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Inflammation as a common factor in the occurrence of symptoms of anxiety, depression and cardiovascular risk factors: results from an Italian cross-sectional study.

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Abstract:	Cardiovascular Diseases and anxiety-depressive symptoms are among the most frequent clinical conditions in the Western World, often in comorbidity. Evidence about a shared pathophysiology suggests a mediating role by chronic systemic inflammation. Aims of this study were to measure the association between anxiety and depressive symptoms, cardiovascular risk factors and inflammatory markers. Outpatients aged≥40 years undergoing colonoscopy after positive faecal occult blood test were enrolled; the following data were collected: BMI, blood pressure, glycaemia, lipid profile, CRP (C Reactive Protein), carotid thickness, scores at the Hospital Anxiety and Depression Scale (HADS), Temperament and Character Inventory (TCI), INTERMED-Self Assessment (IMSA) and SF-36. 54 patients were enrolled; 30.2% had anxiety symptoms, 18.9% depressive symptoms and 9.4% concomitant anxiety-depressive symptoms. Anxiety symptoms were associated with low HDL. Depressive symptoms were associated with CRP. Our results provide further support to evidence on the role of inflammation in the pathophysiology of depression.
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The Journal of Mental and Nervous Disease
Editorial Office

Dear Sir/Madame,

Please find enclosed a copy of a manuscript entitled “Inflammation as a common factor in the occurrence of symptoms of anxiety, depression and cardiovascular risk factors: results from an Italian cross-sectional study”, which we submit for consideration for publication in *The Journal of Mental and Nervous Disease*.

We decided to submit our work to your Journal in view of its implications on the topic of the comorbidity between psychiatric symptoms of anxiety and depression and cardio-metabolic risk factors. Our results seem to provide a further confirmation of the so called “theory of inflammation” as the common pathophysiological ground of anxiety, depression and chronic medical conditions. Moreover, our study explores a relatively recent and, in our opinion, relevant field of research, that is, patients’ self-perception of their physical and mental health, and its correlations to symptoms of anxiety and depression, providing new results which we think could be of interest to the Journal’s readers.

The manuscript has not been submitted elsewhere. Abstracts concerning this work have been presented at the 25th European Congress of Psychiatry (Florence, 1-4 april 2017).

No conflict of interest has to be declared by any of the authors.

Authors of this article had access to all study data, are responsible for all contents of the article, and had authority over manuscript preparation and the decision to submit the manuscript for publication.

All listed authors have approved of the submission of the manuscript to your Journal.

If convenient, we can be contacted by e-mail at giulyrioli@hotmail.it.

Thank for considering our manuscript for publication, we look forward to your response in due course.

On behalf of the Authors,

Yours sincerely,

Giulia Rioli, M.D.

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Anxiety, depression and CVD risk.

Full Title:

Inflammation as a common factor in the occurrence of symptoms of anxiety, depression and cardiovascular risk factors: results from a cross-sectional study.

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ABSTRACT

Cardiovascular Diseases and anxiety-depressive symptoms are among the most frequent clinical conditions in the Western World, often in comorbidity. Evidence about a shared pathophysiology suggests a mediating role by chronic systemic inflammation. Aims of this study were to measure the association between anxiety and depressive symptoms, cardiovascular risk factors and inflammatory markers. Outpatients aged≥40 years undergoing colonoscopy after positive faecal occult blood test were enrolled; the following data were collected: BMI, blood pressure, glycaemia, lipid profile, CRP (C Reactive Protein), carotid thickness, scores at the Hospital Anxiety and Depression Scale (HADS), Temperament and Character Inventory (TCI), INTERMED-Self Assessment (IMSA) and SF-36. 54 patients were enrolled; 30.2% had anxiety symptoms, 18.9% depressive symptoms and 9.4% concomitant anxiety-depressive symptoms. Anxiety symptoms were associated with low HDL. Depressive symptoms were associated with CRP. Our results provide further support to evidence on the role of inflammation in the pathophysiology of depression.

Keywords: anxiety; bio-psycho-social complexity; cardiovascular risk factors; depression; inflammation.

INTRODUCTION

Despite significant advances in diagnosis and treatment, Cardiovascular Diseases (CVDs) are among the leading causes of mortality and morbidity in the world (Roth et al., 2015). Also known as "silent killers", they may be responsible for asymptomatic or pauci-symptomatic physiopathology until the onset of a full-blown cardiovascular event (Perk et al., 2012).

Therapy and prevention of CVDs is now increasingly feasible by means of: regular monitoring of established modifiable cardiovascular Risk Factors (RFs) (hypertension, smoking, dyslipidaemia, obesity/physical inactivity, diabetes mellitus); the study of emerging RFs (hyper lipoprotein(a), hyper homocysteinaemia, increased blood levels of C-Reactive Protein (CRP), and bacterial Lipopolysaccharides (LPS), metabolic syndrome (MS) (Wood, 2001; Grundy et al., 1999; Goff et al., 2014); non-invasive ultrasonographic measurements, such as FMD (Flow Mediated Dilatation) (Stain et al., 2008) and IMT (Intima-Media Thickness) (Polak et al., 2011), typically of the carotid artery. Up to 80% of prevention of CVDs may be achieved by effective improvements of lifestyle and monitoring of RFs (WHO, 2004).

Anxiety and depression too are highly prevalent clinical conditions, esteemed to become the second leading cause of disability worldwide by 2030 (WHO, 2017), with very high health care-related and social costs (Andrade et al., 2012).

Cardiovascular RFs and symptoms of anxiety and depression have a huge epidemiological impact, both independently considered and, even more, when comorbid (Suls & Bunde, 2005). Such strong evidence justifies the increasing amount of clinical research investigating the possible mechanisms underlying their association (Seldenrijk et al., 2010; Kollia et al., 2017).

Anxiety would act as an independent RF not only for CVDs, but also for the subclinical cardiovascular damage, measured either as carotid IMT (c-IMT), or AS (Arterial Stiffness), or ABI (Ankle-Brachial Index) (Roest et al., 2010). Anxiety seems to increase the risk of coronary heart disease (CHD) by 25% and cardiac mortality by almost 50%, compared to control group (Martens et al., 2010).

Similarly, major depression, depressive symptoms and history of major depression all significantly predict cardiac events (Frasure-Smith, 1995) and are associated with subclinical damage, i.e. IMT(Elovainio et al., 2005), especially in males, and with arterial calcification (Tiemeier et al., 2004).

For all these reasons, the inclusion of psycho-social evaluations in the multidimensional assessment of cardiovascular risk is now strongly recommended (Lichtman et al., 2008).

Stress-induced neurotransmitter and biochemical abnormalities accompanying anxiety and/or depression would sustain a subclinical chronic inflammatory state (Vogel, 1997). This contributes to dysregulation of the immunological system (Stein et al., 1985), of the autonomic nervous system, with increased sympathetic activity (Sajadieh et al., 2004), and of the hypotalamic-pituitary system (Akil et al., 1993). All these pathophysiological pathways are also known to be involved in CVD pathogenic factors such as chronic hyperglycemia, atherosclerosis and endothelial dysfunction.

Aim of the study

The primary aim of the study was to measure the association between anxiety and depressive symptoms and atherogenetic (FMD, c-IMT) and metabolic RFs for CVDs in a sample of subjects undergoing screening procedures.

The secondary aim was to measure the association of both anxiety and depressive symptoms and atherogenetic and metabolic RFs for CVDs with an inflammatory marker (CRP), to outline the role of inflammation as possible mediator of their relationship.

METHODS

Ethics

This research work is part of a wider project called "Overweight and inflammation of colorectal mucosa as intestinal marker of risk for cancer" that was approved by the Local Ethics Committee (EC 245/11-Prot.3885 / EC) and conducted according to the Declaration of Helsinki for ethical statement in medical research. Written informed consent was obtained by subjects accepting to be involved.

Study design and population

Cross-sectional design. The sample included 27 males and 27 females (n=54), recruited between March 2015 and July 2016 among patients referred to a screening colonoscopy. Patients were referred for colonoscopy by their GPs after occasional positive faecal occult blood or for suspicious intestinal complaints (abdominal pain, bowel movements abnormalities or haematochezia). Exclusion criteria were: being younger than 40 years; having a positive history for non-colorectal neoplasia, past or current, or systemic diseases in advanced stage, or an inflammatory bowel disease; not being able to fill in psychometric rating scales.

Clinical assessment and measurement methods

Data collection was conducted in three phases, before, during and after the colonoscopy.

Before the colonoscopy, patients were informed about the research project and asked for participation. Those providing consent were interviewed to enquiry about their smoking status, level of physical activity, alcohol consumption, medical history including ongoing medications. Biometric parameters were also measured and registered, including: weight (kg), height (cm), body mass index (BMI, kg/m^2), waist and hips circumference (cm) and their ratio (waist-to-hip ratio, WHR), blood pressure (mmHg) and blood glucose (mg/dl), to establish the diagnosis of MS according to both the International Diabetes Federation (IDF) Consensus Worldwide definition of MS and the National Cholesterol Education Program - Adult Treatment Panel

(NCEP-ATP III) criteria (Grundy et al., 2005).

As part of the wider project, during colonoscopy, three micro-biopsies of ascending, descending and sigmoid colon were performed, stored and sent-off for analysis. A 10 ml-venous blood sampling was collected, with patients fasting for at least 8 hours, and analysed for CPR and lipid profile (total cholesterol, LDL, HDL, VLDL and triglycerides, mg/dl).

One week after undergoing colonoscopy, patients were invited to attend at a clinical meeting aimed at performing ultrasound measurement of left and right c-IMT and FMD. Psychometric assessment was also performed, offering assistance, if needed, to patients filling in the following four self-administered psychometric instruments:

1) The HADS (Hospital Anxiety and Depression Scale, Italian version) is a self-assessment rating scale made of 14 questions, 7 for anxiety and 7 for depression, developed to assess the presence and severity of depressive and anxious symptoms in the week before administration. Scores for each subscale range from 0 to 21, with scores categorized as follows: normal 0-7, mild 8-10, moderate 11-14, and severe 15-21. Although originally designed to be used with hospital populations, it has been found to perform well, with good psychometric properties, also among non-hospitalized subjects (Zigmond & Snaith, 1983; Bjelland et al., 2002; Terluin et al., 2009; Costantini et al., 1999).

2) The TCI (Temperament and Character Inventory, Italian version) is a self-assessment test designed by Cloninger and colleagues, whose list of true/false statements aims at identifying the intensity of and relationships between the basic personality dimensions of temperament (4 dimensions, Novelty Seeking (NS), Harm Avoidance (HA), Reward Dependence (RD) and Persistence (PS)) and character (3 dimensions, Self-Directedness (SD), Cooperativeness (CO) and Self-Transcendence (ST); a 240-item validated Italian version was used (Cloninger, 1994; Fossati e al., 2007).

3) The SF-36 (Short Form-36, Italian version) is a well-known questionnaire assessing patients' perception of own general health and impact on quality of life. It consists of 8 scaled scores, pertaining to as many domains: vitality, physical

functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health (Ware et al., 1993; Apolone & Mosconi, 1998).

4) The INTERMED (INTERdisciplinary MEDicine) Self-Assessment (IMSA) is an instrument to assess bio-psycho-social case complexity in general health care by focusing on past, present and future health needs and risks of patients. Derived as a self-administered tool from the original version (a structured interview), it consists of 27 multiple-choice questions. The total score ranges from 0 to 60, reflecting the level of complexity and the related care needs/risks (van Reedt Dortland et al., 2017). Good psychometric and clinimetric properties were confirmed.

Statistical analysis

Statistical analysis was performed using the program STATA 13.1 (College Station, Texas).

Frequencies and percentages for dichotomous variables and mean, median, range and standard deviation for continuous variables were calculated as part of the descriptive analysis. Univariate and multivariate analyses were then performed as part of the inferential analysis, combining the latter with a parallel Stepwise Regression investigation, to control and enhance accuracy of data. Scores at HADS were selected as response variable (presence/absence of anxiety symptoms, of depressive symptoms and of both anxiety and depressive symptoms – cut-off of 8). For both regression models, the usual $p<0.05$ threshold for statistical significance was used, but only variables reaching a significance level <0.25 at the univariate analysis were included in the multiple analysis, to limit type II errors.

RESULTS

Descriptive statistical analysis

A total of 54 patients (27 males, 50%) were enrolled. Sample characteristics and measures are described in tables I (continuous variables) and II (dichotomic variables).

Anxiety symptoms had a higher prevalence than depressive ones (n=16, 30.2% vs. n=10, 18.9%, respectively). Only 5 patients (9.4% of the sample) simultaneously showed both anxiety and depressive symptoms.

- *Display table I and II about there* –

Univariate inferential statistical analysis

Anxiety symptoms were found to be significantly associated to HDL (OR=0.08; p=0.02), right c-IMT (OR=2.64; p=0.03), the Mental Component Summary (MCS) item of SF-36 (OR=10.5; p=0.01). Depressive symptoms were found to be significantly associated to CRP (OR=6.75; p=0.03) and to MCS SF-36 (OR=13.33; p=0.00). Anxiety and depressive symptoms were found to be significantly associated to MCS SF-36 scale (OR=12.9; p=0.01).

Multivariate inferential statistical analysis

In the multivariate regression analysis, anxiety symptoms were found to be significantly associated to low HDL values (OR=0.30; p=0.01), as shown in table III. Depressive symptoms were confirmed to be significantly associated to MCS SF-36 (OR=26.44; p=0.01) and CRP (OR=13.15; p=0.03), while finally the combined presence of anxious-depressive symptoms was found to be associated only to MCS SF-36 (OR=11.16; p=0.02).

- Display table III about there -

DISCUSSION

The aim of the present research was to measure the association of a range of potential cardio-metabolic RFs, including inflammation, to the presence of symptoms of anxiety and depression in a sub-clinical sample of subjects undergoing colonoscopy as a screening procedure.

More than half of subjects in our sample (64.8%) were found to have a higher BMI than normal, with a frequency of overweight almost double (40.7%) compared to frank obesity (20.4%), according to Italian 2012 ISTAT data. The prevalence of MS was 42.6%, slightly higher than the 20 to 40% rate usually reported in the US and Europe (Ford et al., 2002). This may be related to the age range of the sample and/or to the worse level of glycaemic control, considering that the prevalence of MS is positively related to older age and higher levels of blood sugar. Hypertriglyceridemia was another common feature in our sample (Trenti et al., 2009). Almost two thirds of the sample were affected by hypertension, a result consistent to similar recent Italian epidemiological evidence. The prevalence of diabetes mellitus type II (2 subjects) was in line with Italian epidemiological data (Gnavi et al., 2018); moreover, 12 subjects had poor glycaemic control fulfilling criteria for "pre-diabetes": this is known to be a positive predictor for the development of diabetes within 5-10 years (Dall et al., 2014).

One third of the sample reported being a smoker, a high prevalence when compared-to Italian 2012 population data of 2012 (Tondi, 2011; Pacifici, 2013), and more typical of a younger population than that here described. Smoking status could be coherent with the overall high prevalence of anxious/depressive symptoms, considering the frequent association observed between smoking and emotional distress (Weinberger et al., 2010).

In the sample, 63% of patients described themselves as leading a sedentary lifestyle, a higher prevalence than the one described by ISTAT 2009 survey of the Italian population (ISTAT, 2016). This may be related to the older age of our sample, but also to the over-simplicity of the yes-or-no format of the question, not allowing

respondents to provide further specification.

Psychiatric symptoms of anxiety and/or depression were highly prevalent. While bearing in mind that the HADS is designed as a screening tool and not as diagnostic instrument, the fact that half of a population of out-patients, in a non-psychiatric setting, was found positive for at least mild anxiety and/or depression is nevertheless worth of attention. Even more considering that these symptoms were presumably unrecognized and/or untreated: of the 26 patients affected, only 6 were receiving treatment, suggesting a therapeutic gap consistent with other findings (Corrigan et al., 2014; Mattei et al., in press). This is known to have many potential bio-psycho-social negative consequences (social isolation, decline in work performance, increase in use/abuse of medications, alcohol or drugs, increased hospitalization, self-harm behaviours, worse prognosis of medical conditions) (Wang et al., 2007).

Symptoms of anxiety were associated with subclinical cardiovascular risk (right c-IMT), and the association showed a trend towards statistical significance also for subjects with concomitant anxiety and depressive symptoms (p=0.06). These findings provide further support to the clinical relevance of including assessment of anxiety and depression on a regular basis in medical settings (Santos et al., 2015). Our findings may also contribute further evidence supporting the “theory of inflammation” as the common pathophysiological ground of anxiety, depression and chronic medical conditions including CVDs: symptoms of depression were found to correlate to CRP (Collino et al., 2006).

Moreover, reduced HDL values was found to be a protective factor for anxiety both at the univariate and at the multivariate analysis (OR=0.08 and 0.30 respectively); this finding would fit well a psychogenic theory of obesity, corroborating the role of "comfortable food" as affective compensation, with antidepressant/anti-anxiety effect (Burbatti & Castoldi, 1999).

Finally, increasing levels of anxiety and/or depression were found to correlate to the MCS score of SF-36, consistently with previous evidence reported in various clinical populations (Buendia et al., 2011). This is a highly expectable finding supporting the

evidence that depression and emotional distress have a major impact on quality of life, even more than other chronic conditions (Murray, 1998).

The following limitations in the present research have to be acknowledged. Firstly, the cross-sectional design does not allow causal inferences of the relationship between the psychiatric symptomatology and the cardiovascular changes. Yet, the adoption of such design made the study feasible, and is consistent with the majority of studies currently published in this field. Secondly, the limited sample size and the selected population may affect the generalizability of results. Nonetheless, these results were found to be consistent with evidence provided by international literature. Thirdly, cases were selected not in the general population but among subjects undergoing an anti-cancer screening procedure (colonoscopy) and already presented signs or symptoms. Despite this may limit inference, it provides a "real-world" perspective on patients, reproducing the intertwining of risk factors and causal pathways between different clinical conditions (CVDs, cancer, anxiety and depressive mild-to-moderate conditions). Finally, data were not complete for some of the variables (e.g. TCI dimensions). Yet, the significance level of such variables at the univariate analysis excluded anyway the possibility of including them in the multiple analysis, suggesting that this limitation did not affect the final results. In spite of such limitations, the integration of clinical and instrumental (ultrasound) data in an integrated psycho-neuro-endocrine-immunological perspective is an original approach in psychiatric research and could represent a strength of the study.

CONCLUSIONS

The present research contributes to supporting the need for early detection and management of anxiety and depressive symptoms in a population under study for prevention of cancer and CVDs and provides further elements on the physio-pathological key role of inflammation. Symptoms of anxiety and of comorbid anxiety and depression were associated to subclinical cardiovascular RFs. Emotional symptoms were also found to correlate to inflammatory markers and metabolic RFs.

The exploration of the dimension of self-perceived quality of life and subjective, psychic symptomatology could improve cardiovascular risk assessment, as also Engel's bio-psycho-social model originally suggested (Engel, 1980). Further studies specifically focused on the investigation of inflammatory parameters are needed in order to understand more comprehensively the complex role of chronic inflammation in the association between psychiatric symptoms and CVDs.

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Table I - Descriptive statistical analysis. Demographic and clinical characteristics of the sample (continuous variables).

Variable	N	Mean	SD	Range
Age (years)	**54**	61.3	9.2	44-82
Weight (Kg)	**54**	76.2	15.9	49-113
Height (cm)	**54**	1.7	0.1	150-191
BMI	**54**	27	4.1	18.8-38.1
Waist Circumference	**54**	99.9	14.6	65-129
Hip Circumference	**54**	102.7	9.5	81-120
Total Cholesterol (mg/dl)	**54**	194.8	18.2	156-241
Triglycerides (mg/dl)	**54**	134	44.7	57-220
VLDL Cholesterol (mg/dl)	**54**	26.8	9	11-44
PA Systolic (mmHg)	**49**	146.1	18.2	110-180
PA Diastolic (mmHg)	**49**	82.4	10.1	60-100
Glycaemia (mg/dl)	**54**	95.41	18.6	64-194
CRP (mg/dl)	**54**	0.6	0.45	0.2-2.1
IL 1 beta	**18**	6	9.3	.8 - 41.7
IMT Right	**51**	812.3	274	486-1500
IMT Left	**51**	856.6	313.5	503-2000
FMD 1st minute	**50**	9.4	5.8	0 - 21.1
FMD 3rd minute	**50**	8.3	6.1	-7.2 - 20
FMD 1st -3rd minute	**50**	-1.4	6.4	-22.5-15.5
Psychiatric symptoms (HADS)				
HADS – Anxiety	**44**	5.9	4.1	0 - 15

HADS – Depression	**44**	4.6	3.2	0 - 11
Temperament and Character Dimensions (TCI)				
Novelty Seeking	**37**	22.3	3.7	15- 29
Avoidance	**37**	18.6	3.1	10-24
Reward Dependence	**37**	10.9	2.6	6-16
Persistency	**37**	5.4	1.1	3-8
Self-Directedness	**37**	26.1	4.1	18-34
Cooperativeness	**37**	21.6	4.6	12-31
Self-Transcendence	**37**	20.4	3.3	12-26
INTERMED Self-Assessment (IMSA)				
IMSA total score	**40**	7.6	3.9	0-18
IMSA Biologic domain	**40**	3.2	2.4	0-9
IMSA Psychologic domain	**40**	1.9	1.8	0-7
IMSA Social domain	**40**	1.1	1.1	0-5
IMSA Health Services domain	**40**	1.5	1.6	0-6
IMSA History	**40**	5.2	2.8	0-12
IMSA Present	**40**	2.8	2.9	0-13
IMSA Future	**40**	7.6	3.8	0-18
Quality of life (SF-36)				
Physical Functioning SF-36	**45**	80.4	20.6	25-100
Role limitation because of phyisical health problems SF-36	**45**	75.6	33.1	0-100
Bodily pain SF-36	**45**	70	26.1	0-100

General Health perception SF-36	**45**	65.4	15.2	30-92
Social Functioning SF-36	**45**	79.4	18.9	12.5-100
Role limitations because of emotional problems SF-36	**45**	83.7	29	0-100
General Mental Health SF-36	**45**	74.8	15.1	32-100
Mental Component Summary (MCS) SF-36	**45**	51.7	9.1	22.8- 66.1
Physical Component Summary (PCS) SF-36	**45**	47.1	8.6	26.1-58.8

List of Abbreviations: BMI=Body Mass Index, VLDL=Very Low Density Lipoproteins, PA=Arterial Pressure, CRP=C Reactive Protein, IL1=Interleukine 1, IMT=Intima-Media thickness, FMD=Flow mediated dilatation, HADS-A=Hospital Anxiety and Depressive scale - anxiety subscale, HADS-D=Hospital Anxiety and Depressive scale - depression subscale, SF-36=Short Form 36 Items, IMSA, INTERMED=The INTERMED (INTERdisciplinary MEDicine) Self-Assessment.

Table II - Descriptive statistical analysis. Demographic and clinical characteristics of the sample (dichotomous variables).

Dichotomous variables	N	%
Age		
<62 years	27	50
≥62 years	27	50
Sex		
Females	27	50
Males	27	50
BMI		
<25 kg/m^2	19	35.2
≥25 kg/m^2	22	40.7
≥30 kg/m^2	11	20.4
≥35 kg/m^2	2	3.7
MS ATP III		
No	33	61.1
Yes	21	38.9
MS IDF		
No	32	59.3
Yes	22	40.7
Total cholesterol		
<200 mg/dl	34	63
≥200 mg/dl	20	37
LDL		
<130 mg/dl	39	72.2
≥130 mg/dl	15	27.9
Triglycerides		
<150 mg/dl	34	63

≥150 mg/dl	20	37
HDL		
M≥40 mg/dl; F≥50 mg/dl	35	64.8
M<40 mg/dl; F<50 mg/dl	19	35.2
Hypertension		
<140/90 mmHg	21	38.9
≥140/90 mmHg	33	61.1
Diabetes		
<126 mg/dl	52	96.3
≥126 mg/dl	2	3.7
Hyperglycaemia		
≥100 mg/dl	14	25.9
<100 mg/dl	40	71.1
MAI/cardiopathy		
No	53	98.2
Yes	1	1.9
CRP		
<0.08 mg/dl	30	55.6
≥0.08 mg/dl	24	44.4
Smoke		
No	36	66.7
Yes	18	33.3
Alcohol		
No	17	31.5
Yes	37	68.5
Sedentary		
No	20	37
Yes	34	63
Anxiolytics		
No	50	92.6

Yes	4	7.4
Antidepressants		
No	52	96.3
Yes	2	3.7
Right Intima-Media Thickness		
<900 um	39	73.6
≥900 um	8	15.1
≥1500 um	6	11.3
Left Intima-Media Thickness		
<900 um	40	75.5
≥900 um	9	17
≥1500 um	4	7.6
HADS-A		
<8	37	69.8
≥8	16	30.2
HADS-D		
<8	43	81.1
≥8	10	18.9
HADS A and D		
A or D <8	48	90.6
A or D ≥8	5	9.4
Vitality SF-36		
>40	52	98.1
≤40	1	1.9
MCS SF-36		
>42	45	84.9
≤42	8	15.1
IMSA		
≤21	51	100
>21	0	0

FMD 1st minute		
≥ 9.70%	26	51
<9.70%	25	49
FMD 3rd minute		
≥7.75%	28	54.9
<7.75%	23	45.1
FMD Delta 1st -3rd minute		
≥-0.87%	24	47.1
<-0,87%	27	52.9

List of abbreviations: BMI=Body Mass Index, MS=Metabolic Syndrome, ATP III=Adult Treatment Panel III report, IDF=International Diabetes Federation, LDL=Low Density Lipoproteins, HDL=High density Lipoproteins, MAI=Acute Myocardial Infarction, CRP=C Reactive Protein, HADS-A=Hospital Anxiety and Depressive scale - anxiety subscale, HADS-D=Hospital Anxiety and Depressive scale - depression subscale, SF-36=Short Form 36 Items, IMSA=The INTERMED (INTERdisciplinary MEDicine) Self-Assessment, FMD=Flow Mediated Dilatation.

Table III – Univariate and multivariate inferential statistical analysis for anxiety and/or depressive symptoms.

UNIVARIATE INFERENTIAL STATISTICAL ANALYSIS			
HADS-A	**OR**	**p-value**	**95% CI**
Low HDL	0.08	0.02	0.01-0.7
Right intima-media thickness	2.64	0.03	1.1-6.3
MCS SF-36	10.5	0.01	1.8-60.3
HADS-D	**OR**	**p-value**	**95% CI**
CRP	6.75	0.03	1.3-35.8
MCS SF-36	13.33	0.00	2.4-73.5
HADS-A and D	**OR**	**p-value**	**95% CI**
MCS SF-36	12.9	0.01	1.7-96.8
MULTIVARIATE INFERENTIAL STATISTICAL ANALYSIS			
HADS-A	**OR**	**p-value**	**95% CI**
Low HDL	0.30	0.01	0.00-0.4
HADS-D	**OR**	**p-value**	**95% CI**
MCS SF-36	26.44	0.01	2.5-274.2
CRP	13.15	0.03	1.3-128.4
HADS-A and D	**OR**	**p-value**	**95% CI**
MCS SF-36	11.16	0.02	1.4-89.03

List of abbreviations: HADS=Hospital Anxiety and Depressive scale, HDL=High density Lipoproteins, MCSF SF-36=Mental Component Summary Short Form-36 items, CRP=C Reactive Protein, OR=Odds Ratio, CI=Confidence Interval.

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