean diet and sleep duration, accounted on average for 20% of the examined association.

Mediation analysis outcomes for women with ACS are illustrated in Fig. 3. Diabetes and adherence to medication had the biggest separate mediating effect (PERM = 40% 95% CI 27%, 51% and PERM = 40% 95% CI 29%, 53%, respectively), followed by hypertension (PERM = 38% 95% CI 27%, 48%). Interestingly, disease burden indicators, i.e., patients’ CVD history and discharge status, presented a very low mediating effect size that did not exceed, on average, 10%. Among the examined lifestyle factors, current smoking was revealed the strongest mediator, accounting for 33% (19%, 39%) of depressive symptomatology-aggravating effect on ACS prognosis. Anthropometric parameters in terms of body mass index seemed to modestly mediate the examined association (PERM = 29% 95% CI 19%, 35%). Overall, 46% (23%, 53%) of the excess 10-year recurrent CVD event depressive symptomatology risk was attributed to all adjustment factors.

4. Discussion

In this re-analysis of two epidemiological studies, higher magnitude of association between depressive symptomatology and 10-year first or recurrent CVD event was revealed for women. Furthermore, we estimated that 35% of excess first CVD event risk and nearly half of excess risk for recurrent CVD events due to depressive symptomatology in women subgroup were mediated by conventional factors. Different patterns of ranking were observed regarding the separate mediating effect of adjustment factors oriented by CVD prevention stage. The present work, although exploratory and hypothesis generating, supports that current data for the effect of depression on CVD onset and prognosis along with
the potential underpinnings need being expanded to sex-specific remarks.

4.1. Depressive symptomatology and CVD onset or progression: the gender gap

Women cardiac patients have a twofold higher likelihood to suffer from depressive symptoms. Although this prevalence points to a greater degree of adverse events in women patients with psychological stressors, hitherto literature is not well defined. Sex-based analysis, herein, revealed that depressive symptomatology was an independent prognostic risk factor for recurrent CVD event only in women with ACS. Similarly, in the latest meta-analysis of prospective studies, post-AMI depression presented a twofold higher 2-year risk of impaired outcomes. What should be outlined here is that no sex-stratified analysis was performed while the women patient representativeness did not exceed the 26% of total meta-analysis sample. Interestingly, sex differences in depressive symptomatology and post-AMI prognosis were recently investigated in an individual patient data meta-analysis (MINDMAPS study); the conclusion was that in addition to the more frequent symptoms in women, the aggravating effect was stronger for men. Nonetheless, this “men-privilege” was attenuated by disease status.

Even if it has been four years since when American Heart Association stated depression as a “risk factor” for subsequent cardiac episodes, no convincing evidence exists for CVD onset, even more when it comes to sex interactions. INTERHEART is one of the few large-scale studies suggesting a higher magnitude of psychosocial factors–AMI association in favor of women. An updated meta-analysis revealed that subjects with depressive symptomatology had 1.3 times higher risk for coronary heart disease and AMI. Beyond this pooled effect, that meta-analysis highlighted a remaining literature gap, related to sex-depressive symptoms interaction on CVD onset. Although the men-to-women first CVD relative risk ratio for depressive symptoms was 1.20 [men exceeded women], only eight out of 24 studies provided separate data for women while more than half of them presented men-specific outcomes; this is probably a bias from a sex-related standpoint which seems more evident in European populations. Here, with a European study population, depressive symptomatology was an independent predictor for the first CVD event only in women. Despite the statistical-power limitations, a disproportionally elevated risk for this group is noted. Very few studies, after that meta-analysis, prospectively examined the sex-specific effect of depressive symptoms on CVD onset. Results are mixed ranging from a higher risk in women to similar risk between sexes. Currently, Framingham study revealed an increase in the predictive

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**Fig. 2.** Percentage of excess 10-year first CVD event risk for depressive symptomatology mediated by different risk factors in apparently healthy women [n = 399].

Abbreviations: CVD, Cardiovascular disease; HR, Hazard ratio; 95% CI, 95% Confidence interval, PERM, Percentage of excess mediated risk; SES, Socioeconomic status. "Standard model was adjusted for age, family CVD history, and State Anxiety sub-scale of the Spielberger State-Trait Anxiety Inventory. PERM and corresponding 95% CIs for depressive symptomatology were evaluated for (a) isolated mediators (illustrated as dots and vertical lines) and (b) combinations of mediators (presented in table). Sketched frame represents overall PERM and 95% CI."
ability of Framingham Risk Equation in women after depressive symptomatology addition to the risk-assessment model.18

4.2. Depressive symptomatology and CVD in women: highlights for primary prevention

Although the causality behind these observations has not been established, putative mechanisms have been suggested.5,19,20 Considering men and women differ in CVD manifestation and accompanied risk factors, the attendant metabolic paths should be interpreted separately in all prevention steps.21,22 One hypothesis investigated here was the extent to which the depressive symptoms—CVD association in women was mediated by conventional risk factors. Sex role-related stressors, i.e., role overload, interpersonal orientation, and decreased self-esteem, are the most discussed mediators driven by low socioeconomic status.19 Here, modest mediating effects of socioeconomic factors were revealed, overlapped by clinical/biochemical factors, i.e., excess body weight, abnormal glycemic status, and inflammation; similar underlying mechanisms have been previously suggested as more evident in women.23 Another finding here was that suboptimal adherence to Mediterranean diet and inadequate sleep were the most important behavioral mediators. A bidirectional association between unhealthy nutrition and depressive symptoms has been profoundly proposed in the literature, while this is currently suggested for sleep quality.24,25 Lipid markers are also presented as mediators.5 In the present work, high-density lipoprotein and triglycerides were the lipid markers with the biggest mediating effect; women-specific reports for lipid profile may explain this ranking.21

The important observation here was that all the aforementioned factors accounted for only 35% of the examined association, suggesting a biological relation between the examined disease states, which remains unexplained. Increasing evidence suggests that some psychological factors are influenced by genes and that some of these genes may have cardiac implications.26 Twin-study analyses have shown that various genetic factors contribute to depression-CVD comorbidity, yet interestingly only in women; hence, higher heritability and stronger genetic basis are inferred.27 Another hypothesis that could be performed here is the depressive-symptom chronicity in women. Women predominance regarding psychological stressors begins in adolescence and persists into middle and early old age.2 As there is evidence that depressive symptoms are more persistent and severe for women, this could be considered as an unmeasured confounder. Women-specific conditions have been suggested to exacerbate the effect of depressive symptoms on the vascular system. Serotonin, involved in depression-disrupted behaviors (mood, appetite, and sleep), presents reciprocity with female sex hormones, while an immunological estradiol-mediated path has been currently suggested.27

Fig. 3. Percentage of excess 10-year recurrent CVD event risk for depressive symptomatology mediated by different risk factors in women with acute coronary syndrome [n = 523]. Abbreviations: CVD, Cardiovascular disease; HR, Hazard ratio; 95% CI, 95% Confidence interval, PERM, Percentage of excess mediated risk; SES, Socioeconomic status. *Standard model was adjusted for age and family history of CVD. PERM and the corresponding 95% CIs for depressive symptomatology were evaluated for (a) isolated mediators (illustrated as dots and vertical lines) and (b) combinations of mediators (presented in table). Sketched frame represents overall PERM and 95% CI.
4.3. Depressive symptomatology and CVD in women: highlights for secondary prevention

In women with ACS mentioned in the present work, the effect of examined mediators was higher, interpreting almost the half of depressive-symptomatology-aggravating effect. Among the tested mediators, low adherence to medication came on the top of the rank. This is in accordance with recent highlights from GENESIS-PRAXY and other works, related to very low women’s intention-to-adapt recommendations in their post-ACS period of life, due to depressed mood oriented by cardiac-complication consolidation. Another important observation here was that disease severity indicators were not as important mediators as normally expected. This finding comes in line with recent suggestions that depressive symptoms in women are irrelevant with disease burden.

4.4. Depressive symptomatology and CVD in men

As for men mentioned in the present work, the aggravating effect of depressive symptoms on CVD event rate was observed, yet it did not reach the level of significance. The more prevalent behavioral and clinical risk factors in men along with the lower likelihood to suffer from depressive symptoms might contribute to that outcome. Additionally, men are more likely to suffer from depressive symptoms later in life and after a chronic disease establishment, while in women, the increased subsequent CVD event risk is to be attributed to frailty- and disability-related confounders in advanced age. Finally, different depression features and response to psychological/mental stress have been suggested for men pointing to a non-well-defined and probably underdiagnosed male depression syndrome hypothesis.

4.5. Limitations and strengths

The present study findings should be considered with caution owing to the study’s observational nature. It should also be noted that depressive symptomatology was obtained from self-reporting, validated scales and not from diagnostic interviews. Additionally, as only baseline data were used, long-term shifts were not considered. As for the subsample of the ATTICA study with available psychological metrics, another limitation in the present analysis is the relatively small number of CVD events, which was mainly due to the sampling scheme of this study (i.e., enrolled participants without prior CVD and from all age groups according to the population census). Moreover, statistical power reduction due to sex-stratified analysis should be considered during the interpretation of outcomes.

The present work has several strengths, which compensate the aforementioned limitations. First, this is one of the very few works that correlated depressive symptomatology with major CVD events as the principal endpoint, providing separate outcomes not only for men and women but also for primary (i.e., first event) and secondary (i.e., recurrent event) prevention. Second, the role of impaired psychological health has been largely investigated in the context of established CVD, yet evidence on apparently healthy younger subjects is scarce. Lastly, this work provides highlights on which conventional CVD risk factors mediate the aggravating effect of depressive symptomatology in women with or without CVD history, which expands the obtained knowledge toward the underlying paths on the examined associations.

5. Conclusion

In the interplay between the brain and the heart, many questions still exist to unravel the underlying mechanisms that will support the determination of cost-effective prevention and prognostic strategies. Most importantly, there is need for expansion to the most susceptible groups that exhibit more frequently and/or more aggressively impaired psychological health; studying sex-related associations is oriented toward this approach. Therefore, the present work augments prior evidence that depressive symptomatology is an important driver of CVD onset and progression mainly in women, while it gives rise to additional research toward unmeasured or unidentified paths through which this observation is exerted.

Declaration of interest

None to declare.

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References


