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**FULL RESEARCH PAPER**
*Social-psychological factors*

# Associations between psychosocial burden and prognostic biomarkers in patients with chronic coronary syndrome: a STABILITY substudy

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**Aims** To investigate associations between psychosocial (PS) burden and biomarkers reflecting pathophysiological pathways in patients with chronic coronary syndrome.

**Methods and results** Psychosocial factors were collected from self-assessed questionnaires and biomarkers representing inflammation [high-sensitivity (hs)-C-reactive protein (CRP), interleukin-6 (IL-6), lipoprotein-associated phospholipase A2 (Lp-PLA2)] and cardiac injury/stress [hs-troponin T (hs-TnT), N-terminal pro-B-type natriuretic peptide (NT-proBNP)] were measured in 12 492 patients with chronic coronary syndrome in the STABILITY trial. Associations between level of each PS factor [never–rarely (reference), sometimes, often–always] and biomarkers were evaluated using linear models with adjusted geometric mean ratios (GMR). A score comprising four factors ('feeling down', 'loss of interest', financial stress', and 'living alone') that previously demonstrated association with cardiovascular (CV) outcome was created, and categorized into three levels: low, moderate, and high PS burden. Associations between PS score and biomarkers were evaluated similarly. Greater PS burden was significantly associated with a gradual increase in inflammatory biomarkers [GMR (95% confidence interval) for moderate vs. low PS burden; and high vs. low PS burden]: hs-CRP [1.09 (1.04–1.14); 1.12 (1.06–1.17)], IL-6 [1.05 (1.02–1.07); 1.08 (1.05–1.11)], LpPLA2 [1.01 (1.00–1.02); 1.02 (1.01–1.04)], and cardiac biomarkers hs-TnT [1.03 (1.01–1.06); 1.06 (1.03–1.09)] and NT-proBNP [1.09 (1.04–1.13); 1.21 (1.15–1.27)].

**Conclusion** In patients with chronic coronary syndrome, greater PS burden was associated with increased levels of inflammatory and cardiac biomarkers. While this observational study does not establish causal nature of these associations, the findings suggest inflammation and cardiac injury/stress as plausible pathways linking PS burden to an elevated CV risk that needs to be further explored.

**Lay summary** We studied the association between psychosocial (PS) factors and various circulating protein biomarkers, reflecting different underlying mechanisms of disease, with the hope of shedding light on the link between psychological factors like depression and stress and the risk of cardiovascular (CV) events in patients with chronic coronary syndrome.

- We analysed data from the global large-scale STABILITY trial, which included more than 12 000 patients with chronic coronary syndrome. Participants filled out a questionnaire assessing their level of PS burden, including experiences of depressive symptoms, stress at home, at work and financial stress. Additionally, blood samples were collected in which biomarkers (N-terminal pro-B-type natriuretic peptide, high-sensitive troponin-T, interleukin-6, C-reactive protein, and LpPLA2) were analysed.

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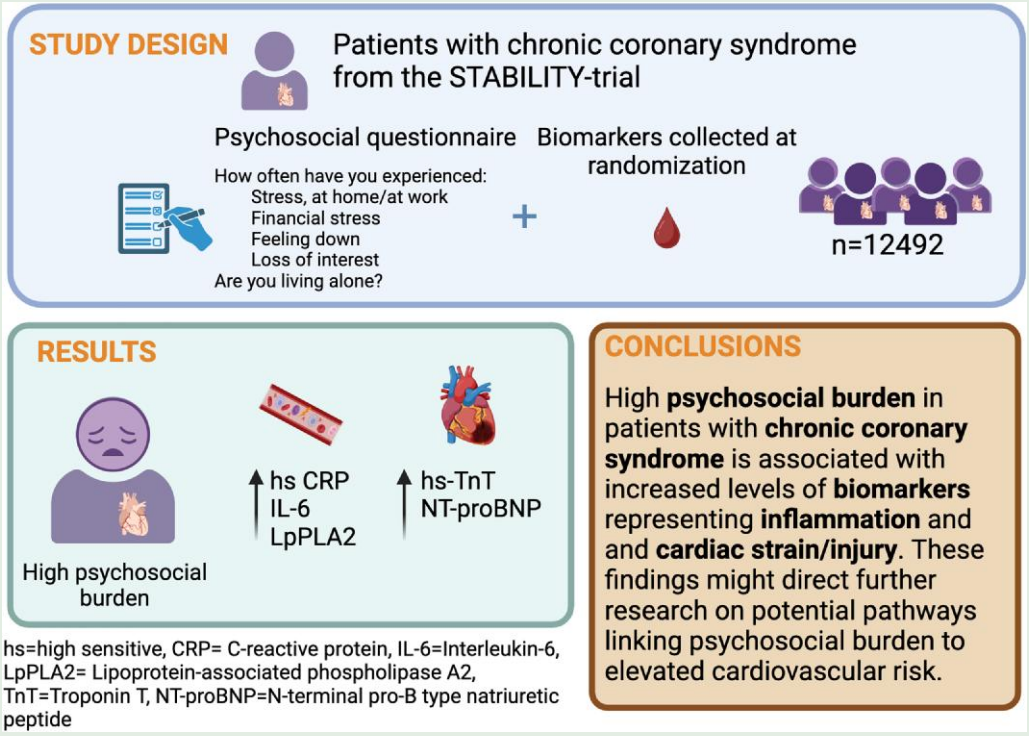
- Our findings revealed a significant association between higher PS burden and increased concentrations of biomarkers in patients with chronic coronary syndrome. These biomarkers reflect both inflammatory processes and cardiac damage or dysfunction which could be potential disease mechanisms explaining the increased risk of adverse events in patients with chronic coronary syndrome and high PS burden. Although causal relationships cannot be determined from this study, the findings suggest that inflammation and cardiac stress may play crucial roles in linking PS factors to heightened CV risk in this patient population. These insights could pave the way for better understanding and managing CV health in individuals with chronic coronary syndrome, offering hope for more targeted interventions in the future.

## Graphical Abstract




**Keywords** Coronary artery disease • Psychosocial factors • Biomarkers

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# Introduction

Psychosocial (PS) factors, such as depression and stress are known risk factors associated with the development of cardiovascular disease (CVD).[1–3] This association was described in the landmark case–control study INTERHEART, wherein six variables representing PS stress (stress at home and/or work, financial stress, stressful life events, locus of control, and depression) were independently associated with an increased risk of myocardial infarction (MI). Furthermore, when the six variables were combined into a PS index, it was considered the fourth strongest risk factor associated with MI, following the major risk factors hypercholesterolaemia, diabetes mellitus, and current smoking.[4,5] Furthermore, our research group has recently shown that depressive symptoms, financial stress, and living alone are associated with increased risk of recurrent cardiovascular (CV) events, including CV mortality, in a large prospective study involving patients with chronic coronary syndrome.[6]

The underlying mechanisms linking PS factors to the development of CVD and increased CV risk are not fully understood. Psychosocial factors may influence the risk of CVD indirectly via unhealthy lifestyle behaviours, such as poor dietary habits, physical inactivity, smoking, alcohol overconsumption, and poor compliance to prescribed medication, leading to CVD risk factors such as hypertension, diabetes, and obesity.[7,8] However, even after adjustments for such behaviours and risk factors, there remains an association with CVD, indicating the involvement of other pathophysiological mechanisms.[9] Experimental and observational studies have shown that depression and stress may contribute to coronary atherosclerosis and endothelial dysfunction through a dysregulated autonomic nervous system. Other possible pathways associated with chronic stress and depression include the activation of the inflammatory and the coagulation systems, leading to atherogenesis.[9–12]

Circulating protein biomarkers play an important role in diagnosis, prognosis, and management of patients with CVD. They also reflect important pathophysiological pathways. Studying the associations between biomarkers and PS burden in CVD patients may provide a better understanding of the potential links between PS burden and CV risk. Commonly used inflammatory biomarkers, such as C-reactive protein (CRP) and interleukin-6 (IL-6), are involved in the progression

of CVD through atherogenesis and are independently associated with the risk of CVD.[13] N-terminal pro-B-type natriuretic peptide (NT-proBNP) and cardiac troponins (c-Tn) reflect cardiac dysfunction and myocardial damage, respectively, and are associated with an increased risk of CVD.[14,15] Additionally, lipoprotein-associated phospholipase A2 (Lp-PLA2), a proinflammatory marker involved in atherosclerosis, is associated with CVD.[16] However, a possible link between these biomarkers and PS burden is less well-established.

The aim of this study was to assess the association between PS factors and circulating protein biomarker levels linked to CV outcomes in patients with chronic coronary syndrome. This might in turn elucidate potential mechanisms connecting PS burden with CVD.

# Methods

## Study population

The current study is based on data collected from the Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy (STABILITY) trial. STABILITY was a randomized, placebo-controlled trial in which the Lp-PLA2-inhibitor darapladib was tested against placebo in 15 828 patients with chronic coronary syndrome from 39 countries included between December 2008 and April 2010.[17] In the trial, darapladib did not significantly reduce the risk of the primary composite endpoint of CV death, non-fatal MI, and non-fatal stroke. The study design and endpoint definitions have been previously published and the inclusion and exclusion criteria are listed in the Supplementary Material (Supplementary material online, *Table S2*).[18] The study was conducted in accordance with the Helsinki Declaration and approved by appropriate regulatory and ethics committees in all participating countries, and all participants provided written informed consent.

## Psychosocial factors

At baseline, all patients included in the STABILITY trial were asked to fill out a questionnaire. The purpose of the questionnaire was to screen for known lifestyle-related risk factors for CVD and explore other potential or novel behavioural risk factors. One section of the questionnaire focused on PS factors, covering questions about whether participants had experienced (A) stress at work, (B) stress at home, or (C) financial stress during the last year. Additionally, patients were asked about characteristic depressive symptoms, such as (D) feeling down and (E) loss of interest. Responses were self-reported using the following scale: 'never or rarely', 'sometimes', 'often', or 'always'. For Question A, there was an alternative answer option for 'I do not work'. The questionnaire also gathered information about current family situation, including whether patients were (F) living alone. In total, six PS factors were selected for a cross-sectional analysis (see Supplementary material online, *Table S1*).

To summarize and quantify the total PS burden, we created a composite PS score. This scoring system has been previously utilized in the STABILITY sub-study analysing the association between PS factors and CV events. The score is based on the PS factors most strongly associated with CV outcomes—specifically, (C) financial stress, (D) feeling down, (E) loss of interest, and (F) living alone.[6] Points were assigned and summed for each patient as follows: 0 points for 'never or rarely' experiencing any of C–E or living with someone, 1 point if experiencing any of C–E 'sometimes', 2 points if experiencing any of C–E 'often' and 3 points for 'always' experiencing any of C–E or if living alone. The resulting score was then categorized into three levels: ≤ 1 point designated low PS burden, 2–3 points labelled moderate PS burden, and >3 points classified as high PS burden.

## Biomarkers

Blood samples were collected at randomization in the STABILITY trial, locally at each site and stored in repositories at −70°C. All blood samples were then sent to the Uppsala Clinical Research Center (UCR) laboratory in Sweden for central analyses. Levels of high-sensitivity (hs)-cardiac troponin T (TnT) and NT-proBNP were analysed by electrochemiluminescence immunoassays using a Cobas Analytics e601 system (Roche Diagnostics) at UCR laboratory, Uppsala, Sweden. Hs-CRP was analysed using a 2-site particle-enhanced immunonephelometric sandwich assay (Dade Behring) at Quest Diagnostics Clinical Laboratories Inc. IL-6 was analysed by Quantikine® HS Human IL-6 Immunoassay, R&D Systems, on a Tecan Freedom EVOlyzer and Lp-PLA2 activity was measured in an automated enzyme assay system by the manufacturer (PLAC Test for Lp-PLA2 Activity; Diadexus).[16] Performance characteristics (limit of quantitation and local coefficient of variation) of all included biomarkers are presented in the Supplementary material online, *Table S3*.

## Statistical analyses

In this cross-sectional analysis, the total study cohort comprised patients with complete observations for all the six PS factors in the lifestyle questionnaire and all the pre-mentioned selected biomarkers at the time of randomization. Baseline characteristics are presented in a tabular format with categorical variables summarized using frequencies and percentages and continuous variables summarized using median and interquartile ranges (IQR). To investigate differences across the groups of patients, categorical variables were compared with the $\chi^2$ test and continuous variables were compared with Mann–Whitney non-parametric tests. Associations between PS factors and biomarker levels (hs-CRP, IL-6, Lp-PLA2 hs-TnT, and NT-proBNP) were evaluated using multivariable linear models with log-transformed biomarkers. The categories 'often' and 'always' were merged into one subgroup 'often–always' due to limited number of patients in these categories when analysing each PS factor separately, though not when calculating the PS score. No imputation was performed for missing data. 'Never–rarely' was selected as reference for all comparisons, except for the question living alone, for which 'no' was selected as the reference. Patients who selected 'did not work' were excluded from the analysis of stress at work. In the PS score, low PS burden was selected as the reference. Results were presented as adjusted geometric mean ratios (GMR) with 95% confidence interval (CI) for comparison between subgroups or to indicate changes in continuous variables. A crude model, without adjustment for potential confounders, was initially presented. In the second model, adjustments were made for well-established CV risk factors. These factors, consistent with those included in our prior study examining associations between PS factors and CV events,[6] encompassed age, sex, geographic region, smoking status, body mass index (BMI), years of education, family history of CVD, hypertension, diabetes mellitus, previous MI, previous coronary artery bypass grafting (CABG), prior percutaneous coronary intervention (PCI), multivessel disease, polyvascular disease, renal dysfunction, and randomized treatment (darapladib or placebo).

All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA). A two-sided *P*-value of <0.05 was considered statistically significant.

# Results

Baseline characteristics for the total study cohort ($n = 12\,492$) and by each PS score level (low–moderate–high PS burden) are presented in *Table 1*. All global geographical regions were represented in the study. The majority of the patients were men (82.1%), and median age was 65 years (*Table 1*). Patients with higher PS burden according to score level were more likely to be younger, female, obese, diagnosed with diabetes mellitus, and current smokers. Demographics of each PS factor are presented in *Table 2*.

Biomarker concentrations according to the level of the PS score are presented in *Figure 1*, demonstrating a stepwise increase in hs-CRP, IL-6, LpPLA2, and NT-proBNP-levels except for hs-TnT. Crude biomarker concentrations for all biomarkers, categorized by each PS factor

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**Table 1 Baseline characteristics in the total cohort and by psychosocial score level[a]**

| Characteristics | Total cohort $n = 12\,492$ | Low PS burden $n = 5098$ | Moderate PS burden $n = 4187$ | High PS burden $n = 3207$ | *P*-value |
|---|---|---|---|---|---|
| Age (years) | 65.0 (59, 71) | 66.0 (61, 72) | 64.0 (58, 70) | 62.0 (56, 69) | <0.0001 |
| Sex, male | 10 251 (82.1%) | 4458 (87.4%) | 3426 (81.8%) | 2367 (73.8%) | <0.0001 |
| BMI (kg/m$^2$) | 28.4 (25.6, 31.8) [20] | 28.1 (25.4, 31.3) [9] | 28.5 (25.7, 31.7) [7] | 28.7 (25.9, 32.5) [4] | <0.0001 |
| Current smoker | 2274 (18.2%) | 664 (13.0%) | 786 (18.8%) | 824 (25.7%) | <0.0001 |
| Geographic region | | | | | <0.0001 |
| Asia/Pacific | 2312 (18.5%) | 1112 (21.8%) | 765 (18.3%) | 435 (13.6%) | |
| Eastern Europe | 2925 (23.4%) | 982 (19.3%) | 1106 (26.4%) | 837 (26.1%) | |
| North America | 3363 (26.9%) | 1367 (26.8%) | 1081 (25.8%) | 915 (28.5%) | |
| South America | 742 (5.9%) | 210 (4.1%) | 266 (6.4%) | 266 (8.3%) | |
| Western Europe | 3150 (25.2%) | 1427 (28.0%) | 969 (23.1%) | 754 (23.5%) | |
| Medical history | | | | | |
| Hypertension | 8944 (71.6%) | 3580 (70.2%) | 3012 (71.9%) | 2352 (73.3%) | 0.0076 |
| Diabetes mellitus | 4803 (38.4%) | 1862 (36.5%) | 1618 (38.6%) | 1323 (41.3%) | <0.0001 |
| Prior MI | 7355 (58.9%) | 2896 (56.8%) | 2533 (60.5%) | 1926 (60.1%) | 0.0005 |
| Prior PCI or CABG | 9335 (74.7%) | 3916 (76.8%) | 3105 (74.2%) | 2314 (72.2%) | <0.0001 |
| Multivessel CHD | 1686 (13.5%) | 641 (12.6%) | 605 (14.4%) | 440 (13.7%) | 0.0285 |
| Polyvascular disease | 1883 (15.1%) | 700 (13.7%) | 618 (14.8%) | 565 (17.6%) | <0.0001 |
| Prior stroke | 1063 (8.5%) | 398 (7.8%) | 349 (8.3%) | 316 (9.9%) | 0.0044 |
| Chronic kidney disease | 3747 (30.0%) | 1493 (29.3%) | 1272 (30.4%) | 982 (30.6%) | 0.3476 |
| Level of education | | | | | 0.0681 |
| None | 417 (3.3%) | 180 (3.5%) | 116 (2.8%) | 121 (3.8%) | |
| 1–8 years | 2185 (17.5%) | 870 (17.1%) | 723 (17.3%) | 592 (18.5%) | |
| 9–12 years | 3893 (31.3%) | 1606 (31.6%) | 1278 (30.6%) | 1009 (31.6%) | |
| Trading school | 2349 (18.9%) | 965 (19.0%) | 793 (19.0%) | 591 (18.5%) | |
| College/University | 3611 (29.0%) | 1465 (28.8%) | 1264 (30.3%) | 882 (27.6%) | |
| Biochemical analyses | | | | | |
| hs-CRP (mg/L) | 1.30 (0.60, 3.10) | 1.20 (0.60, 2.70) | 1.40 (0.70, 3.30) | 1.60 (0.70, 3.50) | <0.0001 |
| Hs-IL-6 (ng/L) | 2.10 (1.40, 3.20) | 2.00 (1.40, 3.00) | 2.10 (1.40, 3.20) | 2.20 (1.50, 3.40) | <0.0001 |
| LpPLA2 (µmol/min/L) | 172.5 (143.3, 204.0) | 171.1 (142.8, 202.1) | 173.2 (143.1, 205.1) | 173.6 (144.7, 206.4) | 0.0232 |
| Hs-troponin T (ng/L) | 9.20 (6.20, 14.10) | 9.40 (6.40, 14.00) | 9.30 (6.10, 14.20) | 8.80 (5.90, 14.30) | 0.0040 |
| NT-proBNP (ng/L) | 169.0 (82.0, 366.0) | 162.0 (81.0, 340.0) | 167.0 (81.0, 373.0) | 183.0 (88.0, 413.0) | <0.0001 |

CHD, coronary heart disease.
[a]Values are median (IQR) for continuous variables and *n* (%) for categorical variables. [ ] for number of missing observations.

from 'never–rarely' to 'sometimes' and 'often–always' are presented in Supplementary material online, *Figure S1*.

In the adjusted analysis, associations between PS burden, based on the level of the composite PS score, and biomarkers showed a gradual increase in biomarker levels with PS burden for all studied biomarkers (hs-CRP, IL-6, LpPLA2, NT-proBNP, and hs-TnT), presented in *Figure 2*.

In the adjusted analysis of each individual PS factor, patients experiencing depressive symptoms ('feeling down' and 'loss of interest') or 'financial stress' exhibited higher levels of the inflammatory biomarkers hs-CRP (for 'feeling down', the *P*-value was slightly above significant level), IL-6 and LpPLA2, as well as the cardiac biomarker NT-proBNP. This association showed a graded pattern based on the level of PS burden, as illustrated in *Figure 3*. 'Feeling down' and 'financial stress' were also associated with a gradual increase in hs-TnT levels. Patients living alone had significantly higher levels of the cardiac biomarkers, hs-TnT 1.05 (1.01–1.08), $P = 0.005$, and NT-proBNP 1.11 (1.05–1.17), $P = 0.0003$, compared to those not living alone. However, patients experiencing 'stress at home' did not exhibit the same pattern, showing weaker associations with biomarkers and in several cases lacking a graded pattern based on the level of burden (*Figure 3*). In contrast to the other PS factors, 'stress at work' was associated with significantly lower levels of the biomarker NT-proBNP [GMR (95% CI) sometimes vs. never–rarely and often–always vs. never–rarely 0.96 (0.90–1.02), 0.90 (0.83–0.97), $P = 0.02$]. Crude associations between PS burden and log-transformed biomarker levels are presented in the supplement (see Supplementary material online, *Figure S2*).

## Discussion

Patients with CVD and PS burden face an elevated risk of recurrent CV events. By studying biomarkers that reflect various pathophysiological

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**Table 2 Psychosocial factors by level of burden**

| Psychosocial factor | Total cohort $n = 12\,492$ |
|---|---|
| Feeling down | |
| Never/rarely | 5349 (42.8%) |
| Sometimes | 5725 (45.8%) |
| Often | 1181 (9.5%) |
| Always | 237 (1.9%) |
| Loss of interest | |
| Never/rarely | 7174 (57.4%) |
| Sometimes | 3947 (31.6%) |
| Often | 1044 (8.4%) |
| Always | 327 (2.6%) |
| Feeling stress at work | |
| Never/rarely | 1822 (14.6%) |
| Sometimes | 2493 (20.0%) |
| Often | 1121 (9.0%) |
| Always | 297 (2.4%) |
| Do not work | 6759 (54.1%) |
| Feeling stress at home | |
| Never/rarely | 5244 (42.0%) |
| Sometimes | 5819 (46.6%) |
| Often | 1189 (9.5%) |
| Always | 240 (1.9%) |
| Feeling financial stress | |
| Never/rarely | 6366 (51.0%) |
| Sometimes | 4088 (32.7%) |
| Often | 1440 (11.5%) |
| Always | 598 (4.8%) |
| Living alone | |
| No | 10 797 (86.4%) |
| Yes | 1695 (13.6%) |

pathways, we might shed light on potential mechanisms linking PS burden to CV risk. In the current study, conducted in a large cohort of patients with chronic coronary syndrome, we demonstrated a significant association between PS factors representing depression (feeling down and loss of interest), financial stress and living alone, and elevated biomarkers reflecting inflammation (hs-CRP, IL-6, and LpPLA2) as well as cardiac stress/dysfunction (hs-TnT and NT-proBNP). Stress at home or at work did only show significant associations with some of the biomarkers, and work stress had a negative association with NT-proBNP.

Multiple studies have shown that PS burden is more prevalent in patients with CVD compared to the general population. For instance, in patients with recent MI or established coronary artery disease (CAD), clinical diagnosis of depression is present in approximately 15–20% and an even higher proportion of patients exhibit depressive symptoms.[19–21] The reporting of the proportion of patients experiencing PS stress is more complex. This could partly be due to the definition of stress that can be interpreted differently and may be categorized into diverse subcategories such as acute or chronic stress, stress at work or at home, or financial stress. Nevertheless, numerous studies have shown that PS stress is associated with an increased risk of CV events and mortality. This association holds true for both healthy populations and patients with established CAD, thus establishing PS factors as independent risk factors for CVD.[1,5,6,9,22] Despite this evidence, the underlying mechanisms linking PS burden and CVD remains undetermined.

## Inflammation, cardiovascular disease, and psychosocial factors

In the current study, we demonstrated that a higher PS score was independently associated with higher levels of pro-inflammatory biomarkers, such as hs-CRP, IL-6, and LpPLA2, in patients with chronic coronary syndrome. Previous studies have shown that inflammation plays a key role in the formation and acceleration of atherosclerosis, consequently being associated with the development of CAD and

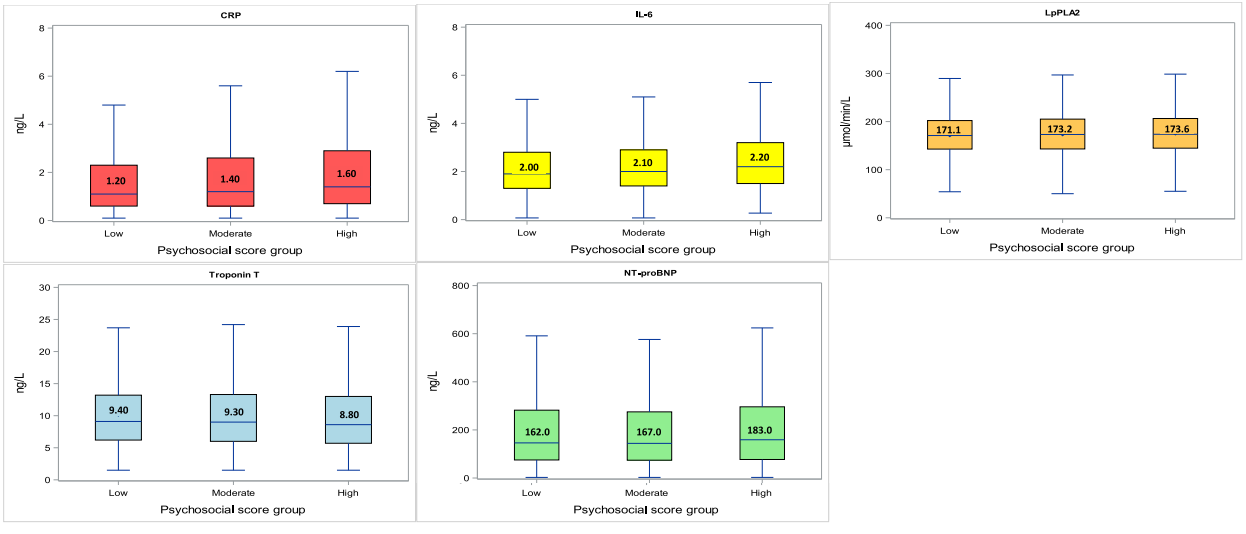


**Figure 1** Concentrations of biomarker by psychosocial score level.

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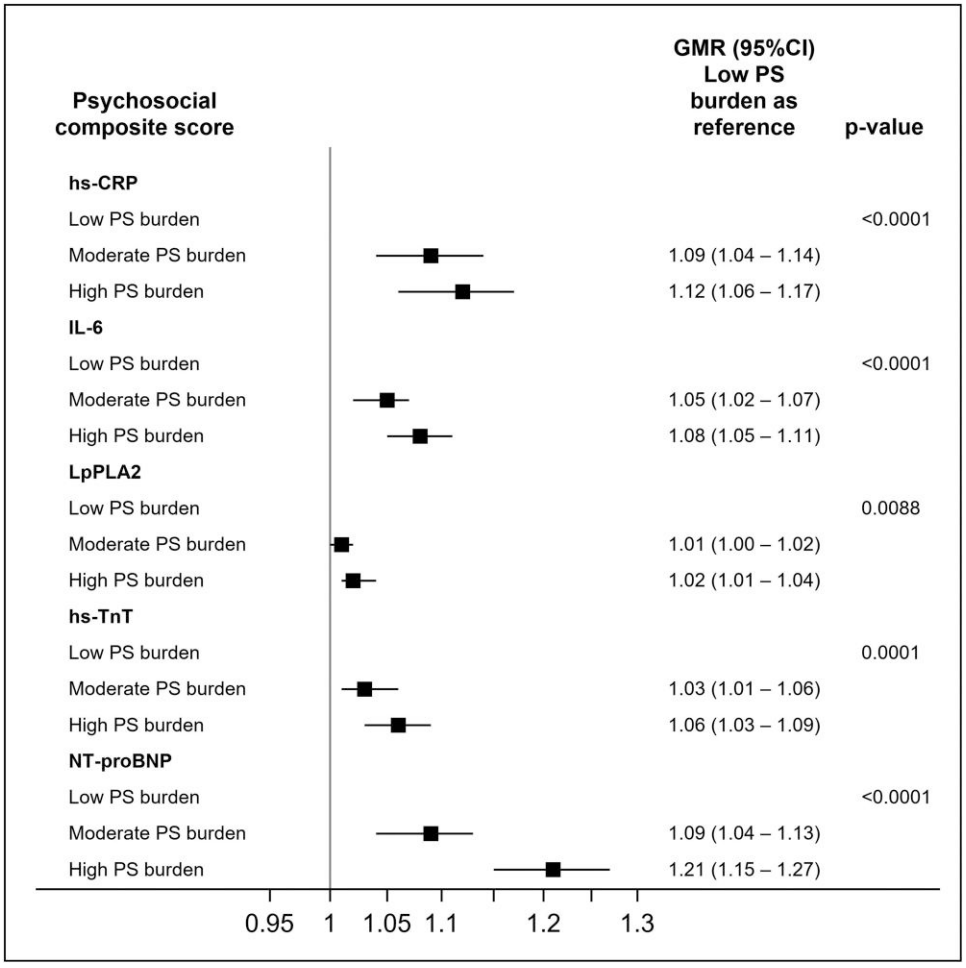


**Figure 2** Adjusted association between level of psychosocial score and biomarkers.

increased risk of CV events.[13,23,24] Nevertheless, conflicting results have been reported on the association between inflammatory biomarkers and subsequent CV events in patients with CAD. In the STABILITY cohort, IL-6 was independently associated with adverse events but not hs-CRP.[13] In contrast, a recent meta-analysis concluded that CRP was predictive of adverse events in patients with chronic coronary syndrome.[25]

The association between PS burden and inflammation has received comparatively limited attention and the underlying mechanisms are largely unknown. However, previous studies have established an association between depression, the most extensively explored PS factor, and inflammatory pathways and observed upregulation of inflammatory biomarkers such as CRP and IL-6 in patients diagnosed with clinical depression, both with and without CVD.[10,11,26] It has been proposed that these entities are related to each other. However, very few prospective studies, and to our knowledge, no interventional studies have been able to determine the causal relationship between depression, inflammation, and CAD. In a recent epidemiological study attempting to answer this question, it was demonstrated that both depressive symptoms and fibrinogen levels, another biomarker representing inflammation, may independently predict the risk of future CV events.[27] This aligns with our findings, which demonstrate that factors representing depressive symptoms, such as feeling down and loss of interest, are associated with inflammatory biomarkers (hs-CRP, IL-6, and LpPLA2). However, in the same study, inflammation did not serve as a mediating factor in the association between depressive symptoms and CAD incidence, nor did depression mediate the relationship between inflammation and CAD incidence.[27] This leaves us with persistent uncertainty regarding the interrelationship between these factors and highlights the need for more research in this area.

## Stress and cardiovascular disease

Stress has been associated with increased risk for incident CVD and recurrent CV events in patients with established CAD, as demonstrated in previous studies.[6,28,29] The definition of stress can be broadly interpreted and therefore challenging to assess. In the INTERHEART study, stress was measured in four dimensions—stress at work, stress at home, financial stress, and major life events in the past year—and each was found to be independently associated with elevated risk of MI.[4,5] While the association between different aspects of stress and CVD is established, there is a gap in large-scale studies examining associations with biomarkers. In a meta-analysis reviewing changes in inflammatory markers in response to laboratory-induced acute stress, IL-6, but not CRP was upregulated. Whether this is generalizable to naturally

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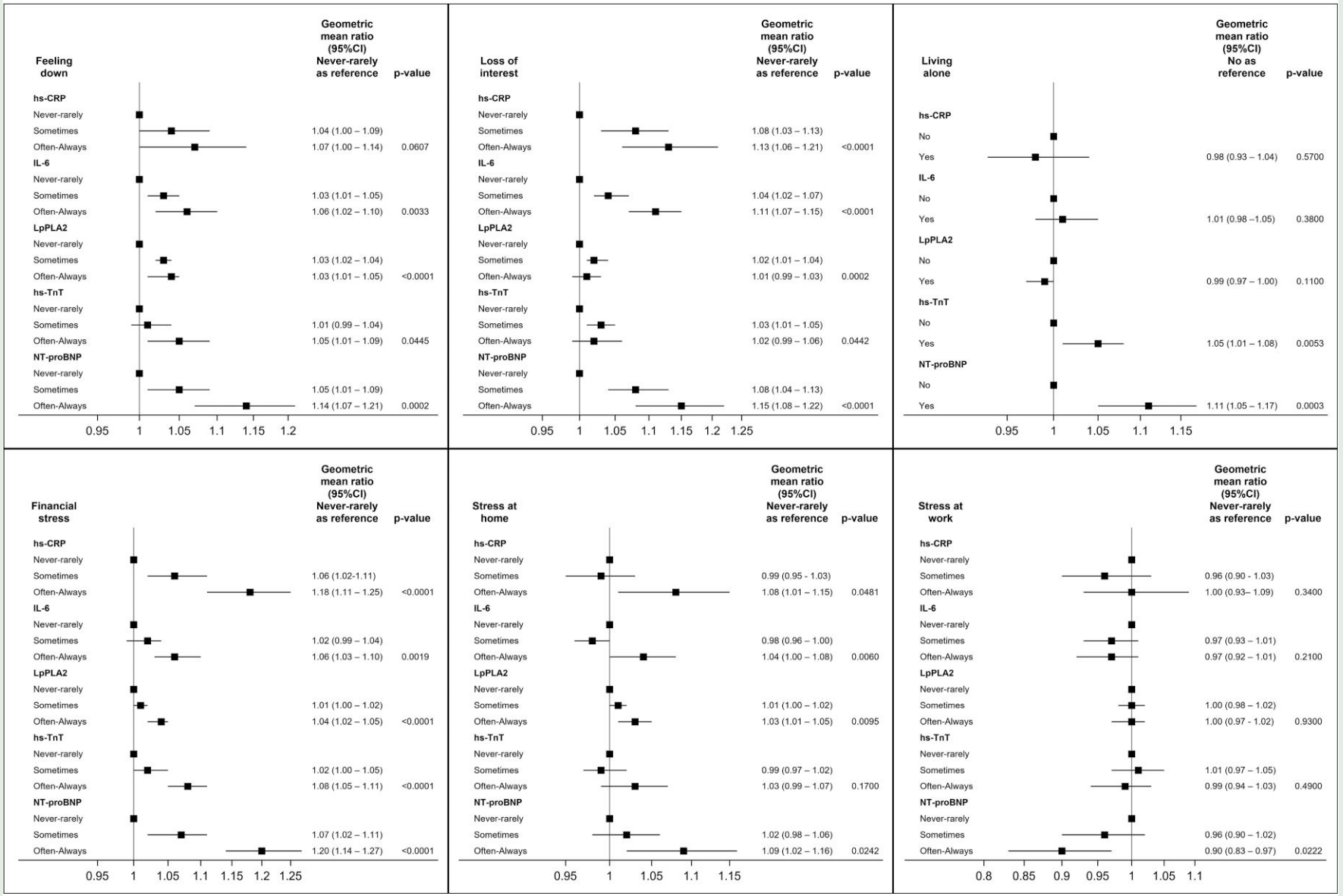


**Figure 3** Adjusted associations between all individual psychosocial factors and biomarkers.



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occurring chronic stressors and patients with CAD remains uncertain.[30] In one study, mental stress induced elevated levels of IL-6 and CRP in patients with CAD, and the increase was larger than in healthy controls.[31] Although the study size was limited, the results were validated in a more recent study investigating IL-6 concentrations in younger women with CAD before and after mental stress.[32] In the current study, three types of stress were measured: financial stress, stress at home, and stress at work. Financial stress was the only stress-factor significantly associated with higher levels of all the studied biomarkers, aligning with previous findings of elevated inflammatory mediators and extends our knowledge suggesting cardiac ischaemia/strain a possible mechanism linking stress and CAD. Conversely, stress at home or at work did not show associations with the studied biomarkers and surprisingly, stress at work was associated with some lower biomarker levels, even though patients who did not work were excluded from the analysis. In other CVD populations, work stress has been associated with an increased CV risk.[8,33] In our previous study based on the STABILITY population, an inverse association between stress at work and CV events and mortality was observed. One possible explanation for this inconsistency might be the rather broad definition of stress and how it may have been interpreted by the patients reporting it. In the STABILITY trial, stress at work was not defined in any particular way and might have been perceived by patients in a more positive light, correlated with having a meaningful and significant work position. In other studies, stress at work has for example been defined as imbalance in job demand vs. job control or as stress that negatively affect health status.[8,33] Stress at home and stress at work did not show convincing results neither in the current study nor in the previous STABILITY study evaluating association with CV outcomes; therefore, these factors were not used when calculating a composite PS stress score.

## Behavioural factors or biological mechanisms

Possible explanations for the association between PS burden and CVD could be clarified by behavioural and lifestyle changes. Indeed, studies have shown that PS factors are linked to an unhealthy lifestyle, leading to an increased risk and prevalence of several traditional CV risk factors such as obesity, smoking, hypertension, and diabetes mellitus.[7] Additionally, patients with depression tend to be less compliant to medication and other health promoting activities after developing CVD, such as exercise and stress control[19,20] Our study similarly observed a trend where patients with higher PS burden were more likely to have CV risk factors such as obesity, current smoking, and diabetes mellitus. However, despite adjusting for these risk factors, we still demonstrated an association between PS burden and biomarkers levels, indicating the potential presence of other pathophysiological mechanisms.

There are few proposed biological mechanisms other than the depression/stress-inflammation-CVD model discussed earlier, and the causal relationship remains unknown. Links between PS burden and cardiac biomarkers such as NT-proBNP and hs-TnT are subject of limited research. One observational study found that mental stress was associated with elevated hs-TnT levels.[34] A potential explanation of this association is the direct impact of cortisol on cardiomyocytes, increased in saliva due to mental stress, through mechanisms such as oxidative stress, modulated ion channels, potentiation of adrenergic signalling, and atherosclerosis leading to ischaemia. Increased NT-proBNP was inversely associated with anxiety and mild depression in one study. This may be explained by the stimulation of vagal afferents by natriuretic peptides, which are known to contribute to internal stress regulation and are used in therapeutic vagus nerve stimulation. Other potential mechanisms by which BNP can be anxiolytic include reduced corticotropin-releasing hormone secretion in limbic structures, which also reduces pituitary and adrenocortical hormone secretion and sympathetic tone.[35]

## Potential future directions

In recent years, the association between inflammation and CVD has gained particular interest due to the possibility of targeting the inflammatory system using anti-inflammatory drugs such as canakinumab and colchicine.[36,37] Nevertheless, there is a need to identify target populations that might benefit the most from treatment with anti-inflammatory drugs. Based on the findings in the current study, patients with chronic coronary syndrome and a high PS burden may represent a suitable target population. However, this needs to be further investigated in a prospective trial before implementation in clinical practice can be done. Overall, the common challenge in patients with chronic coronary syndrome is to identify those with the highest risk of a subsequent CV event who would benefit most from targeted interventions, such as psychological intervention programs and stricter secondary prevention regimes. This study confirms that patients with a high PS burden have elevated biomarker levels, such as NT-proBNP and hs-TnT, both of which are established markers associated with an increased CV risk. Screening for PS factors, as well as measuring specific biomarkers in the blood, might help clinicians make these decisions.

## Limitations

Despite being one of the largest global studies analysing the association between PS burden, CV risk and biomarkers in patients with chronic coronary syndrome, there are limitations. Most importantly since the findings in this study are based on observational data, the relationship between PS factors and biomarker levels cannot be claimed as casually related. Despite adjustments for patient characteristics and known CV risk factors, residual confounding cannot be excluded. Because of the large study population, the demonstrated associations between PS burden and biomarkers are statistically strong, especially for IL-6, hs-CRP, and NT-proBNP. However, the absolute difference in biomarker concentrations between high and low PS burden are relatively modest. Thus, on an individual patient basis it might be difficult to determine the contribution of PS burden on biomarker concentrations. The objective of constructing a PS burden score to reflect the wide-ranging PS factors aimed to facilitate the interpretation of diverse results. Nonetheless, this approach is susceptible to selection bias, as the inclusion of specific factors in the score can possibly influence the outcomes. Consequently, we opted to present each individual association separately, revealing instances of inverse correlation, along with potential elucidations for such observations. Compared with many other biological and lifestyle risk factors, PS factors are difficult to define and, therefore, measure. Nonetheless, there are compelling evidence that PS burden should be considered as an independent risk factor for CVD.[3,4] In this sub-study, self-reported information about PS factors was collected through a questionnaire as part of the STABILITY trial. Many of the questions were based on the INTERHEART trial, which is pivotal in this area. While we acknowledge that there are other validated questionnaires for depression, this may not hold true for other aspects of PS burden. As a result, these are less explored thus even more imperative to incorporate into this study. The advantage of using a self-reported

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questionnaire was that it was easy to utilize and allowed us to collect data from a large proportion of the trial population, thereby limiting the risk of selection and sampling bias. However, this approach has limitations, including introspective ability, response bias, and other issues such as difficulties in interpreting questions and the restrictiveness of rating scales. Consequently, based on the data from the questionnaire, we could not determine whether the patients actually had a clinical diagnosis of depression, and we could not objectively measure the level of stress. However, previous studies have shown that it is the perceived stress level, or even the perception of the stressors on health, and not the actual stress level calculated with complex scores, that correlates with the increased risk of CVD.[33]

# Conclusions

In patients with chronic coronary syndrome, an elevated PS burden including depressive symptoms, perceived financial stress and living alone, was found to be associated with increased levels of inflammatory and cardiac biomarkers. While this study does not establish causal nature of these associations, the findings raise the possibility that inflammation and cardiac stress may serve as potential pathways linking PS burden to an elevated risk of recurrent CV events in patients with chronic coronary syndrome.

# Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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# Authors' contributions

C.W., G.B., and C.H. designed the study, drafted the manuscript, and take responsibility for integrity of the data and accuracy of data analysis. E.H., H.D.W., R.A.H.S., A.S., and L.W. are responsible for data acquisition. N.H. conducted the data analysis. All authors interpreted the results and critically revised and approved the final manuscript.

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**Conflict of interest:** C.W. has nothing to declare. G.B. reports, outside the submitted work, institutional research grants from AstraZeneca and Pfizer, expert committee and consulting fees to his institution from Bayer. Honoraria for lectures and scientific advice from AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Novo Nordisk, Pfizer, and Sanofi. N.H. reports institutional research grants from GlaxoSmithKline. E.H. reports institutional research grant from Pfizer; institutional research grant, speaker fees, and expert committee fees from Amgen; speaker fees from NovoNordisk, Bayer, and AstraZeneca; expert committee fees from Amarin AB and Sanofi; chair of the Swedish secondary prevention registry; National coordinator of DalCore: DAL301 DalGene: R1500-CL-1643; Aegis II/Perfuse. H.D.W. reports research grants from GlaxoSmithKline; grants and steering committee fees from Eli Lilly and Company, Omthera Pharmaceuticals, Eisai Inc., DalCor Pharma UK Inc., American Regent, and CSL Behring LCC; grants, steering committee fees and personal fees from Sanofi-Aventis Australia Pty Ltd, Esperion Therapeutics, and Sanofi-Aventis; personal fees from AstraZeneca; support for attending the clinical trial forum from SAHMRI. R.A.H.S. reports grants from GlaxoSmithKline. A.S. reports institutional research grants from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline, and Roche Diagnostics. L.W. reports institutional research grants from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline, Roche Diagnostics, Merck & Co. C.H. reports institutional grants from Pfizer; consultant/advisory board fees from AstraZeneca, Bayer, Novo Nordisk, Coala Life, Amarin, Pharmacosmos, and Boehringer Ingelheim.

## Data availability

Anonymized individual participant data and study documents can be accessed, if applicable, from GlaxoSmithKline trough the weblink https://www.gsk-studyregister.com/en/, using the search terms 'STABILITY' or 'darapladib' and through application on the Vivli platform.

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