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CLINICAL FEATURE
ORIGINAL RESEARCH

Increased prevalence of depression and anxiety among subjects with metabolic syndrome and known type 2 diabetes mellitus – a population-based study

Alexander Shinkov, Anna-Maria Borissova, Roussanka Kovatcheva, Jordan Vlahov, Lilia Dakovska, Iliana Atanassova and Paulina Petkova

Medical University of Sofia, Clinical Center of Endocrinology, Sofia, Bulgaria

ABSTRACT

Objectives: The metabolic syndrome (MetS) is a cluster of cardiovascular risk factors associated with high cardiovascular morbidity and mortality. The MetS and its elements have been linked to anxiety and depressive disorders. The aim of the current cross-sectional study was to assess the prevalence of depression and anxiety, measured by the Zung Self-Rating Scale in subjects with and without the metabolic syndrome and diabetes.

Methods: A total of 2111 adults were included, 1155 female, age 47.6 (13.7) and 956 male, age 45.2 (13.5). All participants filled questionnaires covering current and past disorders and medication, smoking and family history. Zung self-rating depression and anxiety scales were completed. Body weight, height and waist circumference were measured, BMI was calculated, serum glucose and lipids were measured.

Results: Depression (SDSi) and anxiety scores (SASi) were higher in the females and increased with age ($p < 0.001$). SDSi was higher in the females and males with metabolic syndrome (MetS) (50.9 ± 9.8 vs. 45.9 ± 8.9, $p < 0.001$ and 42.7 ± 9.2 vs. 40.5 ± 7.9 $p < 0.001$, respectively). SASi was higher in the MetS subjects (females 50.59 ± 11.35 vs. 45.97 ± 10.58, $p < 0.001$; males 40.48 ± 10.1 vs. 38.04 ± 8.42, $p < 0.001$). Both SDSi and SASi were higher in the subjects with known diabetes than in those with normal glucose tolerance (Mann-Whitney both $p < 0,001$). Positive depressive scores were more prevalent in subjects with MetS than those without (females 54% vs. 31.6%, $p < 0.001$; males 22.7% vs. 12.3%, $p < 0.001$). Depression and anxiety were more prevalent in the subjects with known diabetes than in those with normal glucose tolerance but not in the newly-diagnosed diabetes. The OR for depressiveness was 2.0 (1.3; 2.6) in subjects with MetS and 4.2 (2.3; 7.8) in those with known diabetes.

Conclusions: In conclusion, depressiveness and anxiety were associated positively with age and female gender and were more prevalent among subjects with MetS and known diabetes mellitus.

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Diabetes mellitus; metabolic syndrome; Zung self-rating scale; depression; anxiety; SASi; SDSi

Introduction

The metabolic syndrome (MetS) is a cluster of cardiovascular risk factors whose coexistence is associated with high cardiovascular (CV) morbidity and mortality [1]. MetS prevalence has been increasing with the increase in diabetes and obesity and is a serious healthcare and social issue [2]. The exact occurrence of the MetS depends on the studied population and the criteria applied. Most definitions include abdominal obesity, high arterial blood pressure, various disorders of lipid metabolism and impaired glucose tolerance or diabetes mellitus type 2 (T2DM). The reported frequencies range widely from about 20% to as high as over 60% [3,4]. It has been demonstrated that the presence of the MetS is associated with an OR of 2.9 for CVD, 1.7 for CV mortality, and 6.9 for T2DM [5,6].

It has been demonstrated by other researchers that some of the components of the MetS like obesity, T2DM, and arterial hypertension are associated with deteriorated quality of life and low self-esteem [7,8]. An association between the MetS and its elements and depressive disorders has also been reported [9–13]. The direction of this association is still debated and some authors do not even confirm it [14]. In a recent meta-analysis Pan A et al. concluded, however, that an association between MetS and depression existed and proposed a bidirectional causality. Obesity, insulin resistance, and chronic inflammation for instance might contribute to depression or, conversely, increased food and alcohol intake and obesity might be brought about by a depressive disorder [15]. In a prospective study Raikkonen K et al. found an increased risk of MetS in women with depressive symptoms or chronic distress, with odds ratios depending on the definition and varying between 1.3 and 1.6 [16]. The association between anxiety and the MetS seems even more elusive. Some data point to higher morbidity and mortality in subjects with a coexistence of MetS and an anxiety disorder [17]. The causal relationship between the two is not clear. Moreover, the complexity of the problem and the multiple factors that might contribute require caution in interpreting these data.

The aim of the present cross-sectional study was to assess the prevalence of depression and anxiety, measured by the Zung Self-Rating Scale in subjects with and without the MetS.

CONTACT Alexander Shinkov shinkovs@abv.bg Medical University of Sofia, Clinical Center of Endocrinology, 2 Zdrave St, Sofia 1431, Bulgaria

Material and methods

The studied cohort was derived from the Survey of the most common endocrine disorders in Bulgaria, 2006 [18]. Subjects with known psychiatric disease and psychoactive treatment, all subjects with thyroid dysfunction (hypothyroidism or hyperthyroidism) and/or taking levothyroxine or antithyroid medication were excluded.

Of the 2406 participants enrolled into the study, 2111 met the inclusion criteria: 1155 female (54.7%, 52.6–56.8) and 956 male (45.3%, 43.2–47.4). All participants signed an Informed consent, approved by the Local Ethics Committee at the University Hospital of Endocrinology before any further procedures. A questionnaire was filled in by the participants, including demographic data and questions on current or past morbidity and medication, smoking and family history of thyroid and CVD and diabetes mellitus. Body weight and height and waist circumference were measured and body mass index (BMI) was calculated by the standard formula (body weight in kg/squared body height in m). The proportion of the subjects with increased waist circumference was assessed using the Caucasian population International Diabetes Federation (IDF) criteria – ≥80 cm for females and ≥94 cm for males.

Arterial blood pressure was measured on the brachial artery in sitting position with an aneroid sphygmomanometer and after at least 5-min rest.

Fasting venous blood samples were collected between 8.00 and 10.00 a.m. and plasma glucose, total cholesterol, HDL cholesterol, triglycerides, and TSH were measured.

The IDF 2005 definition of the MetS was applied – increased waist circumference plus at least two of the following: arterial blood pressure >130/85, fasting plasma glucose >6.0, high-density lipoprotein cholesterol (HDL-c) <1.03 mmol/l for males and <1.29 mmol/l for females, and serum triglycerides >1.7 mmol/l.

All participants filled in the ZUNG Self-rating Depression and Anxiety Scales (SDS and SAS). The resulting raw scores in SDS and SAS were summed and recalculated to 100% Anxiety and Depression indices. The SDS index (SDSi) was interpreted as follows: up to 49 – no depression; 50–59 – mild depression; 60–69 – moderate depression; 70+ – severe depression. Additionally two categories were defined, without criteria for depression (SDSi ≤49) and with criteria for depression (SDSi >49) irrespective of its severity. Similarly, the anxiety Index was interpreted as normal (no criteria for anxiety) if SASi≤44 and as positive for anxiety if SASi>44.

Ultrasensitive TSH was determined by a microparticle immunoenzymatic assay (MEIA) on an automated analyzer AxSYM (ABBOTT, USA). The analytic sensitivity of the method was 0.01 IU/l. The TSH reference range was 0.39–4.20 IU/l. Subjects with TSH level <0.39 IU/l and >4.2 IU/l were excluded.

The plasma glucose was measured by a glucose oxidase method at a Glucose Analyzer II (Beckman, USA). Presinorm (Roche) – glucose 4.9 ± 0.3 mmol/l and Presipath (Roche) – glucose 12.6 ± 0.5 mmol/l standards were used for calibration. If the measured glucose levels exceeded 6 mmol/l, oral glucose tolerance test was performed to further classify the participant.

Serum cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured on an automated analyzer Cobas Mira Plus (ROCHE, Switzerland).

Statistical analysis

The statistical processing was done with IBM SPSS v.19 (IBM, USA). The continuous variables were presented as means and SD, and the categorical as proportions and 95% CI. Kolmogorov–Smirnov test and Normal Q-Q plots were applied to assess the normality of data distribution. T-test and Mann–Whitney U-test were used for continuous variables and Chi-square and Fisher's exact test for proportions. The age-related trends in the SDSi and SASi were explored by Kendal's tau b and ANOVA. Correlations were assessed by Spearman's rho test. Binary univariate and multivariate logistic regression was applied to estimate the association between SASi and SDSi and the other studied variables. The statistical significance of all tests was accepted if $p < 0.05$.

Results

The characteristics of the studied population are presented in Table 1. There were gender differences in all studied variables. The MetS was more prevalent in the males as were most of its components with the exception of the low HDL-c. Both Zung SDSi and SASi were higher in the females.

Both SASi and SDSi correlated moderately with the age in both genders (all $p < 0.001$) and weakly though significantly with BMI, WC and mean blood pressure.

In both genders SASi and SDSi increased with age (Figure 1) as did the proportion of the subjects with criteria for depression and anxiety (Figure 2). SDS and SAS were higher in the females in all age groups. The proportion of SASi and SDSi positive subjects was also higher in the females in all age groups ($p < 0.001$ for all decades).

In both genders, SASi and SDSi were higher in the subjects with MetS, though the differences were smaller in the males (Table 1). The proportion of subjects with criteria for depression and for anxiety was higher in those with MetS and its elements than in those without in both genders (Table 2). The association with high triglyceride levels was significant only in the females. The subjects with low HDL-c did not demonstrate difference in the depression and anxiety prevalence in neither gender (the data are not presented).

We further divided the subjects with diabetes/IGT according to the type of the disorder into known diabetes, newly diagnosed diabetes, impaired fasting glucose and impaired glucose tolerance (Table 3). The proportion of subjects with positive depressive and anxiety scores was higher in both genders in those with known diabetes than in those with normal glucose tolerance and IFG. However, the small number of cases in some groups increased the confidence intervals and did not permit reliable conclusions. The comparison of the SDSi and SASi showed significantly higher values in the subjects with known diabetes than those with normal glucose tolerance or newly diagnosed diabetes.

In the logistic regression models, the ORs for depressiveness among the females and males with the MetS were 2.0 (1.4; 2.6) and 2.2 (1.3; 3.6), the ORs among the subjects with known diabetes – 4.2 (2.3; 7.8) and 3.5 (1.8; 6.7) and in those with abdominal obesity – 2.2 (1.7; 2.8) and 1.9 (1.3; 2.8). Each

Table 1. Characteristics of the studied population. Data are presented as means (SD) or proportions (95%CI).

	Gender		
	Female (n = 1155, 54.7%)	Male (n = 956, 45.3%)	p
Age (years)	47.6 (13.7)	45.2 (13.5)	<0.001
BMI (kg/m2)	26.2 (5.5)	27.8 (4.3)	<0.001
Systolic Blood pressure (mmHg)	129 (19.9)	133.7 (16.6)	<0.001
Diastolic blood pressure (mmHg)	82 (12)	86.4 (11.6)	<0.001
Mean Blood Pressure (mmHg)	97.6 (13.9)	102.1 (12.4)	<0.001
TSH (mIU/l)	1.42 (1.06)	1.28 (0.82)	<0.001
Zung SDSi	47.1 (9.4)	41.4 (8.5)	<0.001
Zung SASi	47.1 (10.9)	39.1 (9.2)	<0.001
MetS	24.7% (22.2–27.2)	41.5% (38.4–44.6)	<0.001
High triglycerides	15.9% (13.8–18)	34.4% (31.4–37.4)	<0.001
Arterial hypertension	38.2% (36.4–41)	45.5% (42.3–48.7)	<0.001
Low HDLc	30.5% (27.8–33.2)	23.5% (20.8–26.2)	<0.001
Increased waist circumference	59.2% (56.4–62)	63.9% (61–66.9)	<0.001
Increased fasting glucose	18% (15.8–20.2)	22.7% (20.1–25.3)	0.001
SDS Index (Mean and SD)			
Subjects without MetS	45.88 ± 8.98	40.47 ± 7.85	
Subjects with MetS	50.87 ± 9.8	42.71 ± 9.17	
p	<0.001	<0.001	
SAS Index (Mean and SD)			
Subjects without MetS	45.97 ± 10.58	38.04 ± 8.42	
Subjects with MetS	50.59 ± 11.35	40.48 ± 10.1	
p	<0.001	<0.001	

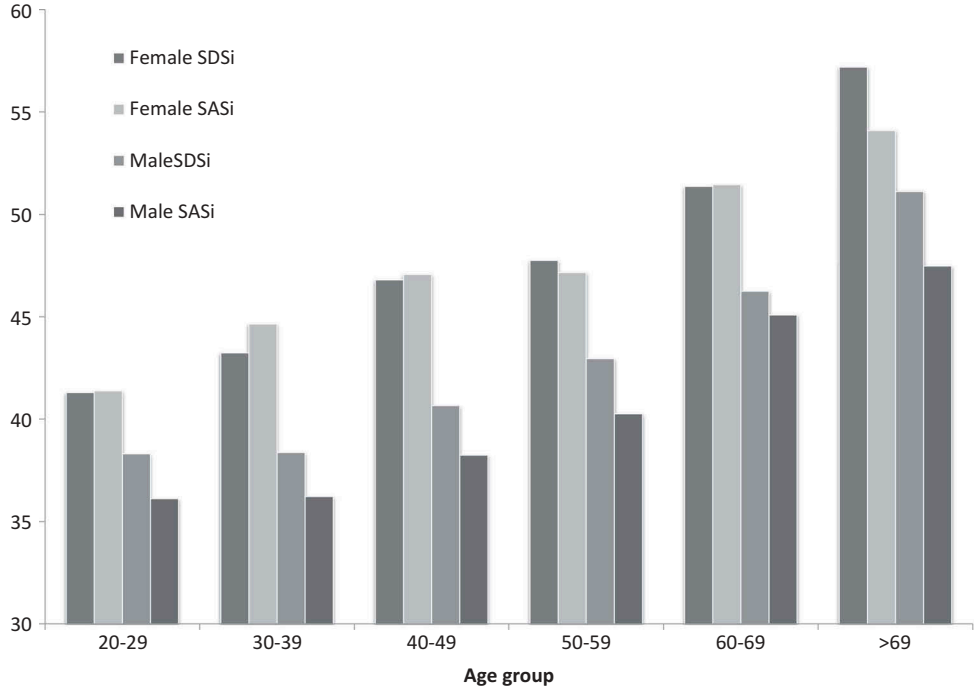

Figure 1. Mean SASi and SDSi by decades.

year increase in the age was associated with a 7% (6–9%) rise in the risk for depression.

Discussion

In this population-based cross-sectional study, we observed higher depression/anxiety scores and higher proportion of positive depression/anxiety scores in the females. The results are consistent with most published data [19,20]. Our data showed also increase in the depressive scores with age which deviates from the majority of published reports. Most authors find the opposite association or no change in the depression rates with age [19,21,22]. One of the reasons for the different result is the diversity of the approaches and assessment tools used. Most authors apply diagnostic criteria for a major depressive disorder or register major depression episodes. We used a self-assessment tool that offers a quantitative measurement of depressive symptoms [23]. Another source of the difference might be the characteristics of the studied population. The socioeconomic factors and social security, employment or retirement conditions and healthcare availability differ among the countries. While in most of Western Europe for instance the time of retirement is associated with a reduction in the stress, Eastern Europe faces the

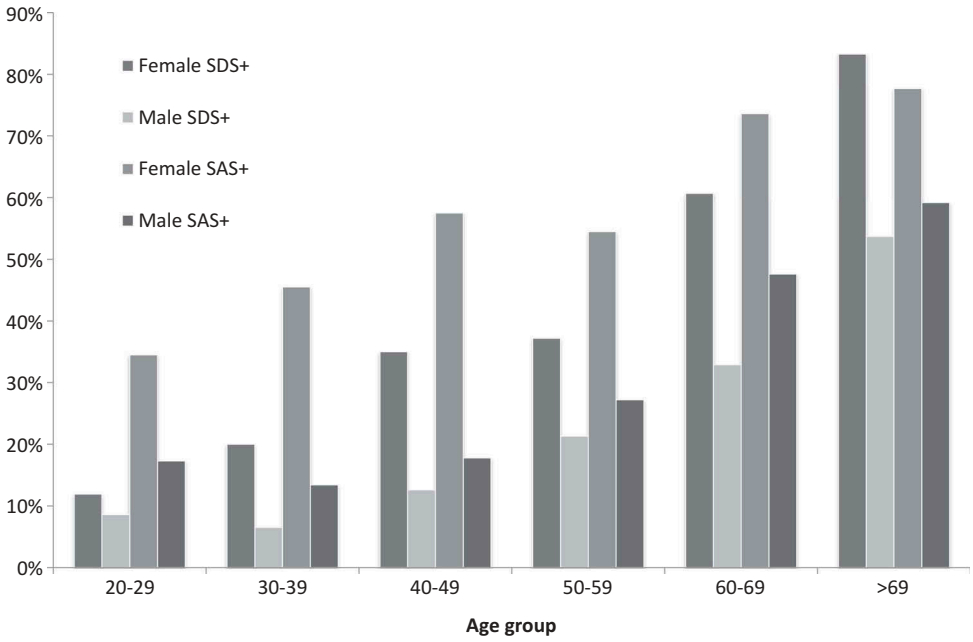

Figure 2. Proportion of the subjects with criteria for depression and anxiety and age by decade. The age-dependent increase was significant for SASi and SDSi for both genders.

Table 2. Proportion of the subjects with criteria for depression and anxiety among those with and without MetS and the separate elements of the MetS and history data of ischemic heart disease.

[% (95% CI)]	AH	DM/IGT	High Tg	High WC	IHD	MetS
Females: SDS+						
No	26.9 (23.6; 30.2)	34.8 (32.2; 37.4)	34.6 (31.6; 37.6)	26.8 (22.8; 30.8)	34.3 (31; 37)	31.8 (28.7; 34.9)
Yes	53.7 (49; 58.4)	47.8 (41; 54.6)	50.8 (43.6; 58)	44.3 (40.6; 48)	74.1 (66; 84)	54 (48.2; 59.8)
P-value	<0.001	0.001	<0.001	<0.001	<0.001	<0.001
Males: SDS+						
No	12.1 (9.3; 14.9)	14.9 (12.3; 17.5)	15.9 (13; 18.7)	11.3 (7.9; 14.6)	15 (12.7; 17)	12.3 (9.6; 15.0)
Yes	22.1 (18.2; 26)	22.7 (17.1; 28.3)	18.7 (14.1; 22.5)	19.7 (16.5; 22.9)	45.3 (32; 58)	22.7 (18.6; 26.8)
P-value	<0.001	0.009	0.36	0.001	<0.001	$P < 0.01$
Females: SAS+						
No	49.6 (45.9; 53.3)	54 (50.8; 57.2)	52.9 (49.8; 56)	47.9 (43.4; 52.4)	18.7 (16.7; 21)	51.8 (48.7; 54.6)
Yes	65.2 (60.7; 69.7)	62.3 (55.7; 68.9)	70.3 (63.7; 76.9)	60.9 (57.2; 64.6)	47 (36; 58)	67.3 (61.8; 72.8)
P-value	<0.001	0.037	<0.001	<0.001	<0.001	<0.001
Males: SAS+						
No	18 (14.7; 21)	21.2 (18.2; 24.2)	23.5 (20.2; 26.8)	19.5 (15.3; 23.7)	4 (3; 5.3)	20.1 (17.1; 23.1)
Yes	30.6 (26.3; 34.9)	32.4 (26.2; 38.6)	24.2 (19.6; 28.8)	26.1 (22.6; 29.6)	22.6 (11; 34)	28.8 (24.3; 33.3)
P-value	<0.001	0.003	0.81	0.022	<0.001	0.003

AH: arterial hypertension; DM/IGT: diabetes mellitus/impaired glucose tolerance; Tg: triglycerides; WC: waist circumference; IHD: ischemic heart disease.

Table 3. Proportion and 95% CI of the subjects with positive depression and anxiety scores and median SDSi and SASi among those with various glucose tolerance disorders.

Anx/Depr	New DM	Known DM	IFG	IGT	Normal GT
Female	***N* = 25**	***N* = 53**	***N* = 74**	***N* = 27**	***N* = 946**
SDS+ **[% (95% CI)]**	52 (32; 72)	69 (56; 82)*	36 (25; 47)	44 (25; 63)	32.3 (29.8; 35.8)
SAS+**[% (95% CI)]**	60 (41; 79)	75 (63; 87)*	54 (43; 65)	70 (53; 87)	54 (50.5; 57)
Male	***N* = 45**	***N* = 43**	***N* = 104**	***N* = 16**	***N* = 735**
SDS+ **[% (95% CI)]**	16 (5; 27)	38 (23; 53)*	19 (11.5; 26)	25 (4; 45)	15 (12.4; 17.6)
SAS+**[% (95% CI)]**	22 (10; 34)	48 (33; 63)*	30 (21; 39)	37 (13; 61)	21 (18; 24)
	N = 70	*N* = 96	*N* = 178	*N* = 43	*N* = 1681
SDSi Median (IQ)	43.7 (16.3)	50 (13.8)[a,b]	42.5 (14.1)	46.3 (12.5)	43.8 (12.5)
SASi Median (IQ)	39.4 (15.3)	47.5 (13.8)[a,b]	41.3 (16.3)	48.8 (13.8)	41.5 (15)

The difference was significant between the cases with normal GT and known diabetes in both genders and for both anxiety and depression (*all $p < 0.001$ compared to the healthy group; [a] $p < 0.001$ known vs. newly diagnosed diabetes; [b] $p < 0.001$ known diabetes vs. normal glucose tolerance).

opposite picture and Milanovich et al. report similar age-dependent increase in the Zung depression scores in Croatia [24]. Social insecurity increases after retirement since pensions are low and frequently cannot sustain a decent living for the elderly [25]. Frustration, low self-esteem and fear for the future all might contribute to an increase in the depressive

symptoms and anxiety. Furthermore, though healthcare is in theory free for the retired persons, in practice the state health funds do not provide fully for all necessary medication or diagnostic procedures and often additional payment is required [26]. As a result most elderly lead existence at the brink of poverty or have to rely strongly on the children for support [27].

We also observed a clear association between positive depressive scores with both the MetS and some of its components. The higher prevalence of the MetS and its components in subjects with major depression and anxiety disorders has been described previously [28–30]. We however examined the opposite association and found higher depressive and anxiety scores and increased prevalence of both depressiveness and anxiety among the subjects with the MetS in both genders. We also found that the depression and anxiety scores were positively associated with some of the components of the MetS, thus corroborating observations from several cross-sectional studies published recently by other teams [31–34].

The data from the large longitudinal Whitehall II Study demonstrated that the presence of the MetS might increase the risk of depressive symptoms in the future [35]. The authors reported an association of the MetS, central obesity and elevated triglycerides with positive depressive scores six years after the initial assessment. A similar association of depression with triglyceride levels particularly in the females was found in our series. It seemed, though, that abdominal obesity was more strongly linked to positive depressive scores as previously observed by Yu S et al. and Ruas LG et al. [36,37]. The latter team studied an older cohort and also reported the strongest association of depressive symptoms being with the elevated triglycerides. Lemche A et al. applied a complex structural equation modeling and concluded that both depression and elevated triglycerides contributed to the elevated CV risk in MetS subjects [38]. We tested a similar assumption by analyzing the prevalence of the subjects with positive depressive and anxiety scores among participants with a history of IHD and found it to be higher than in those without a history of IHD.

One possible explanation of the association between the MetS and depressive disorders is a dysregulation of the hypothalamo-pituitary-adrenal axis (HPAA) that has been described in both disorders [39–41]. The common pathway might pass through chronic psychological stress inducing increased sympathetic tone and an increase in corticotropin-releasing factor (CRF), ACTH and cortisol secretion [42]. Both promote insulin resistance and might contribute to the abdominal fat accumulation. Genetic polymorphisms or dysfunction of the receptors for ACTH, glucocorticoids, and aldosterone have been demonstrated to further predispose to depressive disorders and have been proposed as a neuroendocrine explanation of the relationship between MetS and depression [43].

Increased levels of inflammatory cytokines – IL6, CRP, and TNF-alpha have been found in subjects with mood disorders and MetS [39,44]., It has been suggested that the steroid receptor dysfunction prevents the inhibitory effect of glucocorticoids on lymphocytes and other cells of the immune response and the cytokine production [45]. A recent systematic review demonstrating a complex but convincing link of interferon treatment with major depression offered further support for this hypothesis [46]. Some authors have observed an association of elevated inflammatory markers with particular neuro-vegetative symptoms of depressiveness in MetS subjects such as fatigue, loss of energy, anhedonia [44]. These symptoms might be expected to lead to alteration in the nutritional behavior and reduction in physical activity. Ohmori Y et al., for instance, found an association of depression with lower physical activity and poorer dietetic habits that might contribute to the higher prevalence of abdominal obesity and MetS among depressive subjects [32]. Similarly Salvi V et al. described more prevalent abdominal obesity and lower physical activity among young patients with bipolar disorder [47].

We found significantly higher prevalence of positive depressive and anxiety scores among the subjects with known diabetes than among those with normal glucose tolerance. Positive depression and anxiety scores in the subjects with IFG, IGT and newly diagnosed diabetes were higher than in the healthy ones and lower than in the known diabetic subjects. As seen, known but not newly diagnosed diabetes increased significantly the odds ratios for both depressiveness and anxiety. These findings raise the question of what proportion of the depressiveness in a chronic disorder like diabetes is due to the disease and what – to the knowledge of being chronically ill, the continuous treatment and the lifestyle changes imposed by the disorder and its management.

Moreover health-related quality of life in diabetic subjects is usually decreased which might superimpose on the already discussed pathophysiologic mechanisms. The direction of the association is controversial [48]. 'Diabetes distress' may interfere with self-care and add to the depressiveness [49]. The risk of depression in the diabetic population is further increased by lower occupational status, lower income and food insecurity [50,51]. As a result the coexistence of diabetes/MetS with depression or anxiety contributes to the deteriorated quality of life in these subjects. What is more, the results of the large longitudinal HUNT2 study demonstrated also excess mortality among the diabetic subjects with depression (HR = 3.47) or anxiety (HR = 2.14), though only in the males [52].

The current study is representative for the adult Bulgarian population and the relatively high number of the participants permits generalizability of the observations. The studied disorders are common and associated with significant morbidity and mortality, posing high healthcare, social and economic burden. The study has several limitations. First, the cross-sectional design does not permit conclusions of causality. Second, the data on CV morbidity – IHD is based on history and requires cautiousness in its interpretation. Third, though widely used and recognized as a reliable tool, the Zung Self-rating scales permit a certain bias that is difficult to control for. We tried to improve the quality of the data by assigning a member of the study team to give clear instructions and, when necessary, assist the participants with filling in the questionnaires. Furthermore the Zung self-rating scale does not distinguish endogenous depression which might confound the results.

Conclusions

In conclusion, we found high prevalence of depressiveness and anxiety among the females, the elderly and the subjects

with Mets, diabetes mellitus and a history of ischemic heart disease. Our results corroborate the intimate association between psychiatric and somatic health. Further longitudinal studies are needed to throw more light on the causal relationship between them. Nevertheless, it might be advisable that screening for depression becomes part of the standard work-up in subjects with MetS and diabetes. On the other hand, a somatic assessment of the subjects visiting the psychiatrist with depressive disorders might facilitate the early diagnosis of the metabolic syndrome and diabetes and improve the care in some cases.

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Declaration of Interests

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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