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Original article

Gender differences in Anxious-depressive symptomatology, Metabolic Syndrome and Colorectal Adenomas among outpatients undergoing colonoscopy: a cross-sectional study according to a PNEI perspective

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Abstract. *Background and aim of the work:* To explore gender differences in patients suffering from anxious-depressive symptoms, Metabolic Syndrome (MetS) and Colorectal Adenomas (CRAs) in a sample of outpatients undergoing colonoscopy for screening purposes. *Methods:* Cross-sectional study. 126 consecutive outpatients of both sexes undergoing colonoscopy for non-specific abdominal symptoms between January 2015 and June 2021 at the Modena Policlinico General Hospital (Modena, Northern Italy) were enrolled. MetS was diagnosed according to ATPIII and IDF criteria. Anxiety and depression were assessed with the Hospital Anxiety and Depression Scale (HADS), while the Temperament and Character Inventory (TCI) was used to study personality. The SF-36 was also included as a measure of quality of life perception. *Results:* Among 126 outpatients (51.60% male) undergoing colonoscopy, 51 (44%) had CRAs, 54 (47%) MetS, 41 (41.40%) anxiety symptoms, 22 (22.20%) depressive symptoms and 13 (13.10%) combined anxious-depressive symptoms. HADS-Anxiety (t=2.68, p=0.01) and TCI Reward Dependence (TCI-RD) (t=3.01, p=0.00) mean scores were significantly higher in women; conversely, SF-36 Mental Component Summary scores were higher in men. CRAs were significantly prevalent in men (χ^2=9.32, p=0.00) and were statistically significantly associated with male sex at the univariate logistic regression analysis (OR=3.27; p<0.01). At the multivariate logistic regression, diastolic hypertension (p<0.01) was positively associated with male sex, while TCI-RD (p=0.04) and HDL hypocholesterolemia (p=0.02) were inversely associated with male sex. *Conclusions:* Several significant gender differences in anxious-depressive symptoms, MetS and CRAs were found. These preliminary data suggest the need to consider gender specificities while implementing therapeutic, diagnostic, and preventive strategies. (www.actabiomedica.it)

Key words: anxiety, depression, metabolic syndrome, comorbidity, outpatients

Introduction

In Europe, an estimated 165 million people, over 38% of the adult population, suffer from a mental disorder each year, with depression and anxiety being among the most common mental health issues (1). These disorders account for up to 40% of years lived with disability, with depression as the main cause (2).

Stress-related disorders such as anxiety and depression are extremely prevalent in women (3). Subclinical anxiety and depression symptoms are also more prevalent in women (4).

Several papers have investigated the biological and cultural reasons accountable to the gender gap in the epidemiology and pathophysiology of affective and common emotional disorders (5). First of all, sex differences in brain structure and function could be relevant (6-11). Moreover, the fluctuations in gonadal and stress hormones across the menstrual cycle and during major lifetime hormonal influences (i.e., puberty, pregnancy, lactation, menopause) can play a major role in predisposing females to stress-related diseases (3, 5, 12). Sex differences in the inflammatory response and the inflammation-induced kynurenine pathway (KP) may also be involved (13). Gender related differences in cognitive processes (14, 15) are thought to result in women experiencing more sensitivity to interpersonal stressors, rejection, criticism and separation, key features of depression and anxiety disorders (16-18). Social determinants including gender stereotypes and roles, economical inequalities (19) and exposure to domestic or sexual violence (20), interacting with biological factors, finally, are generally known to contribute to female vulnerability to mental health disorders (21).

In clinical practice, both anxiety and depressive symptoms are frequently comorbid with internal and chronic degenerative diseases, i.e., Metabolic Syndrome (MetS) and Colorectal Adenomas (CRAs). An emerging body of evidence has demonstrated the association between MetS and Colorectal cancer (CRC) (22-25). Conversely, medical literature examining the relationship between MetS and CRAs is more limited (26-28).

Gender differences have been found in the prevalence of both MetS and its diagnostic components (29-31) and CRAs (26, 32). In a recent community-based study, an effect of MetS on CRAs was observed in both genders, whereas the contribution of the individual components of MetS differed between men and women (26).

Clinical (33) and preclinical studies (34) have shown sex differences in inflammatory response in MetS, suggesting the possible different role of inflammatory processes in the pathogenesis of MetS in men and women. Several sex differences were also found in the association between C-Reactive Protein (CRP) and CRAs, suggesting that diet and lifestyle lowering inflammation may be a strategy to prevent neoplasms (28). Interestingly, alterations of the inflammation-induced effects on KP and its metabolites were also found both in MetS (35) and in CRAs patients (36, 37).

Therefore, taking an integrated psycho-neuro -immuno-endocrinological (PNEI) perspective, it is reasonable to hypothesize that sex differences in circulating levels of inflammatory markers such as CRP and metabolites belonging to the KP (38, 39) could eventually influence the development of anxious-depressive symptoms, MetS, CRAs and their associations, further underlining the necessity to investigate gender differences in this field.

The aim of the present study was to investigate gender differences in anxious-depressive symptomatology, MetS and CRAs, in a sample of outpatients undergoing colonoscopy, adopting an integrated PNEI perspective.

Methods

Ethics

All patients enrolled in the study provided written informed consent. The study was conducted in accordance with the Helsinki Declaration for ethical standards in medical research. The study was part of a wider project called *"Sovrappeso e infiammazione della mucosa colorettale come parametri di rischio neoplastico intestinale"* and was approved by the local Ethics Committee (Comitato Etico Provinciale di Modena, prot. No. 4396/C.E.), whose preliminary results on a limited sample has been previously published (27, 40).

Study design

The study followed a cross-sectional design.

Study population

126 consecutive outpatients, of both sexes, who underwent colonoscopy between January 2015 and June 2021 for non-specific abdominal symptoms (abdominal pain, bowel movement abnormalities, or hematochezia) or occasional positive faecal occult blood, were enrolled in the study. Patients with a positive history of colorectal neoplasms, or with a history of, or ongoing systemic condition at an advanced stage, or affected by an inflammatory bowel disease were excluded from the study participation.

Data collection

Before the colonoscopy, biometric parameters were measured and collected, including: weight (kg), height (m), waist circumference (cm) and systolic (SBP) and diastolic (DBP) blood pressure (mmHg). BMI (body weight in kg/height in m^2) and waist-to-hip ratio (WHR) were calculated. Patients were also interviewed regarding their smoking status, alcohol consumption and level of physical activity. A past medical and psychopharmacological history was detailed for each patient.

Before undergoing the colonoscopy, a 10-mL venous blood sample for serological analysis was collected from patients and immediately processed for hs-CRP (mg/L), glycemia (mg/dl) and lipid profile (triglycerides, TRG, mg/dl; total cholesterol, mg/dl; low-density lipoprotein cholesterol, LDL, mg/dl; high-density lipoprotein cholesterol, HDL, mg/dl).

After the colonoscopy, each patient was asked to fulfil the following self-administered tests for the psychometric assessment. Each test was used in its validated Italian-language version.

a. *Hospital Anxiety and Depression Scale, HADS*. It is a 14-items self-rating scale developed to assess the presence and the severity of anxious and depressive symptoms both in hospital populations and in community settings. It is composed of 7 questions for anxiety and 7 questions for depression (41-43), therefore providing both an anxiety (HADS-A) and a depressive (HADS-D) score.
b. The *Temperament and Character Inventory (TCI)*. It is a 240-items self-report test for personality assessment, aimed to evaluate the main temperament (novelty seeking, NS; harm avoidance, HA; reward dependence, RD; persistence, P) and character traits (self-directedness, SD; cooperativeness, C; self-transcendence, ST) (44, 45).
c. *The 36-item Short-Form Health Survey (SF36, Italian version)*. It is a self-reporting questionnaire aimed to assess patient's perception of his or her general health status and quality of life. It refers to the four weeks prior to the completion of the test, regardless of the type of pathology presented. It consists of 36 questions that cover the following 8 domains of health: vitality (energy and fatigue), physical functioning, physical role functioning, social functioning, general health, bodily pain, general mental health and emotional problems. The scores from each domain can be pooled into two components scores, namely Physical Component Summary (SF36-PCS) and Mental Component Summary (SF36-MCS). A third score concerns the change of self-perceived health status (Change Summary, SF36-CS) (46, 47).
d. *The INTERdisciplinary MEDicine (INTERMED)*, in its Self-Assessment version (INTERMED-SA). It is a 27-items clinical multi-dimensional instrument, with good reliability and validity, measuring the bio-psycho-social complexity and healthcare needs of patients (48).

The assessment of the KP metabolites was performed according to the analytical method reported in Borsini and colleagues (49). Briefly, the analyses of tryptophan (TRP), 3-hydrossikynurenine (3HK) and kynurenine (KYN), were performed using an Agilent HP 1200 liquid chromatograph (Agilent, Milan, Italy) consisting of a binary pump, an autosampler

and a thermostated column compartment. Chromatographic separations were carried out using a Discovery HS-F5 column (150 -x4.6 mm, 5 µm, Supelco, Milan, Italy) using 0.1% formic acid in water and acetonitrile (ACN) as mobile phase. The HPLC analyses were carried out using a linear elution profile of 15 min from 5% to 90% of ACN. The column was washed with 90% ACN for 3.5 min, then equilibrated for 5 min with 5% ACN. The flow rate was 0.5 mL/min. The injection volume was 40 mL. An Agilent 6410 triple quadrupole-mass spectrometer with an electrospray ion source operating in positive mode was used for detection.

Liquid chromatography, serological and psychometric tests were performed blind for anthropometric data and other clinical records.

MetS was diagnosed according to both the International Diabetes Federation Consensus Worldwide (50) and the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATPIII) criteria (51).

Statistical analysis

Statistical analysis was performed using STATA 13.1 software (Stata Corp., College Station, Texas) and Microsoft Excel. Mean, median, standard deviation (SD) and range were calculated for continuous variables. Frequencies and percentages were used for dichotomous variables.

To assess data distribution, Kolmogorov-Smirnov normality test (with the Lilliefors' correction) was used. For normally distributed variables, differences among groups were tested by means of Student's t-test. For not-normally distributed variables, Mann-Whitney Rank Sum Test was used. For categorial and dichotomous variables, Chi-square tests were performed to compare proportions in the number of observations. Finally, univariate and multivariate logistic regression analyses were performed as part of the inferential analysis. Sex (male/female) was selected as the response variable; all the above-mentioned clinical, biometric, serological, and psychometric variables were included in the analysis. The statistical significance was set at $p<0.05$.

Results

126 patients were enrolled in the study, 65 of whom (51.59%) were male, with a mean age of 59.88±11.70 years, and 61 (48.41%) were female, whose mean age was 58.61±12.36 years. Demographic, anthropometric and clinical characteristics of patients (both continuous and dichotomous variables) are summarized in Table 1.

Table 2 displays the results at the Student's t-test for means' comparison of continuous normally distributed variables according to gender. Statistically significant differences were also displayed in Figure 1.

Table 1. Description of the total sample.

Continuous Variables	Mean	SD	Min	Max	N
Anthropometric Variables					
Age (years)	59.26	12.00	26	82	126
Weight (kg)	75.50	11.58	44	127	126
Height (m)	1.68	0.09	1.5	1.91	126
BMI (kg/m^2)	26.53	5.04	17.18	44.82	126
Waist circumference (cm)	96.44	15.35	65	129	126
Clinical variables					
SBP (mmHg)	140.92	17.35	104	205	126
DBP (mmHg)	83.04	9.12	60	110	126
Glycemia (mg/dl)	95.95	20.07	64	197	118
Total Cholesterol (mg/dl)	203.28	35.22	118	302	113

Continuous Variables	Mean	SD	Min	Max	N
HDL (mg/dl)	54.50	15.59	30	113.4	113
LDL (mg/dl)	125.79	28.14	61	205	113
TRG (mg/dl)	114.72	45.47	36	220	113
Psychometric variables					
HADS-A	6.92	5.18	0	23	99
HADS-D	4.79	3.72	0	19	99
TCI-NS	22.53	3.64	14	32	85
TCI-A	18.71	2.75	10	26	85
TCI-RD	11.52	2.77	6	18	85
TCI-P	5.25	1.14	3	8	85
TCI-SD	26.76	4.18	13	34	85
TCI-C	22.38	4.57	11	32	85
TCI-ST	20.85	3.46	9	28	85
SF36-CS	2.97	0.92	1	5	92
SF36-PCS	46.94	8.95	21.43	63.10	92
SF36-MCS	48.43	10.63	19.85	66.13	92
Serological variables					
hs-CRP (mg/L)	0.56	0.35	0.00	2.1	115
TRP (μM)	22.96	6.83	10.37	40.35	121
KYN (μM)	1.86	0.59	0.82	4.08	121
KYN/TRP	0.09	0.03	0.04	0.18	121
3HK (μM)	0.02	0.01	0.003	0.102	121
3HK/KYN	0.01	0.004	0.002	0.027	121
3HK/TRP	0.0009	0.00004	0.00009	0.0031	121
Dichotomous Variable		**Presence (n, %)**		**Absence (n, %)**	**N**
Male sex		65 (51.59%)		61 (48.41%)	126
MetS (ATPIII)		54 (46.96%)		61 (53.04%)	115
MetS (IDF)		60 (52.17%)		55 (47.83%)	115
Hypertension		91 (72.80%)		34 (27.20%)	125
Systolic Hypertension		84 (72.41%)		32 (27.59%)	116
Diastolic Hypertension		52 (44.83%)		64 (55.17%)	116
Hyperglycemia		44 (37.29%)		74 (62.71%)	118
Waist circumference (ATPIII)		61 (48.41%)		65 (51.59%)	126
Waist circumference (IDF)		87 (69.05%)		39 (30.95%)	126
Hypertriglyceridemia		34 (29.57 %)		81 (70.43%)	115
HDL Hypocolestherolemia		44 (38.26%)		71 (61.74%)	115
Total Hypercholesterolemia		26 (49.12%)		58 (50.88%)	114
LDL Hypercholesterolemia		67 (58.77%)		47 (41.23%)	114
BMI > 25 kg/m^2		70 (55.56%)		56 (44.44%)	126

Table 1 (*Continued*)

Dichotomous Variable	Presence (n, %)	Absence (n, %)	N
Anxiety Symptoms	41(41.41%)	58(58.59%)	99
Depressive Symptoms	22 (22.22%)	77(77.78%)	99
Anxious-depressive symptoms	13(13.13%)	86(86.87%)	99
CRAs	51(43.97%)	65(56.03%)	116
INTERMED>21	4 (4.49%)	85 (95.51%)	89
hs-CRP > 1 mg/L	37 (32.17%)	78 (67.83%)	115
Alcohol use	49 (38.89%)	77(61.11%)	126
Sedentary lifestyle	67(53.17%)	59(46.83%)	126

List of abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TRG, triglycerides; HADS-A, Hospital Anxiety and Depression Scale, Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale, Depression subscale; TCI, Temperament and Character Inventory; NS, Novelty Seeking; A, Avoidance; RD, Reward Dependence; P, Persistence; SD, Self-Directedness; C, Cooperativeness; ST, Self-Transcendence; SF36, 36-item Short-Form Health Survey; PCS, Physical Component Summary; MCS, Mental Component Summary; hs-CRP, high sensitivity C-Reactive Protein; TRP, tryptophan; KYN, kynurenine; 3HK, 3-hydrossikynurenine; MetS, Metabolic Syndrome; ATPIII, Adult Treatment Panel; IDF, International Diabetes Federation; CRAs, Colorectal Adenomas; INTERMED, The INTERdisciplinary MEDicine.

Table 2. Comparison of continuous normally distributed variables according to gender (Student's t-test).

	Men (mean±SD)	Women (mean±SD)	t	p
Age (years)	60.08±11.72	58.02±12.36	-.957	0.34
Weight (kg)	82.13±16.03	68.23±16.36	-4.807	**0.00**
BMI (kg/m^2)	27.30±4.53	25.66±5.46	-1.827	0.07
Waist Circumference (cm)	101.08±13.05	91.77±15.84	-3.580	**0.00**
SBP (mmHg)	141.77±16.86	140.02±17.84	-.566	0.57
HDL (mg/dl)	50.19±13.14	59.38±16.80	3.209	**0.00**
HADS-A	4.72±3.84	7.21±4.74	2.674	**0.01**
TCI-NS	21.80±3.58	22.86±3.47	1.280	0.20
TCI-A	18.40±2.69	18.92±3.06	.765	0.45
TCI-RD	10.40±2.42	12.14±2.47	3.011	**0.00**
TCI-C	22.63±4.51	22.32±4.71	-.28	0.78
SF36-PCS	49.16±7.54	46.67±9.65	-1.28	0.21
TRP (μM)	23.98±6.89	21.77±6.61	-1.8	0.07
KYN (μM)	1.86±0.49	1.85±0.69	-0.004	1
KYN/TRP	0.08±0.03	0.09±0.04	1.15	0.25
3HK/TRP	0.0008±0.0003	0.001±0.0005	2.63	**0.01**
3HK/KYN	0.01±0.003	0.12±0.005	2.23	**0.03**

List of abbreviations: BMI, body mass index; SBP, systolic blood pressure; HDL, high-density lipoprotein cholesterol; HADS-A, Hospital Anxiety and Depression Scale, Anxiety subscale; TCI, Temperament and Character Inventory; NS, Novelty Seeking; A, Avoidance; RD, Reward Dependence; C, Cooperativeness; SF36, 36-item Short-Form Health Survey; PCS, Physical Component Summary; TRP, tryptophan; KYN, kynurenine; 3HK, 3-hydrossikynurenine.

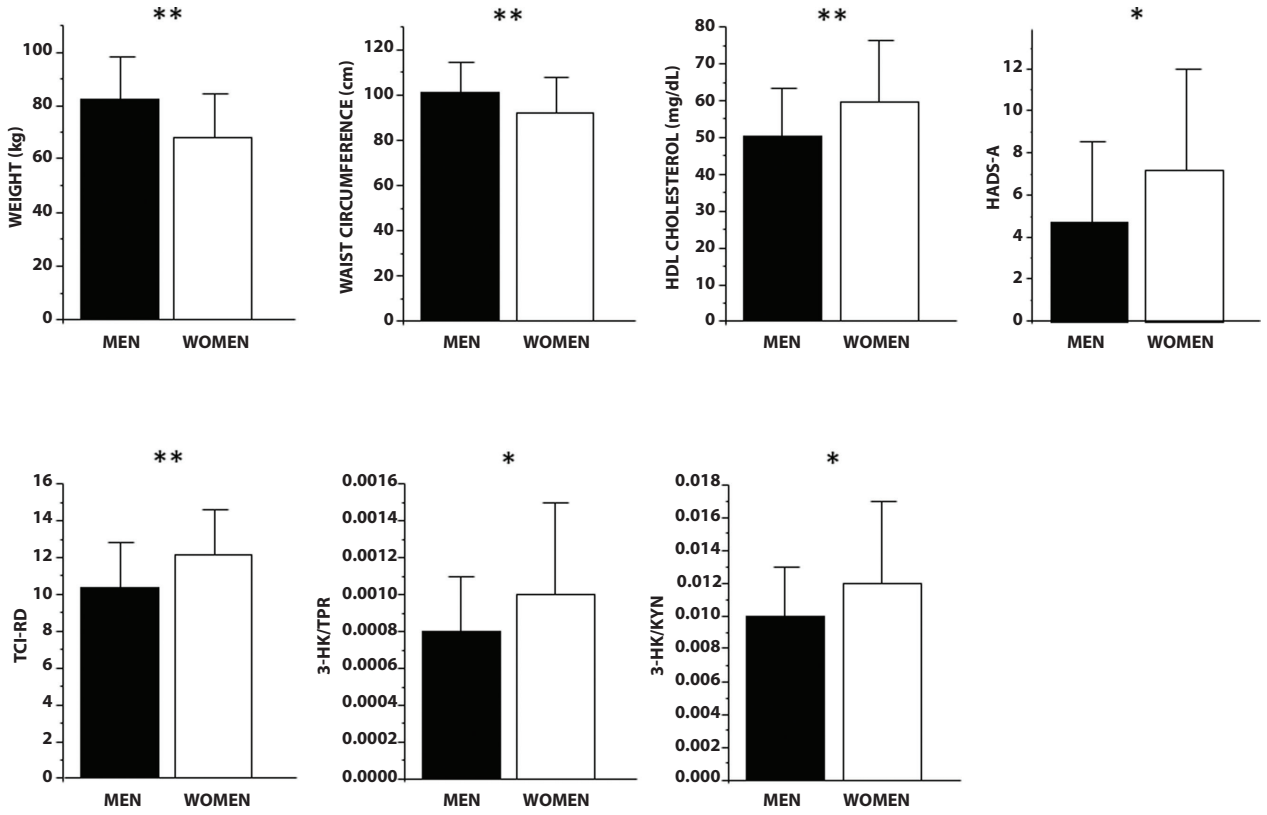

Figure 1. Statistically significant differences for normally distributed continuous variables according to gender.

*=p<0.05; **=p≤0.01. List of abbreviations: HDL, high-density lipoprotein cholesterol; HADS-A, Hospital Anxiety and Depression Scale, Anxiety subscale; TRP, tryptophan; KYN, kynurenine; 3HK, 3-hydrossikynurenine.

According to the U Mann-Whitney test for not normally distributed continuous variables, the distributions were different between males and females for SF36-MCS (men=52.11±7.91; women: 44.90±11.74; p=0.00) and diastolic blood pressure (men: 85.17±9.37; women: 80.85±9.90; p=0.04), as shown in Table 3. Figure 2 also represents these differences.

Table 4 shows the results of the gender-comparison for dichotomous variables as measured by means of Pearson's χ^2. Higher prevalence of CRAs (χ^2=9.32, p=0.00), diastolic hypertension (χ^2=8.88, p=0.003) and LDL hypercholesterolemia (χ^2=5.19, p=0.02) were detected in male than in female subjects. Anxiety (χ^2=5.30, p=0.02) and anxious-depressive (χ^2=4.07, p=0.04) symptoms were prevalent in women *vs*. men. Figure 3 also displays these statistically significant differences.

A statistically significant difference between men and women was detected for the prevalence of visceral obesity (waist circumference above the ATPIII cut-off) in the subgroup of patients affected by anxiety (female: 93.85%, male: 6.3%; χ^2=11.48, p<0.01) and among patients with anxious-depressive symptoms (women: 88.9%, men: 11.1%, χ^2=4.44, p=0.04).

At the Mann Whitney U test for not normally distributed continuous variables, among patients with depression, TCI-Reward Dependence (p=0.03) and SF36-Phisical Component Summary (p<0.01) were significantly different between men and women.

Table 5 displays the statistically significant results of the univariate and multivariate logistic regression analyses, referring to male gender as response variable.

Table 3. Comparison of continuous not normally-distributed variables according to gender (Mann-Whitney U test).

Continuous Variable	Men (mean ±SD)	Women (mean ±SD)	p
DBP (mmHg)	85.17±9.37	80.85±9.90	**0.04**
Glycemia (mg/dl)	95.43±19.93	96.48±20.37	.27
Total Cholesterol (mg/dl)	201.95±33.08	204.79±37.76	.79
LDL (mg/dl)	127.30±27.82	124.08±28.66	.21
TRG (mg/dl)	119.87±48.34	108.89±41.66	.23
HADS-D	4.47±3.66	5.1±3.79	.38
TCI-P	5.02±1.08	5.46±1.17	.16
TCI-SD	26.66±4.50	26.86±3.91	.74
TCI-ST	21±3.07	20.71±3.81	.87
SF36-MCS	52.11±7.91	44.90±11.74	**0.00**
hs-CRP (mg/L)	.61±.33	.51±.37	.09

List of abbreviations: DBP, diastolic blood pressure; LDL, low-density lipoprotein cholesterol; TRG, triglycerides; HADS-D, Hospital Anxiety and Depression Scale, Depression subscale; TCI, Temperament and Character Inventory; P, Persistence; SD, Self-Directedness; ST, Self-Transcendence; SF36, 36-item Short-Form Health Survey; MCS, Mental Component Summary; hs-CRP, high sensitivity C Reactive Protein.

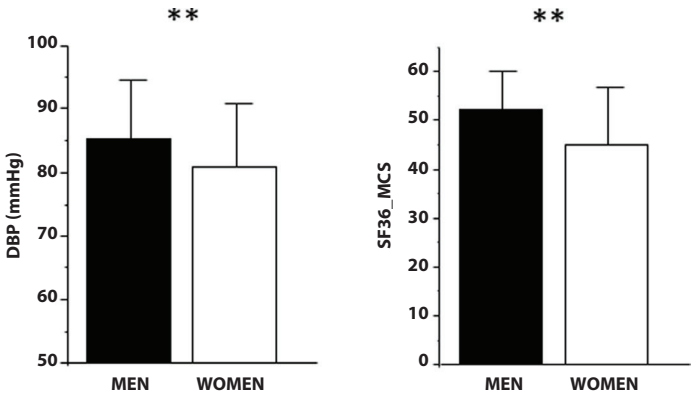

Figure 2. Statistically significant differences for not normally distributed continuous variables according to gender.

**=p≤0.01. *List of abbreviations:* DBP, diastolic blood pressure; SF36, 36-item Short-Form Health Survey; MCS, Mental Component Summary.

Discussion

This study aimed to investigate gender differences in anxious and/or depressive symptoms, MetS and its components, and CRAs in a sample of outpatients undergoing colonoscopy described adopting an integrated PNEI perspective.

In line with our previous findings that included a smaller sample (27, 40), the prevalence of MetS among our sample of outpatients undergoing colonoscopy (49.96% according to ATPIII criteria, and 52.17% according to IDF definition) was higher than the one resulting from epidemiological data measured in general population (52). This finding, though, may represent a selection bias, related to a possibly greater prevalence of MetS among people addressed to colonoscopic screening, given that the association of CRAs and MetS is widely established in the literature (25).

Table 4. Comparison of dichotomous variables according to gender (Pearson χ^2).

	Men (n, %)	Women (n, %)	χ^2	p
CRAs	34 (68%)	16 (32%)	9.32	**0.00**
HADS-A	9 (32.14%)	19 (67.86%)	5.30	**0.02**
HADS-D	8 (42.10%)	11 (57.90%)	0.61	0.44
HADS-AD	2 (20%)	8 (80%)	4.07	**0.04**
INTERMED	0 (0%)	2 (100%)	2.05	0.15
Alcohol use	31 (62%)	19 (38%)	3.08	0.08
Sedentary lifestyle	39 (58.21%)	28 (41.79%)	1.95	0.16
MetS-ATPIII	25 (48.08%)	27 (51.92%)	0.98	0.32
MetS-IDF	27 (48.21%)	29 (51.79%)	1.06	0.30
hs-CRP	22 (59.46%)	15 (40.54%)	1.16	0.28
Hypertension	46 (53.49%)	40 (46.51%)	0.24	0.62
Hyperglycemia	21 (46.67%)	24 (53.33%)	0.74	0.39
Waist-circumference (ATPIII)	27 (44.26%)	34 (55.74%)	3.13	0.07
Waist-circumference (IDF)	43 (48.32%)	46 (51.68%)	2.01	0.16
HDL hypocholesterolemia	16 (32%)	21 (68%)	2.15	0.14
Ipertrygliceridemia	21 (63.64%)	12 (36.36%)	2.08	0.15
Total Hypercholesterolemia	31 (56.36%)	24 (43.64%)	0.46	0.50
LDL Hypercholesterolemia	41 (62.12%)	25 (37.88%)	5.19	**0.02**
BMI>25	40 (57.97%)	29 (42.03%)	1.92	0.17
DBP	34 (68%)	16 (32%)	8.88	**0.003**
SBP	45 (52.33%)	41 (47.67%)	0.003	0.96

List of abbreviations: CRAs, Colorectal Adenomas; HADS-A, Hospital Anxiety and Depression Scale, Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale, Depression subscale; HADS-AD, Hospital Anxiety and Depression Scale, Anxiety and Depression total score; INTERMED, The INTERdisciplinary MEDicine; MetS, Metabolic Syndrome; ATPIII, Adult Treatment Panel; IDF, International Diabetes Federation; hs-CRP, high sensitivity C-Reactive Protein; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

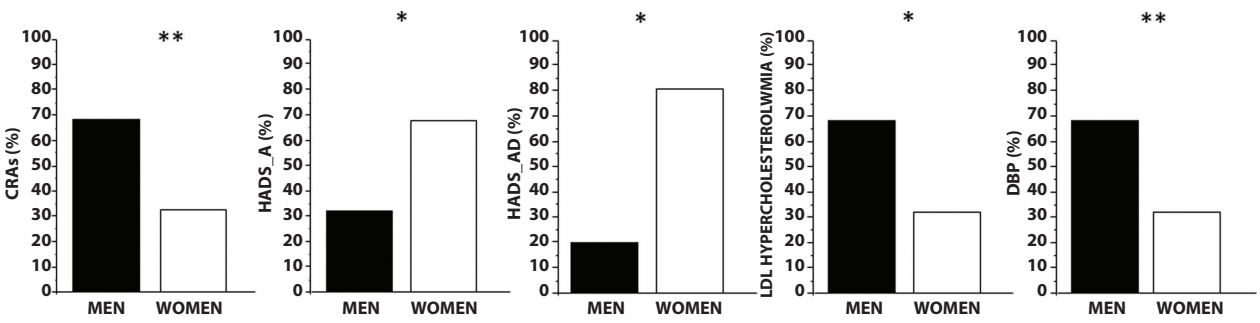

Figure 3. Statistically significant differences for dichotomous variables according to gender.

*=p<0.05, **=p≤0.01. *List of abbreviations:* CRAs, Colorectal Adenomas; HADS-A, Hospital Anxiety and Depression Scale, Anxiety subscale; HADS-AD, Hospital Anxiety and Depression Scale, Anxiety and Depression total score; LDL, low-density lipoprotein cholesterol; DBP, diastolic blood pressure.

Table 5. Statistically significant results of the univariate logistic regression analysis.

UNIVARIATE LOGISTIC REGRESSION ANALYSIS			
Male gender	**OR**	**p**	**95%CI**
CRAs	3.27	<**0.01**	1.51-7.08
HADS-A	0.87	**0.01**	0.79-0.97
HADS-AD	0.92	**0.02**	0.85-0.99
TCI-RD	0.74	<**0.01**	0.60-0.92
SF36-MCS	1.09	<**0.01**	1-03-1.15
Weight	1.06	**0.00**	1.03-1.15
Waist Circumference	1.05	<**0.01**	1.02-1.07
HDL Cholesterolemia	0.958	<**0.01**	0.93-0.99
Diastolic Hypertension	3.19	<**0.01**	1.47-6.91
MULTIVARIATE LOGISTIC REGRESSION ANALYSIS			
TCI-RD	0.67	**0.04**	0.46-0.97
HDL Cholesterolemia	0.94	**0.02**	0.89-0.99
Diastolic Hypertension	10.14	<**0.01**	2.26-45.48

List of abbreviations: CRAs, Colorectal Adenomas; HADS-A, Hospital Anxiety and Depression Scale, Anxiety subscale; HADS-AD, Hospital Anxiety and Depression Scale, Anxiety and Depression total score; TCI, Temperament and Character Inventory; RD, Reward Dependence; SF36, 36-item Short-Form Health Survey; MCS, Mental Component Summary; HDL, high-density lipoprotein cholesterol.

The mean BMI of the total sample was 26.53 kg/m^2, corresponding to an overweight condition (BMI>25 kg/m^2) affecting more than half (55.65%) of the enrolled patients, a result that is slightly higher than the 43% reported by the PASSI (*Progressi delle Aziende Sanitarie per la Salute in Italia*, Progress of Health Authorities in Italy) data for the three-year period 2007-2009 among adults in Emilia-Romagna (53). This difference, again, could be due to the fact that patients undergoing colonoscopy could have a higher BMI, another well-known risk factor for CRAs (54).

CRAs were detected in more than 40% of the sample (43.97%), a result that is higher than figures from the literature (55). This was expected, considering that: 1) the sample was made of people undergoing screening colonoscopy for the detection of colorectal lesions; and 2) almost half of the sample had MetS, as said well-recognized significant risk factor for CRC and CRAs (26). Moreover, the high prevalence of unhealthy lifestyles in our sample, as showed by the percentages of physical inactivity (53.17%) and alcohol consumption (38.89%) – all notorious cancer risk factors (55) – could further explain and justify this finding. CRAs were significantly more prevalent in men (χ^2=9.32, p=0.00) and were statistically significantly associated to male sex at the univariate logistic regression analysis (OR=3.27; p<0.01), in line with epidemiological data showing that women have fewer CRAs and CRC than men (32).

The gender differences detected in waist circumference (men: 101.08±13.05; women: 91.77±15.84; t=-3.58, p=0.00) and in HDL cholesterol mean concentrations (men: 50.19±13.14; women: 59.38±16.80; t=3.21; p=0.00) are consistent with the gender-different cut-points for the detection of abdominal obesity and HDL hypocholesterolaemia both according to IDF and ATPIII MetS definitions (50, 51).

The condition of visceral adiposity (i.e. a waist circumference above the ATP-III criteria cut-off) was significantly prevalent in women with anxiety (χ^2=11.48, p=0.001) and with anxious-depressive symptoms (χ^2=4.44, p=0.035), in comparison with men affected by the same mental disorders. These data are similar to previous findings suggesting that increased waist circumference, an independent predictor of cardiometabolic disease (56) and the most

convenient anthropometric correlate of visceral adipose tissue (57), was associated with an increased depression risk especially in women (58-60). The association between increased waist circumference and anxiety in women is quite disputable: several studies found that anxiety symptoms are associated with variations in body weight and changes in BMI rather than with abdominal adiposity and increased waist circumference (61-63); conversely, other studies detected a positive association between abdominal adiposity and anxiety, particularly in post-menopausal women (64, 65).

The mean level of DBP and the prevalence of diastolic hypertension in our sample were higher in men than in women, consistently with previous evidence (66, 67). The association between male sex and diastolic hypertension at the multivariate logistic regression analysis is also consistent with existing data (67, 68), suggesting the need for implementing gender-specific blood pressure guidelines. According to recent evidence, gender differences in sex steroids could mediate these associations, exacerbating cardiovascular disease in men (69).

To the best of our knowledge, few data are available on psychiatric symptoms and psychopathological characteristics of patients undergoing invasive procedures and colonoscopy, and the impact of emotional disorders on participation in screening colonoscopy is poorly characterized. According to the cross-sectional analysis by Calderwood and colleagues on a large cohort of adults without a history of CRC, depression seems not to be a risk factor for under-utilization of CRC screening (70). Abgrall-Barbry et al. found that comorbid depressive mood may be associated with an increased likelihood of CRC in women undergoing colonoscopy for clinical reasons (71). As far as our sample is concerned, despite the mean scores of anxious and/or depressive psychopathology were generally low, as expected in a non-clinical sample of outpatients, the prevalence of symptoms of anxiety and depression were higher than in the general population (52), in line with our previous research among smaller samples (27, 40). This result could be explained by several factors, including the use of different assessment methods (interview *vs.* self-report) and sampling strategy. Moreover, in our study, we administered the HADS, that is explicitly not intended to be a complete diagnostic instrument, but only a screening tool for symptoms of anxiety and/or depression, though very solidly accounted for (41-43).

Anxiety mean scores were significantly higher in females ($t=2.67$, $p=0.01$) than in male patients; moreover, both symptoms of anxiety ($\chi^2=5.30$, $p=0.02$) and symptoms of comorbid anxiety and depression ($\chi^2=4.07$, $p=0.04$) were significantly higher in women than in men. At the univariate logistic regression analysis, HADS-A (OR=0.87, $p=0.01$) and HADS-AD (OR=0.92, $p=0.02$) were inversely associated to male sex. All these results are in line with the literature, where epidemiological sex differences in anxiety and depressive disorders are clearly documented, independent of race or ethnicity, both in clinical samples (72) and in general population (5).

As far as personality is concerned, significant sex differences were observed in the TCI-RD subscale, with higher scores detected in women than in men, in accordance with previous records (73-77). At the multivariate logistic regression analysis, TCI-RD was inversely associated with male sex. TCI-RD investigates sentimentalism, empathy, and intensity in reward-dependent responses (such as social approval and social support); such traits would fit with the macrosocial characteristics of Western culture as regards the distinction of sexual roles and could also explain the higher predisposition of women towards stress-related diseases (5).

Finally, women reported lower SF36-MCS ($p=0.00$) and SF-36MCS ($p=0.007$) scores, suggesting that women generally self-perceived a worst mental and physical health status than men, consistently to previous studies investigating the impact of gender on health-related quality of life (78, 79).

With regards to KP metabolites, 3HK/KYN and 3HK/TRP ratios were significantly higher in women *vs.* men, suggesting a shift of the KP towards the synthesis of the neurotoxic metabolite 3HK. These data may mirror the findings of a previous study showing lower levels of the neuroprotective Kynurenic Acid (KYNA) and KYNA/3HK ratio in women compared to men (80).

Conversely to previous studies that demonstrated significant gender differences in the distribution of CRP (38), we did not find statistically significant

gender differences in hs-CRP serum levels (p=0.09), and hs-CRP was not associated to sex at the regression analysis. This result may in fact be a consequence of the average low levels of hs-CRP and to the limited sample size of the present study; further studies on larger samples could overcome this limitation.

A second limitation of this study concerns the psychometric assessment, performed using self-administered written questionnaires, rather than face-to-face clinical diagnostic interviews, potentially leading to an over-diagnosis of anxiety and depression in our sample. Though it was specified that the HADS only detects psychiatric symptoms and not full-blown disorders, this tool is one of the most accredited and frequently used in research protocols similar to the present one, providing a reasonable combination of reliability and feasibility. Thirdly, no control group was included, thus limiting the generalizability of our findings. Nevertheless, the sample was enrolled from outpatients performing screening procedures, thus minimizing selection bias from highly selected populations. Finally, the cross-sectional design of the study does not allow to draw causal connections between the variables considered.

Notwithstanding these limitations, the present study represents a preliminary attempt to adopt a clinical multidimensional PNEI approach, increasingly accepted as a validated paradigm in the scientific community. Rather than focusing separately on each single disorders, the PNEI model can help clinicians and researchers in adopting a more holistic and multidisciplinary approach to their patients, taking into account the complex body-mind interconnections.

Conclusions

In conclusion, this study underlines sex differences detected in a sample of outpatients undergoing colonoscopy for screening reasons according to a multidisciplinary PNEI perspective. Additional information on the role of gender differences in the association between anxious and depressive symptoms, MetS and CRAs could result in the implementation of gender-specific recommendations directed to the general population for screening strategies of these highly prevalent and frequently comorbid conditions.

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References

1. Wittchen HU, Jacobi F, Rehm J, et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur Neuropsychopharmacol. 2011;21(9):655-79.
2. World Health Organization. Depression. Available at: https://www.who.int/news-room/fact-sheets/detail/depression. Last access: October 11, 2021.
3. Solomon MB, Herman JP. Sex differences in psychopathology: of gonads, adrenals and mental illness. Physiol Behav 2009;97(2):250-8.
4. Nolen-Hoeksema S, Larson J, Grayson C. Explaining the gender difference in depressive symptoms. J Pers Soc Psychol 1999;77(5):1061-72.
5. Altemus M, Sarvaiya N, Neill Epperson C. Sex differences in anxiety and depression clinical perspectives. Front Neuroendocrinol 2014;35(3):320-30.
6. Marques AA, Bevilaqua MC, da Fonseca AM, Nardi AE, Thuret S, Dias GP. Gender Differences in the Neurobiology of Anxiety: Focus on Adult Hippocampal Neurogenesis. Neural Plast 2016:5026713.
7. Kim J, Gorman J. The psychobiology of anxiety. Clinical Neuroscience Research 2005;4(5-6):335–347.
8. Kaczkurkin AN, Raznahan A, Satterthwaite TD. Sex differences in the developing brain: insights from multimodal neuroimaging. Neuropsychopharmacology 2019;44(1):71-85.
9. Lavretsky H, Kurbanyan K, Ballmaier M, et al. Sex differences in brain structure in geriatric depression. The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry. 2004;12(6):653-657.
10. Ingalhalikar M, Smith A, Parker D, et al. Sex differences in the structural connectome of the human brain. Proc Natl Acad Sci USA 2014;111(2):823-8.
11. de Vries GJ, Södersten P. Sex differences in the brain: the relation between structure and function. Horm Behav. 2009;55(5):589-96.
12. Li SH, Graham BM. Why are women so vulnerable to anxiety, trauma-related and stress-related disorders? The potential role of sex hormones. Lancet Psychiatry 2017;4(1):73-82.
13. Moieni M, Tan KM, Inagaki TK, et al. Sex Differences in the Relationship Between Inflammation and Reward Sensitivity: A Randomized Controlled Trial of Endotoxin. Biol Psychiatry Cogn Neurosci Neuroimaging. 2019;4(7):619-626.

14. Thompson AE, Voyer D. Sex differences in the ability to recognise non-verbal displays of emotion: a meta-analysis. Cogn Emot 2014;28(7):1164-95.
15. Bardeen JR & Stevens EN. Sex differences in the indirect effects of cognitive processes on anxiety through emotion regulation difficulties. Personality and Individual Differences 2015; 81: 180-187.
16. Hammen C. Interpersonal stress and depression in women. J Affect Disord. 2003;74(1):49-57.
17. Cyranowski JM, Frank E, Young E, Shear MK. Adolescent onset of the gender difference in lifetime rates of major depression: a theoretical model. Arch Gen Psychiatry 2000;57(1):21-7.
18. Derdikman-Eiron R, Indredavik MS, Bakken IJ, Bratberg GH, Hjemdal O, Colton M. Gender differences in psychosocial functioning of adolescents with symptoms of anxiety and depression: longitudinal findings from the Nord-Trøndelag Health Study. Soc Psychiatry Psychiatr Epidemiol 2012;47(11):1855-63.
19. Patel V, Araya R, de Lima M, Ludermir A, Todd C. Women, poverty and common mental disorders in four restructuring societies. Soc Sci Med 1999;49(11):1461-71.
20. Patel V, Kirkwood BR, Pednekar S, et al. Gender disadvantage and reproductive health risk factors for common mental disorders in women: a community survey in India. Arch Gen Psychiatry 2006;63(4):404-13.
21. Afifi M. Gender differences in mental health. Singapore Med J 2007;48(5):385-91.
22. Chen H, Zheng X, Zong X, et al. Metabolic syndrome, metabolic comorbid conditions and risk of early-onset colorectal cancer. Gut 2021;70(6):1147-1154.
23. Lee J, Lee KS, Kim H, HW et al. The relationship between metabolic syndrome and the incidence of colorectal cancer. Environ Health Prev Med. 2020;25(1):6.
24. Shen X, Wang Y, Zhao R, Wan Q, Wu Y, Zhao L, Wu X. Metabolic syndrome and the risk of colorectal cancer: a systematic review and meta-analysis. Int J Colorectal Dis 2021;36(10):2215-2225.
25. Wu H, Zhang J, Zhou B. Metabolic syndrome and colorectal adenoma risk: A systematic review and meta-analysis. Clin Res Hepatol Gastroenterol. 2021;45(5):101749.
26. Ku MS, Chiu SY, Chien KL, Lee YC, Chen SL, Chen CD. Gender difference in metabolic syndrome and incident colorectal adenoma: A prospective observational study (KCIS No.42). Medicine (Baltimore) 2021;100(22):e26121.
27. Mancini S, Alboni S, Mattei G, et al. Preliminary results of a multidisciplinary Italian study adopting a Psycho-Neuro-Endocrine-Immunological (PNEI) approach to the study of colorectal adenomas. Acta Biomed 2020;92(1):e2021014.
28. Kim BC, Shin A, Hong CW, et al. Association of colorectal adenoma with components of metabolic syndrome. Cancer Causes Control 2012;23(5):727-35.
29. Regitz-Zagrosek V, Lehmkuhl E, Weickert MO. Gender differences in the metabolic syndrome and their role for cardiovascular disease. Clin Res Cardiol. 2006;95(3):136-47.
30. Rochlani Y, Andries G, Yandrapalli S, Pothineni NV, Mehta JL. Gender Differences in Metabolic Syndrome. In: Mehta J., McSweeney J. (eds) Gender Differences in the Pathogenesis and Management of Heart Disease. 2018. Springer, Cham. https://doi.org/10.1007/978-3-319-71135-5_2
31. Vishram JKK, Borglykke A, Andreasen AH, et al. Impact of Age and Gender on the Prevalence and Prognostic Importance of the Metabolic Syndrome and Its Components in Europeans. The MORGAM Prospective Cohort Project. PLOS ONE 2015; 10(5): e0128848.
32. Ferlitsch M, Reinhart K, Pramhas S, Wiener C, Gal O, Bannert C, Hassler M, Kozbial K, Dunkler D, Trauner M, Weiss W. Sex-specific prevalence of adenomas, advanced adenomas, and colorectal cancer in individuals undergoing screening colonoscopy. JAMA 2011;306(12):1352-8.
33. Lai MM, Li CI, Kardia SL, et al. Sex difference in the association of metabolic syndrome with high sensitivity C-reactive protein in a Taiwanese population. BMC Public Health 2010;10:429.
34. Poret JM, Gaudet DA, Braymer HD, Primeaux SD. Sex differences in markers of metabolic syndrome and adipose tissue inflammation in obesity-prone, Osborne-Mendel and obesity-resistant, S5B/Pl rats. Life Sci 2021;273:119290.
35. Oxenkrug GF. Metabolic syndrome, age-associated neuroendocrine disorders, and dysregulation of tryptophan-kynurenine metabolism. Ann N Y Acad Sci. 2010;1199:1-14.
36. Sun XZ, Zhao DY, Zhou YC, Wang QQ, Qin G, Yao SK. Alteration of fecal tryptophan metabolism correlates with shifted microbiota and may be involved in pathogenesis of colorectal cancer. World J Gastroenterol 2020; 26(45):7173-7190.
37. Liu CY, Huang TT, Chen JL, et al. Significance of Kynurenine 3-Monooxygenase Expression in Colorectal Cancer. Front Oncol 2021;11:620361.
38. Khera A, McGuire DK, Murphy SA, et al. Race and gender differences in C-reactive protein levels. J Am Coll Cardiol 2005;46(3):464-9.
39. Badawy AA, Dougherty DM. Assessment of the Human Kynurenine Pathway: Comparisons and Clinical Implications of Ethnic and Gender Differences in Plasma Tryptophan, Kynurenine Metabolites, and Enzyme Expressions at Baseline and After Acute Tryptophan Loading and Depletion. Int J Tryptophan Res. 2016;9:31-49.
40. Marchi M, Mattei G, Mancini S, Roncucci L, Galeazzi GM, Ferrari S. Personality traits and physical activity may be involved in colorectal carcinogenesis: preliminary data from a cross-sectional study on patients undergoing colonoscopy. Minerva Psichiatrica;60(2):100-1.
41. Zigmond AS & Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67(6),361-70.
42. Costantini M, Musso M, Viterbori P, et al. Detecting psychological distress in cancer patients: validity of the Italian version of the Hospital Anxiety and Depression Scale. Support Care Cancer 1999;7(3),121-7.
43. Bjelland I, Dahl AA, Tangen Haug T, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale:

An updated literature review. J of psychosomatic Research 2002;52(2), 69-77.
44. Cloninger CR (1994) The temperament and character inventory (TCI): A guide to its development and use. Center for Psychobiology of Personality. St Louis, MO: Washington University.
45. Fossati A, Cloninger CR, Villa D, et al. Reliability and validity of the Italian version of the Temperament and Character Inventory–Revised in an outpatient sample. Compr Psychiatry 2007; 48:380–3.
46. Apolone G, Mosconi P. The Italian SF-36 Health Survey: Translation, validation and norming. J Clin Epidemiol 1998; 51:1025–1036.
47. Ware JE, Snow KK, Kosinski M, Gandek B (1993). SF-36 Health Survey: Manual and interpretation guide. Boston, MA: The Health Institute.
48. Van Reedt Dortland AKB, Peters LL, Boenink AD, et al. Assessment of biopsychosocial complexity and health care needs: Measurement properties of the INTERMED Self-Assessment Version. Psychosom Med 2017; 79:485–492.
49. Borsini A, Alboni S, Horowitz MA, et al. Rescue of IL-1β-induced reduction of human neurogenesis by omega-3 fatty acids and antidepressants. Brain Behav Immun 2017;65:230-238.
50. International Diabetes Federation, IDF (2006). The IDF consensus worldwide definition of the Metabolic Syndrome. Brussels, Belgium: International Diabetes Federation. Available at: https://www.idf.org/e-library/consensus-statements/60- idf-consensus-worldwide-definitionof-the-metabolic-syndrome.
51. National Cholesterol Education Program (NCEP): Expert Panel on Detection and Treatment of High Blood Cholesterol in Adults. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106, 3143–3421.
52. de Girolamo G., Polidori G., Morosini P., et al. Prevalence of common mental disorders in Italy. Social Psychiatry and Psychiatric Epidemiology 2006; 41, 853-861.
53. PASSI (*Progressi delle Aziende Sanitarie per la Salute in Italia*, Progress of Health Authorities in Italy). Sovrappeso e obesità in Emilia-Romagna: i dati del sistema di sorveglianza PASSI triennio 2007-09. Available at: https://www.epicentro.iss.it/passi/pdf2010/obesita_ER0709.pdf. Last accessed: October, 12th, 2021.
54. Luu HN, Tran MT, Nguyen MV, et al. Association between body mass index and colorectal adenomas: Findings from a case-control study in Vietnam. Int J Cancer 2021;149(11):1898-1909.
55. Wong MCS, Huang J, Huang JLW, et al. Global Prevalence of Colorectal Neoplasia: A Systematic Review and Meta-Analysis. Clin Gastroenterol Hepatol 2020;18(3):553-561. e10.
56. Siren R, Eriksson JG, Vanhanen H. Waist circumference a good indicator of future risk for type 2 diabetes and cardiovascular disease. BMC Public Health 2012;12:631.
57. Despres JP, Lemieux I, Prud'homme D. Treatment of obesity: need to focus on high risk abdominally obese patients. BMJ 2001;322:716-720.
58. Luppino FS, van Reedt Dortland AK, et al. Symptom dimensions of depression and anxiety and the metabolic syndrome. Psychosom Med. 2011;73(3):257-64.
59. Zhao G, Ford ES, Li C, Tsai J, Dhingra S, Balluz LS. Waist circumference, abdominal obesity, and depression among overweight and obese U.S. adults: National Health and Nutrition Examination Survey 2005-2006. BMC Psychiatry. 2011;11:130.
60. Moreira RO, Marca KF, Appolinario JC, Coutinho WF. Increased waist circumference is associated with an increased prevalence of mood disorders and depressive symptoms in obese women. Eat Weight Disord. 2007;12(1):35-40.
61. Labad J, Price JF, Strachan MW, et al. Edinburgh Type 2 Diabetes Study Investigators. Symptoms of depression but not anxiety are associated with central obesity and cardiovascular disease in people with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. Diabetologia 2010;53(3):467-71.
62. Gomes AP, Soares ALG, Menezes AMB, et al. Adiposity, depression and anxiety: interrelationship and possible mediators. Rev Saude Publica 2019;53:103.
63. Guedes EP, Madeira E, Mafort TT, et al. Body composition and depressive/anxiety symptoms in overweight and obese individuals with metabolic syndrome. Diabetol Metab Syndr 2013;5(1):82.
64. Bocicor AE, Buicu G, Varga A, et al. Association Between Increased Waist Circumference and Depression and Anxiety Trend. Acta Medica Marisiensis 2015;61(2):87-90. DOI: 10.1515/amma-2015-0028.
65. Räikkönen K, Matthews KA, Kuller LH. Anthropometric and psychosocial determinants of visceral obesity in healthy postmenopausal women. Int J Obes Relat Metab Disord 1999;23(8):775-82.
66. Bella JN, Palmieri V, Kitzman DW, et al. Gender difference in diastolic function in hypertension (the HyperGEN study). Am J Cardiol. 2002;89(9):1052-6.
67. Alhawari HH, Al-Shelleh S, Alhawari HH, et al. Blood Pressure and Its Association with Gender, Body Mass Index, Smoking, and Family History among University Students. Int J Hypertens 2018;2018:4186496.
68. Gillis EE, Sullivan JC. Sex Differences in Hypertension: Recent Advances. Hypertension 2016;68(6):1322-1327.
69. Maranon R, Reckelhoff JF. Sex and gender differences in control of blood pressure. *Clin Sci (Lond)*. 2013;125(7):311-318. doi:10.1042/CS20130140
70. Calderwood AH, Bacic J, Kazis LE, Cabral H. Association between self-reported depression and screening colonoscopy participation. J Ambul Care Manage 2013;36(4):345-55.
71. Abgrall-Barbry G, Lemogne C, Lamarque D, et al. Depressive mood and subsequent cancer diagnosis in patients undergoing a colonoscopy. Psychosomatics 2012;53(4):356-62.
72. Bangasser DA, Cuarenta A. Sex differences in anxiety and depression: circuits and mechanisms. Nat Rev Neurosci 2021. Epub ahead of print.

73. Calvet B, Péricaud M, Parneix M, Jouette A, Bricaud M, Clément JP. Age and Sex Differences in Temperament and Character Dimensions in a French Nonclinical Population. Journal of Individual Differences 2016; 37, 168-180.
74. Al-Halabí S, Herrero R, Sáiz PA, et al. A cross-cultural comparison between Spain and the USA: temperament and character distribution by sex and age. Psychiatry Research 2011; 186, 397-401.
75. Mendlowicz MV, Jean-Louis G, Gillin JC, et al. Sociodemographic predictors of temperament and character. Journal of Psychiatric Research 2000; 34:221-226.
76. Parker G, Cheah YC, Parker K. Properties of the temperament and character inventory in a Chinese sample. Acta Psychiatrica Scandinavica 2003;108: 367-373.
77. Miettunen J, Veijola J, Lauronen E, Kantojarvi L, Joukamaa M. Sex differences in Cloninger's temperament dimensions—a meta-analysis. Comprehensive Psychiatry 2007; 48:161-169.
78. Liu CC, Chang HT, Chiang SC, et al. Sex differences in relationships between metabolic syndrome components and factors associated with health-related quality of life in middle-aged adults living in the community: a cross-sectional study in Taiwan. Health Qual Life Outcomes 2018;16(1):76.
79. Cherepanonv D, Palta M, Fryback DG, Robert SA. Gender differences in health-related quality of life are partly explained by socio-demographic and socioeconomic variation between adult men and women in the US: Evidence from four US nationally representative data sets. Qual Life Res 2010;19:1115–24.
80. Meier TB, Drevets WC, Teague TK, et al. Kynurenic acid is reduced in females and oral contraceptive users: Implications for depression. Brain Behav Immun 2018;67:59-64.

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