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 (χ²=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)
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-hydroxikynurenine (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.

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/m²)                  | 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 |

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.
### 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

| Variable  | Mean  | SD    | Min  | Max   | N    |
|-----------|-------|-------|------|-------|------|
| 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

| Variable         | Mean  | SD    | Min  | Max   | N    |
|------------------|-------|-------|------|-------|------|
| 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

| 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/m²                        | 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/m²)      | 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-hydrosikynurenine.

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 \(\chi^2\). Higher prevalence of CRAs (\(\chi^2=9.32, p=0.00\)), diastolic hypertension (\(\chi^2=8.88, p=0.003\)) and LDL hypercholesterolemia (\(\chi^2=5.19, p=0.02\)) were detected in male than in female subjects. Anxiety (\(\chi^2=5.30, p=0.02\)) and anxious-depressive (\(\chi^2=4.07, p=0.04\)) 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%; \(\chi^2=11.48, p<0.01\)) and among patients with anxious-depressive symptoms (women: 88.9%, men: 11.1%, \(\chi^2=4.44, p=0.04\)).

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     | 0.27 |
| Total Cholesterol (mg/dl) | 201.95±33.08  | 204.79±37.76    | 0.79 |
| LDL (mg/dl)         | 127.30±27.82  | 124.08±28.66    | 0.21 |
| TRG (mg/dl)         | 119.87±48.34  | 108.89±41.66    | 0.23 |
| HADS-D              | 4.47±3.66     | 5.1±3.79        | 0.38 |
| TCI-P               | 5.02±1.08     | 5.46±1.17       | 0.16 |
| TCI-SD              | 26.66±4.50    | 26.86±3.91      | 0.74 |
| TCI-ST              | 21±3.07       | 20.71±3.81      | 0.87 |
| SF36-MCS            | 52.11±7.91    | 44.90±11.74     | 0.00 |
| hs-CRP (mg/L)       | .61±.33       | .51±.37         | 0.09 |

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 $\chi^2$).

|                     | Men (n, %) | Women (n, %) | $\chi^2$ | 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.
finding. CRAs were significantly more prevalent in men ($\chi^2=9.32$, $p<0.01$) 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±16.80; 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 ($\chi^2=11.48$, $p=0.001$) and with anxious-depressive symptoms ($\chi^2=4.44$, $p=0.035$), 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

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

|                         | OR       | p        | 95%CI       |
|-------------------------|----------|----------|-------------|
| Male gender             |          |          |             |
| 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**

|                         | OR       | p        | 95%CI       |
|-------------------------|----------|----------|-------------|
| 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.
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 disorder, 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.

Acknowledgements: Authors wish to thank all the medical students and residents in Psychiatry involved in the PNEI-MO Research Group for their help in patients’ enrollment.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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Received: 28 October, 2021
Accepted: 16 December, 2021
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