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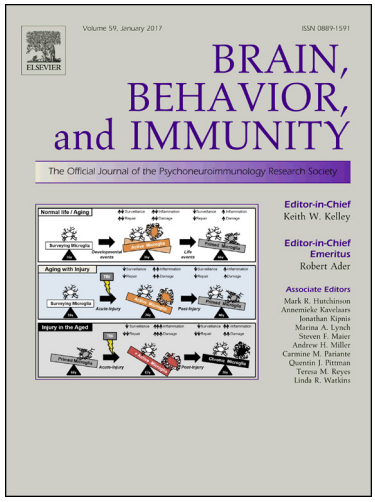

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Short communication

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Inflammation associated with coronary heart disease predicts onset of depression in a three-year prospective follow-up: a preliminary study

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Abstract

Depression frequently co-occurs with coronary heart disease (CHD), worsening clinical outcomes of both, and inflammation has been proposed as a biological link between these two disorders. The aim of the present study was to investigate the role of inflammation in the development of depression in CHD patients during a 3-year follow-up. We examined the inflammatory biomarker, high-sensitivity C-reactive protein (hsCRP), measured at baseline, as a potential predictor of later onset of depression.

We recruited 89 CHD patients, who were assessed at baseline and then every 6 months, for three years. The sample included, at baseline, 25 depressed and 64 non-depressed CHD patients, as confirmed by Clinical Interview Schedule Revised (CIS-R). Depressive symptoms were assessed at baseline and all follow-up points by the Patient Health Questionnaire-9 (PHQ-9).

In all CHD patients (n=89), we found a significant positive correlation between hsCRP levels and the severity of depressive symptoms at baseline (PHQ-9, r=0.23, p=0.032). During follow-up, n=21 patients (of the 64 non-depressed at baseline) developed depression, defined as being PHQ-9 positive (a score ≥10) in at least one follow-up assessment. Of these, n=9 subjects were defined as developing clinically-significant depression, that is, having a positive PHQ-9 in at least 3 of the 6 follow-up assessments, implying a duration of symptoms of at least one year. We found that increased hsCRP values at baseline predicted future onset of depression. Specifically, baseline hsCRP values were higher in patients who later developed clinically-significant depression (mean±SD; 6.76±6.52 mg/L) compared with never-depressed (2.77±3.13 mg/L; F(1,49)=7.13, p=0.010), even after controlling for baseline PHQ-9 scores.

In conclusion, inflammation in CHD patients is associated with future development of clinically-significant depression. HsCRP, a reliable and ready-to-use biological marker of inflammation, may help to identify depression high-risk phenotypes even among CHD patients, who already have high baseline inflammation. Our study conveys important preliminary findings that will require further replication but that have the potential to affect the mental and physical health of a vulnerable group of individuals.

Keywords: *Coronary heart disease; C-reactive protein; Depression; Inflammation; Inflammatory markers.*

1. Introduction

Coronary heart disease (CHD) is the most common cardiovascular disease and frequently co-occurs with depression, in a bidirectional relationship which worsens the clinical outcome of both (Miller et al., 2002; Meijer et al. 2011). Compelling evidence suggests a key role for inflammation in the pathophysiology of both depression and CHD (Khandaker et al., 2019). Hence, immune system dysregulation has been increasingly proposed as a relevant biological link between these conditions (Halaris, 2013), even though the precise mechanism underlying this comorbidity still needs to be clarified (Whooley and Wong, 2013; Wu et al., 2019).

Inflammation is crucial in both diseases. It is a core feature of CHD (Danesh, 2000; Wirtz and von Känel, 2017), and pivotal in all atherosclerosis stages (Tiong and Brieger, 2005), from initiation to propagation and activation of atherosclerotic plaques, ultimately leading to thrombosis. Indeed, CHD patients exhibit higher inflammatory markers, together with higher expression of inflammatory genes, compared with healthy subjects (Libby, 2012; Hansson and Hermansson, 2011). Inflammatory pathways have also been widely studied in depression (Zunszain et al., 2013), and depressed patients frequently exhibit a pro-inflammatory profile (Valkanova et al., 2013; Köhler et al., 2017). Studies from our group have also shown that increased inflammation may be particularly evident in patients with treatment resistant depression (Cattaneo et al., 2016; Chamberlain et al., 2019).

Cross-sectional studies have found an association between depression and increased inflammation in CHD patients (Howren et al., 2009). For example, we have previously shown that C-reactive protein (CRP) levels are elevated in CHD patients with depression compared with CHD patients without depression (Nikkheslat et al., 2015). However, no studies have so far examined this association prospectively, that is, testing whether increased inflammation in

otherwise psychiatrically healthy CHD patients increased the risk of future onset of depression. Previous studies (Steptoe et al., 2013; Lafitte et al., 2015) found no association between baseline CRP levels and future onset of depression in patients with acute coronary syndrome (ACS). ACS is an acute clinical condition that may be considered as a subtype, a symptomatic manifestation of CHD (Singh and Grossman, 2019). Even if ACS could be a result of CHD, they are not the same (Sanchis-Gomar et al., 2016). Indeed, importantly, ACS may lack the chronicity associated with CHD, with substantial clinical and biomarker differences. In previous longitudinal studies of medically healthy cohorts, high levels of inflammation have been found to increase risk of future onset of depression (Valkanova et al., 2013; Smith et al., 2018), however in these samples the average levels of inflammation tended to be much lower than in patients with CHD. Thus, we wanted to examine whether this predictive ability remains true even for a CHD population, who already start with a chronic low-grade baseline inflammation.

The aim of the present study is to analyse the association between CRP levels (at baseline) and the development of new-onset depression in a sample of CHD patients, during a 3-year follow-up study. CRP is one of the most reliable and reproducible markers of inflammation, clinically valuable and easily detected in blood. In healthy adults, serum CRP levels are usually below 1 mg/L, and values above 3 mg/L are indicative of low-grade inflammation, as usually present in patients with CHD even when not acutely ill (Pearson et al., 2003). Being able to recognize specific risk profiles for the development of depression could allow more specific and patient-tailored interventions in these patients, with obvious public health benefits from both clinical and economic perspectives.

2. Materials and methods:

2.1 Study design and sample

The subjects for the present study were recruited from participants of the UPBEAT-UK cohort study (Tylee et al., 2011) designed to evaluate the relationship between CHD and depression in primary care. Participants were recruited from 16 practices in South London. Patients were eligible if included in the official registers of all CHD patients, kept by UK primary care practices under the Quality and Outcomes Framework. CHD registers contain data of patients with documented history of myocardial infarction (MI) up to 20 years previously, or with angina, or who went through some cardiac intervention during their life (for example, angioplasty, stent, or bypass). CHD patients in the UPBEAT-UK cohort who had given prior consent to be contacted for related studies were invited to participate in the present biological project, which received separate Ethical Approval by the National Research Ethics Service, East Kent Local Research Ethics committee (reference number 09/H1103/19) and the Institution Review Boards at the Institute of Psychiatry, King's College London (reference numbers 07/H0809/38 and 322/2003) (Nikkheslat et al., 2015). The sample for the present study comprises 89 patients with documented CHD, who agreed to provide blood samples. The sample is partially-overlapping with that in our aforementioned cross-sectional study (Nikkheslat et al., 2015), albeit larger.

2.2 Clinical assessment

Depression status was assessed at baseline using the Clinical Interview Schedule-Revised (CIS-R) (Lewis et al., 1992). Depressive symptoms were assessed at baseline and then every 6 months for three years through the Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al., 2001), administered via telephone interviews. PHQ-9 is a valuable and reliable instrument to assess depression in various clinical contexts with the advantage of being fast and easy to

administer (Kroenke et al., 2001; Williams et al., 2002). Based on the extensive previous literature, we considered a PHQ-9 score of 10 or above as positive (Kroenke et al., 2001). Results from other analyses of follow-up data which did not include inflammatory biomarkers have been published before (Palacios et al., 2016).

We excluded *a priori* patients with acute infections or with other relevant medical co-morbidity, including asthma, cancer, and arthritis, as well as those taking corticosteroid medications. According to CIS-R assessment, we also excluded patients with a primary diagnosis of obsessive–compulsive disorder, panic disorder, specific phobia, generalised anxiety disorder, and mixed anxiety-depressive disorder.

2.3 CRP and other metabolic assays

Biological assessments were obtained at baseline. Non-fasting blood samples were collected between 8:30 am and 10:30 am. Blood samples were collected in sodium-heparin and clot activator containing tubes and centrifuged to separate plasma and serum. The samples were stored at -80°C until assayed. The levels of serum CRP were determined using the Cormay high sensitivity CRP (hsCRP) assay (P.Z. Cormay, Lublin, Poland) at the biochemistry laboratory, KingsPath, at King's College Hospital. The minimum detectable concentration of hsCRP was 0.01 mg/dL. Inter and intra-assay co-efficients of variations were <10%.

2.4 Data analysis

Statistical analyses were performed using the Statistical Package for Social Sciences, version 25.1 (SPSS Inc., USA). All data were tested for parametric suitability, and analysed as appropriate. Independent *t*-tests or Mann-Whitney *U*-tests were performed for comparing variables between two groups. Categorical variables were compared using Chi-squared test.

One-way analysis of variance (ANOVA) or Kruskal–Wallis *H*-test were executed for comparison of more than two groups. Analysis of covariance (ANCOVA) was conducted in order to control for the effects of covariates. Correlations were assessed using Pearson's correlation coefficient. The values of hsCRP were log-transformed (loghsCRP) in order to correct for positive skew and unequal variances. P-values of <0.05 were considered as significant.

3. Results:

3.1 At baseline, hsCRP levels are positively correlated with severity of depression

At baseline, we had 64 non-depressed CHD patients and 25 depressed CHD patients, based on the CIS-R interview. The main socio-demographical and clinical data of our sample at baseline are summarized in Table 1. Consistent with the literature on cardiovascular diseases, the sample was predominantly male (79%), of older age (mean±SD; 70.7±9.1 years), and with CRP levels (3.60±4.17 mg/L) and BMI (30.1±8) that were in the pathological range when compared with normal values (Libby, 2012; Mongraw-Chaffin et al., 2015). As expected, depressed patients were more likely to be female (40.0% vs. 14.1%, χ^2=7.20, p=0.010) and had higher heart rate (68.00±17.70 vs. 57.16±8.93, U=413.0, p=0.018) compared with non-depressed. No further differences were found in other metabolic and clinical measures (except, of course, for depressive symptoms and antidepressant use, which were both higher in the depressed group).

HsCRP values were higher (4.53±4.47 mg/L) in depressed patients at baseline vs. those non-depressed (3.24±4.03 mg/L). Following logarithmic transformation, there was a statistical trend towards higher hsCRP in the depressed group (t=1.69, p=0.094) compared with non-depressed. In the whole sample, we found a significant positive correlation between loghsCRP and the severity of depressive symptoms assessed by PHQ-9 (r=0.23, p=0.032).

3.2 Non-depressed CHD patients who develop clinically-significant depression during the 3-year follow-up have higher hsCRP levels at baseline

Among our sample of 64 CHD non-depressed patients, 21 individuals (33%) developed new-onset clinically relevant depressive symptoms (PHQ-9≥10) at any time during the follow-up. Although baseline hsCRP was higher in those who developed depression compared with those who did not (mean±SD; 4.21±5.39 vs 2.77±3.13 mg/L), there was no significant difference

between groups after logarithmic transformation (t=0.77, p=0.44). PHQ-9 values at different time points, together with the number of patients who completed each assessment are summarized in Table 2.

To overcome the limitation of using PHQ-9 as the sole measure of depression during the follow-up, we further analysed the data by focusing on a subgroup of patients who developed clinically-significant depression, defined as having a PHQ-9 positive assessment in at least 3 different evaluations out of the 6 time points, indicating that they had been depressed for at least one year. Nine patients (14% of the 64 non-depressed at baseline) developed a clinically-significant depression (Table 3). In our main finding, mean hsCRP baseline values were higher in patients with clinically-significant depression (mean±SD; 6.76±6.52) compared with never-depressed (2.77±3.13 mg/L; t=2.35, p=0.023) and with those who were positive only in 1 or 2 assessments (2.31±3.57; t=2.31, p=0.032).

As expected, PHQ-9 scores were already higher at baseline in patients who later developed clinically-significant depression, compared with never-depressed (6.67±3.87 vs. 2.35±2.61; U=72.5, p=0.003), although interestingly *not* compared with those who were positive only in 1 or 2 assessments (5.08±4.58; U=43.0, p=0.432). Reassuringly, analyses conducted on hsCRP logarithmic values after controlling for PHQ-9 scores at baseline, as well as for gender, confirmed the significant difference in hsCRP baseline levels between clinically-significant depressed patients compared with never-depressed (ANCOVA, F(1,48)=7.29, p=0.010), over and above the potential effects of depressive symptoms at baseline. These further analyses indicate that the difference in baseline inflammation does not simply reflect current mental state but rather the biological processes underpinning future risk.

4. Discussion:

To our knowledge, this is the first study to assess whether peripheral inflammation in CHD patients predicts future mental health outcomes assessed systematically over three years. We found that hsCRP levels at baseline do indeed predict the future development of clinically-significant depression. Overall, the results of the present study confirm the firm connection between depression and inflammation (Pariante, 2017) and the important role of CRP as a potential biomarker of depression (Haapakoski et al., 2015). Remarkably, we found that even in a population with chronic low-grade inflammation, that is, with mean CRP levels above the normal range (>3 mg/L), the highest CRP levels were significantly related to subsequent development of clinically-significant depression. These findings highlight inflammation as a potential target for treatment and prevention of depression in CHD patients and thus, broadly speaking, among patients with chronic medical illnesses.

CRP is the most commonly used inflammatory marker. Even if it is conventionally used as a non-specific marker for peripheral inflammation, patients with high CRP levels show increased levels of inflammation also in cerebrospinal fluid, further corroborating its value as a unique peripheral marker, tapping into both peripheral and central inflammation (Felger et al., 2018). Moreover, it serves as a proxy for cytokines and other inflammatory mediators (Felger et al., 2018), which could be related to the development of depression, but are difficult to measure in the clinic (Miller et al., 2017). Elevated CRP levels in depressed patients have been well described (Haapakoski et al., 2015). Not surprisingly, our baseline findings support previous cross-sectional associations between CRP levels and depressive symptoms in CHD patients (Howren et al., 2009; Nikkheslat et al., 2015).

Furthermore, our results demonstrate a longitudinal association between elevated CRP levels and the development of depression in CHD patients during the follow-up. We confirm and extend previous findings that CHD patients are at risk for development of depressive symptoms (Carney and Freedland, 2003; May et al., 2017) by identifying inflammation as an early biomarker of such risk. Indeed, we observe that more than 30% of non-depressed CHD patients develop depression in at least one follow-up assessment over three years, that is, an average incidence of 10% per year, which is much higher than the incidence in the general population (Waraich et al., 2004), even for similar populations of older males (Büchtemann et al., 2012), and even considering the relatively short time-frame of follow-up.

Bot and colleagues (2011) found no significant association between baseline inflammatory markers, including CRP, and depression scores in a short-term follow-up (10 weeks), but they only analysed CHD patients who were already depressed at baseline. As mentioned above, previous studies tested whether CRP is associated with the onset of depression in non-depressed patients with ACS, that is, in the immediate aftermath of an acute cardiac event. Lafitte et al. (2015) reported a higher (29%) overall incidence of depression in their 9-month follow-up. However, they did not find a significant association with CRP baseline values, suggesting that depression may develop through other mechanisms. As stated before, they specifically considered ACS patients, thus not the same as our CHD patients. Baseline CRP levels were considerably high (mean >8 mg/L) and tended to decrease over time, therefore once again different from the chronic, low-grade inflammation in our sample. Nevertheless, as they only examined the presence of depression in a single follow-up assessment at 9 months, we cannot exclude the idea that they might have reported similar findings to ours if they had focused on long-lasting forms of depression. Similarly, Steptoe and colleagues (2013) found no significant association between CRP and depressive symptoms in a short-term follow-up (3

weeks and 6 months) in ACS patients. Again, ACS was associated with even higher baseline inflammation levels (mean CRP; 17 mg/L). Interestingly, the authors found an association with white cell count, another inflammatory marker. This highlights the importance of using more than one biomarker in order to avoid false negatives, and of identifying the correct one for each specific question (Pariante, 2019).

An association between elevated CRP and future onset of depression has been previously reported in healthy subjects, as also shown by meta-analyses of existing studies (Valkanova et al., 2013; Smith et al., 2018). In the first such study, Gimeno and colleagues (Gimeno et al., 2009) found that baseline CRP in healthy subjects (mean values <1 mg/L) predicted cognitive symptoms of depression in a long-term follow-up (average time 11.8 years), after adjusting for cognitive symptoms of depression at baseline, suggesting that inflammation precedes at least this symptoms' domain. Pasco et al. (2010) reported increased hazard ratios for the development of new-onset depression in a population-based sample of women (median CRP; 1.88 mg/L), followed for a decade or until the first episode of depression, excluding patients with previous major depression but not assessing (or correcting for) depression at baseline. Similarly, another interesting study in a large sample from the general population (Wium-Andersen et al., 2013) found that increased CRP levels were associated with increased risk for depression at follow up (5-year average), with higher odds ratios associated with higher CRP values (categories 3-10 and >10 mg/L). Again, they excluded patients with previous or baseline depression, and did not correct for baseline depression severity. Au et al. (2015) reported that elevated CRP levels (>3 mg/L) at baseline were related to elevated depressive symptoms at a 4-year follow-up in community-dwelling older adults after adjusting for baseline depressive symptoms, even if this association was no longer significant after adjustments for metabolic and health variables. Although some longitudinal studies did not find the significant association

between CRP values and future development of depression, still they found an association between baseline depression and future modifications in CRP levels (Deverts et al., 2010; Shaffer et al., 2011; Copeland et al., 2012; Huang et al., 2019), again confirming the bidirectional association between inflammation and depression. As we do not have follow-up CRP values, we cannot test this association in our sample.

Despite the important strengths already discussed, we also have to mention a few limitations of the present study. First, the sample size is small, although we did manage to complete a fairly long (3-year) follow-up with multiple assessments of depressive symptoms. Another potential limitation is the lack of a structured diagnostic instrument for the diagnosis of depression in the follow-up. Accordingly, we created a single measure of depression that conveys both severity and chronicity over the follow-up period, based on the multiple PHQ-9 assessments. We have a small amount of missing data for the variables that are crucial to the purpose of the present study (Table 1). However, we have to acknowledge several missing values for additional descriptive parameters at baseline, including blood pressure and heart rate. Finally, we were not able to provide a stratification based on the severity of CHD. Even though this does not undermine the validity of our findings, we believe it could further help to better characterize the patients at risk of developing depression, and should therefore be analysed in future studies.

Being the first evidence of successful use of CRP values in predicting future onset of depression in CHD patients – a population where the onset of depression may worsen both morbidity and mortality (Wu et al., 2019) – our study conveys important preliminary findings that will require further replication but that have the potential to affect the mental and physical health of a vulnerable group of individuals.

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Table 1: Characteristics of CHD patients at baseline in relation to depression status

	CHD non-depressed patients n=64	**CHD depressed patients n=25**	**Group tests**
Age, years *mean (± SD)*	n=64 70.78 (±8.98)	n=23 69.91 (±9.70)	U=706.5, p=0.776
Gender *n (%)*	n=64 Female: 9 (14.1%) Male: 55 (85.9%)	n=25 Female: 10 (40%) Male: 15 (60%)	χ^2=7.203, **p=0.010**
CRP (mg/L) *mean (± SD)*	n=64 3.24 (±4.03)	n=25 4.53 (±4.47)	t=1.69, p=0.094
Plasma glucose (mmol/L) *mean (± SD)*	n=58 5.72 (±1.68)	n=24 6.62 (±4.20)	U=695.0, p=0.992
Cholesterol (mmol/L) *mean (± SD)*	n=64 4.39 (±0.83)	n=25 4.31 (±0.61)	t=0.428, p=0.670
Triglycerides (mmol/L)	n=64	n=25	U=766.0, p=0.756

mean (± SD)	1.60 (±0.73)	1.51 (±0.65)	
LDL (mmol/L) *mean (± SD)*	n=64 2.43 (±0.69)	n=25 2.34 (±0.55)	U=744.5, p=0.612
HDL (mmol/L) *mean (± SD)*	n=64 1.23 (±0.31)	n=25 1.31 (±0.34)	U=885.5, p=0.431
BMI (Kg/m2) *mean (± SD)*	n=62 30.41 (±8.70)	n=22 29.13 (±5.72)	U=666.5, p=0.875
Waist-to-hip ratio *mean (± SD)*	n=25 0.96 (±0.12)	n=16 0.97 (±0.07)	U=201.5, p=0.968
Heart rate (bpm) *mean (± SD)*	n=31 57.16 (±8.93)	n=19 68.00 (±17.70)	U=413.0, **p=0.018**
Systolic pressure (mmHg) *mean (± SD)*	n=32 135.94 (±13.53)	n=18 134.00 (±19.64)	t=0.412, p=0.682
Diastolic pressure (mmHg) *mean (± SD)*	n=32 80.00 (±10.92)	n=18 76.78 (±10.32)	t=1.021, p=0.312
Smoking status *n (%)*	n=34 **Active:** 6 (17.6%) **Ex**: 17 (50%) **Never:** 11 (32.4%)	n=20 **Active**: 4 (20%) **Ex:** 10 (50%) **Never:** 6 (30%)	χ^2 =0.060*, p=1.000
Antidepressants use *n (%)*	n=34 0 (0%)	n=12 8 (66.7%)	χ^2=15.965, **p<0.001**

PHQ-9 score *mean (± SD)*	n=64 3.47 (±3.59)	n=25 14.20 (±5.72)	U=1513.5, **p<0.001**

BMI=body mass index; CRP=C-reactive protein; HDL=high-density lipoprotein cholesterol; LDL=low-density lipoprotein cholesterol; PHQ-9= patient health questionnaire-9.

t=t-value; U=Mann-Whitney U; χ^2 =Pearson Chi-Square, *[*16.7% expected count less than 5]*. CRP values were log-transformed for group test. Significant tests ($p < 0.05$) are in bold.

Table 2: Patients completing each follow-up assessment and PHQ-9 scores at each time point.

Follow-up time points	PHQ-9 scores *mean (± SD)*	Depressed vs non-depressed (PHQ-9 ≥10) (%)*
6 months	n=64 4.42 *(± 4.93)*	n=11 (17.2%)
12 months	n=63 3.87 *(± 4.83)*	n=10 (15.9%)
18 months	n=63 3.63 *(± 4.66)*	n=4 (6.3%)
24 months	n=60 3.28 *(± 4.50)*	n=7 (11.7%)
30 months	n=58 3.98 *(± 4.96)*	n=9 (15.5%)
36 months	n=55 3.96 *(± 5.03)*	n=7 (12.7%)

*valid percent values.

Table 3: Characteristics of CHD non-depressed patients at baseline in relation to depression development

	Never-depressed **n=43**	**Clinically-significant depression** **n=9**	**Only 1 or 2 PHQ-9 positive score** **n=12**	**Group tests**
Age, years *mean (± SD)*	n=43 72.05 (±8.36)	n=9 70.11 (±8.10)	n=12 66.75 (±11.06)	F(2,61)=1.70, p=0.191
Gender *n (%)*	n=43 Female: 4 (9%) Male: 39 (91%)	n=9 Female: 2 (22%) Male: 7 (78%)	n=12 Female: 3 (25%) Male: 9 (75%)	χ^2=2.49*, p=0.288
CRP (mg/L) *mean (± SD)*	n=43 2.77 (±3.13)	n=9 6.76 (±6.52)	n=12 2.31 (±3.57)	F(2,61)=3.58, **p=0.034**
Plasma glucose (mmol/L) *mean (± SD)*	n=39 5.91 (±1.82)	n=8 5.71 (±1.81)	n=11 5.06 (±0.68)	H=3.16, p=0.206
Cholesterol (mmol/L) *mean (± SD)*	n=43 4.32 (±0.80)	n=9 4.22 (±0.72)	n=12 4.73 (±0.96)	F(2,61)=1.38, p=0.260
Triglycerides (mmol/L) *mean (± SD)*	n=43 1.62 (±0.82)	n=9 1.60 (±0.43)	n=12 1.53 (±0.60)	H=0.48, p=0.788
LDL (mmol/L) *mean (± SD)*	n=43 2.37 (±0.65)	n=9 2.24 (±0.56)	n=12 2.77 (±0.84)	H=2.63, p=0.269

HDL (mmol/L) *mean (± SD)*	n=43 1.20 (±0.31)	n=9 1.24 (±0.30)	n=12 1.29 (±0.30)	F(2,61)=0.42, p=0.662
BMI (Kg/m2) *mean (± SD)*	n=42 30.34 (±10.01)	n=9 31.91 (±6.24)	n=11 29.48 (±4.13)	H=1.86, p=0.395
Waist-to-hip ratio *mean (± SD)*	n=20 0.99 (±0.79)	n=2 1.00 (±0.03)	n=3 0.79 (±0.25)	H=4.06, p=0.131
Heart rate (bpm) *mean (± SD)*	n=26 56.69 (±8.66)	n=2 56.00 (±11.31)	n=3 62 (±12.49)	F(2,28)=0.48, p=0.626
Systolic pressure (mmHg) *mean (± SD)*	n=27 132.74 (±11.35)	n=2 162.00 (±16.97)	n=3 147.33 (±2.51)	H=8.98, **p=0.011**
Diastolic pressure (mmHg) *mean (± SD)*	n=27 78.70 (±9.67)	n=2 70.00 (±0)	n=3 98.33 (±2.89)	F(2,29)=7.43, **p=0.002**
Smoking status *n (%)*	n=28 **Active:** 6 (21%) **Ex**: 13 (46%) **Never:** 9 (32%)	n=3 **Active**: 0 **Ex:** 2 (67%) **Never:** 1 (33%)	n=3 **Active**: 0 **Ex:** 2 (67%) **Never:** 1 (33%)	χ^2 =1.69**, p=1.000
Antidepressants use *n (%)*	n=28 0 (0%)	n=3 0 (0%)	n=3 0 (0%)	//

PHQ-9 score *mean (± SD)*	n=43 2.35 (±2.61)	n=9 6.67 (±3.87)	n=12 5.08 (±4.58)	H=10.93, **p=0.004**

BMI=body mass index; CRP=C-reactive protein; HDL=high-density lipoprotein cholesterol; LDL=low-density lipoprotein cholesterol; PHQ-9= patient health questionnaire-9.

F= ANOVA F-test; H= Kruskall-Wallis *H*-test; χ^2 =Pearson Chi-Square, *[*16.7%, **77.8%, expected count less than 5]*. CRP values were log-transformed for group test. Significant tests ($p < 0.05$) are in bold.

Highlights:

- High levels of high-sensitivity C-reactive protein (hsCRP) predict future onset of depression in patients with coronary heart disease (CHD).