Depression symptoms and the progression of carotid intima-media thickness: A 5-year follow-up study

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Abstract

Objective

Only a few studies have investigated the changes in carotid intima–media thickness (IMT) over time, and uncertainties remain on the underlying mechanisms linking depression and subclinical atherosclerosis. We carried out a prospective cohort study to evaluate whether depression is associated with changes in carotid IMT in subjects with cardiac risk factors but free from coronary heart disease (CHD), and to what extent the atherogenicity of depression can be explained by inflammatory markers and autonomic nervous system dysfunction.

Methods

During baseline and follow-up visits: all participants were asked to provide blood samples and compile a structured questionnaire; trained physicians assessed depression symptoms using Beck Depression Inventory (BDI); altered cardiac autonomic tone was measured using time-domain components of heart rate variability in 24 h Holter recordings; measurements of carotid IMT were carried out using B-mode ultrasound image acquisition. Logistic and linear regression analyses were used to adjust for potential confounders and explore potential mediators.

Results

A total of 381 subjects completed the 5-year follow-up. The mean carotid IMT significantly increased in all subjects but the amount of increase was significantly larger among subjects with depression symptoms: mean IMT increased by 0.16 ± 0.14 mm; 0.31 ± 0.28 mm and 0.61 ± 0.54 mm among the subjects with no, mild and moderate/severe depression, respectively (all $p < 0.01$). The association between moderate/severe depression and IMT increase remained highly significant even after controlling for all the variables considered, however when both IL-6 and CRP were included in multivariate models the regression coefficient decreased by 42.3%. Some of the inflammation markers and autonomic nervous system dysfunction were also independently correlated with carotid IMT increase.

Conclusion

Depression symptoms are independently associated with an accelerated progression of carotid IMT in subjects with CHD risk factors, and inflammation may substantially modulate the association between depression and carotid IMT progression.

Keywords:

Depression, Coronary heart disease, Intima media-thickness, Autonomic nervous system, Inflammation

Introduction

Depression symptoms are independently associated with cardiovascular events in healthy subjects and in patients with heart disease [[1], [2], [3]]. In the last decade, depression symptoms have also been related to the progression of subclinical atherosclerosis [[4], [5], [6], [7], [8], [9]]. However, only a few studies with short follow-up have investigated the changes in carotid intima–media thickness (IMT) over time [[4], [5], [6], [7]], and uncertainties remain on the underlying mechanisms linking depression and subclinical atherosclerosis.

Among the potential explanations that have been advocated for the observed association there are lifestyle [10], modifications in platelet function [11] and endothelial dysfunction [12]. In addition, depression symptoms have been associated with autonomic nervous system dysregulation, due to sympathetic activation and/or vagal withdrawal [13]. Heart rate variability [HRV] imbalance, an index of the autonomic nervous system, might increase the risk of mortality in depressed patients through myocardial ischemia and ventricular arrhythmia, and could stimulate inflammation [[14], [15]]. Furthermore, depression symptoms have been related to an inflammation response in the general population and in patients with heart disease. Indeed, the relationship between autonomic nervous system dysfunction and inflammation is well documented and is one of the earliest steps in the development of atherosclerosis. Thus, it is plausible that depression exerts an effect on the progression of atherosclerosis through autonomic nervous system imbalance and higher levels of inflammation [16].

To our knowledge, only the Pittsburgh Healthy Heart Project study has examined the correlation between subclinical atherosclerosis, depression symptoms and cardiac risk factors [7]. The authors found that depressive symptoms were associated with the progression of atherosclerosis as measured by a change in carotid intima–media thickness. Such finding, however, was not accounted for some important potential confounders including baseline IMT, demographic factors, cardiovascular risk factors, medication use, and medical conditions. We carried out a prospective cohort study to evaluate whether depression is associated with changes in carotid IMT after 5 years of follow-up in subjects with cardiac risk factors but free from coronary heart disease (CHD), and to what extent the atherogenicity of depression can be explained by inflammatory markers and autonomic nervous system dysfunction.

2. Methods

2.1. Study population and design

All CHD-free individuals presenting to our department (from primary care referral) between September 2003 and November 2005 were asked to participate. The initial eligibility criteria included the presence of at least two among the following CHD risk factors: age ≥60 years, male gender, current smoking (≥1 cigarette per day), hypertension (systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg or current treatment for hypertension), dislipidemia (serum cholesterol > 240 mg/dL, or triglycerides > 150 mg/dL, or current treatment for dislipidemia) and family history of CHD (if at least one of the parents or siblings aged ≤55 years had CHD). Exclusion criteria were the presence of a neoplasm, kidney or liver failure, systemic inflammatory disease and/or current antidepressant treatment, left bundle block, paced rhythm, Wolff–Parkinson–White syndrome or pathophysiological conditions which could alter the analysis of heart rate

variability: diabetes mellitus, peripheral neuropathy, atrial fibrillation and an ejection fraction <45% [17]. We also excluded subjects with an IMT > 1.5 mm at baseline because such values are indicative of plaque according to the joint European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines [18].

The study had a prospective cohort design, and all participants were requested to undergo follow-up examinations 5 years after baseline evaluation (between September 2008 and November 2010). All participants provided written informed consent and the study protocol was approved by the local ethical committee.

2.2. Interview and measurements

During baseline and follow-up visits, all participants were asked to compile a structured questionnaire including items on socio-demographic characteristics, CHD risk factors, medical history, and current medication use. In addition to the questionnaire, information was collected by means of blood sampling. Total cholesterol and triglycerides were measured using commercial kits in an automatic analyzer (Boehringer); HDL cholesterol using enzymatic methods (Boehringer), and LDL cholesterol was computed according to the Friedewald formula. We also recorded C-reactive protein (CRP) (Latex/BN II, Dade Behring) and Interleukin-6 (IL-6, Quantikine human IL-6).

At both baseline and follow-up examination, we also separately assessed depression symptoms, IMT and indices of the autonomic nervous system.

2.3. Depression

Depression was evaluated using the Beck Depression Inventory (BDI), a 21-item self-reported measurement of depressive symptomatology. The BDI score can be divided into three categories ranging from no depression to severe depression (score ≤10-no depression; score >10–18-mild depression, score ≥19-moderate/severe depression) [19].

2.4. Assessment of heart rate variability

To measure altered cardiac autonomic tone, we used the time-domain components of Heart Rate Variability in 24-h Holter recordings as previously described [[13], [16]]. The following parameters were considered in the analysis: standard deviation (SD) for the time between normal-to-normal complexes in the entire 24 h electrocardiographic recording (SDNN), SD of the average normal-to-normal intervals for each 5-min period (SDANN), root-mean square of the differences in successive R wave to R wave (RR) intervals (RMSSD), and the percentage of adjacent RR intervals >50 ms apart (pNN50). Under these conditions, SDNN and SDANN were indices of both parasympathetic and sympathetic tone as mediated by baroreflex activity; RMSSD and pNN50 were measurements of the modulation of parasympathetic tone [16].

2.5. Carotid artery studies

Ultrasound exams were carried out using an Esaote Caris Plus machine (Rome, Italy) with 7.5–10.0 MHz linear array transducers. The measurement of the carotid IMT was carried out using B-mode ultrasound image acquisition. The sonographer was also the reader of the exam for all

measurements, and was blinded to patients' identity. The left and right carotid artery were scanned by ultrasound technicians following a standardized protocol. In brief, image acquisition included the evaluation of the right and left common carotid arteries, 1 cm proximal to the carotid bulb. The far left and right walls of the carotid artery segments were imaged in a standardized magnification (2 × 2 cm). The sonographer used different scanning angles to identify the maximum thickness of the IMT, 1 cm proximal to the carotid bulb. Carotid IMT measurements were performed offline with IMAGE-Pro version 5.1 (Microsoft) image-analysis software. Recorded image sequences (on S-VHS tapes) were reviewed frame by frame to select the best-quality images for measurement. IMT for the common carotid artery was defined as the mean of the maximum wall thicknesses for the near and far walls on the right and left common carotid segments: (maximum near left wall + maximum far left wall + maximum near right wall + maximum far right wall)/4. For each segment, IMT was defined as the average of 3 measurements [[17], [20]]. Inter-observer comparisons showed a mean measurement variation equal to 0.04 mm (SD = 0.07 mm; range −0.13 to 0.13 mm).

2.6. Statistical analyses

Standard univariate analyses were initially used to compare the baseline characteristics of subjects with no (BDI < 10), mild (9 < BDI < 19) or moderate/severe depression symptoms (BDI ≥ 19); one-way ANOVA with a Sidak correction was used for continuous variables and the chi-squared test for categorical variables. For all inflammatory markers, heart rate variability and subclinical atherosclerosis, the percentage of change between the end and the start of the follow-up was also computed and compared across depression groups using ANOVA with a Sidak correction.

As regards the main outcome of the study, namely the mean IMT increase from baseline to the end of the five-year follow-up (±2 months), separate analyses were initially carried out for left and right IMTs. However, given the collinearity between the left and the right IMTs, both at baseline and at the end of the follow-up (Spearman rho = 0.93 and 0.96, respectively), we based all analyses on the mean IMT value between the right and the left side to avoid redundancy.

The independent predictors of IMT increase were investigated in separate steps using multiple regression: 1) depression group as the only explanatory variable; 2) adding demographic and CHD risk factors (age, gender, body mass index, current smoking, familial history of CHD, systolic blood pressure, total cholesterol, HDL cholesterol, triglycerides and global CHD risk at ten years according to the SCORE [21] system); 3) adding the use of selected drugs (beta-blockers, ACE-antagonists, calcium-antagonists, diuretics, sartans, statins, selective serotonin reuptake inhibitors (SSRIs), aspirin); 4) adding time-domain measurements of heart-rate variability (heart rate, SDNN, SDANN, RMSSD, pNN50) and 5) adding Interleukin-6 and C-Reactive Protein. At each step, the association between the depression group and the IMT was re-examined. The depression status – BDI score – was treated either as a continuous or categorical variable: given R2 values, likelihood ratio test results, clinical relevance and easiness of interpretation, finally substantially different coefficients, depression was considered categorical into the final model, including three levels of symptom severity as dummy variables: no, mild, and moderate/severe depression [19].

Some of the covariates were skewed and transformed (logarithm: C-Reactive Protein and SDNN; square root: SDANN and RMSSD; cubic: Interleukin-6). To facilitate the interpretation of the complex autonomic indices, however, their values were transformed back to the original units

yielding geometric means. In addition to regression coefficients, standardized coefficients were also computed to investigate the most important domains in predicting IMT increase.

Once the final fully-adjusted model was fit, its validity was assessed as follows. The assumption of constant error variance was checked graphically, plotting Pearson residuals versus fitted values, and formally, using Cook and Weisberg's test for heteroskedasticity. High leverage observations were identified by computing Pearson, standardized and studentized residuals, Cook's D influence, Welsch distance and DFBETA. We found 32–50 high leverage observations and repeated the analysis excluding those observations with no substantial changes. However, given that the number of outliers was larger than 5% of the sample, all models were conservatively based upon robust standard errors. Finally, since the dependent variable was slightly skewed, we repeated all the analyses using its square root as the dependent variable, with no appreciable changes; IMT increase was thus kept in the models in its original form to facilitate interpretation.

As a secondary additional analysis, we investigated whether depressed subjects had a higher likelihood of developing carotid wall thickening (defined as a IMT > 0.9 mm) during the follow-up [[18], [20]]. We excluded the subjects who already had IMT > 0.9 mm at baseline, and compared the proportion of subjects developing carotid wall thickening according to the depression group using logistic regression. Covariates were selected a priori according to their clinical relevance, and were limited to 16 to reduce the risk of overfitting. The goodness of fit of the logistic model was assessed using the Hosmer–Lemeshow test, and the predictive power was evaluated computing the area under the Receiving Operator Curve. In the logistic model, depression was treated ordinally because mild and moderate/severe depression adjusted odds ratios (ORs) were substantially similar.

Statistical significance was defined as a two-sided p-value <0.05 for all analyses, which were carried out using STATA software, version 10.1 (Stata Corp., College Station, Texas, USA, 2007).

3. Results

3.1. Baseline characteristics

A total of 590 subjects were asked to participate; 391 of them fulfilled the selection criteria and composed the final sample. The present analysis examined the data from the 381 subjects who had complete baseline and follow-up data on ultrasound examinations, depression, heart rate variability and inflammation markers. The reasons for exclusion were death (n = 6), unwillingness to participate (n = 2) and unknown (n = 2).

At baseline, a total of 87 (22.8%) subjects showed depressive symptomatology (n = 47 with mild and n = 40 with moderate/severe depression). At univariate analysis (Table 1, Table 2, Table 3), as compared with subjects without depression, individuals with depression symptoms were more likely to be obese, have higher levels of inflammatory markers, triglycerides, total and LDL cholesterol, and to experience some degree of autonomic nervous system dysfunction (SDNN and SDANN).

3.2. Follow-up characteristics

During the follow-up, only seven subjects improved, but none progressed from depression (either mild or moderate/severe) to normality. Of the seven who improved, four were assuming SSRIs (out of 24; 16.7%), and three were not assuming SSRIs (out of 63; 4.8%).

At the end of the 5-year follow-up, the BMI of subjects with depression remained substantially stable (from 26.5 ± 4.0 to 27.2 ± 3.6 kg/m2), LDL cholesterol decreased by 16%, HDL cholesterol by 21%, systolic blood pressure by 8%, and diastolic blood pressure by 19% (all $p < 0.01$). Although there were no subjects with diabetes at baseline, 10% (n = 9) of them had diabetes five years later. The use of drugs for hypercholesterolemia increased from 27 to 31%, and the number of subjects on antihypertensive treatment rose from 57 to 61%. At baseline, the patients with depression were not taking SSRIs; however, at the end of the follow-up, 24 patients with depression symptoms were being treated with SSRIs.

By the end of follow-up, baseline CRP and IL-6 increased among moderate/severe depression patients but did not change or decreased into the no/mild depression groups. However, heart rate tended to decrease in moderate/severe depression patients (Table 2). Compared with non-depressed subjects, those with depression showed the lowest SDNN and SDANN values at the end of follow-up.

3.3. IMT progression

The mean carotid IMT significantly increased in all subjects during the 5-year follow-up (all $p < 0.001$ – Table 3). However, the amount of increase significantly differed by depression status at baseline: the average IMT increases were 0.16 ± 0.14 mm; 0.31 ± 0.28 mm and 0.61 ± 0.54 mm among the subjects with no depression, mild depression and moderate/severe depression, respectively (all $p < 0.01$). Such values, expressed as the percentage of IMT increase, corresponded to 21.8%, 39.8% and 59.9%, respectively.

At multivariate analysis, moderate/severe depression showed a significant association with an IMT increase in all models, even after controlling for all the variables considered (Table 4). Also mild depression showed a significant positive coefficient of IMT increase during the follow-up, however the significance was lost ($p = 0.068$) when the model was adjusted to also include IL-6 and CRP. Importantly, the latter variables were the only covariates which relevantly influenced the association between depression and IMT increase: when both IL-6 and CRP were included in the multivariate model, the regression coefficients decreased by 51.3% and 42.3% for mild and moderate/severe depression, respectively (Table 4). With regard to mild depression, in any case, the lack of significance might also be due to a sample which was relatively scarce for a multivariate model including more than 20 variables.

Unsurprisingly, the subjects with depression symptoms also showed a significantly higher likelihood of developing carotid wall thickening (IMT > 0.9 mm) during the follow-up (adjusted OR: 1.96 – $p = 0.032$ – Table 5).

Other than depression, the only significant independent predictors of an increase in IMT were increasing CRP, aspirin use, familial history of CHD, and decreasing SDNN (all $p < 0.05$; Table 4).

The statistical power to detect a difference in mean IMT change (or in the proportion of IMT > 0.9 mm during follow-up) between no depression and mild depression groups was higher than 90% in both linear and logistic regression models.

4. Discussion

To date, only a few studies have examined the relationship between depression symptoms and change in carotid IMT over time, with contrasting results [[4], [5], [6], [7]]. To our knowledge, however, this is the first study in which the analyses were adjusted for the main potential confounders and underlying mechanisms (CHD risk factors, inflammation and autonomic nervous system dysfunction). In our sample of subjects with CHD risk factors but free from CHD disease, we found that, as compared to non-depressed subjects, the individuals with moderate/severe depression symptoms showed a significantly larger IMT increase during the 5-year follow-up. This finding remained highly significant after adjusting for several potential confounders or mediators including age, gender, main CHD risk factors, inflammatory markers and indices of autonomic nervous dysfunction. Importantly, the magnitude of the association between depression and subclinical atherosclerosis substantially decreased (halved) when some of the inflammation markers – CRP and IL-6 – were also included in the multivariate analyses.

Our findings confirm and expand those by Stewart et al. on a sample of 464 adults [7], but are in contrast with the conclusions by Rice et al. [4]. These different results, however, can be explained by the differences in the definition of depression, participants, and length of follow-up. In fact, Rice et al. evaluated depressive symptoms according to the Center for Epidemiological Studies-Depression, in the general population, who was followed for an average of 3.9 ± 2.28 years [4]. Finally, their conclusions might also have been influenced by a potential lack of statistical power, due to the relatively small sample size (n = 68).

As regards the autonomic nervous system and inflammation markers, in addition to the above-mentioned role in mediating (or not) the association between depression and subclinical atherosclerosis, we found an independent association between IMT increase and CRP and SDNN, an index of autonomic nervous system dysfunction. Our results are in line with previous findings suggesting that an imbalance of the autonomic nervous system is related to the extent and progression of carotid atherosclerosis in type 2 diabetic patients [22] and in healthy subjects [23]. Indeed, it has been suggested that autonomic nervous system dysfunction, a reflection of both sympathetic hyperactivity and/or parasympathetic withdrawal, favors several factors promoting atherogenesis: insulin resistance, platelet aggregation, lipoprotein metabolism, gene expression and the protein production of several inflammatory cytokines [16]. In fact, recent studies have suggested that a low grade of inflammation was modulated by autonomic nervous system dysfunction [[16], [24]]. This relationship was found in both depressed [19] and non-depressed patients [24]. Conversely, pro-inflammation cytokines, such as IL-6 and tumor necrosis factors, potentially influence nervous autonomic activity.

Several issues remain to be elucidated on the relationship between depression and inflammation [25]. Our findings suggest that depression symptoms and inflammation have some degree of interaction; however they may separately and independently predict the progression of carotid IMT. This finding is again in line with previous studies reporting an independent association of inflammation and depression [[26], [27]]. Vaccarino et al. observed that the cardiovascular mortality risk associated with depression is reduced by 13% when adjusting for CRP, and by 4% when adjusting for IL-6 [26]. In the study carried out by Whooley et al., depressive symptoms remained associated with a 31% greater rate of cardiovascular events after being adjusted for comorbid conditions and cardiac disease severity. However, additional adjustment for C-reactive protein nullified this association. Importantly, these studies have suggested that inflammation markers explain only a small portion of the CHD risk associated with depression symptoms [27].

Our findings suggest that aspirin may attenuate the progression of intima–media thickness of the carotid artery wall of subjects with coronary risk factors but free from disease. However, our study was not focused on such hypothesis and had an observational design. Therefore, specifically targeted randomized controlled trials would be needed to confirm the above association.

4.1. Study limitations

Strengths of the study are the relatively large sample and the prospective design, a well-characterized cohort and the collection of several variables of different domains that may be related to the effects of depression and to the progression of atherosclerosis. However, this study also had some limitations which must be considered in interpreting the results. First, the follow-up lasted five years, which is a reasonable time to detect variations in the risk of subclinical atherosclerosis but does not allow definitive conclusions. Second, the carotid IMT reflected the cumulative effects of risk factors acting over a period of many years, whereas we measured risk factors only at baseline and at the end of the follow-up. It is also true that it would be extremely difficult to carry out a life-long trial to study the progression of atherosclerosis in depressed patients. Third, a statistical association between a risk factor and atherosclerotic changes does not prove that the risk factor directly promotes atherogenesis. However, we adjusted for a large number of factors in the analysis, including most of the known CHD risk factors (and potential confounders). Fourth, excluding the subjects with IMT values indicative of plaques (>1.5 mm), we may have selected a subgroup of subjects particularly protected against the disease. However, given that we hypothesized that autonomic dysregulation and inflammation play a role in depression, these mechanisms may come into play not only in the amplification and complication of advanced forms of disease, but also in the initiation and progression of the early disease in bridging depression and vascular atherosclerosis. Consequently, it was preferred to include only asymptomatic patients, without clinically overt forms of CHD and carotid plaque, that may have provided the highest signal and reinforced our hypothesis.

5. Conclusions

In subjects with coronary risk factors but free from CHD, depression symptoms were independently associated with carotid IMT progression during the follow-up. Some of the inflammation markers and autonomic nervous system dysfunction were also independently correlated with carotid IMT increase. Our findings suggest that inflammation may substantially modulate the association

between depression and carotid IMT progression. Our results should be confirmed by additional research, which is strongly needed to enhance our comprehension of the multifactorial pathophysiological pathways linking depression to atherosclerosis.

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Table 1General characteristics of the sample at baseline.

	No depression (*n* = 294)	**Mild depression (*n* = 47)**	**Moderate–severe depression (*n* = 40)**	***p* < 0.05**
Continuous variables (mean ± SD)				
Age, y	57.7 ± 8.8	56.2 ± 8.6	56.8 ± 9.3	
BMI, kg/m^2 (median, IQR)	26.2 ± 3.9	25.5 ± 6.6	24.7 ± 6.2	
Systolic blood pressure, mmHg	143 ± 21	145 ± 16	145 ± 20	
Diastolic blood pressure, mmHg	81 ± 7	83 ± 11	82 ± 4	
Total cholesterol, mg/dL	207 ± 23	215 ± 26	219 ± 24	**
HDL-cholesterol, mg/dL	53 ± 12	51 ± 20	54 ± 16	
LDL-cholesterol, mg/dL	124 ± 24	136 ± 22	134 ± 18	*, **
Triglycerides, mg/dL	138 ± 31	138 ± 40	155 ± 25	**, ***
Categorical variables, n (%)				
CHD risk factors				
Male gender	52.4	42.6	57.5	
Obesity (BMI ≥ 30)	8.5	34.0	30.0	*,**
Dyslipidemia	44.9	40.4	52.5	
Hypertension	48.0	70.2	42.5	*
Current smoking	29.3	34.0	35.0	
Family history	32.7	36.2	47.5	
Diabetes mellitus (follow-up)	2.4	4.3	5.0	
High-risk for fatal CHD (score ≥ 5%)	11.3	15.2	18.2	
Medications				
β-Blockers	34.4	34.0	37.5	
Calcium channel blockers	21.8	31.9	25.0	
ACE-inhibitors	30.6	36.2	40.0	
Statins	25.2	21.3	35.0	
Antiplatelet drugs	38.1	42.6	35.0	

*No depression versus mild depression; **No depression versus moderate/severe depression; ***Mild depression versus moderate/severe depression. For continuous variables: all comparisons tested using one-way ANOVA with a Sidak correction. For categorical variables, the *p*-values were computed using the chi-squared test. IQR = Interquartile range.

Table 2. Selected inflammatory markers and indices of heart rate variability by depression status.

	No depression (*n* = 294)	Mild depression (*n* = 47)	Moderate/severe depression (*n* = 40)	*p* < 0.05
	Mean ± SD	Mean ± SD	Mean ± SD	
Inflammation markers				
C-Reactive protein, mg/dL (baseline)	0.76 ± 0.27	1.01 ± 0.33	1.61 ± 0.83	*, **, ***
C-Reactive protein, mg/dL (end of follow-up)	0.77 ± 0.27	0.91 ± 0.39	1.67 ± 0.83	**, ***
% of change (end of follow-up – baseline)	8.9 ± 73.9	−13.4 ± 14.7	4.5 ± 14.5	
Interleukin-6, pg/mL (baseline)	1.7 ± 0.6	1.9 ± 0.7	2.1 ± 0.4	*, **
Interleukin-6, pg/mL (end of follow-up)	1.7 ± 0.7	1.8 ± 0.7	2.2 ± 0.5	**, ***
% of change (end of follow-up – baseline)	−1.4 ± 14.4	−6.3 ± 8.3	2.7 ± 8.0	**
Time-domain measurements of heart rate variability (baseline)				
Heart rate, bpm/min (baseline)	66 ± 10	68 ± 10	67 ± 13	
Heart rate, bpm/min (end of follow-up)	66 ± 8	64 ± 8	62 ± 6	***
% of change (end of follow-up – baseline)	3.1 ± 21.0	−4.9 ± 15.5	−4.6 ± 22.8	*
SDNN, ms (baseline)	115 ± 18	107 ± 15	101 ± 10	*, **
SDNN, ms (end of follow-up)	110 ± 23	90 ± 12	90 ± 8	*, ***
% of change (end of follow-up – baseline)	−3.6 ± 15.7	−14.7 ± 7.8	−11.0 ± 10.5	*, **
SDANN, ms (baseline)	108 ± 23	92 ± 12	92 ± 8	*, **
SDANN, ms (end of follow-up)	116 ± 19	105 ± 15	99 ± 10	*, ***
% of change (end of follow-up – baseline)	10.2 ± 19.8	13.3 ± 10.0	9.4 ± 15.5	
RMSSD, ms (baseline)	19.3 ± 5.9	18.0 ± 6.0	16.6 ± 4.8	**
RMSSD, ms (end of follow-up)	19.7 ± 10.1	16.0 ± 6.0	14.6 ± 4.8	*, **
% of change (end of follow-up – baseline)	1.1 ± 35.7	−12.6 ± 5.0	−13.3 ± 4.7	*, **
pNN50, % (baseline)	6.5 ± 3.3	5.8 ± 3.3	5.6 ± 2.7	
pNN50, % (end of follow-up)	6.4 ± 3.4	6.5 ± 4.3	3.9 ± 2.3	**, ***

% of change (end of follow-up – baseline)	−1.7 ± 22.6	20.3 ± 64.2	−26.2 ± 39.5	*, **, ***

*No depression versus mild depression; **No depression versus moderate/severe depression; ***Mild depression versus moderate/severe depression (all comparisons tested using one-way ANOVA with a Sidak correction).
SDNN = standard deviation of the mean value of time between normal complexes. SDANN = standard deviation of the average of NN intervals for each 5 min period. RMSSD = square root of mean square successive difference of RR intervals. pNN50 = mean percentage of successive NN interval differences >50 ms.

Table 3 Selected indices of subclinical atherosclerosis by depression status.				
	No depression (*n* = 294)	**Mild depression (*n* = 47)**	**Moderate/severe depression (*n* = 40)**	***p* < 0.05**
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
Indices of subclinical atherosclerosis, mm				
Intima–media thickness – left (baseline)	0.76 ± 0.14	0.85 ± 0.20	1.08 ± 0.29	*, **, ***
Intima–media thickness – left (end of follow-up)	0.92 ± 0.20	1.16 ± 0.29	1.69 ± 0.59	*, **, ***
Intima–media thickness – right (baseline)	0.76 ± 0.13	0.83 ± 0.19	1.07 ± 0.30	*, **, ***
Intima–media thickness – right (end of follow-up)	0.93 ± 0.20	1.15 ± 0.31	1.68 ± 0.60	*, **, ***
Intima–media thickness – mean (baseline)	0.76 ± 0.13	0.84 ± 0.19	1.08 ± 0.29	*, **, ***
Intima–media thickness – mean (end of follow-up)	0.92 ± 0.20	1.12 ± 0.31	1.69 ± 0.60	*, **, ***
Δ (end of follow-up – baseline)				
Mean intima–media thickness – mean change	0.16 ± 0.14	0.31 ± 0.28	0.61 ± 0.54	*, **, ***
Mean intima–media thickness – % of change	21.8 ± 20.6	39.8 ± 39.4	59.9 ± 56.6	*, **, ***

*No depression versus mild depression; **No depression versus moderate/severe depression; ***Mild depression versus moderate/severe depression (all comparisons tested using one-way ANOVA with a Sidak correction).

Table 4 Relationship between depression symptoms (reference category = no depression) and intima media thickening (IMT) increase (in mm) during follow-up.

	Coefficient	Standardized coefficient	Robust standard errors	*p*
Adjusted for age and gender				
Mild depression (9 < BDI < 19)	0.150	0.180	0.042	<0.001
Moderate and severe depression (BDI ≥ 19)	0.452	0.506	0.085	<0.001
Adjusted for demographic and CHD risk factors[a]				
Mild depression (9 < BDI < 19)	0.149	0.179	0.042	<0.001
Moderate and severe depression (BDI ≥ 19)	0.446	0.499	0.084	<0.001
Also adjusted for drug use[b]				
Mild depression (9 < BDI < 19)	0.156	0.187	0.043	<0.001
Moderate and severe depression (BDI ≥ 19)	0.445	0.498	0.083	<0.001
Also adjusted for autonomic indices[c]				
Mild depression (9 < BDI < 19)	0.156	0.187	0.043	<0.001
Moderate and severe depression (BDI ≥ 19)	0.433	0.485	0.082	<0.001
Also adjusted for C-reactive protein and IL-6				
Mild depression (9 < BDI < 19)	0.073	0.088	0.040	0.068
Moderate and severe depression (BDI ≥ 19)	0.259	0.290	0.069	<0.001
Other significant predictors of IMT increase (fully adjusted model)				
Logarithm of C-reactive protein (mg/dL)	0.207	0.385	0.035	<0.001
Aspirin use	−0.058	−0.104	0.022	0.010
Familial history of CHD	0.062	0.107	0.026	0.017
SDNN	−0.003	−0.203	0.001	<0.001

Variables not reported in the table were not significant in the regression models.

[a]Age, gender, body mass index, current smoking, familiarity for CHD, systolic blood pressure, total cholesterol, HDL-cholesterol and triglycerides, and global CHD risk at ten years according to the SCORE system.
[b]Beta-blockers (yes versus no), ACE-antagonists, calcium-antagonists, diuretics, sartans, statins, SSRIs, and aspirin.
[c]Heart rate (1-bpm increase), SDNN (standard deviation of the mean value of time between normal complexes), SDANN (standard deviation of the average of NN intervals for each 5 min period), RMSSD (square root of mean square successive difference of RR intervals), and pNN50 (mean percentage of successive NN interval differences >50 ms).

Table 5 Relationship between depression symptoms and Intima media thickening. Subjects with carotid wall thickening (>0.9 mm) at baseline were excluded.			
	OR	**IMT > 0.9 mm (95% CI)**	***p***
Unadjusted analysis			
Depression group, ordinal (no depression as the ref. category)	3.05	(1.76–5.31)	<0.001
Adjusted analysis[a]			
Depression group, ordinal (no depression as the ref. category)	1.96	(1.05–3.63)	0.032

OR = odds ratio; CI = confidence interval. Logistic regression model with 314 observations. Hosmer–Lemeshow goodness of fit *p*-value = 0.52; Area under the ROC curve = 0.76.

aIncluding age, gender, body mass index, current smoking, familiarity for CHD, systolic blood pressure, aspirin use, Interleukin-6 level, SDNN (standard deviation of the mean value of time between normal complexes), SDANN (standard deviation of the average of NN intervals for each 5 min period), RMSSD (square root of mean square successive difference of RR intervals), and pNN50 (mean percentage of successive NN interval differences >50 ms).