# ILLNESS INTRUSIVENESS IS ASSOCIATED WITH DEPRESSION SEVERITY AMONG PATIENTS WITH UNIPOLAR DEPRESSIVE DISORDERS

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**Abstract**

**Purpose:** We sought to characterize the relationship between depression severity and illness intrusiveness in a large sample of outpatients with major depression disorders.

**Method:** Six hundred ninety-two patients with unipolar depressive disorders recruited in 19 Italian centers answered a self-administered survey including sociodemographic and clinical data. Illness Intrusiveness Ratings Scale (IIRS). A psychiatrist completed a standardized data collection form concerning depression severity (MADRS).

**Results:** According to MADRS score, 12.7% of patients were on clinical remission, 34.8% had mild symptoms, 44.4% had moderate severity, and 8.1% had severe depression. Significant predictors of IIRS global scores were frequency of physical exercise ($\beta$ = -5.86; p = 0.02), number of drugs prescribed ($\beta$ = -4.06; p<.0001), frequency of relapses in the past 10 years ($\beta$ = -4.77; p = 0.02), primary psychiatric diagnosis ($\beta$ =-5.64; p=0.03). Effect size of depression severity for each IIRS total scale was $\omega^2$ = 0.24 and $\omega^2$ = 0.16 for unadjusted and adjusted models respectively. Patients in clinical remission reported a mild level of distress on all IIRS scales (IIRS = 33.8; IIRS:ins = 2.50; IIRS:int = 2.92; IIRS:dev = 2.58).

**Conclusion**: We found a strong graded association between depression severity and life style disruptions in all dimensions of the Illness Intrusiveness Rating Scale. Our results suggest a persistent residual impairment even after partial or complete clinical recovery. Polypharmacy strongly contributes to life domains' disruption, thus suggesting further efforts to reduce regimen complexity.

**Key words:** Depressive disorders, illness intrusiveness, depression severity, MADRS

## Introduction

There is substantial evidence that adaptations of patients' everyday activities, interests and life-styles to both treatment and disease factors (Illness Intrusiveness) partially mediate the effect of chronic medical conditions on subjective well-being and perceived-health among patients with different medical conditions [1-3]. Previous studies have shown that psychiatric conditions including obsessive-compulsive disorder and other anxiety syndromes impose dramatic limitations to patients' life and are felt as intrusive as life threatening diseases such as acquired immunodeficiency infection and cancer [1].

Depression is a primary determinant of years lost due to disability [4] and exerts a detrimental impact on functional impairment and health-related quality of life (HRQOL) compared to the general population and other

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medical conditions [5-8]. Additionally previous studies have found that depression severity is strongly associated with functional disability [9 10].
Despite depressive symptoms had often been implicated as a mediator in the relationship between chronic medical condition and health-related quality of life impairment, the relationship between the severity of depressive symptoms and illness intrusiveness among working-age adults with major depressive disorder (MDD) is still scarcely characterized. Hence, we sought to characterize the relationship between depression severity and illness intrusiveness in a large sample of outpatients with major depression disorders.

## Methods

### *Participants and Setting*

ILDE study was carried out between June and July 2013 in 19 outpatient referral centers for diagnosis and treatment of psychiatric disorders across all Italian regions. Patients referred to the centers for psychiatric conditions were screened for eligibility by a psychiatrist during a regular follow-up visit at the clinic. We included adult patients with a clinical diagnosis of depression with the exclusion of bipolar disorders. According to International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD10; WHO 1990) classified diagnosis in our sample were: Adjustment Disorder (AD; ICD10:F43.2), Dystimia (DYS; ICD10:F34.1), Recurrent Depressive Episode (RDE; ICD10:F33), Depressive Episode (DE; ICD10:F32), Mixed Anxiety and Depressive Disorder (ADD; ICD10:F41.2), Other Persistent Mood Disorder (OTHER; ICD10:F34.8, F34.9).
Patients completed a self-administered questionnaire while the same psychiatrist recorded relevant clinical characteristics in a standardized data collection form. To preserve anonymity of data collection while matching clinical and patient-reported information, the psychiatrist handed the data collection form to the patient at the end of the visit. The patients sealed both the data collection form and the self-administered questionnaire in an anonymous envelope to return to the research team.

## Measures

### *Depression severity*

The Montgomery-Asberg Depression Rating Scale [11] (MADRS) consists of ten rating items that can be clinician-administered in a short period of time. Each item is scored on a 0-6 scale, with 6 indicating maximum symptom severity; the total score is constructed by summing the ten item scores. The ten items were designed to track treatment change; hence, the MADRS provides a sensitive instrument for measuring patient responses to antidepressant medications and other treatments [12 13]. According to the score, depression severity was classified as remission (MADRS: 0-6), mild (MADRS: 7-19), moderate (MADRS: 20-34), severe (MADRS: ≥ 35).

### *Illness intrusiveness*

Illness intrusiveness results from disease- and treatment-induced disturbance on every-day life, activities and interests. The Illness Intrusiveness Ratings Scale [14] (IIRS) is a self-report questionnaire built on 13 items that ask respondents the extent to which their "illness and/or its treatment" interfere with 13 life domains central to quality of life. Each item ranges from 1 (not very much) to 7 (very much). Subscales are "Relationships and Personal Development", "Intimacy", and "Instrumental" life domains.

### *Demographic and Medical Information*

The survey included a section on sociodemographic characteristics, patients' age, gender, Body Mass Index, frequency of physical activity, education level, marital status were recorded, employment, inactivity, retirement, and unemployment status were classified using the International Labour Office definition [15]. Medical information included number of depressive episodes in the last ten years, time since disorder onset, number of comorbidities in the last twelve months, specifications about therapy and drugs prescribed.

## Statistical Analysis

Analyses were conducted with SAS 9.2. Means and standard deviations or absolute and relative frequencies were computed for continuous or categorical variables, respectively. The association between MADRS score classes and socio-demographic characteristics has been evaluated with 1-way ANOVA or $\chi^2$ test. The association between MADRS score classes and cognitive impairment was evaluated with $\chi^2$ test. The unadjusted and adjusted association between outcomes and MARDS has been assessed with generalized linear models. We used an identity or logarithmic link function were appropriate depending on outcomes distribution for each analysis. We adjusted each model for socio-demographic characteristics (age, gen-

der, education, occupation, marital status) and clinical characteristics (disease vintage, treatment, primary diagnosis, number of comorbidities, BMI). P < 0.05 was considered statistically significant.

## Results

### *Sample Characteristics*

Sample characteristics are shown in Table I. The mean age was 46.0 ± 10.9 and the majority of patients were women (n = 446; 65.3%). Among 692 patients with complete MARDS scores, 12.7% were on clinical remission, 34.8% had mild symptoms, 44.4% had moderate severity, and 8.1% had severe depression. There were 188 patients with no or mild cognitive impairment (27.2%), 487 with moderate impairment (70.4%) and 17 with severe impairment (2.5%). We found a strong association between attention deficits and MADRS scores (no/mild impairment: 9.6 ± 6.9; moderate impairment: 23.4 ± 8.7; severe impairment:

**Table I.** Sample characteristics across classes of depression severity.

| | Depression severity | | | | | |
|---|---|---|---|---|---|---|
| **Characteristics** | **Whole sample N = 692** | **Remission N = 88** | **Mild N = 241** | **Moderate N = 307** | **Severe N = 56** | |
| Socio-demographic | N (%) or mean (STD) | | | | | p |
| **Age** | | | | | | 0.43 |
| < 40 | 186 (26.9) | 25 (28.4) | 69 (28.6) | 80 (26.1) | 12 (21.4) | |
| 40-50 | 175 (25.3) | 26 (29.6) | 66 (27.4) | 71 (23.1) | 12 (21.4) | |
| > 50 | 331 (47.8) | 37 (42.0) | 106 (44.0) | 156 (50.8) | 32 (57.2) | |
| Women | 440 (65.2) | 55 (64.7) | 142 (61.2) | 202 (66.7) | 41 (74.5) | 0.26 |
| Tertiary education | 118 (17.0) | 19 (21.6) | 47 (19.5) | 46 (15.0) | 6 (10.7) | 0.18 |
| Living with partner | 381 (55.9) | 52 (59.8) | 133 (56.1) | 167 (55.3) | 29 (52.7) | 0.83 |
| Children | 442 (63.9) | 58 (65.9) | 142 (58.9) | 203 (66.1) | 39 (69.6) | 0.24 |
| **Employment** | | | | | | 0.29 |
| Employed | 339 (49.0) | 52 (59.1) | 117 (48.6) | 141 (45.9) | 29 (51.8) | |
| Inactive | 177 (25.6) | 14 (15.9) | 62 (25.7) | 84 (27.4) | 17 (3.0) | |
| Retired | 61 (8.8) | 5 (5.7) | 20 (8.3) | 31 (10.1) | 5 (8.9) | |
| Unemployed | 115 (16.6) | 17 (19.3) | 42 (17.4) | 51 (16.6) | 5 (8.9) | |
| Physical activity (≥ 3 days/week) | 83 (12.0) | 23 (26.1) | 38 (15.8) | 22 (7.2) | 0 | < 0.01 |
| **Clinical** | | | | | | |
| Years since diagnosis | 6.3 (7.3) | 5.0 (5.6) | 6.3 (6.9) | 6.4 (7.5) | 7.1 (9.8) | 0.33 |
| Recurrent depression (≥ 3 episodes/10 years) | 302 (46.3) | 26 (29.9) | 90 (39.6) | 157 (54.9) | 29 (55.8) | < 0.01 |
| **Primary diagnosis** | | | | | | 0.01 |
| AD | 53 (7.7) | 11 (12.5) | 22 (9.1) | 18 (5.9) | 2 (3.6) | |
| DYS | 53 (7.7) | 7.0 (8.0) | 14 (5.8) | 28 (9.12) | 4 (7.14) | |
| RDE | 298 (43.0) | 33 (37.5) | 88 (36.5) | 149 (48.5) | 28 (50.0) | |
| DE | 122 (17.6) | 12 (13.6) | 46 (19.1) | 48 (15.6) | 16 (28.6) | |
| ADD | 154 (22.2) | 22 (25.0) | 65 (27.0) | 61 (19.9) | 6 (10.7) | |
| Other | 12 (1.7) | 3 (3.4) | 6 (2.5) | 3 (1.0) | 0 | |
| Other Axis I diagnoses | 34 (4.9) | 6 (6.8) | 21 (8.7) | 7 (2.3) | 0 | < 0.01 |
| **Body Mass Index** | | | | | | 0.13 |
| Underweight | 22 (3.2) | 0 | 12 (5.0) | 8 (2.6) | 2 (3.7) | |
| Normal weight | 366 (53.7) | 55 (63.2) | 131 (55.0) | 149 (49.2) | 31 (57.4) | |
| Overweight | 214 (31.4) | 23 (26.4) | 73 (30.7) | 105 (34.6) | 13 (24.1) | |
| Obesity | 80 (11.7) | 9 (10.3) | 22 (9.24) | 41 (13.5) | 8 (14.8) | |
| N. of comorbidities | 0.92 (1.20) | 0.77 (1.03) | 0.84 (1.18) | 0.98 (1.27) | 1.14(1.38) | 0.04 |

*(continues)*

*Table I (Follows)*

| | Depression severity | | | | | |
|---|---|---|---|---|---|---|
| **Comorbidities**: | | | | | | |
| None | 344 (49.7) | 45 (13.0) | 126 (36.6) | 148 (43.0) | 25 (7.27) | 0.66 |
| Serious injuries | 18 (2.60) | 3 (3.41) | 4 (1.66) | 8 (2.61) | 3 (5.36) | 0.43 |
| Surgery | 57 (8.24) | 2 (2.27) | 25 (10.4) | 24 (7.82) | 6 (10.7) | 0.10 |
| Osteo-articular | 97 (14.0) | 9 (10.2) | 30 (12.4) | 49 (16.0) | 9 (16.1) | 0.44 |
| Hypertension | 87 (12.6) | 6 (6.82) | 20 (8.30) | 53 (17.3) | 8 (14.3) | < 0.01 |
| CAD | 7 (1.01) | 0 | 5 (2.07) | 1 (0.33) | 1 (1.79) | 0.14 |
| Other CVD | 26 (3.76) | 3 (3.41) | 6 (2.49) | 12 (3.91) | 5 (8.93) | 0.15 |
| Diabetes | 28 (4.05) | 3 (3.41) | 5 (2.07) | 17 (5.54) | 3 (5.36) | 0.21 |
| Thyroid diseases | 54 (7.80) | 7 (7.95) | 13 (5.39) | 30 (9.77) | 4 (7.14) | 0.30 |
| Dyslipidemia | 44 (6.36) | 5 (5.68) | 13 (5.39) | 19 (6.19) | 7 (12.5) | 0.26 |
| Anemia | 14 (2.02) | 1 (1.14) | 5 (2.07) | 8 (2.61) | 0 | 0.56 |
| CKD | 3 (0.43) | 0 | 2 (0.83) | 1 (0.33) | 0 | 0.66 |
| Lung diseases | 18 (2.60) | 1 (1.14) | 6 (2.49) | 5 (1.63) | 6 (10.7) | < 0.01 |
| Gastrointestinal | 66 (9.53) | 10 (11.4) | 25 (10.4) | 23 (7.49) | 8 (14.3) | 0.21 |
| Other | 59 (8.53) | 9 (10.2) | 22 (9.13) | 26 (8.47) | 2 (3.57) | |
| **Therapy** | | | | | | 0.08 |
| Pharmacotherapy | 565 (81.6) | 72 (81.8) | 183 (75.9) | 262 (85.3) | 48 (85.7) | |
| Psychotherapy | 11 (1.59) | 2 (2.27) | 8 (3.32) | 1 (0.33) | 0 | |
| Drugs & psychotherapy | 101 (14.6) | 12 (13.6) | 43 (17.8) | 40 (13.0) | 6 (10.7) | |
| None | 15 (2.17) | 2 (2.27) | 7 (2.90) | 4 (1.30) | 2 (3.57) | |
| Association regimens (≥ 2 prescription drugs) | 464 (67.0) | 40 (45.5) | 142 (58.9) | 237 (77.2) | 45 (80.4) | < 0.01 |
| N. of drugs | 1.98 (1.01) | 1.59 (0.97) | 1.70 (0.87) | 2.24 (1.00) | 2.41 (1.20) | 0.02 |
| **Antidepressant therapy** | | | | | | |
| NASSA | 36 (5.20) | 3 (3.41) | 10 (4.15) | 20 (6.51) | 3 (5.36) | 0.53 |
| SSRI | 390 (56.4) | 44 (50.0) | 149 (61.8) | 169 (55.1) | 28 (50.0) | 0.14 |
| SARI | 21 (3.03) | 2 (2.27) | 4 (1.66) | 11 (3.58) | 4 (7.14) | 0.15 |
| SNRI | 145 (20.9) | 23 (26.1) | 42 (17.4) | 68 (22.1) | 12 (21.4) | 0.32 |
| TCA | 47 (6.79) | 5 (5.68) | 7 (2.90) | 29 (6.45) | 6 (10.7) | 0.01 |
| Other | 48 (6.94) | 2 (2.27) | 10 (4.15) | 27 (8.79) | 9 (16.1) | < 0.01 |
| **Other psychotropic drugs** | | | | | | |
| Anti-anxiety | 388 (56.1) | 35 (39.8) | 121 (50.2) | 195 (63.5) | 37 (66.1) | < 0.01 |
| Anti-epileptics | 97 (14.0) | 8 (9.09) | 26 (10.8) | 52 (16.9) | 11 (19.6) | 0.06 |
| Neuroleptics | 131 (18.9) | 15 (17.1) | 24 (9.96) | 78 (25.4) | 14 (25.0) | < 0.01 |

Antidepressant Therapy: NASSA: Noradrenergic and Specific Serotonin Antidepressants; SSRI: Selective serotonin reuptake inhibitors; SARI: Serotonin antagonist and reuptake inhibitors; SNRI: Serotonin-Norepinephrine Reuptake Inhibitors; TCA: Tricyclic antidepressants. Primary Psychiatric Diagnosis. AD: Adjustment Disorder (ICD10:F43.2); DYS: Dystimia (ICD10:F34.1); RDE: Recurrent Depressive Episode (ICD10:F33); DE: Depressive Episode (ICD10:F32); ADD: Mixed Anxiety and Depressive Disorder (ICD10:F41.2). Other Persistent Mood Disorder (OTHER; ICD10:F34.8. F34.9). P values represent confidence levels of $\chi^2$ for categorical variables, one-way ANOVA for continuous variables.

34 ± 6.7, p for trend < 0.01; r = 0.71, p < 0.01). RDE was the most frequent diagnosis (43%), followed by mixed anxiety and depressive disorder (22%) and single major depressive episode (17%). The average duration of depression was 6.28 ± 7.34 years and 58% of patients consulted more than one physician after symptoms onset before receiving a diagnosis of depressive disorder. More than 45% (n = 302) of subjects had more than 2 major depressive episodes in the previous 10 years. Combined pharmacological

treatment and psychotherapy were prescribed in a minority of cases (14%). About half of the sample had no comorbid condition (n = 344; 49.7%). Patients with severe depressive symptoms had a higher number of comorbidities (1.14 *vs* 0.77, p for linear trend = 0.04), received more complex treatment regimens (80.1% *vs* 45.5%, p < 0.01), had more depressive episodes (55.8% *vs* 29.9%, p for trend < 0.01), more likely were occupationally inactive (30.4% *vs* 15.9%, p for trend < 0.05), carried out less physical activity (0% *vs* 26.1%, p for trend < 0.01), and had lower education (graduates: 10.7% *vs* 21.6%, p for trend < 0.05) compared to patients in clinical remission (Table I). Patients with RDE and DE had more severe symptoms compared to patients with ADD, AD, DYS or other depressive disorders (Table I, p < 0.011).

### *Socio-Demographic and Clinical correlates of Illness Intrusiveness*

The pattern of association observed was partially different across subscales of illness intrusiveness (Table II). Global scores were associated with the frequency of physical exercise, the number of psychotropic drugs prescribed in the treatment regiment, the frequency of relapses in the past 10 years, the primary psychiatric diagnosis and was marginally associated with patients' employment status. The personal development scale was associated with physical exercise, the number of psychotropic drugs prescribed in the treatment regiment, the frequency of relapses in the past 10 years, the primary psychiatric diagnosis, patients' employment status, and was marginally associated with patients' marital status. The intimate relationship scale was associated with physical exercise, the number of psychotropic drugs prescribed in the treatment regimen and was marginally associated with the frequency of relapses in the past 10 years and the presence of children in the household. The instrumental domain subscale was associated with the number of comorbidities, the number of psychotropic drugs prescribed in the treatment regimen, the frequency of relapses and was marginally associated with patients' employment.

### *Depression Severity and Illness Intrusiveness*

The average IIRS scores in the whole sample and

**Table II.** Socio-Demographic and Clinical Correlates of Illness Intrusiveness.

| | IIRS | IIRS: Ins. | IIRS: Int. | IIRS: Dev. |
|---|---|---|---|---|
| **Demographics** | | β (p) | | |
| Age | -0.06 (0.51) | -0.01 (0.29) | -0.01 (0.32) | -0.00 (0.97) |
| Women | 1.89 (0.27) | 0.13 (0.35) | 0.02 (0.92) | 0.20 (0.16) |
| Living with partner | -2.75 (0.16) | -0.23 (0.14) | 0.14 (0.50) | -0.31 (0.06) |
| Children | 1.04 (0.63) | -0.01 (0.97) | -0.41 (0.07) | -0.04 (0.81) |
| Employed | -3.19 (0.05) | -0.24 (0.07) | -0.10 (0.55) | -0.30 (0.03) |
| **Clinical** | | | | |
| *Primary diagnosis* | | | | |
| AD | -0.41 (0.90) | 0.01 (0.96) | 0.12 (0.74) | -0.12 (0.67) |
| DYS | -0.89 (0.79) | -0.35 (0.19) | 0.20 (0.58) | 0.08 (0.77) |
| RDE | 0.15 (0.94) | -0.07 (0.68) | 0.05 (0.81) | 0.07 (0.71) |
| DE | 5.64 (0.03) | 0.18 (0.40) | 0.62 (0.03) | 0.58 (0.01) |
| ADD | ref | ref | ref | ref |
| Other depressive syndromes | 9.44 (0.21) | 0.44 (0.46) | 1.26 (0.11) | 0.78 (0.22) |
| Recurrent depression (≥ 3 episodes/10 years) | 4.77 (0.02) | 0.34 (0.04) | 0.41 (0.06) | 0.38 (0.03) |
| Physical Activity (≥ 3 days/week) | -5.86 (0.02) | -0.24 (0.22) | -0.52 (0.04) | -0.60 (0.004) |
| Number of psychotropic drugs | 4.06 (< 0.01) | 0.36 (< 0.01) | 0.23 (< 0.01) | 0.30 (< 0.01) |
| Number of comorbidities | 0.48 (0.50) | 0.16 (< 0.01) | -0.06 (0.41) | -0.03 (0.62) |

Coefficient estimates and p values are based on generalized linear models (normal distribution with identity link function). For continuous variables, association estimates represent the change in the IIRS score associated with a 1-point increase in the independent variable. For categorical variable, association estimates represent the difference in the IIRS score between patients with a characteristic compared to the reference category.

**Table III.** Illness intrusiveness scale and subscales mean scores in the whole sample and across levels of depression severity.

| | | Depression Severity | | | | | |
|---|---|---|---|---|---|---|---|
| | Whole N = 692 | Remission N = 88 | Mild N = 241 | Moderate N = 307 | Severe N = 56 | | |
| HRQOL score | Unadjusted Mean Scores | | | | | $\omega^2$ | p |
| IIRS | 49.0 | 30.4 | 44.9 | 54.8 | 64.6 | 0.24 | < 0.01 |
| IIRS: development | 3.7 | 2.3 | 3.4 | 4.1 | 5.0 | 0.21 | < 0.01 |
| IIRS: intimacy | 4.1 | 2.7 | 3.7 | 4.5 | 5.1 | 0.12 | < 0.01 |
| IIRS: Instrumental | 3.7 | 2.3 | 3.4 | 4.2 | 4.9 | 0.22 | < 0.01 |
| HRQOL score | Adjusted Mean Scores a | | | | | $\omega^2$ | p |
| IIRS | 48.6 | 33.8 | 47.5 | 55.6 | 64.7 | 0.16 | < 0.01 |
| IIRS: development | 3.67 | 2.50 | 3.54 | 4.18 | 4.97 | 0.14 | < 0.01 |
| IIRS: intimacy | 3.99 | 2.92 | 3.94 | 4.69 | 5.19 | 0.09 | < 0.01 |
| IIRS: Instrumental | 3.72 | 2.58 | 3.67 | 4.24 | 4.89 | 0.13 | < 0.01 |

Unadjusted and adjusted mean scores and p values are based on generalized linear models (normal distribution with identity link function); $\omega^2$ represents effect size for the F-test. Adjusted model included age, gender, tertiary education, presence of partner, number of children, employment status, recurrent episodes, physical activity, number of drugs, Body Mass Index, duration of disorder, number of comorbidities).

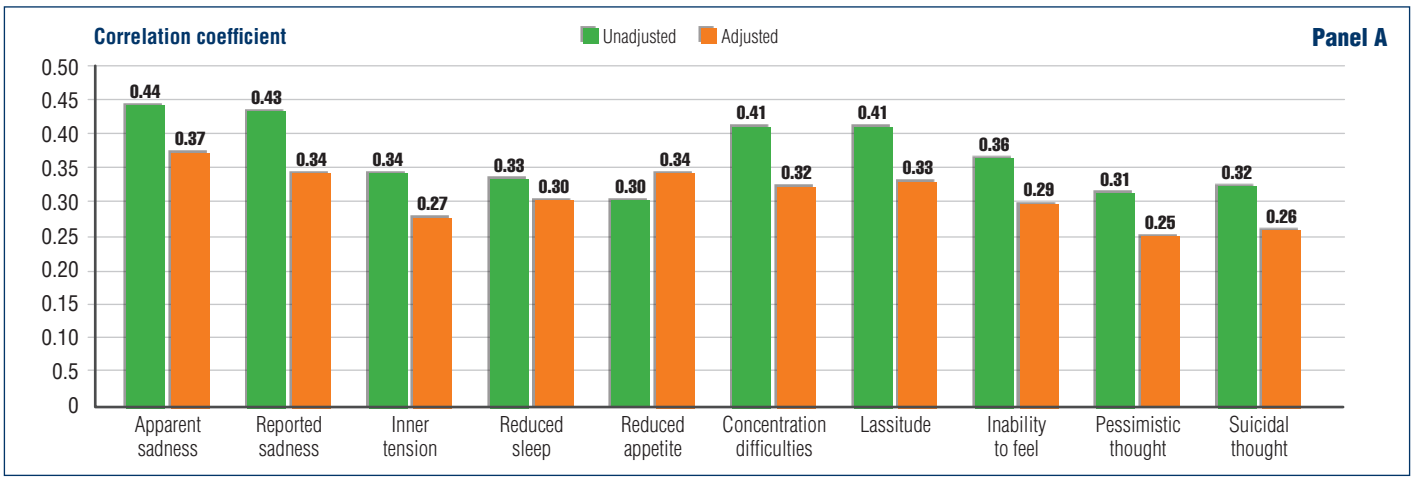
across MADRS classes are reported in Table III. We found a strong, graded association between depression severity and each HRQOL outcome. These associations were robust to adjustment for several confounders (Table III). The interaction between MADRS classes and diagnostic groups was not statistically significant and was removed from the model (not shown). Effect sizes in the full model ranged between $\omega^2 = 0.12$ (IIRS: intimacy subscale) and $\omega^2 = 0.24$ (IIRS: total score). To further explore the association between MADRS scores and IIRS, we evaluated the relationship between individual facets of depression and patients' perception of life-limitation (Figure 1).

## Discussion

The primary objective of our study was to characterize the relationship between symptoms severity and perceived Illness Intrusiveness in a large national sample of working age patients with major depressive disorders. The results outlined the disruption of symptoms severity on patients life domains pivotal to health-related quality of life such as intimate relationships, personal development, work and social participation. Depression in the IIRS literature has been primarily studied as a specific complication of other disabling diseases and is considered a key mediator of subsequent quality of life impairment [16 17]. Indeed, depressive mood is common in chronic and life-threatening disease, as a result of illness-induced disruptions to lifestyle, activities, and interests [18-20].
We advanced current knowledge concerning the relationship between depressed mood and quality of life by demonstrating a strong graded association between depression severity and life-style disruption in all dimensions tapped by the Illness Intrusiveness Rating Scale. We observed a large effect size of depression severity for each IIRS total scale, both in the unadjusted ($\omega^2 = 0.24$) and adjusted ($\omega^2 = 0.16$) models. Adjusted IIRS mean scores in the whole sample (48.6) was higher compared to those found among patients with other severe chronic diseases

FIGURE 1

(Panel A-D). Unadjusted and Partial Correlations between facets of depression and illness intrusiveness. Bars represent the zero order and partial Spearman's Correlations coefficients estimating the association facets of individual item scores of the MADRS scale and IIRS scores (Panel A: global IIRS scores; Panel B: Instrumental Domain scores; Panel C: Intimacy Domain scores; Panel D: Development Domain scores). Partial correlations have been adjusted for age, sex, education, marital status, having children, employment, primary psychiatric diagnosis, frequency of relapses in the past 10 years, frequency of physical exercise, BMI, number of comorbidities, disease vintage, number of psychotropic medications.


Correlation coefficient
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Apparent sadness
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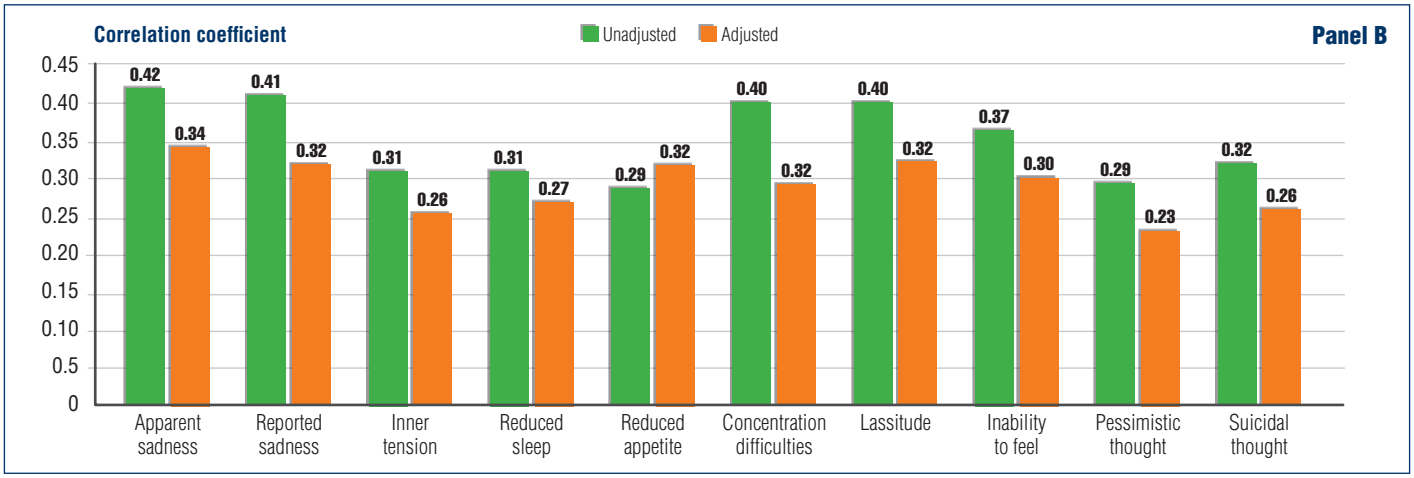
Reduced sleep
Reduced appetite
Concentration difficulties
Lassitude
Inability to feel
Pessimistic thought
Suicidal thought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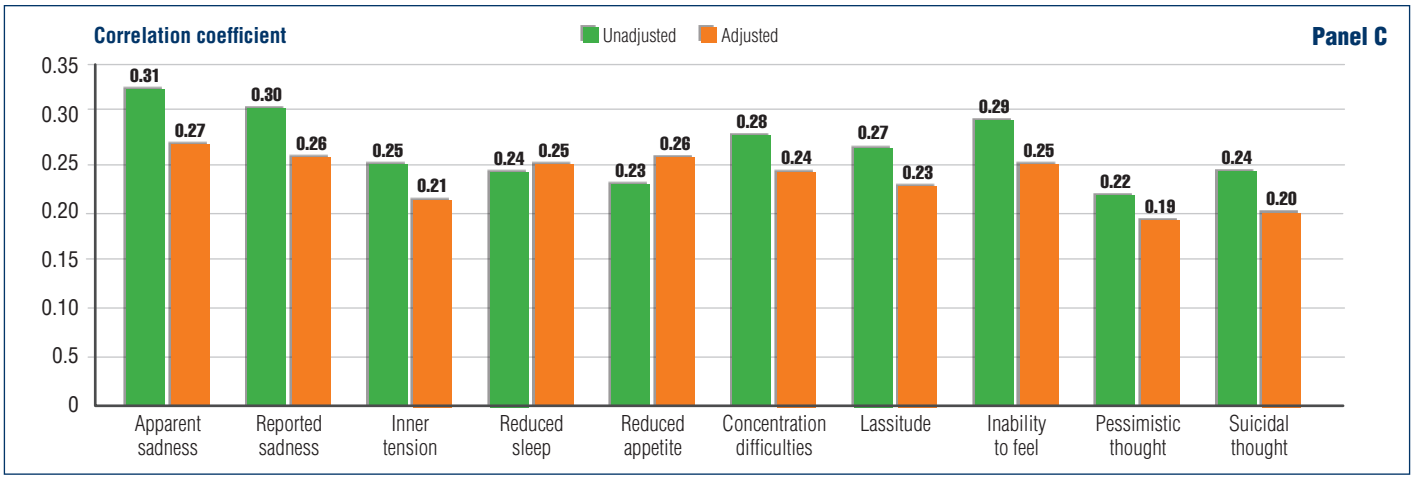
Inner tension
Reduced sleep
Reduced appetite
Concentration difficulties
Lassitude
Inability to feel
Pessimistic thought
Suicidal thought


Correlation coefficient
Unadjusted
Adjusted
Panel C
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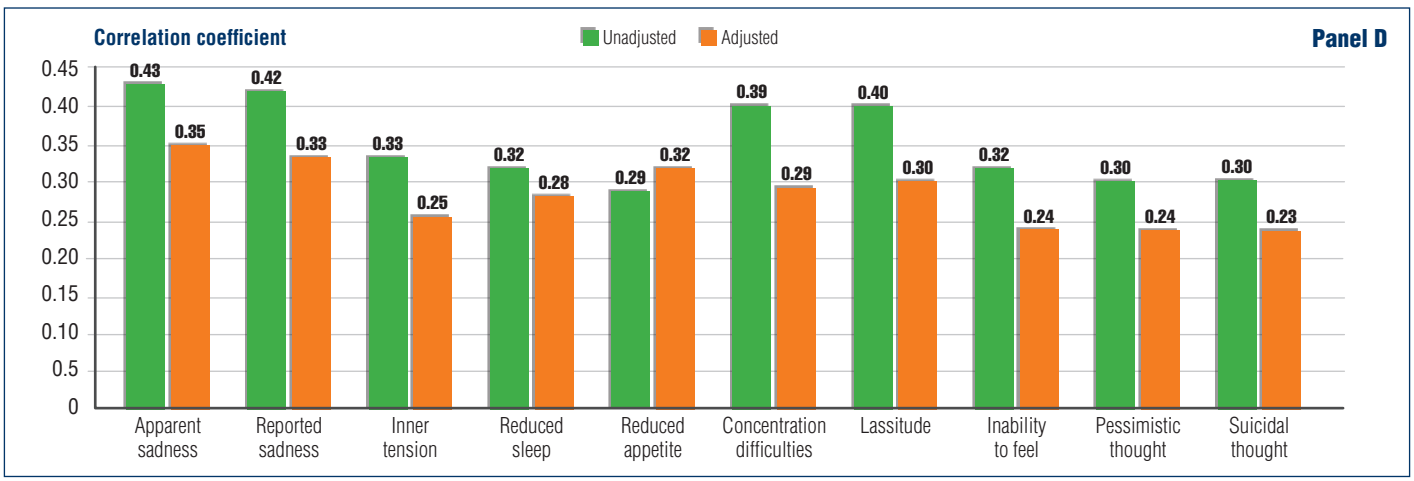
0.30
0.25
0.20
0.15
0.10
0.5
0
0.31 0.27
0.30 0.26
0.25 0.21
0.24 0.25
0.23 0.26
0.28 0.24
0.27 0.23
0.29 0.25
0.22 0.19
0.24 0.20
Apparent sadness
Reported sadness
Inner tension
Reduced sleep
Reduced appetite
Concentration difficulties
Lassitude
Inability to feel
Pessimistic thought
Suicidal thought


Correlation coefficient
Unadjusted
Adjusted
Panel D
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0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.5
0
0.43 0.35
0.42 0.33
0.33 0.25
0.32 0.28
0.29 0.32
0.39 0.29
0.40 0.30
0.32 0.24
0.30 0.24
0.30 0.23
Apparent sadness
Reported sadness
Inner tension
Reduced sleep
Reduced appetite
Concentration difficulties
Lassitude
Inability to feel
Pessimistic thought
Suicidal thought

such as bipolar disorder (43.8), multiple sclerosis (42.6), epilepsy (38.8), rheumatoid arthritis (37.9) end stage renal disease (38.8) [21 22]. To our knowledge, patients with severe symptoms showed the highest IIRS score compared to any other chronic condition investigated so far [3 22]. Further, we found that MDD patients on clinical remission still reported a mild level of distress on all IIRS scales. These subjects (mean IIRS: 33.8) scored similarly to patients with Insomnia (mean IIRS: 34.9) and Biliary cirrhosis (mean IIRS: 32.2) [22]. Our findings are consistent with previous research suggesting that a residual impairment of patients' functioning persists even after complete clinical recovery [23-26].

Interestingly, we found no evidence that any MADRS attribute drives the association between depression severity and IIRS. Our results suggest that all facets of depression are equally contributing to overall lifestyle disruption caused by the disease. It may be surprising that reporting of suicidal thoughts does not seem to provide a major contribution to illness-related interference on daily life. However only few patients in our sample reported such symptom and its overall effect might then be underestimated.

The secondary aim of our study was evaluating socio-demographic and clinical correlates of IIRS. Our data showed that patients reporting more than 2 depressive episodes in the last 10 year had poorer IIRS scores. Treating depression to full symptoms resolution and maintenance of remission is a key endpoint of therapy since the disability related to chronic depression and recurrent pattern of disease is substantial. However, this has been an elusive target of therapy for many patients so far. Adherence issues, inappropriate treatment and late referral to specialized healthcare are often reported as key barriers to successful induction and maintenance of remission among MDD patients [27].

An important finding of our study was that regimen complexity (i.e. number of prescription psychotropic drugs) was strongly associated with illness intrusiveness independent of depression severity. Our results are consistent with a large body of evidence showing that treatment factors are key drivers of HRQOL and life-style interference [22] which in turn might hamper medication adherence [28]. The management of complex regimens require greater organizational accommodations in patients' daily life and need significant self-care abilities [28]; additionally psychotropic drugs are burdened with significant side-effects, and their use may be associated with self-stigma issues [28], all factors leading to reduced adherence and persistence on treatment for the full course of therapy.

Finally, we did not find any significant interaction between depression severity and IIRS scores across different depressive unipolar diagnosis: our sample size achieved 80% power of detecting a small effect size interaction ($f \geq 0.12$), thus making additional stratified analysis not justified. However, the aim of our study was to evaluate the association between depression severity and Illness intrusiveness independent of the underlying disease, since scores of depression severity scales are often the primary endpoint in RCTs.

This study has several strengths worth mentioning. First, assessment severity relied on clinician-rated scales, which help overcome common method bias. Second, the large sample size allowed us to adjust for several potential confounders. Third, heterogeneity in symptoms severity among our sample let us estimate the relative burden of patients on remission and compare a wide range of symptoms severity.

However, our study has some weaknesses to be taken into account. The cross-sectional design does not allow to draw causal inferences; moreover, the diagnosis of depressive disorders was based on psychiatrists' clinical evaluation carried out during a regular outpatient visit and standardized methods were not uniformly adopted (e.g. Structured Clinical Interview for DSM Disorders; SCID). Consequently we cannot rule out the possibility of classification bias.

Additionally, despite IIRS scale has been extensively used in several chronic conditions worldwide, it has not received formal validation in the Italian psychiatric population. The Italian version of the IIRS has been used in 3 previous published studies with patients suffering from chronic and autoimmune diseases [29-31]: IIRS scale was translated by professional translators, and back-translation was carried-out to corroborate the validity of the process. Although cross-cultural validation studies have generally demonstrated excellent reliability and criterion validity of the total IIRS score, the trans-national stability of the Intimacy subscale has been questioned in French and Asian studies [14]. Hence, results pertaining this subscale should be interpreted cautiously.

Finally, we cannot discount the possibility that selection bias occurred. In order to capture potentially important regional variation, we selected centers located in each Italian region, operating both in university and community hospitals, with both large and relatively small catchment area: however, we could not evaluate the reasons for two cases of non-participation nor we could estimate the attrition rate for the study. Therefore, our results may not be fully generiz-

able to the Italian population of patients with major depressive disorders seeking care in outpatient mental health services.

## Conclusion

We demonstrated wide differences in life-style disruption across depression severity classes, suggesting that the potential quality of life improvement achievable with appropriate therapy is substantial. However we showed that residual impairment due to illness intrusiveness might persist among patients on clinical remission. Additionally we showed that treatment related issues such as the excessive regimen complexity often required to treat the multifaceted manifestations of the disease, might be associated with substantial life-interference irrespective of symptoms severity. Since increased treatment-related illness intrusiveness might lead to poor adherence, the symptom-reducing potential of any additional medication should be carefully considered by clinicians vis-à-vis the risk for increased therapy burden and its impact on quality of life.

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The conduct of this study has been funded by DoxaPharma s.r.l. The investigators had full access to the data and vouch for data integrity. FA and NL contributed equally to this work. NL contributed to study concept development, study design, data interpretation, manuscript drafting, performed data analysis and approved the final version of the manuscript. FA contributed to data interpretation, drafted the first version of the manuscript, and approved the final version of the manuscript. BA, VM, MC contributed to study concept development, study design, data interpretation, supervised the scientific conduct of the study and approved the final version of the manuscript. Members of the ILDE Study Group design, data interpretation and approved the final version of the manuscript.

## Take home messages for psychiatric care

- Depression is a primary determinant of years lost due to disability and exerts a detrimental impact on functional impairment and quality of life. However. the relationship between the severity of depressive symptoms and illness intrusiveness is still scarcely characterized
- We demonstrated a strong graded association between depression severity and life-style disruption in all dimensions tapped by the Illness Intrusiveness Rating Scale (IIRS)
- All facets of depression are equally contributing to overall lifestyle disruption caused by the disease
- Patients with severe symptoms showed the highest IIRS score compared to any other chronic condition investigated so far. A residual impairment persists even after partial or complete clinical recovery
- The potential quality of life improvement achievable with appropriate therapy is substantial
- Polypharmacy strongly contributes to life domains' disruption. thus suggesting further efforts to reduce regimen complexity

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## Appendix I

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