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*(No title)*
Bianca Santini
Porto Alegre, Brazil, 2015
Graphite, oil pastel, dust, sand, and watercolor on canson paper, 40x59cm
Photograph: Babilônica/Letícia Lau
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## Sobre a capa

# Bianca Santini

O trabalho artístico de Bianca Santini é um reflexo da sua percepção do cotidiano, e por muito tempo o foco foi a paisagem e a natureza, observando como ela se renova ao passar dos dias, suas linhas, texturas e formas. A partir de caminhadas pela cidade, percorrendo ruas, praças e parques com foco no olhar sobre a paisagem, onde galhos, raízes, troncos de árvores vislumbram esse desenho, Bianca compõe um acervo com os elementos registrados ou coletados que funcionam como um laboratório de pesquisa a céu aberto para desenvolver pinturas, desenhos, objetos e instalações.

Foto: Lisa Roos

> *"Cada pequeno deslocamento ao redor de uma árvore produz imagens diferentes. E isso me interessa. O ponto de partida é sempre o mesmo. Os suportes para minha obra mudam na busca de encontrar diferentes linguagens para me comunicar."*

A poética do seu trabalho traduz elementos do real (galhos secos, troncos, cipós) para o imaginário, do lado externo (da paisagem) para o lado interno (ateliê e salas de exposições), provocando uma ativação do espaço e um desenho da paisagem mediado pelo corpo.

A artista registra, através da fotografia e da memória, as imagens de paisagens que percorre e caminha, observando galhos, texturas, troncos e linhas. Estes servem de inspiração para suas pinturas e desenhos. Com o tempo sentiu a necessidade de experimentar outros materiais e suportes, desenvolvendo as Paisagens Portáteis, simulação de galhos secos feitos com folhas de revistas, tinta spray e algodão ou tecido acondicionados em caixas de acrílico. Em seguida, sua vontade de transpor o desenho da paisagem para dentro do ateliê e para o campo da arte incentiva uma produção maior com outros materiais e, assim, surgem as instalações de árvores. As primeiras árvores, da série Transposição da Paisagem, foram criadas com cordas de sisal e galhos secos suspensos pelo teto, e as últimas, da série Além da Paisagem, foram construídas com folhas de catálogos e revistas de moda e roupas usadas sobre um suporte de tela de arame.

Bianca Santini se dedica à sua produção artística desde 1985, estudando, pintando e desenhando. No entanto, é a partir de 2014 que sua produção ganha maior visibilidade no circuito de arte gaúcha. Sua mais recente exposição individual, Risco & Ar - Uma exposição de Bianca Santini, foi realizada na principal instituição de arte do estado, o Museu de Arte do Rio Grande do Sul Ado Malagoli (MARGS), com curadoria de Gabriela Motta. Nessa mostra, encerrada em janeiro deste ano, a artista revela uma nova proposição – seu interesse na paisagem migra para outro foco, surge uma vontade de investigar, do ponto de vista material e conceitual, o universo do consumo e da moda.

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Bianca Santini é natural de Porto Alegre, onde vive e trabalha. Possui seu ateliê na zona sul da cidade. Formada em direito, decide não seguir a carreira para auxiliar seu pai no comando da Casa do Desenho (antiga loja de materiais para arte, design e arquitetura em Porto Alegre). A proximidade com os materiais artísticos aguça seu interesse em pintura e desenho, já despertado anteriormente no Centro de Desenvolvimento da Expressão (CDE), aos 6 anos de idade. Mais tarde busca aprimoramento com cursos ministrados por importantes artistas da cena gaúcha, como Malu Soeiro, Maria Aparecida Peixoto, Paulo Porcela, Iara Burle, Dayse Viola, Ana Petini, Elizethe Borghetti, Clara Pechansky, Julio Ghiorzi, entre outros. Hoje estuda História da Arte com Maria Helena Bernardes e Jailton Moreira.

Em seu currículo coleciona 7 exposições individuais e 21 coletivas nos principais centros culturais do estado e galerias de Porto Alegre, Caxias do Sul, Florianópolis, Rio de Janeiro e Montevidéu. Participou de três salões de arte: 19º Prêmio de Incentivo à Produção Chico Lisboa, no MARGS; Salão de Arte da América Latina, no Museu de Arte de Santa Maria; e 20º Salão de Arte da Câmara Municipal de Porto Alegre. Possui obras no acervo do Museu de Arte Contemporânea do Rio Grande do Sul (MACRS), no MARGS, ambos em Porto Alegre, RS, e no Centro Cultural Dr. Henrique Ordovás Filho, em Caxias do Sul, RS.

Bianca Santini - www.biancasantini.com.br
Babilônica Arte e Cultura - www.babilonica.com

# **“Thank you”** to all 2017 reviewers

We are grateful to our colleagues listed below for their generous and anonymous participation in the peer-review process of **Revista Brasileira de Psiquiatria** in 2017. These colleagues have donated their time and knowledge to enhance the quality of our publication. Thank you for your outstanding job.

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# Instructions for Authors

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## ORIGINAL ARTICLES

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## ORIGINAL ARTICLE

# Mood disorder, anxiety, and suicide risk among subjects with alcohol abuse and/or dependence: a population-based study

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**Objective:** To evaluate the prevalence of alcohol abuse and/or dependence in a population-based sample of young adults and assess the prevalence of comorbid mood disorders, anxiety, and suicide risk in this population.
**Methods:** This cross-sectional, population-based study enrolled 1,953 young adults aged 18-35 years. The CAGE questionnaire was used to screen for alcohol abuse and/or dependence, with CAGE scores $\geqslant 2$ considered positive. Psychiatric disorders were investigated through the structured Mini International Neuropsychiatric Interview (MINI).
**Results:** Alcohol abuse and/or dependence was identified in 187 (9.60%) individuals (5.10% among women and 15.20% among men). Alcohol abuse and/or dependence were more prevalent among men than women, as well as among those who used tobacco, illicit drugs or presented with anxiety disorder, mood disorder, and suicide risk.
**Conclusion:** These findings suggest that alcohol abuse and/or dependence are consistently associated with a higher prevalence of psychiatric comorbidities, could be considered important predictors of other psychiatric disorders, and deserve greater public heath attention, pointing to the need for alcohol abuse prevention programs.

**Keywords:** Alcohol abuse and/or dependence; anxiety; mood disorder; depression; suicide risk

## Introduction

Alcohol consumption is highly prevalent worldwide and has numerous negative consequences for health and quality of life, especially in the young population.[1] Alcohol use disorders (AUDs) are among the most frequently diagnosed disorders, with a 12-month prevalence rate of 8.5%.[2] In the United States alone, according to the 2013 National Survey on Drug Use and Health, 37.9% of young adults reported binge drinking (four or more drinks for women and five or more drinks for men on an occasion) at least once in the past 30 days.[3] Moreover, studies have shown a higher prevalence of cigarette smoking or drug abuse among subjects who engage in heavy or frequent binge drinking.[3-5]

AUDs are highly comorbid with mood and anxiety disorders in adults and are associated with substantial societal and personal costs. In a study conducted by Grant et al., among adults seeking treatment for an AUD, 40.69% and 33.3% were diagnosed with at least one current comorbid mood disorder and anxiety disorder, respectively.[6] The diagnosis of current mood or anxiety disorders among individuals with AUD is challenging, because many symptoms of intoxication, for example, resemble those of mood and anxiety disorders.[7]

In addition to mood disorders and anxiety, other serious problems that can develop in people with AUDs include violent behavior and suicide attempts.[8] Alcoholics are 60 to 120 times more likely to attempt suicide compared to the general population.[9] Furthermore, studies demonstrate that 85 out of every 100 individuals who complete suicide had comorbid depression and/or alcoholism.[10] Individuals with AUDs should be evaluated for the risk of suicide whenever they present with depressive symptoms,[11]

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since proper treatment can achieve remission of depressive symptoms, reduce the odds of relapse, and mitigate suicide risk.

Within this context, the aim of this study is to evaluate the prevalence of alcohol abuse and/or dependence in a population-based sample of young adults and ascertain the prevalence of co-occurring mood disorders, anxiety, and suicide risk in the same population.

## Methods

This is a cross-sectional population-based study that identified young adults between 18 and 35 years of age. The sample consisted of 1,953 participants living in the city of Pelotas, state of Rio Grande do Sul, Brazil. Sample selection was performed by clusters, from June 2011 to October 2012, considering a population of 97,000 in the age range of interest in the 448 sectors of the city according to the latest census. To ensure the necessary sample size, 86 census-based sectors were systematically drawn.

Individuals were included in the sample after receiving information about the objectives of the study and providing written informed consent for participation. Those who were unable to understand and/or respond to the instruments, due to physical or cognitive reasons, were excluded from the study. This study was approved by the Universidade Católica de Pelotas (UCPel) ethics committee (protocol no. 15/2010).

Sociodemographic information was collected through a questionnaire. Economic status was assessed with the National Wealth Score, which considers ownership of material goods and educational attainment of the head of the household.[12] For anthropometric assessment, height was measured using a stadiometer, and weight, with a Tanita® BC-554 bioimpedance body composition monitor. The body mass index (BMI) was calculated as weight (in kg) divided by height (in m) squared, as recommended by WHO. Participants were stratified into two groups, normal-weight or obese/overweight, considering a BMI cutoff of 25. The International Physical Activity Questionnaire (IPAQ),[13] version 8.0, was used to evaluate engagement in leisure-time physical activities. Participants who reported over 150 minutes of weekly physical activity were considered active.

To evaluate alcohol abuse and/or dependence, the participants completed the CAGE questionnaire, which asks about the four consequences of drinking and is a validated screening test for alcohol abuse and dependence.[14] Briefly, patients score 1 point for each "yes" on the CAGE questionnaire and 0 points if all questions are answered "no." A score of 2 or higher (CAGE $\geqslant$ 2) is usually considered to be a positive screen for moderate-to-severe alcohol abuse and/or dependence.[14] The participants also answered about use of tobacco and illicit substances (marijuana, cocaine, and crack).

To screen for psychiatric disorders, trained psychologists administered the Mini International Neuropsychiatric Interview 5.0 (MINI), according to DSM-IV criteria.[15,16] All individuals with current depression and bipolar disorder were included in the mood disorder group. All anxiety disorders covered by the MINI were included: social phobia, posttraumatic stress disorder, obsessive-compulsive disorder, panic disorders, and generalized anxiety disorder. The suicidality section inquires about several components of suicide risk with the following questions: "Over the last month: 1) Have you wished you were dead?" (Score: 1 point); 2) "Have you wanted to harm yourself?" (2 points); 3) "Have you thought of committing suicide?" (6 points); 4) "Have you planned how to commit suicide?" (10 points); 5) "Have you attempted suicide?" (10 points), and 6) "Have you ever attempted suicide?" (4 points). Risk of suicide was classified as low (score 1-5), moderate (score 6-9), and high (10 or higher). For analysis, scores were dichotomized as no suicide risk (low or absent risk) or suicide risk (moderate or high risk), as recommended by the MINI authors.[15] Respondents were questioned about the current presence of chronic diseases, which included systemic arterial hypertension, diabetes mellitus, heart disease, lung disease, cancer, renal disease, and thyroid dysfunction.

In this study, the following independent variables were considered: sex, ethnicity, age, marital status, employment, income, education level, obesity, and physical activity; suicide risk, tobacco use, illicit drug use, anxiety disorder, mood disorder, and chronic disease were included as comorbidities. The outcome was alcohol abuse and/or dependence.

Statistical analyses were performed in SPSS version 22.0 and Stata version 13.0. Initially, data were described as absolute and relative frequencies. The *t* and chi-square tests were used for comparisons as appropriate. Poisson regression was used for multivariate analysis. Confounders were defined as variables associated with alcohol abuse and/or dependence at a significance level of 20% or less. Association was considered significant at 5%.

## Results

The sample comprised 1,953 individuals with a mean (SD) age of 25.78 (5.21) years. Table 1 describes the sample according to sociodemographic characteristics, life habits, and morbidity. The majority of subjects were female (54.9%) and white (75.9%). In terms of habits, 21.7% reported tobacco use and only 26.5% were classified as physically active. Regarding comorbidities, 7.5% reported the use of other illicit drugs, 10.6% had a chronic disease, 27% had anxiety disorder, 4.7% had mood disorder and 13% reported suicide risk.

Alcohol abuse and/or dependence was identified in 187 (9.60%) individuals overall (5.10% of women and 15.20% of men) (Table 2). In Table 2 the results of the crude analysis are presented, as well as the adjusted results for alcohol abuse and/or dependence and confounders variables ($p < 0.020$) in this study. In the crude analysis, the factors that were statistically significant for alcohol abuse and/or dependence were: sex ($p < 0.001$), ethnicity ($p = 0.035$), education level ($p = 0.015$), tobacco use ($p < 0.001$), illicit drugs use ($p < 0.001$), anxiety disorder ($p < 0.001$), mood disorder ($p < 0.001$) and suicide risk ($p < 0.001$).

Table 2 also shows the results of analysis adjusted for alcohol abuse and/or dependence. Alcohol abuse and/or

**Table 1** Sociodemographic and clinical characteristics of the sample

| Variables | Sample distribution |
|---|---|
| Sex, female | 1,073 (54.90) |
| Age, mean (SD) | 25.78 (5.21) |
| Ethnicity (self-reported) | |
| White | 1,483 (75.90) |
| Income* | |
| Low | 648 (33.30) |
| Middle | 655 (33.70) |
| High | 641 (33.00) |
| Education level | |
| Years of schooling, mean (SD) | 11.45 (3.46) |
| Marital status | |
| Single | 1,186 (60.80) |
| Married/cohabiting | 720 (36.90) |
| Separated/divorced | 46 (2.40) |
| Currently working | 1,158 (59.30) |
| Physically active | 518 (26.50) |
| Alcohol abuse/dependence (outcome variable) | 187 (9.60) |
| Obesity | 860 (44.00) |
| Current comorbidities | |
| Tobacco use | 421 (21.70) |
| Illicit drug use | 146 (7.50) |
| Chronic disease, any | 207 (10.60) |
| Anxiety disorder | 527 (27.00) |
| Mood disorder | 349 (17.90) |
| Suicide risk | 253 (13.00) |
| Total | 1,953 (100.00) |

Data presented as n (%), unless otherwise specified.
SD = standard deviation.
* Income was classified in sample terciles, according to the National Wealth Score.[12]

dependence remained more prevalent among men than women (prevalence ratio [PR] 2.97; 95%CI 2.17-4.06; $p < 0.001$), as well as among those who used tobacco (PR 1.76, 95%CI 1.31-2.37; $p < 0.001$) and illicit drugs (PR 1.72, 95%CI 1.22-2.43; $p = 0.002$). In terms of comorbidities, alcohol abuse and/or dependence were also more prevalent among those with anxiety disorder (PR 1.66, 95%CI 1.25-2.20; $p < 0.001$), mood disorder (PR 2.13, 95%CI 1.46-3.11; $p < 0.001$), and suicide risk (PR 1.52, 95%CI 1.08-2.16; $p = 0.016$).

## Discussion

The present study evaluated the prevalence of alcohol abuse and/or dependence and associated factors in young adults. We found that 9.6% of individuals in our sample had alcohol abuse and/or dependence, which is consistent with previous studies.[6,17] Moreover, in our study, alcohol abuse and/or dependence were associated with male gender, tobacco use, and illicit drug use, and was often comorbid with anxiety disorders, mood disorder, and risk of suicide.

Several studies have discussed the relationship between AUD and gender, in which males are more likely than females to engage in binge drinking, and therefore, to have AUDs.[18,19] A study performed in 2013 involving 6,478 subjects found that alcohol abuse and/or dependence were more prevalent among males (22.0%) than females (9.8%).[19] In our study, AUDs were also more prevalent among males: the prevalence of alcohol abuse and/or dependence among men was three times higher than in women.

Alcohol consumption is socially acceptable and, in most cases, is the gateway to consumption of and addiction to other drugs (tobacco, marijuana, cocaine, etc.) In our sample, the prevalence of alcohol abuse and/or dependence among illicit drug users and tobacco users was higher than among those with no illicit drug or tobacco use. Our results are consistent with previous studies that have found higher prevalence of smoking and illicit drug use among individuals who consume too much alcohol.[20,21]

Alcohol abuse can have negative effects on mental health, in that it is frequently comorbid with mood disorders; in fact, this comorbidity can be a cyclic process.[6,21-23] According to Watts, most individuals with mood disorders abuse alcohol in search of pleasure and disinhibition or to reduce emotional, behavioral, and cognitive symptoms of depression.[24] However, the state of intoxication induced by alcohol abuse can increase impulsivity and promote thoughts and feelings of hopelessness and sadness, thus worsening mood disorder symptoms.[24] In a recent review, Pompili et al. found that mood disorders are frequently precursors of alcohol abuse, but alcoholism may also trigger or exacerbate mood disorders.[10] In our study, mood disorders were associated with alcohol abuse and/or dependence. However, we could not infer a causal relationship between these disorders. Likewise, we found a high prevalence of anxiety among individuals with alcohol abuse and/or dependence. It is important to note that having a comorbid diagnosis of anxiety or elevated sensitivity of anxiety has been associated with increased alcohol use severity, decreased likelihood to seek treatment, and higher rates of AUD treatment dropout.[25-27]

Furthermore, alcohol abuse can increase the risk of suicide.[8] A meta-analysis conducted recently by Darvishi et al. found evidence that AUD significantly increases the risk of suicidal ideation, suicide attempt, and completed suicide. The authors report that suicidal ideation and suicide attempt are two and three times more frequent in alcohol abusers than in the general population. Thus, AUD was considered an important predictor of suicide.[8] In our study, we also observed that the suicide risk was twofold among individuals with alcohol abuse and/or dependence (PR of alcohol abuse and/or dependence: 2.12 among those with suicide risk versus those with no suicide risk).

Some limitations must be acknowledged. First, we did not evaluate the frequency or quantity of intake in current or former alcohol abusers. Second, due to the study design, causality cannot be inferred. On the other hand, strengths of our study include the population-based design, which provides sample representativeness.

In conclusion, our study suggests that alcohol abuse and/or dependence are consistently associated with a higher prevalence of mood disorders, anxiety, and suicide risk. The comorbidity between alcohol abuse and psychiatric disorders warrants greater attention in public health and points to an unmet need for alcohol abuse prevention programs.

**Table 2** Factors associated with alcohol abuse among young adults, Pelotas, Rio Grande do Sul, Brazil, 2011-2012

| Variables | Alcohol abuse/dependence (%) | Crude PR (95%CI) | Adjusted PR (95%CI) |
|---|---|---|---|
| Sex | | p < 0.001 | p < 0.001 |
| Female | 54 (5.10) | - | - |
| Male | 133 (15.20) | 3.00 (2.21-4.07) | 2.97 (2.17-4.06) |
| Age, years | | p = 0.957 | |
| 18-23 | 66 (8.70) | 1.02 (0.71-1.46) | |
| 24-29 | 72 (11.60) | 1.36 (0.96-1.92) | |
| 30-35 | 48 (8.50) | - | - |
| Ethnicity (self-reported) | | p = 0.035 | p = 0.183 |
| White | 130 (8.80) | - | - |
| Nonwhite | 57 (12.30) | 1.39 (1.03-1.86) | 1.21 (0.91-1.61) |
| Income* | | p = 0.800 | |
| Low | 64 (10.00) | 1.02 (0.73-1.42) | |
| Middle | 58 (9.00) | 0.91 (0.65-1.29) | |
| High | 63 (9.80) | - | |
| Education level | | p = 0.015 | p = 0.899 |
| Primary school diploma and/or incomplete secondary school | 115 (8.50) | - | - |
| Secondary school or college diploma | 72 (12.20) | 1.42 (1.08-1.88) | 1.01 (0.76-1.35) |
| Marital status | | p = 0.090 | p = 0.239 |
| Single/divorced | 128 (10.50) | 1.30 (0.95-1.77) | 1.19 (0.88-1.61) |
| Married/cohabiting | 59 (8.30) | - | - |
| Currently working | | p = 0.159 | p = 0.438 |
| No | 66 (8.30) | - | - |
| Yes | 121 (10.50) | 1.23 (0.92-1.64) | 1.11 (0.84-1.46) |
| Current tobacco use | | p < 0.001 | p < 0.001 |
| No | 116 (7.60) | - | - |
| Yes | 71 (38.00) | 2.20 (1.67-2.90) | 1.76 (1.31-2.37) |
| Current illicit drug use | | p < 0.001 | p = 0.002 |
| No | 150 (8.40) | - | - |
| Yes | 37 (19.80) | 3.03 (2.20-4.16) | 1.72 (1.22-2.43) |
| Current physical activity | | p = 0.074 | p = 0.399 |
| No | 126 (8.90) | - | - |
| Yes | 60 (11.60) | 1.30 (0.97-1.73) | 1.14 (0.83-1.55) |
| Obesity | | p = 0.719 | |
| No | 90 (9.80) | - | |
| Yes | 88 (10.30) | 0.95 (0.71-1.25) | |
| Current chronic disease | | p = 0.096 | p = 0.283 |
| No | 174 (10.00) | 1.58 (0.96-2.74) | 1.34 (0.78-2.33) |
| Yes | 13 (6.30) | - | - |
| Current anxiety disorder | | p < 0.001 | p < 0.001 |
| No | 113 (8.00) | - | - |
| Yes | 74 (14.20) | 1.78 (1.35-2.34) | 1.66 (1.25-2.20) |
| Current mood disorder | | p < 0.001 | p < 0.001 |
| No | 130 (8.10) | - | - |
| Yes | 57 (25.80) | 2.91 (1.99-4.27) | 2.13 (1.46-3.11) |
| Current suicide risk | | p < 0.001 | p = 0.016 |
| No | 142 (8.40) | - | - |
| Yes | 45 (17.90) | 2.12 (1.55-2.88) | 1.52 (1.08-2.16) |
| Total | 187 (9.60) | - | - |

95%CI = 95% confidence interval; PR = prevalence ratio.
* Income was classified in sample terciles, according to the National Wealth Score.[12]

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## Disclosure

The authors report no conflicts of interest.

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## ORIGINAL ARTICLE

# Bipolar disorders: is there an influence of seasonality or photoperiod?

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**Objective:** To increase understanding of the influence of photoperiod variation in patients with bipolar disorders.
**Methods:** We followed a sample of Italian bipolar patients over a period of 24 months, focusing on inpatients. All patients admitted to the Psychiatric Inpatient Unit of San Luigi Gonzaga Hospital in Orbassano (Turin, Italy) between September 1, 2013 and August 31, 2015 were recruited. Socio-demographic and clinical data were collected.
**Results:** Seven hundred and thirty patients were included. The admission rate for bipolar patients was significantly higher during May, June and July, when there was maximum sunlight exposure, although no seasonal pattern was found. Patients with (hypo)manic episodes were admitted more frequently during the spring and during longer photoperiods than those with major depressive episodes.
**Conclusions:** Photoperiod is a key element in bipolar disorder, not only as an environmental factor but also as an important clinical parameter that should be considered during treatment.

**Keywords:** Bipolar disorder; seasonality; photoperiod; sunlight

## Introduction

It is well known that climatic variations affect human behavior, and over the last decade a number of researchers have thoroughly studied the influence of environmental factors on the onset and course of major psychiatric disorders, as well as on their treatment and prognosis.[1]

The main focus of these studies has been circadian rhythm, since a strong correlation has been observed between seasonal variation and impaired adaptation. Circadian rhythms are, above all, variations in physiological and behavioral processes, temperature, hormone secretion, food intake, sleep, and mood[2,3] and are closely related to chronotype preference. Chronotype, or morningness-eveningness, is an individual's preferred period of activity,[4] reflecting a circadian or ultradian propensity for alertness or somnolence. Three different chronotypes have been identified: morning, evening and neither (indifferent).[5] These rhythms are generated by endogenous processes and are regulated by external stimuli, such as daylight, in a 24-hour interval.

Numerous studies agree that bipolar patients display biological clock abnormalities, which lead to circadian rhythm alterations, impaired adaptation to environmental stimuli, and an unstable and hypersensitive mood.[1,6,7] These features not only present serious clinical implications, such as an higher suicide rates and lower response to treatment, but also imply the presence of a seasonal pattern.[8]

Bipolar disorder has long been suspected to involve sensitivity to the effects of seasons and climate, especially luminosity. Seasonality and sunlight exposure have been demonstrated to play a role in the onset of affective recurrences in bipolar patients and could be considered core symptoms of bipolar disorder.[9] Specifically, patients with (hypo)manic episodes have higher rates of hospitalization during spring and summer, when sunlight exposure (i.e., the photoperiod) is longer,[10-14] while patients with major depressive episodes are mainly admitted during the winter.[10,15-17]

Photoperiod is defined as the number of hours of daylight, which can influence an individual's physiology and metabolic cycles. Ideal photoperiods are approximately 14 hours in summer and 8 to 9 hours in winter. Studies have highlighted how sunlight exposure, which varies by season and latitude, has a positive correlation with peak admission rates for (hypo)manic and major depressive episodes. Amr & Volpe conducted a study comparing bipolar and schizophrenic patients in terms of monthly hospitalization rates: the authors reported that sunlight exposure had no influence on schizophrenic patients, whereas different admission patterns were observed for affective recurrences (manic or depressive episode) in bipolar patients.[10]

More recent studies, however, suggest that the seasonal variation in sunlight exposure is insufficient to explain circadian rhythm disruption and that other climatic variables, such as ultraviolet exposure levels, temperature, snow, rain, and light exposure during early life should be taken into consideration.[18-21]

Thus, the aim of our study was to increase understanding about the influence of photoperiod variation by following a sample of Italian bipolar patients over a period of 24 months, focusing on inpatients.

## Methods

### *Sample*

All patients consecutively admitted to the Psychiatric Inpatient Unit of San Luigi Gonzaga Hospital in Orbassano

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(University of Turin), Italy, over a 24-month period (September 1, 2013 until August 31, 2015) were included. All of these patients were from northwest Italy. To avoid the inclusion of patients who were readmitted during the same episode, hospitalizations occurring less than 8 weeks after a previous admission were not considered.

In Italy, the type of psychiatric admission is based on the subject's clinical conditions and is regulated by a mental health law passed in 1980: involuntary treatment occurs when a patient refuses treatment and immediate non-hospital treatment cannot be considered under the circumstances. For this reason, the sample included patients both voluntarily and involuntarily admitted. During hospitalization, the status of an inpatient can shift from involuntary to voluntary, and after 7 days a reassessment is required to maintain involuntary hospitalization status.[22]

After the study's aim and procedures had been thoroughly explained to them, recruited patients expressed their willingness to participate by signing a written consent form. The study design was reviewed by the local Ethics Committee.

### *Assessment*

Psychiatric diagnoses were made in accordance with the DSM-5[23] at discharge. All diagnoses were made by clinicians with at least 5 years of postgraduate clinical experience and were carefully reviewed by a senior psychiatrist.

Sociodemographic characteristics were collected in a semi-structured interview and consisted of the patient's gender, age, education level, and marital and employment status, while the clinical characteristics included age of onset, total length of voluntary and involuntary hospitalization, diagnoses, current suicide ideation and/or attempts, month and season of admission to the psychiatric ward (autumn was defined as September 21st to December 20th, winter as December 21st to March 20th, spring as March 21st to June 20th, and summer as June 21st to September 20th). The hospitalization periods were classified according to sunlight exposure: spring-summer (s-s) (highest solar intensity) and autumn-winter (a-w) (lowest solar intensity).

### *Statistical analysis*

All statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL); statistical significance was set at $p < 0.05$.

The subjects' sociodemographic and clinical characteristics were represented as mean and standard deviation (SD) for continuous variables and as frequency and percentage for categorical variables.

The total sample was divided in two groups, one of patients with bipolar disorder, the other of patients with any other diagnosis.

Since the Kolmogorov-Smirnov test, which determines whether parametric or non-parametric tests are required, indicated normal sample distribution, intergroup differences were analyzed using the Pearson chi-square test with Yates correction for categorical variables, while the *t*-test for independent samples was used for continuous variables. Comparative analyses of the number of admissions were adjusted for age and gender.

## Results

During the 24-month study period, 730 patients were included, with a mean age of 43.4±13.9 years. Of this total, 311 subjects (42.6%) were female; slightly more than half of the patients (55.6%) were single, and 33.6% were employed.

Regarding clinical characteristics, the mean age of onset was 28.5±13.3 years, while the mean duration of hospitalization was 11.4±8.9 days. A total of 112 (15.3%) patients were involuntarily admitted.

The longitudinal diagnoses were distributed as follows: 251 (34.4%) patients had bipolar or related disorders, 192 (26.3%) had schizophrenia, 134 (18.3%) had depressive disorders and 153 (21.0%) had other diagnoses, such as personality or substance-related disorders.

Further details about the clinical and sociodemographic characteristics are summarized in Table 1.

As previously mentioned, the sample was divided into two subgroups: patients with bipolar disorder (n=251, 34.4%), and patients with other diagnoses (n=479, 65.6%). When these two groups were compared, as shown in Table 2,

**Table 1** Sociodemographic and clinical characteristics of the total sample

| | Total sample (n=730) |
|---|---|
| Gender (female) | 311 (42.6) |
| Age (years), mean ± SD | 43.42±13.91 |
| Education level | |
| Elementary school | 67 (9.2) |
| Middle school | 352 (48.2) |
| High school | 257 (35.2) |
| Higher education | 54 (7.4) |
| Marital status | |
| Single | 406 (55.6) |
| Married | 190 (26.0) |
| Divorced | 106 (14.5) |
| Widowed | 28 (3.9) |
| Employment status: currently employed | 245 (33.6) |
| Age at onset (years), mean ± SD | 28.47±13.30 |
| Suicide | |
| Ideation | 122 (16.7) |
| Attempt | 77 (10.5) |
| Admission | |
| Involuntary | 112 (15.3) |
| Voluntary | 618 (84.7) |
| Duration of hospitalization, mean ± SD | 11.42±8.91 |
| Diagnosis | |
| Bipolar and related disorders | 251 (34.4) |
| Schizophrenia and related disorders | 192 (26.3) |
| Depressive disorders | 134 (18.3) |
| Others | 153 (21.0) |

Data presented as n (%), unless otherwise specified.
SD = standard deviation.

**Table 2** Sociodemographic and clinical characteristics in the two subgroups

| | Bipolar disorder (n=251) | Other diagnoses (n=479) | $t/\chi^2$ | df | p-value |
|---|---|---|---|---|---|
| Gender (female) | 124 (49.4) | 187 (39.0) | 7.23 | 1 | 0.007 |
| Age (years), mean ± SD | 46.11±12.57 | 42.01±14.37 | -3.82 | 728 | < 0.001 |
| Education level | | | | | |
| Elementary | 14 (5.6) | 53 (11.1) | 25.46 | 3 | < 0.001 |
| Middle school | 102 (40.6) | 250 (52.2) | | | |
| High school | 105 (41.8) | 152 (31.7) | | | |
| Higher education | 30 (12.0) | 24 (5.0) | | | |
| Marital status | | | | | |
| Single | 113 (45.0) | 293 (61.2) | 17.96 | 3 | < 0.001 |
| Married | 79 (31.5) | 111 (23.2) | | | |
| Divorced | 48 (19.1) | 58 (12.1) | | | |
| Widowed | 11 (4.4) | 17 (3.5) | | | |
| Employment status: currently employed | 98 (39.0) | 147 (30.7) | 5.16 | 1 | 0.023 |
| Age at onset (years), mean ± SD | 28.76±11.89 | 28.32±13.99 | -0.42 | 728 | 0.676 |
| Suicide | | | | | |
| Ideation | 44 (17.5) | 78 (16.3) | 0.18 | 1 | 0.668 |
| Attempt | 31 (12.4) | 46 (9.6) | 1.32 | 1 | 0.251 |
| Admission | | | | | |
| Involuntary | 57 (22.7) | 55 (11.5) | 15.98 | 1 | < 0.001 |
| Voluntary | 194 (77.3) | 424 (88.5) | | | |
| Duration of hospitalization (days), mean ± SD | 14.72±8.65 | 9.68±8.56 | -7.52 | 728 | < 0.001 |

Data presented as n (%), unless otherwise specified.
df = degrees of freedom; SD = standard deviation.

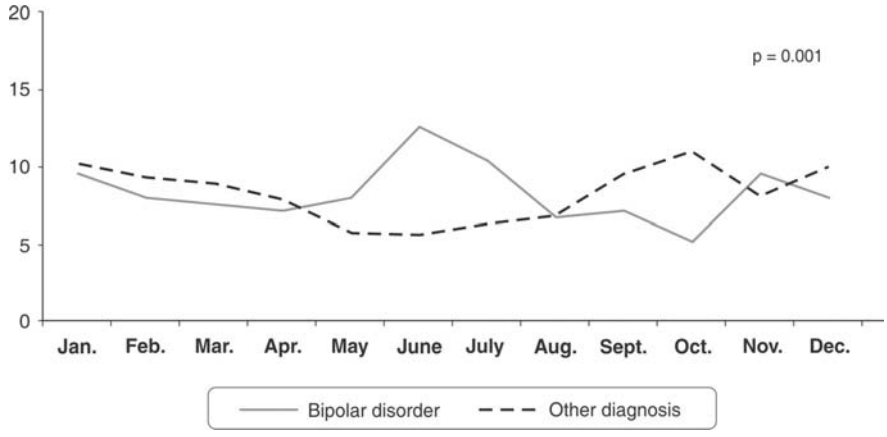


**Figure 1** Inpatient admission rates by month: comparison between bipolar and other mental disorders.

patients with bipolar disorder included more females (49.4 vs. 39.0%, p = 0.007) and had a significantly higher mean age (46.1±12.6 vs. 42.0±14.4 years, p < 0.001). Additionally, patients with bipolar disorder had a higher education level (41.8 vs. 31.7%, p < 0.001) and were more likely to be employed (39.0 vs. 30.7%, p = 0.023) and married (31.5 vs. 23.2%, p < 0.001).

Regarding the clinical characteristics, the bipolar group was admitted involuntarily more frequently (22.7 vs. 11.5%, p < 0.001) and for significantly longer durations (14.7± 8.6 vs. 9.7±8.6 days, p < 0.001). No significant differences were found with respect to suicide ideation and/or attempts.

Figure 1 shows the monthly admission prevalence according to longitudinal diagnosis. The hospitalization of bipolar patients showed significant peaks during the months with more sunlight: the greatest differences with the mixed control group were in May (8.0 vs. 5.8%), June (12.7 vs. 5.6%), and July (10.4 vs. 6.3%).

No significant differences were found for seasonality, despite the slightly higher admission prevalence in spring for patients with bipolar disorder, as shown in Table 3. However, patients with bipolar disorder reported a significantly higher prevalence of (hypo)manic episodes during spring-summer (i.e., the greatest period of solar intensity) than the mixed control group (51.4 vs. 42.4%, p = 0.020).

**Table 3** Number of admissions divided by season and photoperiod

| | Bipolar disorder (n=251) | Other diagnoses (n=479) | $t/\chi^2$ | df | p-value |
|---|---|---|---|---|---|
| Season | | | | | |
| Spring | 67 (26.7) | 99 (20.7) | 5.74 | 3 | 0.125 |
| Summer | 62 (24.7) | 104 (21.7) | | | |
| Autumn | 61 (24.3) | 139 (29.0) | | | |
| Winter | 61 (24.3) | 137 (28.6) | | | |
| Photoperiod | | | | | |
| Spring-summer | 129 (51.4) | 203 (42.4) | 5.40 | 1 | 0.020 |
| Autumn-winter | 122 (48.6) | 276 (57.6) | | | |
| | Manic episode (n=140) | MDE (n=111) | | | |
| Season | | | | | |
| Spring | 46 (32.8) | 21 (18.9) | 7.73 | 1 | 0.049 |
| Summer | 36 (25.7) | 26 (23.4) | | | |
| Autumn | 28 (20.0) | 33 (29.7) | | | |
| Winter | 30 (21.4) | 31 (27.9) | | | |
| Photoperiod | | | | | |
| Spring-summer | 82 (58.5) | 47 (42.3) | 6.27 | 1 | 0.012 |
| Autumn-winter | 58 (41.5) | 64 (57.7) | | | |

Data presented as n (%).
df = degrees of freedom; MDE = major depressive episode.

When the analyses were restricted to the bipolar group, patients undergoing a (hypo)manic episode were more frequently hospitalized during spring (32.8 vs. 18.9%, p = 0.049) and during longer daylight periods (58.5 vs. 42.3%, p = 0.012) than those undergoing a major depressive episode.

Analyses adjusted for age and gender confirmed these findings.

## Discussion

The primary aim of our study was to increase understanding about the influence of photoperiod variation by following a sample of Italian bipolar patients over a period of 24 months, focusing on inpatients.

The first difference that should be highlighted was gender: bipolar patients were more frequently female than patients in the mixed control group. This result agrees with a recent epidemiological study[24] and is likely due to a strong link between the female reproductive hormonal axis and regulatory mechanisms of sunlight sensitivity.[17]

Second, a difference in mean age was found. Although substance intoxication usually involves adolescent patients, the greater age observed for the bipolar group could be attributed to the peculiar course of the disorder, with long free intervals and a progressive worsening of the symptoms after every affective recurrence; thus, treatment is often delayed. During the first (hypo)manic and/or major depressive episode, for example, patients with bipolar disorder usually do not feel the need to be treated. Moreover, bipolar patients usually achieve better social and work functioning than patients with other diagnoses (such as schizophrenia, personality disorder or substance abuse disorder), which is corroborated by the overall higher education level and prevalence of married and working subjects.[25-27]

Regarding suicide attempts in the bipolar group, our results were similar to international averages, which range from 11 to 19%.[28-30] However, we found no significant difference between bipolar patients and those with other diagnoses, in contrast with the literature.[30,31] This might be explained by the different suicide risk rates of the psychiatric disorders included in the mixed control group.

Finally, higher involuntarily admission rates were observed for bipolar patients. This also agrees with the international data, which indicates that bipolar disorder is one of the main causes of involuntary admission.[10,15,32]

The focus of our study, however, was on analyzing admission rates during different months and seasons among the two subgroups. Seasonality has been defined as "a driving force that has a major effect on the spatio-temporal dynamics of natural systems and their populations."[33] The fact that our results showed a slightly higher prevalence in admission rates during autumn and winter months could be explained by two factors: on the one hand, a slightly higher rate of admission in autumn-winter for unipolar major depression (17.2 vs. 19.3%) and for schizophrenic and other psychoses (23.8 vs. 28.4%) and, on the other hand, the greater length of admissions for manic episodes during spring-summer, which reduced hospital bed turnover and, consequently, the number of admissions in these months.

Numerous studies have indicated that sunlight intensity is positively correlated with the number of mania admissions and negatively correlated with bipolar depression admissions.[8,14,21] Considering monthly admission rates, our results agreed with the international literature: the most interesting finding was the peak of admissions during May, June and July for patients with bipolar disorder. This result underscores the higher probability of admission during the pronounced photoperiod change between spring and summer, which agrees with numerous recent studies confirming a strong seasonal pattern in bipolar disorder.[9-16,21,34-37]

This finding, in light the DSM-5's focus on seasonal pattern in bipolar disorder, prompted the following question: is seasonality really the most incisive clinical parameter for assessing the onset of bipolar disorder, or is it, rather, greater exposure to sunlight?

The answer is both, if we consider the current affective recurrence in bipolar disorder, namely subdividing the bipolar group into (hypo)manic and major depressive episodes. Our study showed that (hypo)manic episodes were significantly more sensitive to photoperiod variation, since admissions peaked during maximum sunlight exposure (i.e., spring-summer). When we assessed the effect of seasonality (admission rates by single season), the results showed that patients with (hypo)manic episodes were admitted more frequently in spring than bipolar patients with depressive recurrences.

This result agrees with recent reviews[9,38] and clinical trials.[8,14,21] Manic episodes peak during spring/summer and, to a lesser extent, in the autumn, depending on climatic variations, whereas depressive episodes peak

during early winter and, to a lesser extent, in summer, with mixed episodes peaking in early spring or mid/late summer.[9] Furthermore, Yang et al. conducted a population-based study showing that young adults presented a higher degree of seasonality in acute admissions than middle-aged adults, and the polarity of a patient's admission index predicted the seasonality of relapse admissions.[16] Symptom dimensions, such as psychosis, suicidality/aggression, or sex differences follow seasonal variations and are also influenced by climatic conditions.[9] Finally, a recent study conducted on 148 bipolar I patients found that a seasonal pattern of manic episode admissions was associated with male gender and psychotic features.[13]

However, when we compared the bipolar group with the mixed-diagnosis control group, we found no differences in seasonality, which was probably due to the counterbalancing effect of depressive recurrences in bipolar disorder, whose admissions particularly increased in autumn.

We could conclude that if bipolar disorder is considered as single affective recurrences, it shows both seasonality and photoperiodic patterns. When we consider the diagnosis of bipolar disorder as a whole, the significant clinical variable for the onset of an affective episode is not seasonal pattern but, rather, greater sunlight exposure, which has also been shown in recent reviews[9,36] and clinical trials.[14,21,37]

In a clinical study assessing climatic variables and admissions for mania, Volpe et al., concluded that the most frequent association is with luminosity: higher temperatures were only significantly involved in regions where the hottest months coincide with the more daylight.[39] So, it is important to point out that exposure to sunlight could be considered a useful and significant clinical parameter for evaluating the course of the illness and affective recurrences in patients with bipolar disorder rather than seasonality.

Furthermore, there is emerging evidence that seasonal effects may vary with latitude, varying more strongly in the northern hemisphere than in the southern hemisphere.[40] Therefore, photoperiod length has a primary mood-altering role: its variation during different seasons leads to biorhythm adaptation in humans and animals. The photoperiod reaches its maximum extension during summer and its minimum during winter; this environmental pattern reveals biological and clinical implications for human beings, since the light stimulus is received by the retina and transformed into an electrical signal that interacts with the suprachiasmatic nucleus of the hypothalamus (SCN), known as the main endogenous pacemaker. The SCN regulates the activity of many organs, the pineal gland above all, in order to modify biorhythms to better fit seasonal variations.[41,42] Bipolar subjects present circadian-related gene mutations that compromise normal synchronization to environmental stimuli, such as sunlight, which ultimately leads to neurotransmitter dysregulation that mainly affects the noradrenergic, serotoninergic, dopaminergic and melatoninergic systems. The timing of melatonin secretion interacts with gene transcription in the pituitary pars tuberalis to modulate the production of TSH (thyrotropin), hypothalamic T3 (triiodothyronine), and tuberalin peptides, which modulate the production of regulatory gonadotropins and other hormones in the pituitary gland. Pituitary hormones largely mediate seasonal physiological and behavioral variations. Thus, altered interaction between the SCN and the rest of the body could have repercussions on every level, from metabolic, circadian and sleep-wake rhythm dysregulations (due to hypothalamus-pituitary-adrenal gland axis malfunction), to altered and compromised immune response, to increased oxidative stress on a cellular level.[1,43]

Furthermore, certain authors have indicated other climatic factors, such as humidity, day length, ultraviolet radiation and temperature, which represent a significant role in the admission of patients with bipolar disorder, particularly for (hypo)manic episodes.[21,35]

Our study has several limitations: first, seasonal, environmental and/or psychological factors that could contribute to the onset of an acute clinical event (e.g., holidays, stressful life events, general medical condition, poor adherence to treatment, humidity, temperature, ultraviolet radiation) have not been taken into consideration and could not be ruled out as contributing factors. Second, our findings on seasonality are based on hospital admission date, rather than actual onset of the acute episode. Third, our data are limited to a single hospital, and the control group was a mixed sample of psychiatric diagnoses. Fourth, clinical variables, such as the number of previous hospitalizations, predominant polarity and a structured interview for diagnoses are lacking.

In conclusion, bipolar disorder seems to be strongly linked to compromised communication between biorhythm pathways, since these patients exhibited an increased probability of (hypo)manic episodes during maximum sunlight exposure. Infradian rhythm abnormalities, such as seasonal aspects in bipolar patients, are well documented. However, the mechanisms underlying the effects of the natural seasonal environment on bipolar symptoms remain unclear. Various aspects, such as the nature and intensity of environmental factors or the temporal relationship between symptoms and these environmental factors, need to be investigated.

Identifying patients with such susceptibilities would enable the development of personalized therapeutic strategies to prevent affective recurrences[38] or of chronotherapeutic interventions such as sleep deprivation, the blue-blocking regime in mania ("a virtual darkness therapy"), or interpersonal or social rhythm therapy.[6,38]

## Disclosure

The authors report no conflicts of interest.

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## ORIGINAL ARTICLE

# Analysis of suicide mortality in Brazil: spatial distribution and socioeconomic context

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**Objective:** To perform a spatial analysis of suicide mortality and its correlation with socioeconomic indicators in Brazilian municipalities.
**Methods:** This is an ecological study with Brazilian municipalities as a unit of analysis. Data on deaths from suicide and contextual variables were analyzed. The spatial distribution, intensity and significance of the clusters were analyzed with the global Moran index, MoranMap and local indicators of spatial association (LISA), seeking to identify patterns through geostatistical analysis.
**Results:** A total of 50,664 deaths from suicide were registered in Brazil between 2010 and 2014. The average suicide mortality rate in Brazil was 5.23/100,000 population. The Brazilian municipalities presenting the highest rates were Taipas do Tocantins, state of Tocantins (79.68 deaths per 100,000 population), Itaporã, state of Mato Grosso do Sul (75.15 deaths per 100,000 population), Mampituba, state of Rio Grande do Sul (52.98 deaths per 100,000 population), Paranhos, state of Mato Grosso do Sul (52.41 deaths per 100,000 population), and Monjolos, state of Minas Gerais (52.08 deaths per 100,000 population). Although weak spatial autocorrelation was observed for suicide mortality (I = 0.2608), there was a formation of clusters in the South. In the bivariate spatial and classical analysis, no correlation was observed between suicide mortality and contextual variables.
**Conclusion:** Suicide mortality in Brazil presents a weak spatial correlation and low or no spatial relationship with socioeconomic factors.

**Keywords:** Suicide; epidemiology; social and political issues; community mental health; statistics

## Introduction

Suicide is the act of taking one's life in a deliberate and voluntary manner in the full knowledge of its fatal outcome.[1] Suicidal behavior ranges from the ideation of killing oneself to forming a plan and obtaining the means to execute the act; it is currently a major public health problem worldwide, causing more deaths than homicides and wars together.[2] Ingestion of pesticides, hanging and firearms are among the most common suicide methods.[3]

It is estimated that about one million people committed suicide in the year 2000, with suicide among the ten leading causes of death in all countries. One in three of these suicides was in the 15 to 35 age group.[4] In 2012, there were approximately 800,000 deaths from suicide worldwide, representing an annual global age-standardized rate of 11.4 per 100,000 population (15.0 for males and 8.0 for females).[3] In Brazil, suicide rates are low compared to most countries, ranging from 3.50 to 4.00 per 100,000 population, in contrast with its much higher homicide rates.[5]

The literature indicates that suicide statistics are unevenly distributed around the world, within countries, between genders, and between age groups.

In richer countries, the suicide rate is three times higher among men, but in low- and middle-income countries, the male-to-female ratio is much lower, at 1.5 men to each woman.[3] There is a discrepancy between the number of suicides and attempted suicides, with one possible explanation being the preferred methods of each gender: despite more suicide attempts, women use less efficacious methods than men.[6]

Although suicide rates are higher among young people, ranking as the second leading cause of death among 15- to 29-year-olds, a considerable increase has recently been observed among the elderly in almost every region of the world.[5]

The suicide rate is significantly higher among men than women in Brazil, with a 3.7:1 ratio in 2012. People over 60 have the highest suicide rate in Brazil: in 2012, the mortality in this group was 8.0/100,000 population. The greatest rise in mortality, however, occurred in the 25 to 59 and the 10 to 24 age groups, increasing 22.7% and 21.8, respectively, over rates from year 2000. The major causes of suicide in Brazil are hanging, firearm injury, and

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deliberate self-poisoning with pesticides, which account for approximately 80% of the cases.[7]

According to official statistics, Brazil's suicide rate is far below the world's highest, which is over 16/100,000 population in France, China, Switzerland, Belgium, Austria, the United States, Eastern Europe and Japan. Its current world raking is 71st in rate and 9th in absolute number of deaths from suicide.[8] However, even in countries with good vital registration data, suicide can often be mistakenly attributed to accidents or other causes of death. Although it is relatively easy to measure mortality in a well-organized country, including mortality from injury, diagnosing suicide involves determining intent, which makes unambiguous statistical data more difficult to obtain.[9]

To a large extent in Brazil, only the mode of death (e.g. falls or drownings) – not the intent – is recorded for deaths from external causes. Such recordkeeping practices can mask a considerable proportion of suicide cases, especially among young male adults.[7] However, national mortality records show that the incidence of suicides among young adults, particularly males, is increasing, even considering possible underreporting.[8]

The risk of suicidal behavior is usually calculated according to sociodemographic and clinical indicators.[10] There are also genetic factors, whose accuracy is still subject to speculation, though such data can be considered in light of an individual's family history.[11] Risks associated with community and relationships include war and disasters, acculturation stress (e.g. among indigenous or displaced people), discrimination, affective separation, isolation, abuse, violence, and conflicting relationships.[3]

Among the individual risk factors, mental disorders stand out as an important cause of suicide.[12] Patients with a long history of mental or physical illness are at higher risk of committing suicide. Other risk factors on an individual level include previous suicide attempts, alcohol abuse, financial loss, chronic pain, and a family history of suicide.[13]

Social, psychological, cultural, and other factors may interact to lead a person to suicidal behavior, but the stigma associated with mental disorders and suicide prevents many people from seeking help. In recent decades, and particularly since 2000, a number of suicide prevention strategies have been developed.

In 1999 the WHO launched its Suicide Prevention Program (Supre), which is a worldwide suicide prevention initiative aimed at reducing the morbidity and mortality associated with suicidal behavior.[4] In in 2006, the Brazilian Ministry of Health inaugurated its National Strategy for Suicide Prevention, whose purpose is to reduce deaths, attempts, associated damage and impacts on families. Also in 2006, a Suicide Prevention Handbook for Mental Health Professionals was published in Brazil, whose objective is early detection of associated conditions and implementation of preventive measures.[14] Short-term measures have also been proposed, such as expanding mental health service coverage and increasing social and spatial accessibility to Psychosocial Care Centers (Centros de Atenção Psicossocial – CAPS). Long-term proposals include educational initiatives promoting holistic health for individuals and communities.[15] In 2009, the Brazilian Ministry of Health began its National Strategy for Suicide Prevention, whose purpose is to reduce the incidence of cases in Brazil, thus reducing the suicide death rate and the damage caused to those directly and indirectly involved.[8]

Studies on suicide in Brazil have described different scenarios and associated factors that, taken together with other results, may contribute to a better understanding of the phenomenon. Nevertheless, few studies have addressed the phenomenon's spatial behavior or its geographic relationship with extrinsic factors, data that could be applied to health services management and contribute to strategies for reducing the morbidity/mortality of the population. Considering both the importance of suicide as a cause of death in Brazil and the need to strengthen understanding of this phenomenon, this study's purpose was to evaluate the distribution of mortality from suicide in Brazilian municipalities and correlate it with socioeconomic indicators.

## Methods

This is an ecological study of multiple groups, using Brazilian municipalities as a unit of analysis. The dependent variable or response was mortality from self-inflicted injuries, represented by the standardized mortality rate (SMR). Deaths occurring from January 1, 2010 to December 31, 2014 were used to calculate the SMR. The number of deaths was obtained from the Mortality Information System of the Brazilian Unified Health System's IT Department (Sistema de Informação sobre Mortalidade, Departamento de Informática, Sistema Único de Saúde – SIM/DATASUS).

Municipal population and age data were obtained from the 2010 Census and projections published on the Brazilian Institute of Geography and Statistics website. The gross rates were standardized through the direct method, considering the total Brazilian population and expressed per 100,000 population per year.[16]

The independent variables were the socioeconomic indicators of the Brazilian municipalities: (V1) Municipal Human Development Index (HDI-M); (V2) dependency ratio; (V3) aging rate; (V4) illiteracy rate among those $\geqslant$25 years of age; (V5) percentage of vulnerable poor; (V6) income ratio between the richest 10% and the poorest 40%; (V7) Gini index; (V8) unemployment rate among those $\geqslant$18 years of age; (V9) percentage of the population living in households with a density $>$2. The socioeconomic indicators for the year 2010 were collected from the United Nations Development Programme's (UNDP) Atlas of Human Development in Brazil (www.atlasbrasil.org.br).

A descriptive analysis of the variables used in the study was conducted and, to evaluate of the relationship between the selected socioeconomic indicators and the suicide SMR in Brazil, Pearson's correlation and Simple Linear Regression tests were applied. SPSS version 22.0 was used for data processing and statistical analysis.

The spatial dependence analysis was performed with the global Moran index, which estimates the spatial autocorrelation on a scale of -1 to +1. After the general

analysis, the presence of clusters was evaluated using local indicators of spatial association (LISA), which were then presented in BoxMap regardless of their statistical significance. To validate the global Moran index, a random permutation test with 99 permutations was employed.[17]

Bivariate LISA analysis was performed to evaluate the spatial correlation between the outcome variable (suicide SMR) and the independent variables. To do this, thematic maps were constructed with each pair of variables and their autocorrelation value was verified. These analyses were performed in GeoDa version 1.6.61.

Since this study used secondary data available on Brazilian Ministry of Health official websites, which does not identify individuals, it was exempt from evaluation by a research ethics committee, in accordance with Resolution 466/2012 of the National Health Council.

## Results

The mean suicide mortality rate in Brazil from 2010 to 2014 was 5.23/100,000 population. The five Brazilian municipalities with the highest rates were: Taipas do Tocantins, state of Tocantins (79.68 deaths per 100,000 population); Itaporã, state of Mato Grosso do Sul (75.15 deaths per 100,000 population); Mampituba, state of Rio Grande do Sul (52.98 deaths per 100,000 population); Paranhos, state of Mato Grosso do Sul (52.41 deaths per 100,000 population); and Monjolos, state of Minas Gerais (52.08 deaths per 100,000 population).

The Midwest and the South had the highest mean suicide mortality rates. Of the socioeconomic indicators analyzed, the worst conditions were concentrated in the North and Northeast, which are characterized by low life expectancy, income inequalities, low education and low income. The most developed regions of the country, South and Southeast, were considerably different from the poorest ones (Table 1).

A weak correlation, very close to zero, was found between all independent variables and the dependent variable (Table 2).

The bivariate linear regression analysis between sociodemographic variables and suicide SMR confirmed that these variables have low explanatory power over SMR, as evident in the adjusted $R^2$ values obtained. On the other hand, in the spatial autocorrelation analysis, all sociodemographic variables had global Moran index values above 0.5, which shows a moderate to strong spatial autocorrelation distributed in clusters. The highest autocorrelation values were recorded for illiteracy rate among those $\geqslant$25 years of age (I = 0.87359) and percentage of vulnerable poor (I = 0.87359) (Table 3).

A pattern of spatial autocorrelation was not confirmed for suicide SMR. The global Moran index values showed a weak spatial autocorrelation (I = 0.2608) (Figure 1). Figure 1A shows that the highest municipal suidcide SMRs were in the Midwest and the South, along with a grouping in the Northeast and the North. In the mortality rate cluster analysis, shown as a MoranMap in Figure 1B,

**Table 1** Descriptive analysis of socioeconomic indicators and suicide SMR (per 100,000 population) in Brazil and its macroregions: 2010-2014

| Variables* | Geographical area | | | | | |
|---|---|---|---|---|---|---|
| | Brazil | North | Northeast | Midwest | Southeast | South |
| suicide SMR | 5.23 | 5.43 | 5.14 | 7.34 | 6.13 | 10.74 |
| V1 – HDI-M | 0.727 | 0.607 | 0.590 | 0.689 | 0.698 | 0.714 |
| V2 – Dependency | 45.92 | 63.35 | 57.39 | 47.55 | 47.05 | 45.83 |
| V3 – Aging | 7.36 | 5.23 | 8.08 | 7.14 | 9.08 | 9.58 |
| V4 – Illiteracy | 11.82 | 22.38 | 34.97 | 15.38 | 13.58 | 9.76 |
| V5 – Vulnerable poor | 32.56 | 61.99 | 66.93 | 33.46 | 32.04 | 23.43 |
| V6 – Income ratio | 22.78 | 25.35 | 17.13 | 13.66 | 11.20 | 11.01 |
| V7 – Gini | 0.600 | 0.567 | 0.525 | 0.495 | 0.465 | 0.459 |
| V8 – Unemployment | 7.29 | 7.36 | 8.30 | 5.52 | 6.00 | 3.09 |
| V9 – Density | 27.83 | 45.13 | 33.06 | 20.78 | 20.45 | 13.83 |

HDI-M = Municipal Human Development Index; SMR = standardized mortality rate.
* Mean observed values.

**Table 2** Correlation between suicide SMR (per 100,000 population) and socioeconomic variables in Brazil from 2010-2014

| | SMR suicide | HDI-M | Dependency | Aging | Illiteracy | Vulnerables | Income ratio | Gini | Unemployment | Density |
|---|---|---|---|---|---|---|---|---|---|---|
| SMR suicide | 1 | | | | | | | | | |
| HDI-M | 0.163 | 1 | | | | | | | | |
| Dependency | -0.144 | -0.811 | 1 | | | | | | | |
| Aging | 0.222 | 0.238 | -0.285 | 1 | | | | | | |
| Illiteracy | -0.181 | -0.889 | 0.720 | -0.134 | 1 | | | | | |
| Vulnerables | -0.210 | -0.936 | 0.832 | -0.279 | 0.883 | 1 | | | | |
| Income ratio | 0.048 | -0.391 | 0.544 | -0.308 | 0.330 | 0.455 | 1 | | | |
| Gini | -0.113 | -0.424 | 0.551 | -0.345 | 0.401 | 0.562 | 0.775 | 1 | | |
| Unemployment | -0.260 | -0.322 | 0.285 | -0.299 | 0.342 | 0.445 | 0.189 | 0.296 | 1 | |
| Density | -0.259 | -0.645 | 0.774 | -0.605 | 0.554 | 0.709 | 0.532 | 0.552 | 0.442 | 1 |

HDI-M = Municipal Human Development Index; SMR = standardized mortality rate.
All results were statistically significant ($p < 0.001$).

**Table 3** Global Moran index and bivariate linear regression between socioeconomic indicators and suicide SMR (per 100,000 population) in Brazil from 2010-2014

| | Bivariate analysis | | | | | |
|---|---|---|---|---|---|---|
| Variable | Coefficient | Default error | p-value | F | Adjusted $R^2$ | Moran Index |
| HDI-M | 14.303 | 1.162 | < 0.001 | 151.5 | 0.026 | 0.71075 |
| Dependency | -0.102 | 0.009 | < 0.001 | 117.7 | 0.021 | 0.77160 |
| Aging | 0.508 | 0.034 | < 0.001 | 289.0 | 0.049 | 0.63707 |
| Illiteracy | -0.090 | 0.017 | < 0.001 | 189.4 | 0.033 | 0.87359 |
| Vulnerables | -0.059 | 0.004 | < 0.001 | 14.009 | 0.044 | 0.88896 |
| Income ratio | 3.016 | 0.350 | < 0.001 | 74.2 | 0.013 | 0.44526 |
| Gini | -10.84 | 1.27 | < 0.001 | 72.3 | 0.013 | 0.46629 |
| Unemployment | -0.449 | 0.022 | < 0.001 | 402.6 | 0.067 | 0.51899 |
| Density | -0.126 | 0.006 | < 0.001 | 400.4 | 0.067 | 0.85111 |

HDI-M = Municipal Human Development Index.

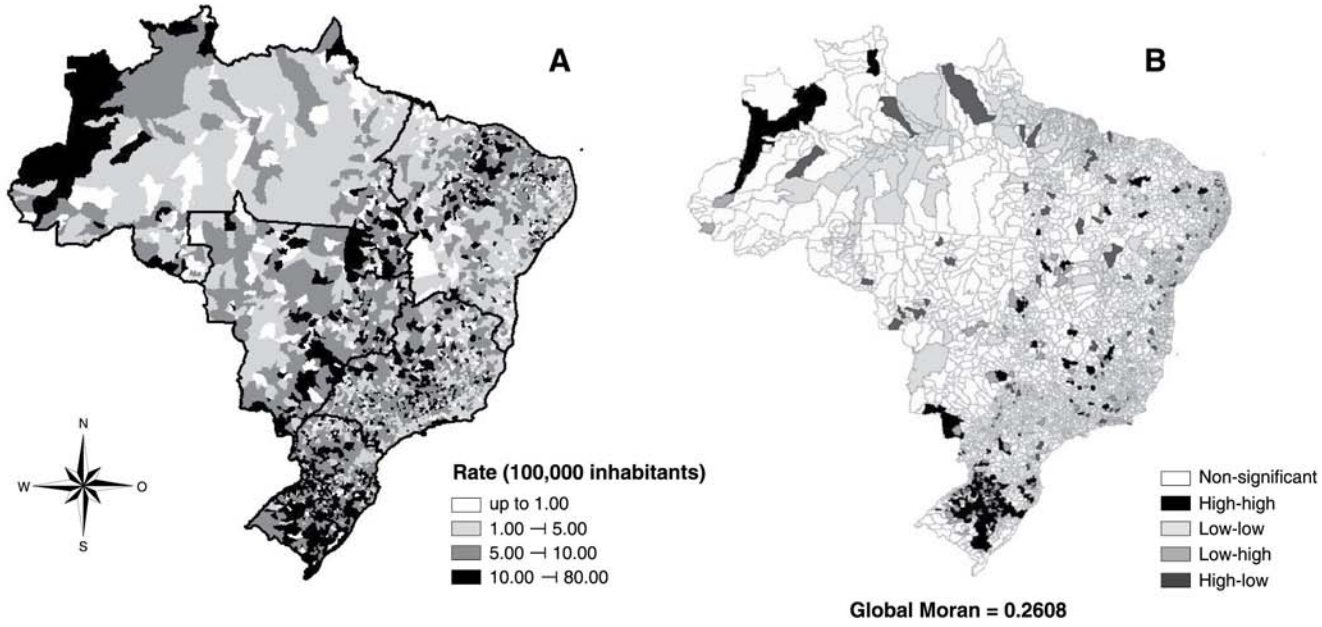


**Figure 1** Analysis of suicide mortality in Brazil. A) Spatial distribution of suicide SMR in Brazilian municipalities; B) Spatial distribution of clusters of suicide SMRs with statistically significant local indicators of spatial association (LISA) (MoranMap), Brazil, 2010-2014.

a cluster of high mortality rates was identified in the South.

In the bivariate spatial analysis, the LISA/Moran's I value of all variables was close to zero, which indicates no spatial autocorrelation between the socioeconomic variables and suicide SMR (Figure 2). Even without spatial autocorrelation, cluster formations were observed in the distribution pattern of these variables. Outstanding among these cluster results was the formation of high mortality rate clusters with the variables dependency ratio, HDI-M, and aging rate, all in the South. Conversely, in the Northeast, SMR clusters were formed with the variables illiteracy, vulnerabe poor and Gini.

## Discussion

Although this study on the spatial distribution of suicide mortality in Brazil found high mortality cluster formations in the South, there were neither significant spatial autocorrelation values nor associations with the analyzed socioeconomic factors.

Results that corroborate the findings of the present study were observed in a study on the spatial and socioeconomic determinants of suicide in Brazil between 1998 and 2002. This exploratory analysis found a strong global spatial association for mean suicide rate, with the Moran index values indicating a positive spatial autocorrelation that included cluster formation in the South and Midwest, where the two highest mortality rates in the country are found.[18]

However, it should be noted that in recent years different regional suicide mortality trends have been observed, especially in the Northeast and the North. Machado & Santos found that between 2000 and 2012, suicide mortality increased by 37.2% in the North, from 3.8 to 5.3 per 100,000 population. The Northeast, however, had the highest increase in suicide rate during the same period,

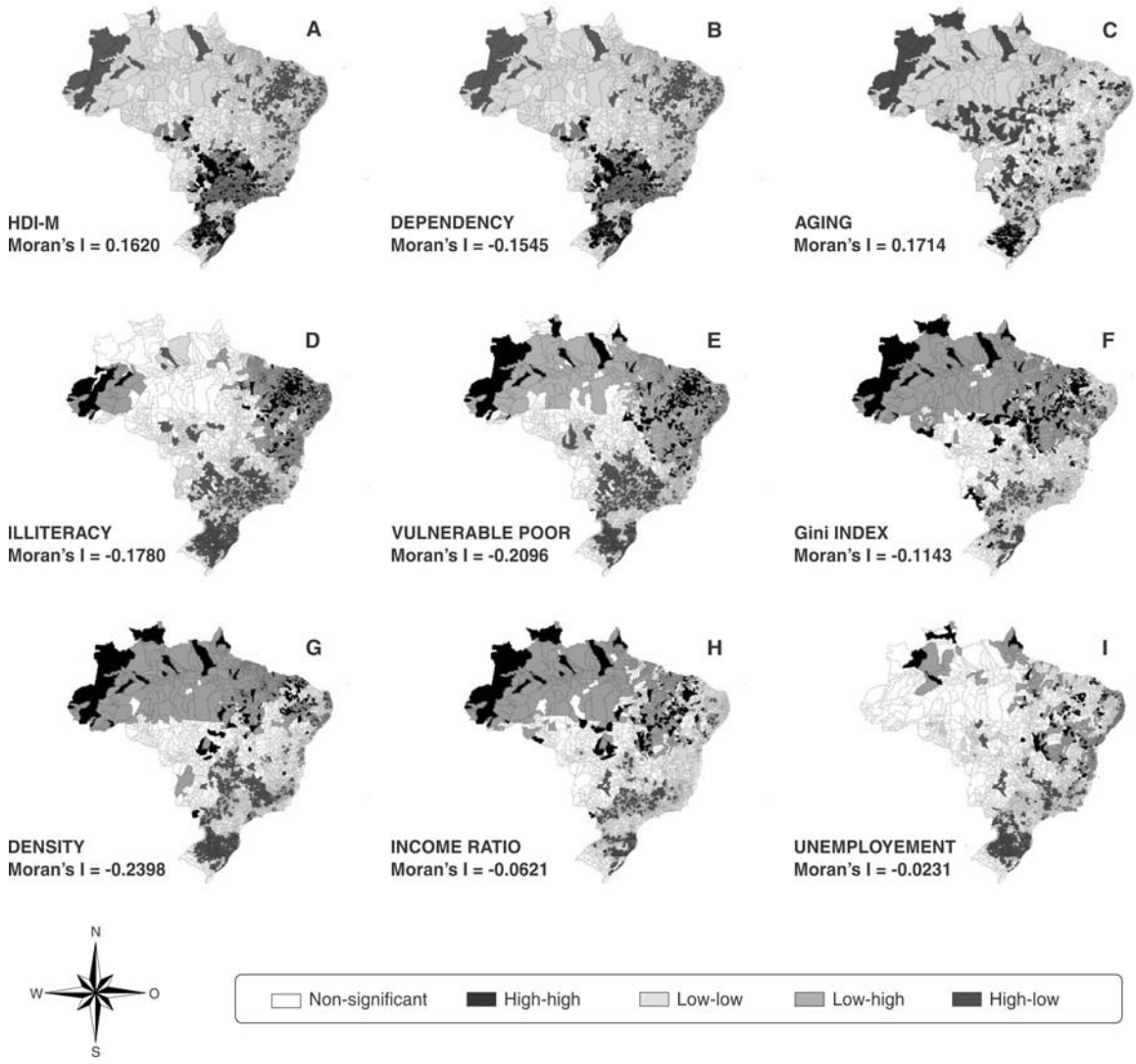


**Figure 2** Bivariate local indicators of spatial association (LISA)/Moran's I between suicide SMR and socioeconomic variables in Brazilian municipalities, 2010-2014. A) Municipal Human Development Index (HDI-M); B) dependency ratio; C) aging rate; D) illiteracy rate; E) vulnerable poor; F) Gini index; G) population in households with density $>2$; H) income ratio between the richest 10% and the poorest 40%; I) unemployment rate.

rising 72.4% (from 3.0 in 2000 to 5.2 in 2012).[19] This is reinforced by the Map of Violence in Brazil (2014), which shows that suicide has been progressively increasing in the country: the rate rose 2.7% between 1980 and 1989, another 18.8% by 1999, and a further 33.3% by 2012.[20]

These data were corroborated in a study by Mota that mapped suicide in Brazil.[15] The author's spatiotemporal analysis of suicide considered groupings of deaths in three-year periods from 1979 to 2011, finding that the highest suicide rates were concentrated in the South and Southeast between 1979 to 1990, which subsequently expanded to the Northeast and Midwest in the following triennia and increased in certain microregions of the North and Northeast beginning in 2004-2006. These results indicate that suicide has become an important public health problem the Northeast and North, which was also demonstrated in the present study.

The suicide phenomenon is studied in several fields, being approached with two main types of analysis: the first involves factors related to the social and interpersonal contexts of the victims, i.e., the intrinsic determinants, while the second focuses on extrinsic determinants such as social and economic factors; the latter are the main focus of the present study.

One point to be considered is that no consensus exists in the literature about the relationship between suicide and socioeconomic status. High quality studies have proposed a direct relationship between high suicide rates and high regional socioeconomic status, while others have proposed an inverse relationship (low suicide rates in an area of high socioeconomic status) or no relation.[21]

The ecological proposal of the present study emphasizes multiple causes of violence and an interaction of risk factors that operates in a broader community context,

including social, cultural and economic dimensions. In such a developmental context, the ecological model shows how violence can stem from different factors at different stages of life.

Other ecological studies conducted in Brazil present important contextual factors related to suicide mortality. One study conducted in the state of Rio de Janeiro found an inverse correlation between suicide mortality rates and factors such as the percentage of Pentecostal residents, an individual's mean years of schooling, the percentage of people living on minimum wage, and the percentage of unmarried individuals.[1]

Lovisi et al.[22] claimed that sociodemographic characteristics such as poverty, unemployment and low education level are important factors that may be associated with suicide, especially in countries with serious socioeconomic problems, such as Brazil. These authors found that suicide was associated with sociodemographic characteristics such as low education level and lack of a partner.

In a study using data from Porto Alegre (state of Rio Grande do Sul), Recife (state of Pernambuco), Salvador (state of Bahia), Belo Horizonte (state of Minas Gerais), Rio de Janeiro and São Paulo – all with populations over one million and among the ten largest metropolitan areas of the country – a correlation was observed between suicide and certain work-related variables, such as occupation, sub-minimum wage income, and employment in the private sector or in construction, i.e., the suicide rate was inversely associated with unemployment.[23]

According to Durkheim,[24] society plays a fundamental role in the construction of the individual. Social factors[24] such as family, school, social groups, and friends have an acute positive or negative influence on the occurrence of suicidal episodes. The proposition that individuals are integrated into a social group regulated by norms and conventions has influenced the development of control theory. Durkheim's work is often referred to as a classic sociological study on suicide.

A relationship between lower education level and suicide was found in one Brazilian study,[19] which agrees with the findings of the present study, mainly due to the relationship between suicide SMR and illiteracy. In different regions of the world, there has been an increase in suicide rates among younger[9] and older populations,[5] data that may be related to the income and dependency ratios. Loureiro et al.[25] emphasize that purely economic factors, such as unemployment and income, have a greater impact on the suicide rate of younger people in society and that high occupational pressure and job market competitiveness are factors that make the young Brazilian population particularly vulnerable to the risk of suicide.

However, according to Durkheim,[24] there is a positive relationship between advancing age and suicide. He explained that old age is associated with the highest suicide rate due to the fact that devastating situations, such as social isolation, unemployment, economic setbacks and loss of loved ones, are experienced in this period.

A study carried out in Campinas, SP found a higher suicide mortality rate among men. In deaths from suicide, although the victim's underlying mental health is frequently compromised, family or economic relationship problems are often present. In situations of economic crisis and unemployment, a man's failure to perform as a provider could lead to family friction, exacerbated alcohol and drug consumption and even to family dissolution, which could be associated with suicide.[26]

The results of a study on the economic determinants of suicide suggest that economic factors are relevant as an explanation for suicide in Brazil. It is noteworthy that income was found to have a negative effect on the suicide rate, while inequality and unemployment had a positive impact. Poverty, moreover, was negatively correlated with suicide.[25]

Some analyses point out that the higher the income, the greater the consumerism, which creates a high degree of personal satisfaction and lowers the risk of suicide.[27] Durkheim, however, refuted this idea, claiming that increased income intensifies the suicide rate, since it increases personal independence and, thus, family degeneration.[28]

Mapping the distribution of suicide cases in Brazil by municipality makes it possible identify suicide risk areas, an approach currently relevant in the social determinants of health field, which seeks explanations for suicide index variations in their local context. There is a need for more organized epidemiological surveillance and research focused on higher occurrence areas to better understand this serious public health problem, as well as to improve the possibility of prevention.

In this perspective, when analyzing the spatial distribution results for suicide in Brazil and their relationship with social and economic indicators, it should be considered that there are multiple risk factors for suicide, which may be defined through epidemiological studies that utilize individualized information, such as suicide method, demographic factors, psychiatric factors, medical factors, factors related to suicidal behavior, hospitalization and medical treatment; further research addressing other aspects not identified in the present study can thus be developed.

This study's main limitation the use of secondary mortality data, which is subject to underreporting, although in recent years it has been recognized that the Mortality Information System in Brazil has substantially increased in quality. Other limitations involve the study design: although an ecological association may correctly reflect a causal association between exposure and a health-related condition/disease, the possibility of ecological bias is always perceived as a limitation on the use of ecological correlations.

This study's contribution, however, lies in the data provided for preventive territorially-determined campaigns that can more equitably distribute public resources by prioritizing regions with the worst indicators.

## Disclosure

The authors report no conflicts of interest.

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## ORIGINAL ARTICLE

# Telomere length and hTERT in mania and subsequent remission

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**Objective:** The findings of telomere length (TL) studies in bipolar disorder (BD) are controversial. The aim of the present study was to detect TL, human telomerase reverse transcriptase (hTERT), and brain derived neurotrophic factor (BDNF) in severe mania and subsequent remission.
**Methods:** Twenty-one medication-free male patients and 20 age and gender matched controls were recruited. The patients were followed in the inpatient clinic, and comparisons were made between the same patients in their remission state and controls. Patients received lithium plus antipsychotics during the follow-up period. Quantitative real-time polymerase chain reaction was performed to verify leukocyte TL and whole blood hTERT gene expression levels. Serum BDNF levels were verified by enzyme-linked immunosorbent assay (ELISA).
**Results:** Compared to controls, manic patients presented shorter telomeres ($p < 0.001$) whose length increased with treatment ($p = 0.001$). Patients in the late stages showed shorter TL than those in the early stages and controls ($p < 0.001$). hTERT gene expression levels were up-regulated in mania and remission compared to controls ($p = 0.03$ and $p = 0.01$, respectively). BDNF changes did not reach statistically significant levels.
**Conclusions:** TL and hTERT gene expression might reflect a novel aspect of BD pathophysiology and TL might represent a novel biomarker for BD staging.

**Keywords:** Bipolar disorder; telomere; TERT protein

## Introduction

Bipolar disorder (BD) is characterized by alternating manic and depressive episodes.[1] Neuroprogression in BD results in worsening cognitive performance and increased risk of suicide.[2] Cumulative damage to the brain and body caused by stress and/or inefficient stress management in an effort to maintain homeostasis is called the "allostatic load,"[3] and is hypothesized to influence neuroprogression in BD.[4] In patients with BD, recurrent mood episodes may be responsible for allostatic load, which, in turn, may result in accelerated aging.[5] BD is associated with reduced life expectancy, premature mortality, and high prevalence of comorbid age-related disorders, such as cardiovascular conditions, metabolic imbalance, and immunosenescence.[6] In light of these findings, clarifying the dynamics of stress response is important for improving both clinical and psychiatric prognosis.

Telomere length (TL) is an important biological marker of cellular aging.[7] Telomeres are nucleoprotein structures present at the ends of eukaryotic chromosomes formed of long nucleotide repeats (TTAGGG) that protect chromosome ends from depredation and fusion. They shorten with each cell division and prevent replication of damaged or genomically unstable cells. Accelerated telomere shortening can be caused by exposure to stress and has been observed in several chronic and age-related disorders, including psychiatric disorders.[8,9] Telomerase, an enzyme that extends telomeric nucleotide repeats, consists of two core components: telomerase reverse transcriptase (TERT) and telomerase RNA component (TERC). Telomerase, with its catalytic subunit TERT, counteracts telomere shortening.[7] Human TERT (hTERT), a catalytic subunit bearing the enzymatic activity of telomerase, is the rate-limiting determinant of human telomerase activity, whereas the other subunits are constitutively expressed.[10]

hTERT and brain derived neurotrophic factor (BDNF) are both neurotrophic factors that have roles in neuronal survival, inhibition of apoptosis, and reduction of excitotoxicity.[11] hTERT has been demonstrated to successfully immortalize various types of cells.[12] TERT mediates the neuroprotective effects of BDNF via inhibiting apoptotic pathways.[13] Lithium promotes the expression of BDNF, which, in turn enhances TERT expression.[14] Even TERT- and BDNF-modified umbilical cord blood mesenchymal stem cells may promote the recovery of neurological function following hypoxic-ischemic brain damage.[11]

Shorter leukocyte TL(LTL) has been associated with major depressive disorder, bipolar disorder, schizophrenia, and anxiety disorders (especially post-traumatic stress disorder).[9] In a meta-analysis of the association between psychiatric disorders and TL, a robust effect size was observed, with a smaller effect size for BD than depressive and anxiety disorders.[15] A recent meta-analysis about TL in BD found no differences between patients and controls,

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and concluded that studies should control for potential confounders such as clinical characteristics, the assays used to measure TL, and age-gender matching of BD patients with healthy control samples.[16]

The purpose of this study was to compare LTL in unmedicated patients with mania and matched healthy controls, and to determine whether the stage of the disorder has any effect on LTL. To assess whether TL change is due to increased shortening or decreased length replenishment by telomerase, we determined hTERT gene expression levels. Serum BDNF was also assessed due to known interaction with TERT. LTL, hTERT, and BDNF were also evaluated during the same patients' subsequent remission state.

## Methods

### *Sample*

The sample comprised 21 medication-free, manic male patients and 20 age and gender matched healthy control subjects who resided in the same region as the patients. Males were selected for the study group to eliminate menstrual cycle effects on the studied parameters. Clinical diagnosis of BD type I was ascertained using the Structured Clinical Interview for DSM-IV (SCID-I). Inclusion criteria for the manic patients were a Young Mania Rating Scale (YMRS) total score $\geqslant$ 25 (signifying that a patient is markedly ill)[17] and lithium response documentation. Remission was defined as a YMRS total score of $< 4$.[18] Early stage BD was defined as having less than 5 previous episodes, and late stage BD was defined as having more than 10 episodes.[19] The control subjects were volunteers with no history of psychiatric disorder or medical illness and who had no first-degree relatives with BD, schizophrenia, or other psychotic disorders.

Patients who had used oral psychotrophic drugs within the last 2 weeks or parenteral psychotrophic drugs within the last month were excluded. Patients who used mood stabilizers were not accepted for the study unless their blood levels were 0. Patients with comorbid axis I disorders (except from nicotine dependence), mental retardation, neurological and/or medical illnesses including metabolic syndrome were excluded. An attempt was made to minimize the factors affecting TL by excluding females, people below age 20 or above 40, and patients with body mass index (BMI) scores below 18.5 kg/m$^2$ or above 24.9 kg/m$^2$.

All of the patients and controls stated that they were not on a diet, had not recently engaged in heavy exercise, and were not on any kind of medication, including vitamins, dietary supplements, and/or energy drinks. Selected patients also stated that they had not been exposed to viral or bacterial pathogens or radiation or had used alcohol or illegal substances in the past week. Patients or controls with abnormal blood analyses (complete blood count, alkaline phosphatase, aspartate aminotransferase, gama glutamil transpeptidase, blood urea nitrogen, creatinine, uric acid, total protein, albumin, sodium, potassium, chloride, c-reactive protein, sedimentation rate, or thyroid function tests) were also excluded from the study.

The study was approved by the local ethics committee (TÜTF-BAEK 2014/198) and was supported by the Trakya University Scientific Research Project Committee (TÜBAP 2015/08). The study conforms to the provisions of the Declaration of Helsinki; only subjects who gave informed consent participated in the study.

### *Measures*

All 41 participants completed the study. Blood samples were taken from the patients and controls by trained nurses between 08:00 and 10:00 a.m. The patients' first blood samples were taken the day after they were admitted to the inpatient clinic. Only lorazepam was allowed before blood collection. The second blood samples were taken when the patients had fulfilled the remission criteria. The patients were followed in the inpatient clinic and comparison between the same patients in their remission state and controls were made. The patients received lithium and antipsychotics during the follow-up period.

The measurements were done at the laboratories of the Technology Research and Development Center of Trakya University (TÜTAGEM). For TL measurement and hTERT gene expression analysis, peripheral blood samples were collected in tubes with ethylenediaminetetraacetic acid.

For TL measurements, DNA was extracted from frozen whole blood using standard methods. TL was measured using quantitative real-time polymerase chain reaction (qRT-PCR) via a previously used and described method.[20] The beta-hemoglobin gene (36B4) served as a reference single-copy gene. TL was expressed as a ratio of telomere copy number over single gene copy number (T/S). SYBR Select Master Mix (Life Technologies, Carlsbad, CA, USA) on an ABI Step One Plus Real-Time PCR system was used for TL and hTERT gene expression measurements. Cycle threshold 21 calculations were made. The relative amounts of TL and hTERT were calculated according to the $2^{-\Delta\Delta Ct}$ method.[21] Each reaction was performed in triplicate for each sample.

For hTERT gene expression measurements, total RNA was isolated using a PureLink RNA Mini Kit (Thermo Fisher Scientific, Waltham, MA, USA) according to manufacturer instructions. The extracted RNA concentrations were measured with a Qubit Fluorometer (Thermo Fisher Scientific, Waltham, MA, USA). The first strand of cDNA was synthesized using a High Capacity cDNA Reverse Transcription Kit (Thermo Fisher Scientific, Waltham, MA, USA) in a Veriti™ 96-well thermal cycler (Thermo Fisher Scientific, Waltham, MA, USA). TERT gene expressions were determined as fold changes compared to controls.

For determination of BDNF serum level, peripheral blood samples were collected in tubes with heparin. BDNF serum levels were assessed using enzyme-linked immunosorbent assay kits (Boster Biological Technologies, Fremont, CA, USA) according to manufacturer instructions.

### *Statistical analysis*

All statistical analyses were conducted with SPSS version 20.0 for Windows with $\alpha = 0.05$. The statistics were done on the level of $\Delta$Ct (cycle treshold) values for the analysis

of TL and hTERT gene expression measurements. The Kolmogorov-Smirnov test was used to check for normal sample distribution. The demographic variable with normal distribution (age) was tested using an independent samples *t*-test. Demographic variables without normal distribution (BMI, smoking, years of education, paid employment) were tested using the Mann-Whitney test. Comparisons of studied parameters between groups were made using an independent samples *t*-test. The manic and remission samples were compared to controls using a paired samples *t*-test. One-way analysis of variance (ANOVA) was used to compare early-BD, late-BD, and controls. Correlations between variables were assessed using Pearson's or Spearman's correlation coefficients.

## Results

### *Demographics*

Both patient (n=21) and control (n=20) groups were composed of male subjects. No subject from either group had comorbid diseases. The mean age between groups was similar ($t$ = -0.66, p = 0.50). Both the patients and the controls had BMI within the normal range (z = -0.69, p = 0.48). The smoking rate between groups was similar (z = -0.76, p = 0.44). Years of education between groups were similar (z = -1.72, p = 0.08). Occupational status between the groups was similar (z = -1.38, p = 0.16) (Table 1). All patients were treated with lithium plus one antipsychotic drug and none of the patients received electroconvulsive therapy. All patients fullfilled the remission criteria. Demographic characteristics, including BD duration and number of manic and depressive episodes, are shown in Table 1.

### *Baseline (manic sample) comparison with controls*

Baseline LTL was significantly shorter in the manic sample (mean ± standard error of mean [SEM] = 311.27±22.94) than in controls (430.43±91.01) (independent samples *t*-test: $t$ = -3.89, p < 0.001, d = 1.79) (Figure 1A). Baseline LTL correlation with baseline YMRS scores was not significant (r = 0.33, p = 0.16), but when the staging effect was removed the negative correlation became significant (r = -0.63, p = 0.02). A significant negative relationship existed between smoking and LTL (rho = -0.39, p = 0.01). The number of depressive and manic episodes and the number of suicide attempts showed no significant relationship with LTL or other studied parameters. Age, BMI, years of education, and occupational status also showed no significant relationship with LTL or other studied parameters.

Baseline hTERT gene expression in the manic sample was 2.2 fold (120%) higher than the controls, calculated according to the $2^{-\Delta\Delta Ct}$ method. This difference was significant (mean ± SEM manic sample hTERT = 10.16± 0.43; control sample hTERT = 11.36±0.34; independent samples *t*-test: $t$ = -2.19, p = 0.03, d = 3.09) (Figure 2).

Baseline serum BDNF level (ng/ml) in the manic sample was lower (mean ± SEM = 18.25±3.17) than the controls (27.23±4.96), but this difference was not statistically significant (independent samples *t*-test: $t$ = -1.52, p = 0.13). There were no significant correlations between baseline manic hTERT or BDNF and the other variables. Baseline LTL, hTERT, and BDNF levels were not significantly correlated with each other.

### *Treatment-associated changes*

LTL was significantly longer in the remission state (mean ± SEM = 400.68±24.01) than in the baseline manic state of the same patients (311.27±22.94) (paired samples *t*-test: $t$ = -3.94, p = 0.001) (Figure 1B). YMRS ratings significantly declined over the course of treatment, demonstrating an improvement (mean ± standard deviation YMRS scores at baseline = 27.57±8.62; YMRS scores at week 8 = 2.10±1.22; paired samples *t*-test: $t$ = 15.20, p < 0.001). The correlation between remission

**Table 1** Demographic characteristics of the patients and controls

| | Patient group (n=21) | Control group (n=20) | p-value |
|---|---|---|---|
| Age in years | 30.64 (8.07) | 32.30 (7.54) | 0.50* |
| Body mass index | 24.34 (3.98) | 24.85 (2.11) | 0.48† |
| Cigarette smoking, % | 71 | 60 | 0.44† |
| Years of education | 8.47 (3.77) | 10.50 (3.59) | 0.08† |
| Current paid employment, % | 38 | 60 | 0.16† |
| BD duration (years) | 8.10 (1.86) | - | |
| Number of manic episodes | 4.57 (3.31) | - | |
| Number of depressive episodes | 3.57 (3.26) | - | |
| Subjects with previous suicide attempts, n (%) | 8.00 (38.09) | - | |
| Time until remission (weeks) | 8.04 (1.93) | - | |
| Baseline YMRS | 27.57 (8.62) | - | |
| Endpoint YMRS | 2.10 (1.22) | - | |
| Antipsychotics used, n (%) | | | |
| Olanzapine | 2.00 (9.52) | - | |
| Quetiapine | 9.00 (42.85) | - | |
| Risperidone | 7.00 (33.33) | - | |
| Haloperidol | 3.00 (14.28) | - | |

Data presented as mean (standard deviation), unless otherwise specified.
BD = bipolar disorder; YMRS = Young Mania Rating Scale.
* Independent samples *t* test; † Mann-Whitney test.

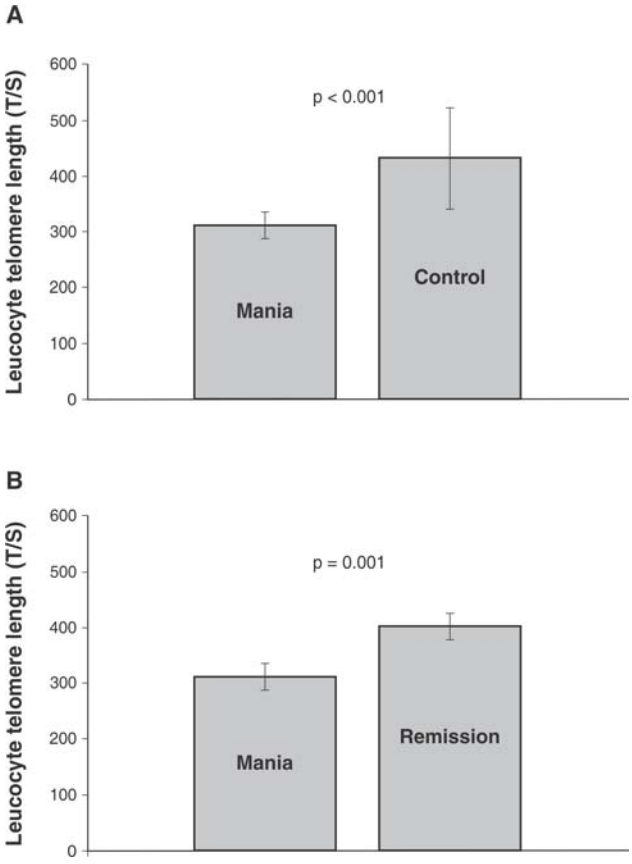


**Figure 1** A) Leucocyte telomere length (T/S) comparison between mania and controls; B) leucocyte telomere length (T/S) comparison between mania and remission.

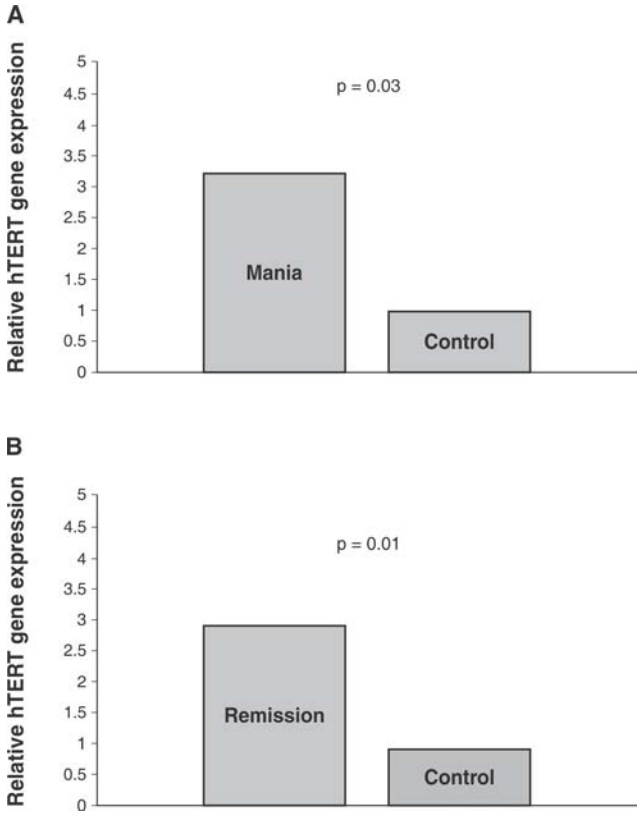


**Figure 2** A) hTERT gene expression as fold changes relative to controls in mania; B) hTERT gene expression as fold changes relative to controls in remission.

state LTL and YMRS scores at week 8 was not significant (r = 0.16, p = 0.46). However, a positive relationship existed between antipsychotic use and remission state LTL (r = 0.52, p = 0.01).

hTERT gene expression in the remitted patients was 3.2 fold (220%) higher than in controls, which was statistically significant (mean ± SEM remission sample hTERT = 9.66±0.55; control sample hTERT = 11.36±0.34; independent samples *t*-test: *t* = -2.60, p = 0.01) (Figure 2).

Although serum BDNF level (ng/mL) in the remission sample was higher (mean ± SEM 22.41±4.03) than the baseline (18.25±3.17), the difference was not statistically significant (paired samples *t*-test: *t* = -0.08, p = 0.40) (Figure 2B). There were no significant correlations between remission state hTERT or BDNF and the other variables. Post-treatment LTL, hTERT, and BDNF levels were not significantly correlated with each other.

*Early vs. late stage comparison with controls*

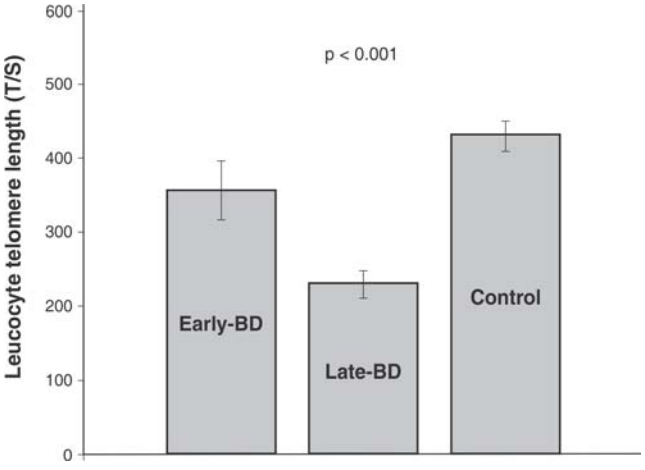


**Figure 3** Leucocyte telomere length (T/S) comparison between early-stage patients, late-stage patients and controls.

Baseline measurements from early stage (n=9) and late stage (n=12) patients and controls were compared. The LTL results were significant: late stage patients had the shortest LTL (mean ± SEM = 270.33±17.82) in comparison with early stage patients (356.76±40.14) and controls (430.43±20.35) (one way ANOVA F = 10.35, $p < 0.001$, $\eta p^2 = 0.18$) (Figure 3). hTERT gene expression and serum BDNF level were lower in late stage patients than in early stage patients and controls, although not statistically significant (one way ANOVA F = 3.03, p = 0.06, and F = 1.25, p = 0.29, respectively). The only significant correlation between the variables was a positive correlation between years with the disorder and baseline YMRS scores (r = 0.76, $p < 0.001$).

## Discussion

We found that LTL was significantly lower in unmedicated manic patients than in age- and gender-matched healthy controls. Late-stage patients had the shortest LTL compared to early-stage patients and controls. LTL significantly increased with treatment (lithium + antipsychotics) but did not reach healthy control levels. hTERT gene expression levels were significantly higher in manic subjects than in controls and were even higher in the remission state. These results were interpreted as increased hTERT levels in mania and remission, possibly to counteract LTL decreases. LTL and hTERT gene expression might reflect a novel aspect of BD pathophysiology, and LTL might represent a novel biomarker for BD staging.

Several studies have found evidence for accelerated cell aging in bipolar patients, as demonstrated by the shortened telomeres.[22-26] These studies differed in terms of methodology and patient selection. TL was measured in DNA isolated from either leucocytes or peripheral blood mononuclear cells (PBMCs). Euthymic or depressed patients with various different disease durations, episode numbers and treatment protocols constituted the majority of the participants. BD type was not specified in some of the studies, so the association between TL and BD I is still unclear. The first study reported lower LTL in patients with chronic mood disorder (major depressive disorder and bipolar disorder-state not specified) than in controls.[22] Rizzo et al. found shorter PBMC TL in 22 euthymic female BD type I patients than in 17 age-matched controls.[24] Lima et al.[23] found shorter PBMC TL in (moderately depressed) BD patients than in age, gender and, educational-level matched controls.

The impact of the number of BD episodes on TL has also been studied. The hypothesis is that if recurrent mood episodes constitute key stressors in the allostatic load model, patients with more episodes should present shorter telomeres. We found no significant association between the number of episodes or suicide attempts and the studied parameters. Our data is supported by the findings of previous studies investigating the effects of the number of manic/hypomanic episodes or suicide attempts on TL.[23,27] Elvsåshagen et al.[26] found that lifetime number of depressive episodes positively correlated with the load of short telomeres (PBMC) in BD type II (euthymic and mildly/moderately depressed patients).

In a study by Martinsson et al.,[28] patients (outpatients diagnosed with BD type I or II) who had experienced more than five episodes were grouped together and compared with those who had experienced fewer episodes. The findings showed that LTL was significantly shorter in patients who had experienced a larger number of depressive episodes, and that this effect was even more pronounced for males. The results of the present study support this finding, since early-stage patients had longer LTL than late-stage patients. Barbé-Tuana et al.[25] compared TL in early- and late-stage euthymic BD patients with controls in a cross-sectional study and found that TL was shorter in both the early and late stages of the disorder. These results were similar to those of the present study, and suggest that telomere shortening occurs early in the course of BD and could precede and lead to all of oxidative stress changes and inflammatory responses in BD.

Martinsson et al.[28] also found that LTL was higher in lithium-treated BD patients than in healthy controls. In this study, almost all of the patients were treated with lithium, an important factor not controlled for in previous studies. LTL was positively correlated with duration of lithium treatment. After correcting for age, number of depressive episodes, and duration of lithium treatment, LTL was 10% greater in lithium responders than in non-responders. Lima et al.[23] found no difference in LTL between patients treated with lithium versus patients treated with valproic acid or other medications. The present study found that post-treatment LTL and hTERT levels were greater than pre-treatment levels. All of the patients were taking lithium + antipsychotics, so it was not possible to rule out the effects of antipsychotics. Use of psychotropic drugs had been shown to have antioxidative effects and, thus, a protective effect on telomeres.[29]

Mechanistic support for an association between lithium treatment and TL has recently been provided. A correlation may exist between lithium, β-catenin, and telomerase activity. β-Catenin is indirectly regulated by lithium, with the main mediator between lithium and β-catenin being glycogen synthase kinase-3β.[30] Lithium has also been reported to promote expression of BDNF, which, in turn, enhances TERT expression.[14,31] In general, hTERT is considered to be regulated primarily on the transcriptional level. Specifically, transcription of hTERT has been found to be activated by β-catenin, resulting in increased telomerase activity and longer TL in human cancer cell lines and human embryonic kidney cells.[31]

In studies measuring telomerase in stressed individuals, post-treatment (approximately 3 months) telomerase activity was found to be greater than pre-treatment levels. Epel[32] concluded that an increase in telomerase activity may be due to cessation of stress and/or change in circulating blood cells. Recently, Li et al.[33] found a protein (telomeric zinc finger-associated protein [TZAP]) that triggers deletion of telomeric repeats and seems to be involved in TL regulation in mammalian cells. The binding of TZAP to long telomeres triggers telomere trimming, setting the upper limit for TL. In the present study, the TL difference found between BD and controls may be controlled by hTERT as well as other proteins in the telomere system, one of which is TZAP.

The present study found a significant negative relationship between smoking and LTL. Years of disorder and baseline YMRS scores also demonstrated a significant positive relationship. Factors such as BMI and smoking have an influence on TL and telomerase activity, and these factors could have hypothetically added to oxidative and inflammatory stress states, which may trigger cellular responses that ultimately lead to senescence and telomere shortening. It has thus been suggested that TL may be a response to cellular stress.[34] Shorter LTL has been reported to be associated with smoking, obesity, inflammation, and several somatic diseases.[35,36] The present study focused on male participants because TL is also effected by gender.[37]

A major strength of the present study was the selection of physically healthy, middle-aged men as participants. Although the patients were medication-free for the first measurements, it was not possible to control for the medication effect in the latter measurements. Previous treatments (before the medication-free period) were not analyzed, and these treatments could have affected LTL. It should also be noted that cognitive evaluations were not performed. The sample size was small for a study evaluating LTL using qPCR, and larger samples with prolonged follow-up periods must be considered in future studies. LTL and hTERT might even be biomarkers of treatment response. This is a question arising from our findings that could be resolved through proper study designs.

There does not appear to be any data about medication-free bipolar manic patients, their remission states, and TL. Studies postulating that decreased TL could be a marker of BD could not demonstrate whether or not this is truly the case based upon their data, since a wide variety of traumas and pathologies reduce TL. Considering that only a few studies have investigated TL in BD and even fewer have analyzed the clinical features related to it, it is important to target these aspects. Although the findings of the present study are novel and should be replicated, they still raise the possibility that LTL is involved with hTERT in BD. Whether a shorter LTL in mania reflects shorter brain tissue TL in bipolar individuals is unknown, but blood TL measurement is easy and may be useful as a state marker.

## Acknowledgements

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## Disclosure

The author reports no conflicts of interest.

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## ORIGINAL ARTICLE

# Effectiveness evaluation of mood disorder treatment algorithms in Brazilian public healthcare patients

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**Objective:** To assess the effectiveness of three mood disorder treatment algorithms in a sample of patients seeking care in the Brazilian public healthcare system.
**Methods:** A randomized pragmatic trial was conducted with an algorithm developed for treating episodes of major depressive disorder (MDD), bipolar depressive episodes and mixed episodes of bipolar disorder (BD).
**Results:** The sample consisted of 259 subjects diagnosed with BD or MDD (DSM-IV-TR). After the onset of symptoms, the first treatment occurred ~6 years and the use of mood stabilizers began ~12 years. All proposed algorithms were effective, with response rates around 80%. The majority of the subjects took 20 weeks to obtain a therapeutic response.
**Conclusions:** The algorithms were effective with the medications available through the Brazilian Unified Health System. Because therapeutic response was achieved in most subjects by 20 weeks, a follow-up period longer than 12 weeks may be required to confirm adequate response to treatment. Remission of symptoms is still the main desired outcome. Subjects who achieved remission recovered more rapidly and remained more stable over time.
**Clinical trial registration:** NCT02901249, NCT02870283, NCT02918097

**Keywords:** Mood disorders; bipolar; mood disorders; unipolar; clinical drug studies; economic issues; epidemiology

## Introduction

Mood disorders are highly prevalent and are related to psychological, social and functional impairment. A number of studies have associated mood disorders with high economic costs and public healthcare system overload.[1,2] Major depressive disorder (MDD) is one of the main causes of morbidity in the world,[3] with lifetime prevalence rates varying from 3% in Japan to 17% in the United States to 18.3% in Brazil.[4] According to the Global Burden of Disease Study, unipolar depression is currently considered the third leading cause of medical conditions and is predicted to be the leading cause in 2030.[3] Bipolar disorder (BD) is the eighth leading cause of disability worldwide, with prevalences of about 3% globally[5] and 0.9% in Brazil.[6]

Brazil is the largest country in South America, with a population of approximately 190 million.[7] About 70% of the population uses the public healthcare system, called the Sistema Único de Saúde (Unified Health System), or SUS, which provides free medical care to all citizens. According to DATASUS, the National Database of Healthcare Services, health care expenditures have increased significantly in recent years. Between 1995 and 1996 the total cost was R$ 12 billion (~US$ 7 billion), while in 2006 it reached R$ 40 billion (~US$ 23 billion).[8] Despite this growth, the resources devoted to health care are still insufficient for the demands of the population, causing serious equity problems.[9] In 2010, only I$ 1.06 million of the I$ 36.7 million spent on healthcare in Brazil, about 3% of the total, went to mental health care.[10]

In addition to limited financial resources, there are still few treatment guidelines for mood disorders that take the specificities of the Brazilian public health care system into account.[11] Due to insufficient financial resources, the Brazilian government developed a family health care strategy for primary health care units that provides greater coverage for mental health care, reaching 95% of Brazilian municipalities and more than 50% of the population.[12] The strategy includes a basic list of free medications that can be prescribed to patients.

A high prevalence of mental disorders has been observed among patients at Brazilian primary health care clinics, with around 52% presenting symptoms suggestive of a mental disorder and 25% presenting symptoms suggestive of depression, although the recognition of mood disorders is still precarious.[12] According to Castelo et al., 7.6% of patients seeking primary healthcare at clinics in a large Brazilian city screened positively for BD, although

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only 3.6% were actually diagnosed the disorder.[13] There are few guidelines for primary health care practitioners regarding mental health, and no data are available to evaluate the impact of interventions.[14]

In order to systematically study the effectiveness of treatment choices for patients with mood disorders in the Brazilian public health system, the authors developed pharmacological treatment algorithms for unipolar depressive episodes, bipolar depressive episodes, and mixed episodes based on the list of drugs provided by SUS (Figure 1). The aim of this study was to verify the effectiveness of these three algorithms for treating mood disorders in a sample of patients seeking care in the Brazilian public health care system.

## Methods

A quasi-experimental study design was developed to evaluate the effectiveness of treatments for mood disorders in a public health care context in the city of Porto Alegre, RS,

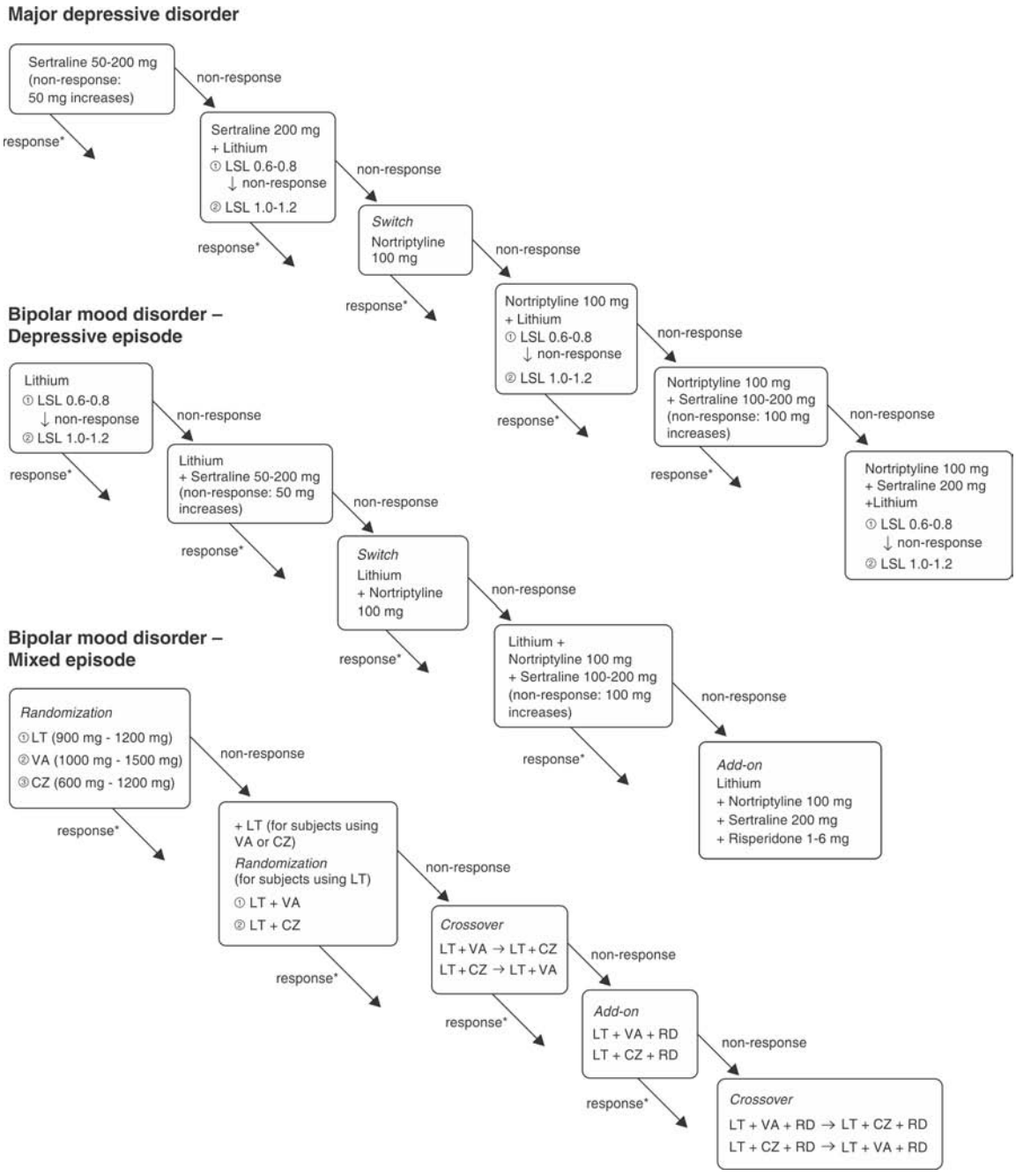


**Figure 1** Treatment algorithms. CZ = carbamazepine; LT = lithium; LSL = lithium serum level; RD = risperidone; VA = valproic acid.* Response was considered a 50% decrease in Hamilton Rating Scale for Depression baseline scores for major depressive disorder and bipolar depressive episodes, and a 50% decrease in Hamilton Scale and Young Mania Rating Scale baseline scores for mixed episode bipolar disorder.

southern Brazil. Patients with mood disorders were enrolled through general practitioner referrals or social media advertisements. The evaluations were performed between October 2010 and October 2014 at a public health outpatient clinic in Porto Alegre (Hospital Psiquiátrico São Pedro). Trained medical students and psychiatry residents provided clinical care and conducted the evaluations. Three algorithms were originally developed for treating mood disorders: one each for unipolar depressive episodes, bipolar depressive episodes, and mixed episodes. For unipolar and bipolar depressive episodes, a single-group, pretest-posttest trial approach was employed. For mixed bipolar episodes, a multi-arm, randomized, non-blinded, crossover, pragmatic trial was conducted. Following simple randomization procedures (i.e., computer-generated random numbers), mixed bipolar episode patients were assigned to 1of 3 treatment groups in a 1:1:1 allocation ratio to initially receive lithium, valproic acid or carbamazepine. The algorithms were developed by a Delphi panel of experts. The treatment sequence was carried out according to episode status, as described in Figure 1. Only medications available in the Brazilian public healthcare system were used: a) sertraline, nortriptyline, and lithium for unipolar depressive episodes; b) lithium (or valproic acid when the use of lithium was contraindicated), sertraline, nortriptyline, and risperidone for bipolar depressive episodes; c) lithium, carbamazepine, valproic acid, and risperidone for mixed bipolar episodes (Figure 1).

All participants provided written informed consent prior to participation in this study protocol. The institutional ethics committee approved all ethical aspects of this human subject study. The clinical trial registry numbers are NCT02901249, NCT02870283 and NCT02918097.

### *Sample*

The following eligibility criteria applied to all participants: a) aged between 18 and 65 years; b) current acute episode of BD or MDD; c) full capacity to understand and answer self-applied instruments; d) the presence of symptoms in the last 30 days; e) at least 30 days of abstinence for drug addicts. The exclusion criteria included: a) the presence of organic brain syndrome (OBS); b) pregnancy or lactation; c) fulfilling the criteria for psychiatric hospitalization.

### *Procedures and measurements of the study*

The study procedures were as follows: 1) sample selection began by referral from primary municipal health care clinics; 2) potential participants were given an informative lecture regarding mood disorders and the parameters of this study, after which the informed consent forms were distributed; 3) screening was conducted for BD or MDD symptoms with the Patient Health Questionnaire (PHQ-9) for depressive symptoms and the Hypomania Symptom Checklist Brazilian Version (HCL-32-BV) for manic/hypomanic symptoms; 4) diagnostic evaluation was through a Mini International Neuropsychiatric Interview (MINI) and a clinical interview for individuals whose screening results indicated BD or MDD; 5) patients with OBS were excluded (as recommended by the Mini-Mental State Examination); 6) participants were assigned to a treatment algorithm upon confirmation of diagnosis; 7) mixed-episode BD participants were randomized into one of three treatment alternatives in that algorithm; 8) baseline and demographic assessments were conducted using standardized semi-structured interviews during the first and second visits; 9) in each clinic visit, the severity of the symptoms were evaluated using the Clinical Global Impression Scale (CGI), the Hamilton Rating Scale for Depression (HRSD), and the Young Mania Rating Scale (YMRS), although individuals diagnosed with MDD were only evaluated with the CGI and HRSD; 10) participants were followed-up biweekly and then monthly after stabilization (the maximum follow-up period was 52 weeks).

The individuals included in the treatment protocols received medications that were already available in the public healthcare system, obtaining them from the hospital's dispensing pharmacy according to the previously-described algorithms (Figure 1).

### *Instruments and measures*

#### Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 is derived from the Primary Care Evaluation of Mental Disorders (PRIME-MD) instrument, which was originally developed to identify five common mental disorders in primary healthcare: depression, anxiety, alcohol abuse, somatoform disorders, and eating disorders. The PHQ-9 contains nine self-applied questions and is considered a relatively quick instrument. It has been validated for the Brazilian population with adequate sensitivity and specificity.[15]

#### Hypomania Checklist-32 (HCL-32)

The HCL-32, consisting of 32 questions, is a self-administered instrument that screens for symptoms suggestive of lifelong hypomania. It is a widely used tool for research and has demonstrated adequate psychometric characteristics regarding reliability and validity for the Brazilian population.[16]

#### Mini-Mental State Examination

This instrument is widely used to assess cognitive impairment for clinical and research purposes. The first two sections explore questions regarding orientation, memory, and attention. The second section tests the ability to name objects, follow verbal and written commands, and copy a polygon. This instrument is easily applied, lasting 5-10 minutes. It has demonstrated reliability, validity, and acceptance in the clinical field.[17]

#### Mini International Neuropsychiatric Interview (MINI) version 5.0

This is a short (15-30 minutes) semi-structured diagnostic instrument that allows diagnoses consistent with the DSM-IV-TR and ICD-10. It is available in over 30 languages, including Brazilian Portuguese.[18]

Demographic data sheet

The demographic data included age, gender, education (number of years of schooling), and socioeconomic status. To determine the latter, the Critério Brasil economic classification system was used. This system estimates the purchasing power of urban individuals and families based on a socioeconomic survey. It characterizes the physical characteristics of each respondent's dwelling, the demographics of all residents, the various household goods possessed, the public services available (e.g., sewer, water, power etc.), and household income according to a points system that determines the economic class.[19]

Hamilton Rating Scale for Depression (HRSD)

This scale was developed to evaluate and quantify depression in patients with mood disorders. Its validity and reliability are well established, being of worldwide use. Its abbreviated version, which was used in this study, consists of 17 items. The cutoff points are: 7-17 for mild depression, 18-24 for moderate depression, and 25 or more for severe depression.[20]

Young Mania Rating Scale (YMRS)

This is the most widely used assessment tool for manic symptoms. The scale consists of 11 items and is based on a patient's subjective report of his or her clinical condition over the past 48 hours. Additional information is obtained from clinical observations made during the course of the interview. Each item is related to a severity score. Four items are graded 0-8 (irritability, speed/amount of speech, thought contents, and aggressive and disruptive behavior), while the remaining seven items are graded 0-4 (elevated mood, increased activity and energy, sexual interest, sleep, language-thought disorder, appearance, and insight). Although baseline scores can vary, it is assumed that a YMRS score of 12 indicates mania. Clinical trials generally require YMRS $\geqslant$ 20 for inclusion.[21]

*Outcomes*

The main outcomes were response to treatment and remission of symptoms. Treatment response for each diagnostic protocol was measured in aggregate steps; individual steps were not assessed. Response to treatment was defined as a 50% reduction of baseline HRSD results for MDD and BD depressive episodes, and 50% reductions in both scales (HRSD and YMRS) for mixed episode BD. Remission was considered as obtaining three consecutive asymptomatic scores on the HRSD scale ($<$ 7 points) for MDD and BD depressive episodes, and on both scales (HRSD $<$ 7 points and YMRS $<$ 6 points) for mixed bipolar episodes. Participants who remained asymptomatic for 6-8 months were considered to be in remission, in agreement with the DSM-IV-TR criteria for partial and complete remission.[22]

The sample size was calculated to detect a response to pharmacological intervention with a confidence level of 95% and a statistical power of 90%. Power calculations revealed that a minimum sample size of 39 patients was needed in each drug treatment group (total 117 patients). For mixed bipolar episodes, the expected response rates were 50% in the lithium group, 50% in the valproic acid group, and 20% in carbamazepine group. For bipolar depression treatment, a minimum sample of 93 patients was calculated to provide an expected response rate of $\sim$30-40%. For unipolar depression treatment, a minimum sample of 81 patients was calculated to provide an expected response rate of 70%. These expected response rates were based on major clinical trials and diagnostic guidelines. An alpha level of .05 determined significance in all statistical analyses, which were performed in SPSS version 19 for Windows. The chi-square test was used to evaluate categorical variables. Continuous variables were analyzed using Student's *t*-test or ANOVA. Kaplan-Meier time-event curves were used to analyze response to treatment and remission of symptoms. The response maintenance and remission results were obtained through intent-to-treat analysis, using a marginal approach for handling missing data through generalized estimating equations. The HRSD and YMRS ratings over time were weighted by the inverse of the estimated probability of being observed. Changes in scores were compared to baseline.

## Results

The sample consisted of 259 subjects, the majority of whom were female. The average age was $\sim$40 and the average schooling was nine years. The most common marital status was cohabitation and the most prevalent socioeconomic category was class C (lower middle). The diagnostic prevalences were n=68 (26%) for major depression, n=78 (30%) for bipolar depression, and n=113 (44%) for mixed episode BD.

Regarding clinical variables, there was a delay of approximately six years between the onset of symptoms and the first treatment. After bipolar symptoms had been identified, there was an additional $\sim$6-year delay until mood stabilizers were used. Although most patients had moderate depressive symptoms according to HRSD scores, at least 46% had been hospitalized at least once due to mood symptoms. All subjects were similar in terms of educational level, occupational status, clinical characteristics and baseline symptom scores. These characteristics are described in Table 1.

Regarding the response to treatment over time, there was a satisfactory response to the protocols used (Figure 2). By approximately 20-30 weeks, $\sim$80% of the mixed episode BD patients, $\sim$83% of bipolar depression patients, and $\sim$85% of the unipolar depression patients had responded to treatment. The data suggest that patients with mixed episode BD take longer than those with depression to respond. It should be noted that the rates for change in mental state (mood elevation) were around 13% in subjects with bipolar depression.

With respect to maintaining treatment gains (Figure 3), the unipolar depression patients remained more stable and had lower HRSD scores than those with other disorders. Around 71% of the unipolar depression patients maintained their response over time, which was higher

**Table 1** Clinical and demographic characteristics

| | Unipolar depression | Bipolar depression | Mixed episode | p-value* |
|---|---|---|---|---|
| Age | 40.4 (11.4) | 41.9 (14.7) | 41.7 (11.5) | 0.736 |
| Education (years) | 8.6 (3.5) | 9.9 (3.9) | 9.4 (3.8) | 0.116 |
| Onset of symptoms (age) | 25.2 (13.9) | 20.5 (8.1) | 22.9 (11.1) | 0.081 |
| First treatment (age) | 32.4 (12.7) | 30.4 (10.9) | 30.6 (9.6) | 0.567 |
| Time between onset of symptoms and first treatment (years), median (IQR) | 4 (0-12) | 7 (1-15) | 6 (0-14) | 0.564 |
| Time between onset of symptoms and first use of mood stabilizers (years), median (IQR) | - | 12 (4-24) | 13 (5-23) | 0.808 |
| YMRS (baseline) | 3.2 (2.7)† | 4.0 (3.1)† | 10.1 (5.7)‡ | < **0.001**§ |
| HRSD (baseline) | 20.5 (6.6) | 19.1 (5.9) | 19.7 (7.2) | 0.418 |
| Female, n (%) | 53 (77.9) | 61 (78.2) | 90 (80.4) | 0.905 |
| Marital status (with partner), n (%) | 45 (67.2) | 54 (71.1) | 81 (74.3) | 0.593 |
| Employment, n (%) | | | | |
| Unemployed | 26 (38.8) | 17 (22.4) | 38 (34.9) | 0.279 |
| Employed | 19 (28.4) | 27 (35.5) | 32 (29.4) | |
| Retired/on leave | 22 (32.8) | 32 (42.1) | 39 (35.8) | |
| Socioeconomic status[19], n (%) | | | | |
| A and B | 20 (29.9) | 15 (19.7) | 24 (22.0) | 0.196 |
| C | 43 (64.2) | 47 (61.8) | 70 (64.2) | |
| D and E | 4 (6.0) | 14 (18.4) | 15 (13.8) | |
| History of psychiatric hospitalization, n (%) | 28 (56.0) | 28 (60.9) | 33 (46.5) | 0.282 |
| Family history of psychiatric disorder, n (%) | 53 (94.6) | 50 (89.3) | 83 (95.4) | 0.322 |

Data presented as mean (standard deviation), unless otherwise specified.
HRSD = Hamilton Rating Scale for Depression; IQR = interquartile range; SD = standard deviation; YMRS = Young Mania Rating Scale.
*Quantitative variables with symmetrical distribution are described as mean (standard deviation) and compared with ANOVA, followed by the Tukey test. Quantitative variables with asymmetric distribution are described by median (IQR) and compared using the Kruskal-Wallis test. Categorical variables are described by n (%) and compared with the chi-square test.
†No significant statistical difference between unipolar and bipolar depression YMRS scores.
‡Mixed episode YMRS scores were significantly different from unipolar and bipolar depression YMRS scores.
§$p < 0.05$.

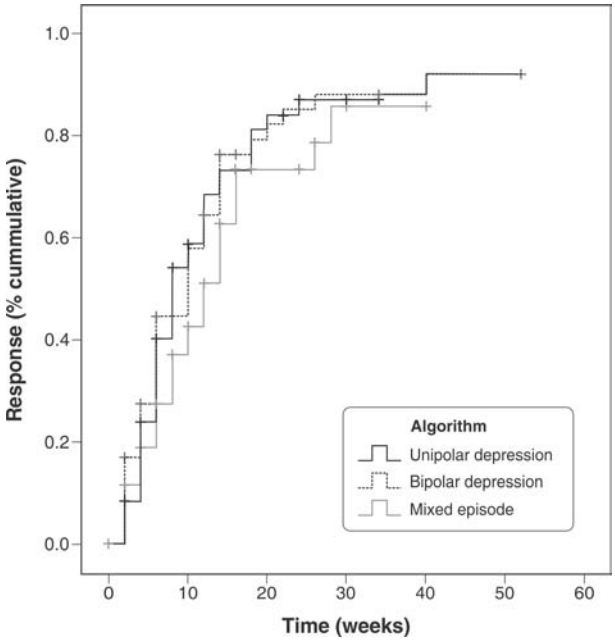


**Figure 2** Kaplan-Meier time-event curves (treatment response).

than those with mixed episode BD (47%) or bipolar depression (66%). There was a statistically significant difference between unipolar and mixed episode BD response maintenance (chi-square $p < 0.05$).

The time-event curves in Figure 4 show the number of weeks required for the subjects to present a single asymptomatic measurement on the symptom scales. For the protocols used in this study, this was expected to occur at around 20 weeks for 60% of the subjects. However, regarding the remission maintenance curves (Figure 5), it was evident that subjects who fulfilled the remission criteria did so at around 10 weeks, remaining stable thereafter. Of all the participants in the study, 34.5% achieved complete remission. Of these, 47.1% had MDD, 34.2% had depressive episode BD, and 26.9% had mixed episode BD; the difference between MDD and mixed episode BD was statistically significant (chi-square $p < 0.05$).

## Discussion

Our findings show that the proposed treatment algorithms for these three mood disorder subtypes were effective as a whole, with response rates around 80%. This is the first study using Brazilian data to evaluate an algorithm for treating mood disorders with medication available in the public health care system. Although the effectiveness of these medications has already been demonstrated in several studies, it is relevant to search for interventions that are appropriate for Brazil's economic and social conditions.[23-26] These data suggest that the public healthcare system still has major difficulties in treating these disorders properly, which is probably due to problems of access, equity, and/or identifying such cases. Despite the

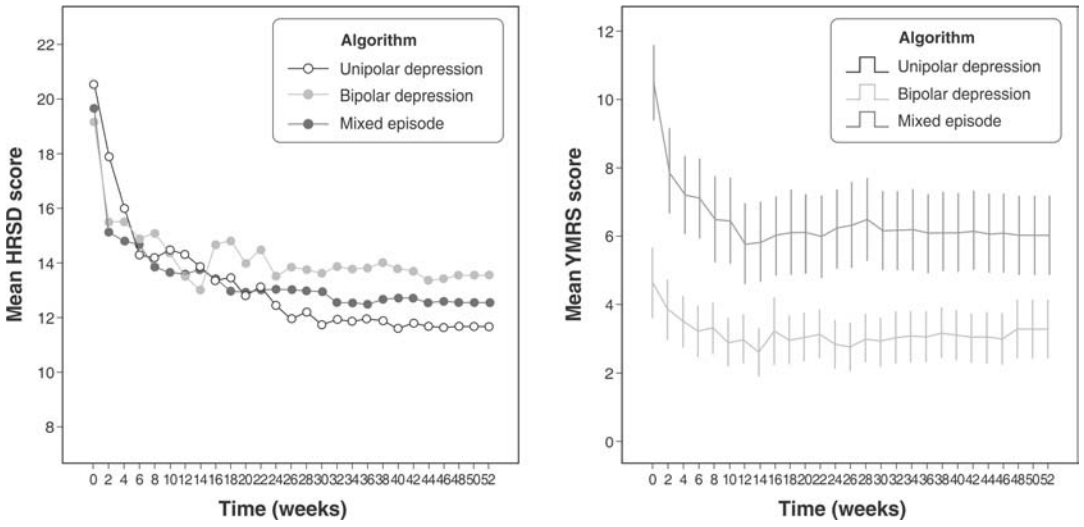


**Figure 3** Hamilton Rating Scale for Depression (HRSD) and Young Mania Rating Scale (YMRS) mean scores (follow-up).

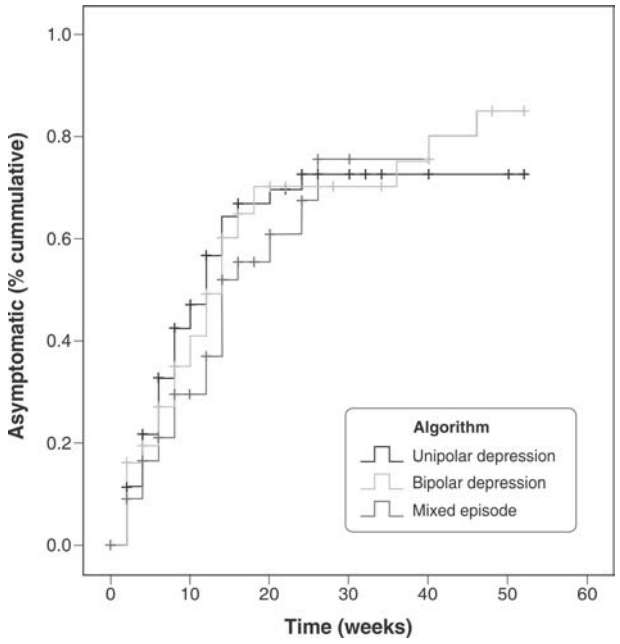


**Figure 4** Kaplan-Meier time-event curves (first asymptomatic measure).

satisfactory results obtained in this study, it was surprising to find that after symptom onset, the subjects had taken an average of six years to begin treatment and an average of 12 years to begin taking mood stabilizers.

A recent study of 5,037 adult residents of the city of São Paulo found that the prevalence of mental disorders in the 12 months prior to the evaluation was ~30%. Mood disorders were the second most frequent type of disorder, affecting 11% of the population. We observed higher prevalence rates for mood disorders than Andrade et al.[27] In our study, around 44% of subjects had mixed episode BD, followed by 30% with bipolar depression, and 26% with major depression. This was probably due to the sample type, which was derived from a secondary healthcare service involving psychiatry specialists. The lower percentages of major depression patients were probably due to the ease of identification and treatment of these subjects in primary healthcare clinics, which is in accordance with previous findings. Castelo et al. observed that doctors more easily recognized depressive symptoms in patients who tested positive on a BD screening at a primary healthcare clinic. Depressive symptoms were observed in 18.1% of the bipolar patients, while symptoms suggestive of BD were recognized in only 2 subjects (3.6%).[13] It is also surprising that, in spite of the high prevalence of psychiatric disorders in big cities like São Paulo, healthcare resources are still scarce. According to Andrade et al., only 8.7% of the Brazilian population has ever received treatment for psychiatric disorders, and only 5.3% have received treatment from a sector employing mental health experts.[27] These data help explain the treatment delay observed in our study.

Regarding the effectiveness of the algorithms, high response rates were found for the different subtypes of mood disorders. However, since the algorithms are sequential interventions, featuring combinations of more than one pharmacological option, the response rates are justified for being as high as 85% for unipolar depressive episodes, 83% for bipolar depressive episodes, and 80% for mixed episode BD. According to the (UK) National Institute for Health and Care Excellence, combining different classes of antidepressants and adjusting doses are effective strategies in depression treatment, with response rates to the first antidepressant ranging from 50 to 75%.[28,29] A number of medications are used to treat BD[30]: ample evidence indicates that lithium is effective in treating acute manic episodes and for preventing relapses, while valproate is becoming more commonly prescribed and also represents an effective treatment.[31-33] Studies on carbamazepine, however, suggest that it is less effective in preventing relapse than lithium or valproate.[34]

The literature on bipolar depressive disorder is still very controversial.[35,36] Some studies do not recommend using antidepressants, since they do not accelerate recovery

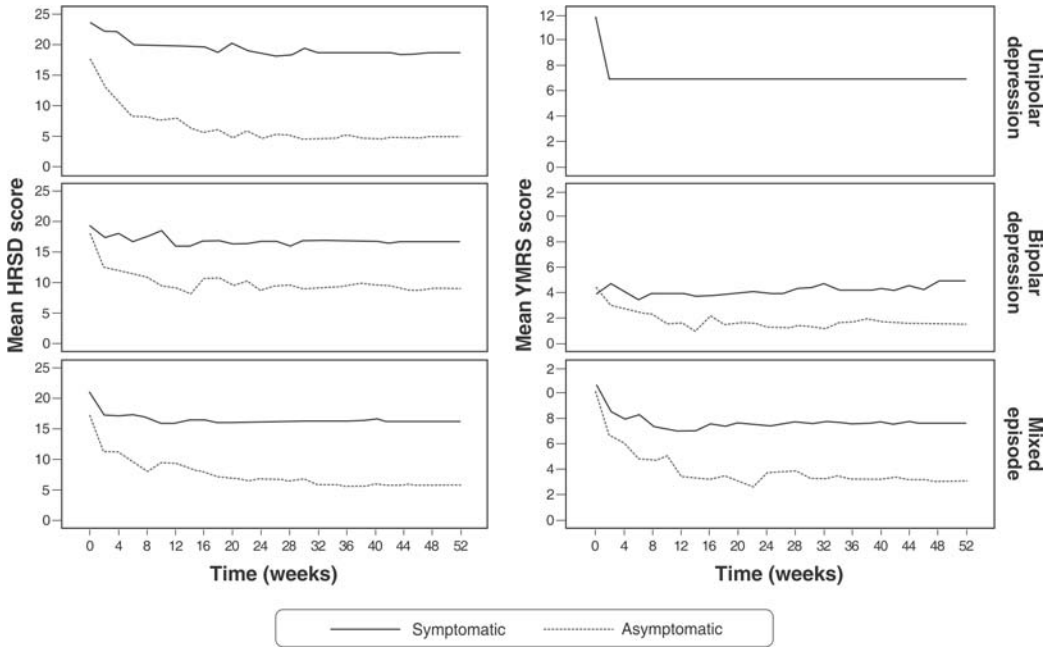


**Figure 5** Hamilton Rating Scale for Depression (HRSD) and Young Mania Rating Scale (YMRS) mean remission scores (follow-up).

time compared to monotherapy and may increase the risk of manic symptom onset.[26] Several studies have suggested monotherapy treatment with drugs such as lamotrigine and quetiapine as the first choice for treating bipolar depression.[24,37,38] On the other hand, The International Society for Bipolar Disorders (ISBD) set up a task force in 2013 featuring experts on antidepressant use in BD patients, which found that antidepressants can bring some benefit to patients who have responded to them previously during the acute phase of treatment.[39,40] For the purposes of our study, however, given that neither of these medications are made available by SUS, we started patients on lithium. If they were unresponsive after 8 weeks, lithium was associated with sertraline and so forth, as described above. The mood symptom change rate was around 13% in subjects with bipolar depression. This finding is similar to those described by the ISBD, in which changes in mood state due to antidepressant use ranged from 3.7 to 29%. According to the consensus, the tri- or tetracyclic classes, as well as the use of venlafaxine, are most associated with changes in mood state.[40]

Another important finding was the time necessary to obtain a therapeutic response. Our findings indicate that most subjects responded by the 20th weeks of treatment. Since this was a sample of individuals who had undergone previous treatment, the results may be due to their more chronic profile, in which an association of different pharmacological strategies was necessary. Subjects with mixed bipolar episodes took longer than subjects with major depression to respond to the treatment algorithms. Most obtained a response within 30 weeks. This could be because the response to treatment was only considered valid if there was a 50% reduction in both the HRSD and YMRS scales. No other study with this criterion could be found in the literature. Thus, the response may seem delayed in comparison to studies that assessed only manic or depressive symptoms.

In addition to the response to therapy, our findings suggest that obtaining complete remission is an important outcome for individuals with mood disorders. In our study, the complete remission rates were not high (47.1% of MDD, 34.2% of depressive episode BD, and 26.9% of mixed episode BD, with significant differences between MDD and mixed episode BD). These data are similar to those found in the literature.[23,24,38] Nonetheless, participants who achieved complete remission did so in approximately 10 weeks and were more stable over time than those whose symptoms did not go into remission.

Our findings should be considered in light of the study limitations: i) the study design did not provide comparisons with a control or placebo group; ii) neither the interventions nor the outcomes were blinded; iii) the study protocol was developed so that only the entire algorithm could be evaluated rather than individual steps; iv) due to missing cases , there is a level of uncertainty about longitudinal data; v) there were no dose-dependent or side effect evaluations. Despite these limitations, as a real-life assessment, many of the challenges found in clinical mental health practice were present, and the limited therapeutic choices provided by SUS were addressed. Hence, the results could contribute to the body of knowledge on public health and mental disorders, especially regarding mood disorder treatments for primary care providers.

In conclusion, great strides have recently been made in understanding mood disorders. Since these disorders have extremely heterogeneous presentations, identifying cases and prescribing appropriate treatment can still be a challenge. Our study showed response rates around 80%, suggesting that treatments can be more effective if they are coupled with longer follow-up periods. The

remission of symptoms is still the main desired outcome. In our findings, participants who achieved remission recovered more rapidly and remained more stable over time. In a country of continental dimensions such as Brazil, in which at least 11% of the population is affected by mood disorders, the development of guidelines to assist in obtaining proper treatment for these symptoms should be highly beneficial and could provide better quality of life for these people. It is our expectation that the findings of this pragmatic trial could facilitate the development of future studies and guidelines, providing useful hypotheses toward the implementation of mental health policies for SUS users.

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## Disclosure

The authors report no conflicts of interest.

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ORIGINAL ARTICLE

# Schizophrenia and work: aspects related to job acquisition in a follow-up study

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**Objective:** Work is considered one of the main forms of social organization; however, few individuals with schizophrenia find work opportunities. The purpose of this study was to evaluate the relationship between schizophrenia symptoms and job acquisition.
**Method:** Fifty-three individuals diagnosed with schizophrenia from an outpatient treatment facility were included in an 18-month follow-up study. After enrollment, they participated in a prevocational training group. At the end of training (baseline) and 18 months later, sociodemographic, clinical data and occupational history were collected. Positive and negative symptoms (Positive and Negative Syndrome Scale – PANSS), depression (Calgary Depression Scale), disease severity (Clinical Global Impression – CGI), functionality (Global Assessment of Functioning – GAF), personal and social performance (Personal and Social Performance – PSP) and cognitive functions (Measurement and Treatment Research to Improve Cognition in Schizophrenia – MATRICS battery) were applied at baseline and at the end of the study.
**Results:** Those with some previous work experience (n=19) presented lower scores on the PANSS, Calgary, GAF, CGI and PSP scales ($p < 0.05$) than those who did not work. Among those who worked, there was a slight worsening in positive symptoms (positive PANSS).
**Conclusions:** Individuals with less severe symptoms were more able to find employment. Positive symptom changes do not seem to affect participation at work; however, this calls for discussion about the importance of employment support.

**Keywords:** Schizophrenia; work; symptom; support

## Introduction

An essential characteristic of schizophrenia is its impact on psychosocial functioning, which includes impairment of self-care, independent life skills, quality of social relations and the capacity to work or study.[1] Although multiple facets of the disorder may contribute to functional incapacity, cognitive functioning and the severity of negative symptoms have been more commonly associated with impaired performance in activities related to social functioning, work or study.[2-4] In a systematic review, Shamsi et al.[5] reviewed predictors of functional incapacity in schizophrenia and found that attention, processing speed, language and memory are predictors of employability and impairments in social functioning and social skills.

According to several studies, schizophrenics who are employed report greater life satisfaction than those who are unemployed.[6-8] One of the main goals of people with mental disorders is access to activities that are satisfying and give meaning to life, including work. Most people with severe mental disorders are willing and able to work[9]; however, unemployment rates in this population remain excessively high, ranging from 80 to 90%.[1] These numbers reflect a combination of psychological and social barriers, such as stigma and lack of support and professional guidance.[10-14]

In a review, Bond & Drake[10] highlight a schizophrenia diagnosis and psychiatric symptoms as predictors of low employability, while remission is a predictor of favorable work outcomes. They emphasize that attitudes towards individuals with schizophrenia, especially from employers, and lack of access to support services act as barriers to employment.

A preparatory group is a type of prevocational training to improve work habits and personal skills. This model considers that people with mental disorders need a preparation period before seeking competitive jobs. This strategy includes participation in sheltered workshops, transition jobs, skills training and other preparatory activities.[15]

It has been argued that using support strategies during the employment process of individuals with schizophrenia is important.[11,14,16] However, most individuals with serious mental disorders do not receive supported

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employment.[10,16] According to Boycott et al.,[17] the main obstacles to implementing supported employment are organizational and systemic barriers, as well as barriers related to employment specialist competencies and attitudes. Due to policy and funding restrictions within the current Brazilian mental health care system, supported employment for individuals with schizophrenia is still in its incipient phase. Since supported employment programs are generally unavailable, prevocational programs can be a promising strategy for those who want to work.[18]

This study aimed to identify and analyze the relationship between symptomatology and job acquisition and retention. Individuals with schizophrenia were enrolled in a prevocational training group and then followed up for 18 months to analyze the relationship between achievement and permanence at work and the central features of the disorder, such as symptomatology, functionality, social functioning and cognitive aspects. We hypothesized that more favorable symptomatology profiles would present higher rates of job acquisition and retention.

## Materials and methods

### *Participants*

All individuals undergoing treatment in the Schizophrenia Program (Programa de Esquizofrenia – PROESQ) of Universidade Federal de São Paulo (UNIFESP) and the Integrated Center for Mental Health (Centro de Atenção Integrada à Saúde Mental – CAISM) of Santa Casa de São Paulo who expressed a desire for employment were invited by their psychiatrist to participate in the study. The psychiatrists were previously informed of the study's inclusion and exclusion criteria: age between 18 and 45 years (mean age: 34.24±7.42), stable psychiatric symptoms for at least 2 months prior to enrollment, and good treatment adherence in the psychiatrist's opinion. The referring psychiatrists used DSM-IV criteria for schizophrenia to determine the diagnosis.

All prospective participants were interviewed and allocated into groups for prevocational training. Groups of 10 to 15 individuals were formed until a 1-year preset deadline had expired (2012-2013). Those who had participated in at least 6 meetings were included in the study.

A convenience sample was formed of 53 of schizophrenics desiring employment, each of whom was followed up for 18 months. All participants were informed that participation in this study was voluntary and would not affect his/her treatment. All participants provided voluntary written informed consent, and the study was approved by the Ethics Committee of the Universidade Federal de São Paulo (180.554/12).

### *Instruments*

#### Clinical diagnosis data

Clinical data included onset age and duration of the disorder, medications, and alcohol and drug use.

#### Socio-occupational background

Information was obtained about the participant's last three periods of employment, including work hours and type of work, social security benefits and participation in interviews.

#### Positive and Negative Syndrome Scale (PANSS)

This scale is used to identify and quantify positive and negative symptoms in schizophrenia. The scale is divided into three sections: a) positive symptoms: 7 items; b) negative symptoms: 7 items; c) general symptoms: 16 items. All items are rated from 1 to 7 according to symptom severity (1 = absent; 2 = minimal; 3 = mild; 4 = moderate; 5 = moderately severe; 6 = severe; 7 = very severe). Higher scores indicate greater severity.[19]

#### Remission criteria

Eight items on the PANSS scale are used to define remission in schizophrenia (P1 – delusions; P2 – conceptual disorganization; P3 – hallucinatory behavior; N1 – affective blunting; N4 – social withdrawal passive/apathetic; N6 – lack of spontaneity and fluency; G5 – mannerism/posture; G9 – unusual thought content). Two factors are considered necessary to fulfill remission criteria: 1) symptomatic, all eight items must present scores $\leqslant 3$; 2) temporal, remission should be sustained for 6 months.[20] In the present study, both criteria were used, except that the temporal criterion was extended to 18 months.

#### Calgary Depression Scale

This nine-item scale assesses depression in schizophrenia. For each item, the symptom is scored as absent, mild, moderate or severe. Higher scores indicate greater severity of depression.[21]

#### Global Assessment of Functioning (GAF)

This numeric scale (0 to 100) is used as a scoring system for the severity of psychiatric disorders. It is a subjective assessment of the social, occupational and psychological functioning of patients. The scale is shown and described in the DSM-IV-TR. The score is often given in intervals of ten points.[22]

#### Clinical Global Impression (CGI)

This well-established rating tool is applicable to all psychiatric disorders and can be easily used by practicing clinicians.[23] The CGI has two components: CGI-Severity (CGI-S), which rates illness severity, and the CGI-Improvement (CGI-I), which rates change from baseline. The CGI-S rates the severity of a patient's illness on a 7-point scale ranging from 1 (normal) to 7 (extremely ill), according to the clinician's experience of patients suffering from the same condition. The CGI-I assesses the extent of a patient's clinical change at the point of assessment compared to baseline and also involves a 7-point range, from 1 (very much improved) to 7 (very much worse).[24]

Personal and Social Performance (PSP)

This scale measures four areas of individual functioning and social performance (usual social activities, personal and social relationships, self-care, aggressive and disturbed behavior). Higher scores indicate better performance.[25]

The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) cognitive battery

This recently validated instrument was an initiative to develop a standard battery of cognitive tests for use in clinical trials on schizophrenia.[26] It consists of a set of 10 tests developed through a consensus of experts and was designed to establish an acceptable way to evaluate cognition-enhancing agents, thereby providing a pathway for the approval of new medications by the U.S. Food and Drug Administration (FDA). It was also meant to aid standardized evaluations of other interventions to treat the core cognitive deficits of schizophrenia. The battery should be completed in about an hour and a half. Grouped by cognitive domains, the battery consists of the following tests (9 of the 10 tests were used): processing speed – Trail Making Test, Digit Symbol Coding Subtest, and Category Fluency Test; attention/vigilance – Continuous Performance Test (CPT); working memory – Letters and Numbers Span Test (SPAN L N) and Spatial Span Subtest (SPAN S); verbal learning – Hopkins Verbal Learning Test (HVLT); visual learning – Brief Visuospatial Memory Test (BVMT); reasoning and problem solving – Mazes. The social cognition test was not used due to lack of reasonable reliability in the Brazilian version.[26,27]

*Study design*

An exploratory study involving an 18-month follow-up was conducted. The initial evaluation took place at the end of participation in the prevocational training group (baseline), with a subsequent evaluation 18 months later. The participants' clinical, sociodemographic and employment history were assessed through a socio-occupational questionnaire.

Over the 18 months, all individuals were followed monthly through in-person meetings or telephone calls to report their participation in job interviews, study and work. Specific interventions to support job retention were not performed during the study. All individuals continued psychosocial treatment in the aforementioned services throughout the study period. Of the 53 participants, 45 were followed up for 18 months by phone, email or in person to report the circumstances of their job search. All participated in initial clinical evaluations and 41 participated in a final evaluation. Among those who did not do undergo the final clinical evaluation, three were employed and could not miss work, and one was incarcerated. However, there was a greater dropout rate with the MATRICS battery, eight unexcused absences, which left only 37 evaluations at the end of the study.

*Prevocational training*

The prevocational training program was carried out in three stages: 1) weekly 1-hour meetings with those who were as yet unsuccessful in their job search (the main barriers identified were lack of documentation, insecurity and fear about revealing their diagnosis); 2) support material about the issues raised in the previous stage was developed and shared in eight 90-minute sessions; 3) a pilot project was carried out, followed by support team training.

The main topics of the eight support sessions were: 1) the goals of the group; 2) how to communicate assertively; 3) the importance of a good résumé; 4) how to write a résumé; 5) how to behave in an interview; 6) stigma, stressors and group work; 7) the importance of relationships at work; 8) a farewell meeting.

All participants (n=53) completed the prevocational training group, produced a new résumé and acquired the necessary documentation to be hired for a formal job. It was outside the scope of the program to offer or recommend jobs.

*Data analysis*

For the analysis, baseline clinical and neuropsychological data were compared between those who worked for at least 1 month during the 18-month follow up (employed group [EG]) and those who did not (unemployed group [UG]). Previous studies have considered 1 day[12,14] or 1 week[11] as the job acquisition criterion, although Vauth et al.,[28] used a 3-month cutoff point. In the present study, job acquisition was defined as 1 month of employment to enable analysis of the relationship between work experience and possible changes in symptomatology. To analyze symptom changes in both groups during follow-up, assessments from two different points (baseline and 18 months later) were compared.

*Statistical analysis*

The sample was divided into two groups based on job acquisition: those who obtained any kind of paid work, either formal or informal, for at least 30 days (EG), n=19, and those who did not (UG), n=26. Analysis included a frequency analysis and chi-square test for categorical data, as well as the Kolmogorov-Smirnov test to determine sample distribution. To compare means, an independent *t*-test for parametric data and the Mann-Whitney test for nonparametric data were used. For repeated measures, a paired *t*-test was used for parametric data and the Wilcoxon test was used for nonparametric data. Binomial logistic regression analysis was performed to analyze job acquisition predictors.

## Results

*Sociodemographic data*

The mean age of the original sample (n=53) was 34.23 (standard deviation [SD] = 7.42) years; the majority of participants were men, n=38 (71.7%); 45 were single (84.9%); the mean years of schooling were 12.51 (SD = 3.34); 37.7% had completed high school and 35.9% had

enrolled in higher education. The mean disorder duration was 11.92 (SD = 6.66) years. A total of 45 patients completed the study; of those, 19 (35.8%) acquired a job, with 10 (52.6%) earning $\geqslant$ minimum wage. There was no statistical difference between EG and UG regarding gender, marital status, education, age or disorder duration (Table 1).

*Job acquisition analysis*

Statistically significant differences between EG and UG were found in most of the scales (Table 2), although there were no significant differences in the MATRICS cognitive battery.

At the beginning of the study, 14 (73.7%) participants from the EG met the criteria for remission and 5 (26.3%) did not. In the UG, 8 (30.8%) were in remission and 18 (69.2%) were not; this difference was statistically significant ($\chi^2$ = 1-8.091, p = 0.004). At the end of the study, 15 (93.7%) individuals from EG met the remission criteria and 14 (56%) from UG were in remission, a statistically significant difference ($\chi^2$ = 1-6.716, p = 0.01).

Baseline PANSS, CGI, GAF and PSP were included in a binomial logistic regression model. An association was found between job acquisition and total PANSS score (OR = 1.15, 95% confidence interval 1.06-1.25, p = 0.001).

The average length of employment in the EG was 11.55 months (SD = 6.48). Three individuals remained employed for less than 6 months (6.8%); six (13.6%) remained employed between 6 and 12 months and 10 (22.7%) for more than 12 months.

*Symptomatic changes*

The mean baseline and final evaluations were compared to identify changes in symptoms and neuropsychology over the follow-up period. Among the EG (n=16), the mean PANSS positive scale was 8.31 (SD = 1.74) at baseline and 9.69 (SD = 2.27) at the final evaluation; this result was statistically significant ($t$ = -2.18, degrees of freedom = 15, p = 0.046). There were no significant changes in PANSS negative, general psychopathology or total score, or in Calgary, GAF, PSP or MATRICS measures. No significant results were found in the UG.

## Discussion

Fifty-three individuals with schizophrenia who participated in a prevocational training program were followed for

**Table 1** Sociodemographic comparison of employed and unemployed schizophrenics followed up for 18 months.

| | Employed | Unemployed | p-value |
|---|---|---|---|
| Gender | | | |
| Male | 14 (73.7) | 18 (69.2) | 0.745 |
| Female | 5 (26.4) | 8 (30.8) | |
| Marital status | | | |
| Single | 15 (78.9) | 23 (88.5) | 0.665 |
| Married | 1 (5.3) | 1 (3.8) | |
| Divorced | 3 (15.8) | 2 (7.7) | |
| Educational (complete or incomplete) | | | |
| Elementary school | 1 (5.3) | 3 (11.5) | 0.102 |
| High school | 11 (57.9) | 15 (57.7) | |
| Higher education | 7 (36.8) | 8 (30.8) | |
| Age, mean (SD) | 33.26 (7.1) | 34.54 (7.6) | 0.570 |
| Disorder duration, mean (SD) | 10.5 (6.6) | 12.9 (6.81) | 0.243 |

Data presented as n (%), unless otherwise specified.
The chi square test was used for comparison between groups, p $\leqslant$ 0.05.
SD = standard deviation.

**Table 2** Comparison of baseline assessments for the employed and unemployed groups.

| | Employed (n=19) | Unemployed (n=26) | Test result* |
|---|---|---|---|
| PANSS P | 8 (7/12) | 12 (7/24) | $U$ = 103.5 |
| PANSS N | 14 (9/25) | 21 (9/28) | $U$ = 130 |
| PANSS G† | 23 (3.94) | 29 (5.81) | $t$ = -3.979 |
| PANSS T | 44 (36/66) | 61.5 (42/94) | $U$ = 74 |
| Calgary | 0 (0/2) | 0.5 (0/10) | $U$ = 154 |
| GAF | 65 (55/85) | 60 (20/80) | $U$ = 115.5 |
| CGI-S | 3 (2/4) | 4 (2/5) | $U$ = 161 |
| PSP | 70 (50/90) | 60 (40/80) | $U$ = 138 |

Data presented as median (minimum/maximum), unless otherwise specified.
Calgary = Calgary Depression Scale; CGI-S = Clinical Global Impression-Severity Scale; GAF = Global Assessment of Functioning; PANSS = Positive and Negative Syndrome Scale (G = General Psychopathology Scale; N = Negative Scale; P = Positive Scale; PANSS T = Total Score); PSP = Personal and Social Performance.
* Independent $t$-test or Mann-Whitney $U$ test. All results were significant (p $\leqslant$ 0.05).
† Mean (standard deviation).

18 months. The purpose of the study was to evaluate factors related to finding and keeping employment and symptom changes during the follow-up period.

We found less clinical impairment among patients in the EG than the UG. Among those who found work (EG), 73.7% met the remission criteria at the beginning of the study. The group also presented fewer symptoms in all PANSS subscales, fewer depressive symptoms, better functionality and better social performance. These results corroborate previous studies[10-14] claiming that individuals with controlled symptoms have better performance in finding work. These results point to remission as a predictor of favorable work outcome.[13,20]

In the binomial regression analysis, total PANSS score was strongly associated with employment, since less symptomatic individuals performed better at finding work. This corroborates the results of previous studies[29-32] indicating that cognitive functioning may be decisive for job acquisition[2]; however, in the present study no statistically significant results were found in the neuropsychological evaluations. This might be explained by the relatively small sample size.

The results suggest a worsening of positive symptoms over time in the EG; however, this worsening – from 8.31 to 9.69 in the positive PANSS scale – is not clinically relevant. In fact, Leddy-Stacy & Rosenheck[33] suggest that further evaluation should be performed to estimate the minimum clinically important difference (MCID) for these symptoms.

Considering that the employment rate for individuals with schizophrenia ranges from 10 to 20%, our results are encouraging, with 35.8% of all individuals gaining some work experience during the follow-up period. These results could be explained by the participants' high level of formal education,[34] as well as their motivation to work[35] and group support.[18] However, simply obtaining a position with satisfying work hours and wages is probably not enough, since job retention remained problematic. At the end of the study, only 7 EG participants (36.8%) were still working.

Despite efforts to improve its rigor, this study has some limitations. The sample size made it impossible to analyze predictors of job retention. The sample size may have also limited analysis of the relationship between changes in positive symptoms and work experience, as well as the cognitive analyses. Moreover, this is a convenience sample of individuals with high education levels and favorable symptomatology who were undergoing treatment at university outpatient clinics, which sets the analysis within a particular context. Another limitation is related to strategy: prevocational training is associated with lower job acquisition rates than supported employment. However, the barriers to implementing supported employment in Brazil made prevocational training more feasible.

This study's findings are an important contribution, especially the favorable symptomatology among patients who found employment. Thus, it is evident that treatment to control symptoms and increase functional capacity is essential. Moreover, the prevocational training program was important for overcoming initial barriers, such as lack of official documents, fear and insecurity. The meeting format increased motivation among members and facilitated an exchange of work-related experiences.[35] Thus, prevocational programs can be considered a feasible strategy for the social insertion of similar populations.

To promote the professional inclusion of individuals with schizophrenia, certain actions are important, such as encouraging new ways to understand schizophrenia and to deal with the stigma and lack of information about the disorder.[36,37] Furthermore, work engagement requires understanding of the disorder's impact on job acquisition and retention, perception of how occupational stress interferes in the disorder's evolution, and consideration of the specificity and combination of choices involved in the job. Finally, job acquisition support entails avoiding occupational risks and minimizing the worsening of symptoms due to the effects of employment. In light of such conditions, a case can be made for developing treatment strategies that enable social participation, normalize social status and advocate for these individuals.[38,39]

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## Disclosure

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## ORIGINAL ARTICLE

# Indirect self-destructiveness in individuals with schizophrenia

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**Objective:** To explore the indirect self-destructiveness syndrome in patients with schizophrenia.
**Methods:** Two hundred individuals with paranoid schizophrenia (117 men and 83 women, mean age 37.15 years), all in remission, were examined using the Polish version of the Chronic Self-Destructiveness Scale. Two hundred well-matched healthy individuals served as a control group.
**Results:** The intensity of indirect self-destructiveness was greater in the schizophrenia group than in controls. The intensity of each manifestation was as follows (in decreasing order): helplessness and passiveness in the face of difficulties (A5), personal and social neglects (A3), lack of planfulness (A4), poor health maintenance (A2), transgression and risk (A1).
**Conclusion:** Patients with schizophrenia displayed more behaviors that were indirectly self-destructive than healthy controls; they scored better than healthy controls only on caring for their own health. The patients showed the lowest intensity of behaviors connected with the active form of indirect self-destructiveness, and the highest intensity of behaviors connected with the passive form. These findings may enable delivery of more effective forms of pharmacological and psychosocial help to patients with schizophrenia.

**Keywords:** Schizophrenia; indirect self-destructiveness; health maintenance; neglects; planfulness; helplessness

## Introduction

Behaviors causing harm to the individual, regardless of the intention, aim, awareness of their negative consequences, and time perspective (i.e., harm occurring immediately vs. later) and object of harm (physical or psychological existence of the individual), can be referred to as self-destructive behaviors. A majority of authors understand the term self-destructive behaviors to mean direct or acute self-destructiveness, i.e., self-injury, self-mutilation, and attempted and completed suicides.

However, there is a distinction between direct and indirect threat and/or harm. The subject of this work is indirect (chronic) self-destructiveness. This category is important because the behaviors it encompasses, although many are considered normal by most people, generate undesired and harmful effects in an almost imperceptible way.[1] To date, research on indirect or chronic self-destructiveness has focused mainly, if not solely, on mentally healthy people.

Kelley defines chronic self-destructiveness as behaviors involving a generalized tendency to engage in acts that increase the probability of experiencing negative future consequences and/or reduce the probability of attaining positive future ones; perhaps some individuals are constitutionally more responsive to affectively toned sensations than to information-oriented cognition.[2,3]

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The present work assumes that indirect self-destructiveness refers to behaviors with negative outcomes intermediated by additional factors, relating behavior and harm. Thus defined, indirect self-destructiveness includes not only undertaking but also abandoning actions (commission and omission); it concerns engaging in dangerous and risky situations (i.e., active form) or neglecting one's own safety or health (i.e., passive form). Furthermore, indirect self-destructiveness involved a great distance between the action and its outcome. Whereas acute/direct self-destructive behavior involves conscious and willful intent to self-inflict painful and injurious acts, sometimes with fatal consequences, chronic/indirect self-destructiveness refers to actions extended over time and across situations, with the individual being unaware of or disregarding their long-term harmful effects.[4,5] Kelley et al.[2] states that "impulsive" individuals, who are mainly motivated by current emotional factors, are more likely to engage in acts that are ultimately self-destructive than are individuals motivated by more distant cognitive considerations. The term indirect refers not only to the time distance between an action and its harmful consequences, but also to the psychological distance between the type of behavior and its psychological and physical consequences.[4]

This phenomenon is of major importance, as manifestations of self-aggression and self-destruction are also observed in individuals with schizophrenia. These patients self-impose changes in their physical appearance, which also causes various self-mutilations. Self-injury and self-mutilation take various forms, concern different parts of their bodies, and are performed in various ways and with different "tools."[6-9] Attempted and completed suicides belong to the behavioral category of actions of greater

significance, because their outcomes are more important and often ultimate.[10-12]

It has been assumed that the intensiveness of indirect self-destructiveness, both as a generalized behavioral tendency and of its discrete categories, is different in individuals with schizophrenia than in healthy individuals. However, there have been few studies on indirect self-destructiveness in individuals with schizophrenia using a holistic, comprehensive approach; the international literature is limited to studies of some discrete manifestations of the phenomenon. Within this context, the present study is a subsequent stage of an earlier project, the preliminary results of which have already been published.[13,14] The aim of this work is to assess and explore indirect self-destructiveness in a holistic, comprehensive manner – i.e., addressing it as a syndrome rather than assessing its discrete symptoms – in individuals with schizophrenia.

## Methods

Permission was obtained from the Bioethics Committee of the Medical University of Lodz, Poland (RNN/266/12/KB according to ICH GPC) before starting the research. The recommendations of the Declaration of Helsinki were followed. The survey was anonymous, participation was voluntary, and consent was obtained from patients beforehand.

### *Participants*

A group of 200 patients (117 male, 83 female) meeting ICD-10 criteria for paranoid schizophrenia, aged 27-58 years (mean 37.15 years), was examined. All patients were clinically stable, had not been hospitalized in the preceding 12 months, and had been on the same medication for at least 6 months. None of the patients was considered acutely unwell or in relapse; all were in partial or complete remission, which facilitated work. The patients were diagnosed by experienced psychiatrists, using instruments such as the Positive and Negative Syndrome Scale (PANSS) to measure symptoms, and recruited at Mental Health Centers, in Lodz voivodeship, Poland. The control group was well matched in terms of sociodemographic characteristics and consisted of 200 healthy individuals. The characteristics of both groups are presented in Table 1.

Examinations were anonymous and participation was voluntary. Consent was obtained from all patients before examination. An experienced clinical psychologist and psychotherapist examined patients and controls using the Chronic Self-Destructiveness Scale (CS-DS) and a sociodemographic questionnaire.

The exclusion criteria for the schizophrenia group were relapse and double diagnosis. Exclusion criteria for the control group were use of narcotic substances and need for psychological and/or psychiatric help on the basis of observation, clinical interview, and self-report on the sociodemographic questionnaire.

### *Materials*

In order to assess indirect (chronic) self-destructiveness, the Polish version of Kelley's CS-DS, as adapted by Suchańska, was used. To examine chronic self-destructiveness as a generalized tendency, Kelley developed a research tool eliciting information for groups or categories of behaviors such as carelessness, poor health maintenance, evidence of transgression, and lack of planfulness. The ultimate version consists of an internally consistent set of 52 items scored on a Likert-type scale; the total score informs about the intensity of indirect self-destructiveness.[2] The Polish version of the scale is characterized by high reliability (Cronbach's alpha: 0.811) and validity (0.823), as was the original instrument, and includes the following subscales: transgression and risk (A1; example items: I like jobs with an element of risk; I have done dangerous things just for the thrill of it; Lots of laws seem made to be broken), poor health maintenance (A2; example item: I am familiar with basic first-aid practices), personal and social neglects (A3; example item: I usually meet deadlines with no trouble), lack of planfulness (A4; example item: I seldom have even minor accidents or injuries), and helplessness and passiveness in the face of difficulties (A5; example item: Sometimes I don't seem to care what happens to me). CS-DS scores between 52 and 104 are considered low, between 105 and 160 are rated as medium, and from 161 to 260 are considered high.[15]

**Table 1** Sociodemographic characteristics of the sample

| Variable | Schizophrenia | Healthy controls |
|---|---|---|
| Sex | | |
| Female | 83 (41.50) | 83 (41.50) |
| Male | 117 (58.50) | 117 (58.50) |
| Age, years | | |
| Mean (SD) | 37.15 (5.10) | 37.50 (6.77) |
| Range | 27-58 | 26-59 |
| Educational level | | |
| Elementary | 35 (17.50) | 34 (17.00) |
| Vocational | 53 (26.50) | 52 (26.00) |
| Secondary | 92 (46.00) | 93 (46.50) |
| Higher | 20 (10.00) | 21 (10.50) |
| Marital status | | |
| Married | 81 (40.50) | 83 (41.50) |
| Divorced | 15 (7.50) | 14 (7.00) |
| Single | 91 (45.50) | 90 (45.00) |
| Widowed | 13 (6.50) | 13 (6.50) |
| Area of residence | | |
| Urban | 110 (55.00) | 111 (55.50) |
| Rural | 90 (45.00) | 89 (44.50) |

Data presented as n (%), unless otherwise specified.
SD = standard deviation.

### *Statistical analysis*

Scores were analyzed statistically by calculation of means and standard deviations and application of the chi-square, Student's *t*, and Mann-Whitney *U* tests. Factor analysis, multiple regression analysis, and hierarchical cluster analysis were also conducted. To explore the factor structure of the indirect self-destructiveness syndrome in schizophrenia group, the scores obtained for the CS-DS subscales were analyzed using factor analysis by the principal

components method with varimax normalized rotation and eigenvalue $\geqslant$ 1.00. To explore relationships (associations) between the variables of interest, the correlation-regression procedure was applied. For all analyses, the maximum acceptable type I error was assumed at $\alpha = 0.05$. Asymptotic two-sided test probability p-values were calculated, and $p \leqslant 0.05$ considered statistically significant. Statistical analyses were conducted using SPSS version 24.0[16] and Statistica version 13.0.[17]

## Results

### *Description of the indirect self-destructiveness syndrome in patients with schizophrenia*

Table 1 reports the characteristics of the case and control groups. Table 2 presents the rank order of patients' scores in particular CS-DS subscales.

As indicated by the data, the intensity of indirect self-destructiveness in patients with schizophrenia remained within the range of mean scores. The intensity of indices of particularly indirectly self-destructive behavior categories seems to be of key importance for considerations in this work. The highest intensity was that of helplessness and passiveness in the face of difficulties and failures (A5). The second highest in intensity, but still much lower, was the score for personal and social neglects (A3), i.e., neglect of many things of various importance. The third highest in intensity was the score for lack of planfulness (A4), which may be related to negative events, apparently without connection with the individual's conduct. The intensity of poor health maintenance (A2) was lower; this scale includes, e.g., non-compliance with professionals' recommendations and advice, and was thus of special importance for the study sample. Among all the indirectly self-destructive behavior classes, the lowest intensity was that of transgression and risk (A1), including transgressive and even risky and dangerous acts.

To determine predictors of indirect self-destructiveness, stepwise multiple regression analysis was used. All five categories of indirectly self-destructive behaviors were included in the initial regression equation model. As shown in Table 3, all categories of indirectly self-destructive behaviors remained in the regression equation and explained 94.25% ($R^2 = 0.9425$) of variance of the indirect self-destructiveness variable in patients with schizophrenia; in other words, the set of these variables best explained the indirect self-destructiveness syndrome in patients with schizophrenia. Furthermore, it can be stated that all particular categories of behaviors had their own contribution to forming the indirect self-destructiveness tendency in patients with schizophrenia. As shown in Table 3, significant contributions to the prediction of indirect self-destructiveness in the study sample were made by transgressive and risky behaviors (A1) and personal and social neglects (A3), with standardized regression coefficients at 0.395 and 0.365 respectively.

**Table 2** CS-DS subscales scores rank order in the patients' population

| CS-DS subscale | | Mean | SD |
|---|---|---|---|
| Indirect self-destructiveness | | 126.257 | 21.815 |
| Rank | CS-DS subscale | Mean ranks | Sum of ranks |
| 1 | A5 - Helplessness and passiveness | 4.228 | 380.500 |
| 2 | A3 - Personal and social neglects | 3.144 | 283.000 |
| 3 | A4 - Lack of planfulness | 2.950 | 265.500 |
| 4 | A2 - Poor health maintenance | 2.517 | 226.500 |
| 5 | A1 - Transgression and risk | 2.161 | 194.500 |

CS-DS = Chronic Self-Destructiveness Scale; SD = standard deviation.

### *The structure of indirect self-destructiveness in patients with schizophrenia*

To explore the factor structure of indirect self-destructiveness in patients with schizophrenia, factor analysis of their scores in the CS-DS was conducted (principal components extraction method, varimax normalized rotation). Two factors emerged from this analysis (Table 4 and Figure 1). Factor I consisted of the following variables: lack of planfulness (A4), personal and social neglects (A3), and poor health maintenance (A2); as the highest factor loading was that of lack of planfulness (A4), factor I was named lack of planfulness. Factor II consisted of two, apparently opposite, variables: helplessness (A5) and transgression (A1); this factor was named helplessness. Similar results were obtained after different types of factor analysis, i.e., oblique, confirmatory, and hierarchical.

Factor analysis of healthy controls' scores yielded only one factor, comprising all the variables/indirect self-destructiveness categories, as was the case in other studies.[2,15]

**Table 3** Determinants of indirect self-destructiveness in patients with schizophrenia

| Variables | Beta ($\beta$) | SE of Beta ($\beta$) | Standard B ($\beta$) | SE of B ($\beta$) | *t* (195) | p-level |
|---|---|---|---|---|---|---|
| A1 - Transgression and risk | 0.395 | 0.029 | 0.724 | 0.053 | 13.155 | $p < 0.001$ |
| A2 - Poor health maintenance | 0.194 | 0.031 | 0.818 | 0.133 | 6.105 | $p < 0.001$ |
| A3 - Personal and social neglects | 0.365 | 0.032 | 1.069 | 0.099 | 10.662 | $p < 0.001$ |
| A4 - Lack of planfulness | 0.297 | 0.030 | 1.201 | 0.120 | 9.957 | $p < 0.001$ |
| A5 - Helplessness, passiveness | 0.157 | 0.029 | 1.267 | 0.238 | 5.285 | $p < 0.001$ |

SE = standard error.
Coefficient of multiple regression: R = 0.972.
Coefficient of determination (R square): $R^2 = 0.9425$.
Corrected coefficient of determination (adjusted R square): $R^2 = 0.940$.
Significance of the regression equation: $F_{5,195} = 275.99$, $p < 0.0000$.
Standard error of the estimate: 5.6305.

**Table 4** Factor analysis of Chronic Self-Destructiveness Scale (CS-DS) scores of patients with schizophrenia

| Factors/variables | Factor loadings | |
|---|---|---|
| I. Lack of planfulness | (Eigenvalue = 3.239) | Explained variance = 53.97% |
| A4 - Lack of planfulness | 0.865 | Cumulative explained variance = 53.97% |
| A3 - Personal and social neglects | 0.782 | |
| A2 - Poor health maintenance | 0.527 | |
| II. Helplessness | (Eigenvalue = 1.005) | Explained variance = 17.72% |
| A5 - Helplessness, passiveness | 0.876 | Cumulative explained variance = 71.69% |
| A1 - Transgression and risk | 0.694 | |

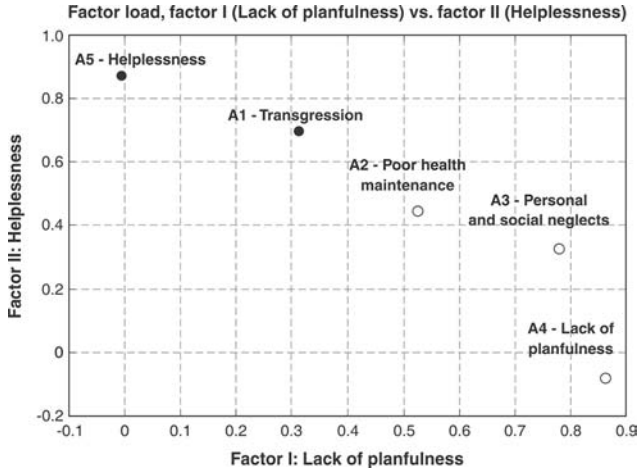


**Figure 1** Factor loadings of patients' scores in the Chronic Self-Destructiveness Scale (CS-DS).

*Indirect self-destructiveness in patients with schizophrenia and in healthy individuals*

To compare the structure of indirect self-destructiveness in patients with schizophrenia and healthy individuals, the CS-DS subscales scores obtained by each group were compared using a *t*-test for normally distributed scores and the Mann-Whitney *U* test otherwise (shown in italic in tables). The results of comparisons are presented in Table 5.

As shown in Table 5, statistically significant differences were found in the following indices: indirect self-destructiveness (global index), poor health maintenance (A2), personal and social neglects (A3), lack of planfulness (A4), and helplessness (A5). Patients with schizophrenia scored higher on all of these (although not always with statistical significance) except poor health maintenance (A2).

## Discussion

The findings of this study indicate that the psychotic process of schizophrenia causes indirectly self-destructive tendencies to be higher in patients with this condition than in healthy individuals. As a matter of fact, the contribution of psychotic experiences to the development of indirect self-destructiveness in patients with schizophrenia has been reported before. Schizophrenic disorders are a predictor of indirect self-destructiveness syndrome in these patients. Among schizophrenic and paranoid disorders and symptoms, persecutory ideas, especially the sense of injustice and experiencing life as an enormous effort, are an important factor in determining indirect self-destructiveness.[14] The structure of indirect self-destructiveness, and which of its components (categories) make it stronger as a generalized behavioral tendency in patients with schizophrenia than in healthy individuals, have yet to be determined.

The highest CS-DS scores of patients with schizophrenia, significantly higher than those of healthy controls, were in the subscale of helplessness and passiveness in the face of difficulties (A5). This means that, more often than healthy controls, patients gave up on an activity in situations in which that activity could stop suffering or prevent a threat. This reflects effects of motivation deficits and learned helplessness, which is associated with attributional style.[18]

As was mentioned before, the indirectly self-destructive tendency includes not only commission of dangerous actions (active form), but also omission or neglect of actions which could improve quality of life (passive form). The situation of patients with schizophrenia is similar to learned helplessness because they often face events or situations which they cannot control (e.g., psychotic experiences, psychosis relapse, drug resistance, and other unpleasant life events).

The above are related to intentional and, at least, "serial" failures, defeats, and helplessness. Previous research has shown that a sense of inferiority seriously affected Abasement and Deference (using Murray's terms[19]) in patients with schizophrenia; furthermore, in patients with schizophrenia, the intensity of "will of power" and achievement was lower.[20,21]

This is consistent with the idea that individuals with uncertain self-esteem may feel strongly threatened in conditions of high social expectations and more safe in conditions of low expectations and standards.[15] Thus, it can be assumed that low motivation and low intensity of need for achievement may constitute a self-defense mechanism to protect the self from self-destructiveness. On the other hand, patients with schizophrenia may also be overwhelmed and exhausted by their struggle. Other studies have also found relationships between chronic (indirect) self-destructiveness and feelings of hopelessness and helplessness.[15,22]

Personal and social neglects (A3) was the next category of indirectly self-destructive behaviors in which patients scored significantly higher. This means that, in the population of patients with schizophrenia, situations of personal and social failures occurred more often because of neglecting activities which could improve their social and

**Table 5** Comparisons of CS-DS scores of patients with schizophrenia vs. healthy controls

| CS-DS subscales | Schizophrenia | Controls | Significance | |
|---|---|---|---|---|
| | Mean (SD) | Mean (SD) | *t* or *U* | p-value |
| Indirect self-destructiveness | 126.257 (21.815) | 121.561 (18.005) | 1.975* | 0.05 |
| A1 - Transgression and risk | *39.202 (12.430)* | *39.151 (8.525)* | *5326.000*† | *ns* |
| A2 - Poor health maintenance | *25.232 (5.361)* | *27.575 (6.369)* | *4423.500*† | *0.01* |
| A3 - Personal and social neglects | *30.958 (7.767)* | *28.356 (5.890)* | *4183.500*† | *0.004* |
| A4 - Lack of planfulness | *21.279 (5.616)* | *19.238 (4.831)* | *4210.000*† | *0.004* |
| A5 - Helplessness, passiveness | *7.658 (2.813)* | *5.879 (2.116)* | *4220.500*† | *0.005* |

CS-DS = Chronic Self-Destructiveness Scale; ns = nonsignificant; SD = standard deviation.
* Student's *t* test; † Mann-Whitney's *U* test.
Italic font indicates non-normal distribution.

life situations or interpersonal relations. This issue of serial failures, noted above, may be explained by the concept of cognitive dissonance: the individual who encounters failures seeks subsequent failures in order to avoid a cognitive dissonance situation which success could cause. This particularly dramatic form of aspiration expectation regulation by so-called strategic failures is evidence of a readiness to incur high psychological costs in order to preserve a feeling of safeness, which is disturbed in patients with schizophrenia.[20,21,23]

Omissions reflect passiveness in the face of negative events and seem to be the opposite of readiness for risk-taking, sensation and stimulation seeking.[4,15] This may be associated with lack of planfulness (A4), a subscale in which patients scored significantly higher than healthy controls. Planning behavior is largely dependent on cognitive functions, especially abstract thinking, an area known to be impaired in schizophrenia since Kraepelin's concept of dementia praecox.[24-26] Motivation, the second type of function on which planning is dependent, is also assumed to be affected by dysfunctions, such as the so-called schizophrenic low motivation.[21,27,28] Similarly to personal and social neglects (A3) and helplessness and passiveness in the face of difficulties and failures (A5), this category belongs to the passive form of indirect self-destructiveness.

Attention should be paid to the category of behaviors in which patients with schizophrenia scored significantly lower than healthy controls, namely, poor health maintenance (A2). It can be assumed that patients comply with professionals' advice concerning therapy and even prevention (e.g., of psychosis relapse) to a greater degree. They accept immediate costs and inconveniences (regular and repeated: appointments with professionals, buying medications, taking medications despite their often unpleasant side effects, participation in socio- and psychotherapeutic activities) to reduce the probability of long-term costs (e.g., acuteness of psychotic symptoms, psychosis relapse, and hospitalization). This may reflect an attempt by patients to improve their own lives by at least avoiding and preventing unpleasant consequences, which is consistent with the statement that lack of punishment (negative reinforcement) is also a reward (positive reinforcement).[29]

Patients with schizophrenia scored lowest in the A1 subscale (transgression and risk), which includes behaviors typically regarded as indirectly self-destructive. Behaviors violating norms are actions which result in the destruction of the *status quo*, i.e., a disturbance of some order. Patients with schizophrenia tend to avoid changes, especially the destruction of some order, because it may disturb their feeling of safeness.[20,21,23]

Based on the findings of the present study, it can be stated that patients with schizophrenia show the lowest intensity of categories of behaviors connected with the active form of indirect self-destructiveness, and the highest intensity for those connected with its passive form; an explanation taking into account psychotic experiences, negative symptoms, and withdrawal seems to be appropriate. In the structure of the indirectly self-destructive tendency of patients with schizophrenia, there is a greater contribution of helplessness and passiveness in the face of difficulties. This finding is consistent with the low motivation and low activity – particularly, the low intensity of need for achievement – found in previous research.[20,21,30]

The factor analysis conducted in this study yielded two factors, with variables belonging to the passive form of indirect self-destructiveness having the highest loading in both factors. Indirect self-destructiveness as a generalized tendency is idiosyncratic in individuals with schizophrenia; it is of a "dual" nature, as demonstrated by the factor analysis. Factor analysis of the scores obtained by healthy controls, as opposed to those of patients, revealed only one factor combining all the variables. This conforms to the results of other studies.[2,15] Based on the foregoing, it can be stated that the specificity of the syndrome of indirect self-destructiveness in patients with schizophrenia consists in the prevalence of its passive form, with a particular contribution of helplessness and passiveness.

The helplessness and passiveness of patients with schizophrenia in the face of problems and difficulties may be determined by a psychological breakdown of defense mechanisms, which may constitute a certain aspect of indirect self-destructiveness, i.e., the deficit in defense. Some confirmation has been found for a deficit in the self-care ego function. The issue of breakdown of the psychological defense system deserves special attention, since indirect self-destructiveness may be considered a manifestation of self-aggression as well as a deficit of the self-care ego function.[5]

Ego and self are important concepts for discussion in this work. Bleuler[25] coined the term schizophrenia (σχιζοφρενεια) from two Greek (Hellenic) words: *schizein* (σχιζειν, to split) and *phrēn* (φρην, mind), i.e., splitting of

the mind; he considered autism (Gr. αυτος, self) as one of the fundamental symptoms of schizophrenia. According to some authors, schizophrenia is a self-disorder or an ipseity disturbance in which one finds certain characteristic distortions of the act of awareness and is best understood as a particular kind of disorder of consciousness and self-experience.[31] (Ipseity refers to the experiential sense of being a vital and self-coinciding subject of experience, or the first-person perspective on the world, from the Latin *ipse*, self or itself[31]). Moreover, the abovementioned autism can be understood as an expression of disturbed selfhood, and it is the clinical essence of schizophrenia, in the sense of a detachment from reality. This disturbance of the basic sense of self may underlie the social cognition difficulties that result in the poor social functioning observed in schizophrenia, i.e., compromised social relationships, social behaviors, and social activities.[32] Some concepts claim that difficulties in self-other processing lie at the core of schizophrenia and pose a problem for patients' daily social functioning – e.g., when confusing self and other, one may project one's own intentions and emotions onto others, or take over the intentions and emotions of others. Abnormal processing of self and other may be an important factor in explaining impaired social functioning in patients with schizophrenia.[33] The above may be reflected in the finding that, in patients with schizophrenia, indirect self-destructiveness was associated with a feeling of being harmed by life, which may cause a suspicious attitude toward people; on the other hand, a sense of injustice, a feeling of being misunderstood by others, and a feeling that life lacks meaning played very important roles in shaping indirectly self-destructive tendencies. Moreover, the perception of life as a tremendous effort, the feeling of being harmed by life, and lack of hope for improvement held great significance for indirect self-destructiveness.[14]

Attention should be paid to a research project implemented in Finland in 1994, in which 670 schizophrenic patients aged 15-64 were interviewed 3 years after discharge from psychiatric hospitals. Poor financial situation and history of alcohol misuse, among others, seemed to be associated with increased risk of violent victimization, with patients constituting a vulnerable subgroup in that respect. This subgroup may need additional care and protection from dangers posed to them by other members of society.[34] Although the topic of that study was not indirect self-destructiveness, the results were consistent with this syndrome: some forms of self-defeating, lack of resourcefulness, serial failure, and being a victim of violence could be considered manifestations of indirect self-destructiveness.

To conclude, it can be stated that indirect self-destructiveness has a significant impact on individual management of everyday life and can lead to directly self-destructive behaviors. It seems that, inasmuch as the pattern of indirect self-destructiveness in healthy individuals includes mainly searching for stimulation, strong sensations, and hedonistic motives, the pattern of indirect self-destructiveness in patients with schizophrenia is based on resignation, withdrawal, and protection of the "self" or a self-defense deficit. It might be assumed that these patients lack motivation to protect themselves and even their own lives.

The results of this study may have preventive and therapeutic implications. As far as the prevention aspect is concerned, not only individuals who tend to engage in dangerous and high-risk situations (active form of indirect self-destructiveness), but also those who neglect their own safety or health (passive form of indirect self-destructiveness), should be the subject of experts' interest. The latter (passive) form, of neglects, is especially neglected in preventive and therapeutic work. In these patients, the motivation to undertake an effort to care for their health by these patients is an encouraging and buoyant result, since self-care is a factor that holds promise for patients, both as a prognostic factor and for the possibility of independent living. Moreover, it should be kept in mind that this is the only category in which patients demonstrate fewer self-destructive behaviors than healthy people do.

The findings of this study may contribute to the provision of more effective forms of pharmacological and psychosocial help to patients with schizophrenia. The differences found in categories of indirect self-destructiveness could provide insights into how patients manage their own illness, how their illness leads to problems in those behaviors, and even support the design of practice guidelines to help patients with their disease and indirect self-destructiveness.

Complex therapeutic (psychiatric, psychological, and social) actions should aim to enhance the defense-of-self and self-care functions in patients with schizophrenia, improve patients' self-image, and evaluate its adequacy and efficiency. Equally important within (psycho)therapy is to work with patients toward enhancing their sense of life, even though life did not spare them suffering. Mobilization and orientation of their activities toward actions that support their development and health seems just as vital.

The findings of this study do not differ substantially from the results obtained at an earlier stage of this research project.[13] This may mean that the general regularities and direction of the relationships remain the same. Some limitations must also be mentioned. One may be the impact of antipsychotics (especially their side effects) on the psychological functioning of individuals with schizophrenia. However, this impact is unavoidable, since, in most cases, patients must take lifelong medication. Another possible limitation could be the self-report design of the study: the healthy controls may have intended to appear better than they actually were. However, this remark could apply to any self-report instrument; besides, social desirability has not been found to correlate significantly with CS-DS.[2] One could argue that this clinically stable sample could mean that patients had good adherence to treatment, which, in turn, could explain why these patients had better health maintenance than even the healthy controls did. On the other hand, some research designs, especially when seeking to address psychological functioning, actually require patients to be clinically stable and in remission. The aforementioned idea is interesting, but the actual relationship may well be inverse: good adherence to treatment may be caused by

low poor health maintenance. However, regardless of causal relationship, could it justify the fact that individuals with schizophrenia neglect their health less than healthy individuals do? Perhaps these patients simply want to be healthy, feel less ill, or both. Another limitation may be the fact that patients were not diagnosed with a specific instrument, (e.g., the Structured Clinical Interview [SCID]) but rather according to the ICD-10 criteria and by the means of PANSS (to measure symptoms). Finally, the scarcity of studies on this topic in the literature makes it difficult to compare and verify the findings of the present investigation.

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## Disclosure

The author reports no conflicts of interest.

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## ORIGINAL ARTICLE

# Prevalence, clinical correlates and maternal psychopathology of deliberate self-harm in children and early adolescents: results from a large community study

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**Objectives:** Little is known about the prevalence and correlates of deliberate self-harm (DSH) in children from low- and middle-income countries. We investigated the prevalence of DSH and its clinical and maternal psychopathological associations in Brazilian children (n=2,508, ages 6-14y) in a community-based study.
**Methods:** Participants of the High Risk Cohort Study for the Development of Childhood Psychiatric Disorders (HRC) and their mothers were assessed in structured interviews. Current (last month) and lifetime DSH were estimated, including analysis stratified by age groups. Logistic regressions were performed to investigate the role of the children's clinical diagnoses and maternal psychopathology on DSH prevalence estimates, adjusting for potential confounding factors.
**Results:** The prevalence of current DSH was 0.8% (children 0.6%, adolescents 1%) and lifetime DSH was 1.6% (1.8% and 1.5%, respectively). Current and lifetime DSH were more frequent in children with depression, attention-deficit/hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD), even in multiple models accounting for demographic variables and co-occurring psychiatric disorders. Maternal anxiety disorder was strongly associated with current and lifetime DSH in offspring; whereas current DSH, specifically in young children, was associated with maternal mood disorder.
**Conclusion:** Diagnoses of depression, ADHD and ODD were consistently associated with DSH, as was having a mother with anxiety disorder.

**Keywords:** Deliberate self-harm; self-injurious behavior; suicide attempt; community survey; family health; psychopathology

## Introduction

Deliberate self-harm (DSH) is defined as any act of self-poisoning or self-injury carried out by an individual, regardless of motivation or desire to die.[1] DSH is one of the strongest predictors of completed suicide,[2-4] which is the second leading cause of death among 10- to 24-year-olds worldwide, accounting for 6.3% of all deaths.[5] Suicide is the third leading cause of death among youth in low- and middle-income countries (LMIC), accounting for 8% of all deaths among 15- to 29-year-olds.[6] According to the World Health Organization, 75% of suicide deaths worldwide occur in LMIC, which have limited resources to address the issue.[6] This personal tragedy also has devastating consequences for families and the community.[7]

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Community studies have demonstrated that DSH is a set of increasingly common behaviors beginning at age 12 and peaking at around age 15, which then decline by young adulthood.[8-10] Adolescents who deliberately self-harm are at increased risk for developing depression and anxiety disorders later, as well as for repeating DSH by 18 years of age.[11] It was also observed that individuals clustered into overlapping high-risk trajectories of DSH, other suicidal behaviors and substance abuse had high scores for borderline personality disorder criteria.[12] Youth DSH prevalence rates are highly variable, with world lifetime estimates ranging from 4 to 42% and 12-month estimates varying from 3 to 21%, depending on the instruments and methods used to assess suicidal behavior.[13]

In 32 LMIC, the pooled 12-month prevalences of suicide ideation among adolescent females and males, respectively, were 16.2% and 12.2%.[14] The reported prevalence of suicide attempts by adolescents in LMIC ranges from 2.9 to 3.2%.[15-17] In Brazil, the few available studies show a prevalence of suicide ideation in adolescents ranging from 8 to 14%,[18-20] suicide planning from 6 to 10%,[20,21] and suicide attempts from 5.5 to 8.6%.[20,22]

DSH varies substantially according to demographic, clinical and familial factors. Although suicide is more common in young males,[23] DSH is more common in young females.[10,15,20,24-26] High rates of this behavior are also found in adolescents from lower socioeconomic groups.[24,27,28] These findings are not consistent across ethnic groups.[10,24,26,29-32] Furthermore, studies have shown a strong relationship between DSH and mood, anxiety, disruptive, substance use and eating disorders.[9,10,24,27,33,34] Finally, DSH is more common among the offspring of individuals with psychiatric disorders.[35-38]

Despite the seriousness of the problem, little is known about the prevalence of DSH among children and early adolescents in LMIC or its demographic, clinical and familial correlates. No studies adjusted for the co-occurrence of DSH and psychiatric diagnosis have been conducted. More importantly, there is little information worldwide about suicidal behavior in children less than 10 years of age. In the present study, we investigated the prevalence of DSH in Brazilian children and adolescents as part of a large community-based study and explored the role of relevant clinical and familial factors related to DSH.

## Methodology

### *Study design and participants*

The High Risk Cohort Study for the Development of Childhood Psychiatric Disorders (HRC) is a large community school-based study of children aged 6 to 14 years from 57 schools in two Brazilian cities: Porto Alegre (n=22) and São Paulo (n=35). During the screening phase, which took place on school enrollment day, 9,937 respondents were interviewed using the Family History Survey.[39] From this pool, two subgroups were recruited using a random selection (n=958) or high-risk selection procedure (n=1,554), which resulted in 2,512 subjects. Four subjects were excluded from the analysis due to missing data for outcome variables, resulting in a total sample of 2,508 subjects with an average age of 9.7 years upon recruitment (standard deviation [SD] = 1.92). Details about the sample and the methodological procedures can be found in Salum et al.[40] This study was approved by the ethics committee of the Universidade de São Paulo (protocol IORG0004884; CONEP no. 15.457; project IRB registration no. 1132/08). Written consent was obtained from all participants' parents, and verbal consent was obtained from all the children. All children with suicidal thoughts were offered consultation with trained psychiatrists and psychologists and were referred to proper services for treatment.

### *Instruments and measures*

#### Outcomes

Interviews were conducted at home with the biological parents. We collected parental reports about current (last month) and lifetime DSH using the following yes/no questions from the suicidal behavior items of the Brazilian Portuguese version of Development and Well-Being Assessment (DAWBA), a structured interview administered by lay interviewers[41]: "Over the last 4 weeks, has s/he tried to harm or hurt himself/herself?" and "In his/her lifetime, has s/he ever tried to harm or hurt himself/herself?."

#### Demographic variables

Age, gender, socioeconomic status and ethnicity data were collected. We adopted the 2009 Associação Brasileira de Empresas de Pesquisa (ABEP) criteria for calculating socioeconomic status and then merged classes A and B into a wealthy stratum, C into a middle stratum, and D and E into a poor stratum. Ethnic groups were divided into a majority group, which included Whites, and a minority group, which included Blacks, mixed-race, Asians, Native South Americans, and people of unknown ethnicity.

#### Child diagnosis

Current child psychiatric diagnoses were assessed using the DAWBA. The responses generated a computerized diagnosis according to DSM-IV-TR criteria. Child psychiatrists evaluated the responses and confirmed, refuted or altered the initial diagnosis proposed by DAWBA algorithms. Diagnoses used for data analysis were: any anxiety disorders (separation, social or generalized anxiety disorder), major depression, attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD) and conduct disorder (CD). A second child psychiatrist rated a total of 200 interviews from the study, which resulted in a high interrater agreement ($\kappa$-value = 0.80, expected agreement = 54.6; rater agreement = 90.95).[40] Insufficient power prevented us from performing any analysis with specific diagnostic categories, such as post-traumatic stress disorder, obsessive-compulsive disorder, specific phobia, other depression, mania/bipolar disorder, other hyperactivity, psychosis or eating disorder. However, an 'any mental disorder' variable (present/absent) was created to encompass disorders included or excluded from the specific analysis.

#### Parental diagnosis

Current parental psychiatric diagnosis was assessed using the Mini International Neuropsychiatric Interview (MINI).[42] Analyses were restricted to mothers, because they represented the vast majority of the respondents (92%). We investigated the following categories: any anxiety disorder (panic, agoraphobia, social or generalized anxiety disorder), any mood diagnosis (the presence of a depressive or manic episode) and psychotic diagnosis. Insufficient power prevented us from performing analyses with specific maternal diagnostic categories, such as substance use disorder and ADHD. An 'any mental disorder' variable (present/absent) was also created to encompass any current anxiety, mood, or substance use disorder, psychosis or ADHD. In eight subjects this variable could not be computed due to missing data regarding psychotic syndrome (n=11) and ADHD (n=16). This discrepancy occurred because the missing data did not impact the 'any mental disorder' value if another maternal

disorder was present, since it would have been tagged as "present" nonetheless. In cases where all other disorders were tagged as "absent," the missing data prevented computation.

### *Data analysis*

DSH prevalence rates were calculated using both unweighted and weighted samples for the oversampling procedure. For details about the HRC's weighting procedure, see Martel et al.[43] Logistic regression models were performed using the survey package from R,[44] taking school clusters into consideration and trimming the weights to fit into an interval between 0.3 and 3 to avoid the inflation of a few cases with too much weight.[45] Associations between DSH and child or parental psychopathology were estimated using three models: 1) bivariate associations (in which each predictor variable was considered individually); 2) multiple associations adjusted for demographic variables; 3) multiple associations adjusted for demographic variables and comorbidity (in which all predictor variables were considered simultaneously). Additional analysis stratified by age was also performed for children (6 to 9y) and early adolescents (10 to 14y). All significance tests were two-sided with a p-level of 0.05.

## Results

The sample mainly consisted of white, middle-class boys. The most common diagnoses were ADHD and ODD, and the most common maternal diagnosis was anxiety disorder (Table 1).

### *Prevalence of deliberate self-harm in children and early adolescents*

The lifetime DSH prevalence in the total sample was 1.6% (1.8% for children and 1.5% for adolescents). DSH prevalence in the last month was 0.8% (0.6% for children and 1% for adolescents). There were no significant differences in prevalence rate between the two age groups (odds ratio [OR] = 1.56, 95% confidence interval [95%CI] 0.8-3.05 for current DSH and OR = 0.86, 95%CI 0.47-1.57 for lifetime DSH).

### *Associations with demographic factors*

The prevalence of lifetime and current DSH did not vary with age, gender or race. However, the chance of reporting a lifetime DSH episode was 70% lower among middle-class children than upper-class children. No associations

**Table 1** Sample description according to age group and total sample

| | 6 to 9 years (n=1,172) | | | 10 to 14 years (n=1,336) | | | Total sample (n=2,508) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Unweighted | | Weighted | Unweighted | | Weighted | Unweighted | | Weighted |
| | n | % | % | n | % | % | n | % | % |
| Gender | | | | | | | | | |
| Male | 639 | 54.5 | 53.5 | 694 | 51.9 | 52.2 | 1,333 | 53.1 | 52.8 |
| Socioeconomic status | | | | | | | | | |
| A/B (the wealthiest) | 239 | 20.4 | 19.5 | 287 | 21.5 | 21.4 | 526 | 21.0 | 20.5 |
| C | 811 | 69.2 | 70.9 | 926 | 69.3 | 70.3 | 1,737 | 69.3 | 70.6 |
| D/E (the poorest) | 122 | 10.4 | 9.5 | 123 | 9.2 | 8.3 | 245 | 9.8 | 8.9 |
| Ethnic group | | | | | | | | | |
| Majority (White) | 699 | 59.6 | 58.3 | 816 | 61.1 | 60.3 | 1,515 | 60.4 | 59.4 |
| Minority (Black, mixed-race, Asian, Native South American or unknown) | 473 | 40.4 | 41.7 | 520 | 38.9 | 39.7 | 993 | 39.6 | 40.6 |
| Outcomes | | | | | | | | | |
| Current DSH | 10 | 0.9 | 0.6 | 18 | 1.3 | 1.0 | 28 | 1.1 | 0.8 |
| Lifetime DSH | 26 | 2.2 | 1.8 | 30 | 2.2 | 1.5 | 56 | 2.2 | 1.6 |
| Psychiatric diagnoses (current) | | | | | | | | | |
| Any mental disorder | 298 | 25.4 | 22.2 | 352 | 26.3 | 21.0 | 650 | 25.9 | 21.6 |
| Anxiety disorder | 58 | 4.9 | 3.8 | 75 | 5.6 | 4.3 | 133 | 5.3 | 4.0 |
| Major depression | 23 | 2.0 | 1.7 | 50 | 3.7 | 2.4 | 73 | 2.9 | 2.1 |
| ADHD | 136 | 11.6 | 10.5 | 137 | 10.3 | 8.5 | 273 | 10.9 | 9.4 |
| ODD | 71 | 6.1 | 5.7 | 60 | 4.5 | 3.8 | 131 | 5.2 | 4.7 |
| Conduct disorder | 14 | 1.2 | 0.9 | 26 | 1.9 | 1.6 | 40 | 1.6 | 1.2 |
| Maternal psychiatric diagnoses (current) | | | | | | | | | |
| Any mental disorder | 315 | 27.0 | 24.6 | 435 | 32.6 | 28.8 | 750 | 30.0 | 26.8 |
| Anxiety disorder | 237 | 20.2 | 17.8 | 347 | 26.0 | 23.2 | 584 | 23.3 | 20.6 |
| Any mood disorder | 205 | 17.5 | 16.2 | 285 | 21.3 | 17.4 | 490 | 19.5 | 16.8 |
| Psychotic syndrome | 61 | 5.2 | 4.6 | 58 | 4.4 | 3.6 | 119 | 4.8 | 4.1 |

ADHD = attention-deficit/hyperactivity disorder; CI = confidence interval; DSH = deliberate self-harm; ODD = oppositional defiant disorder. Anxiety disorder includes generalized anxiety disorder, separation anxiety disorder and social anxiety. For children, any mental disorder includes disorders used in specific analysis and post-traumatic stress disorder, including obsessive-compulsive disorder, specific phobia, other depression, mania/bipolar disorder, other hyperactivity, psychosis or eating disorder. For mothers, any mental disorder encompasses any current anxiety, mood, substance abuse, psychotic or attention-deficit/hyperactivity disorders.

were found between current DSH and socioeconomic status. Associations between DSH and demographic factors were similar between child and adolescent subpopulations (Table 2).

*Clinical associations*

Current and lifetime DSH were more frequent in children with major depression, ADHD and ODD, after controlling for demographic variables and the co-occurrence of psychiatric disorders. For both current and lifetime DSH, there were significant associations with conduct disorders in bivariate and multiple models adjusted for demographic factors, although the associations were fully explained by other diagnoses in multiple models adjusted for comorbidity (Table 3). Stratified analysis according to age-group revealed the same pattern of associations for adolescents (Table 4). For children, current DSH was associated with major depression and ADHD in a fully adjusted model, while associations with ODD and conduct disorder were non-significant. In children, however, lifetime DSH was associated with major depression and conduct disorder, but not with ADHD or ODD (Table 4).

*Associations with maternal diagnosis*

Mothers with anxiety disorders were three times more likely than those without them to report a current or lifetime episode of DSH in their offspring. Current and lifetime associations between offspring DSH and maternal mood disorders were found in bivariate models and models adjusted for demographic factors, although the associations were fully explained by other diagnoses in multiple models adjusted for the co-occurrence of other psychiatric disorders. No associations were found for mothers with a psychotic syndrome (Table 3). According to the completely adjusted models presented in Table 5, with results stratified by age group, we can confirm that maternal anxiety is associated with lifetime DSH among children, as well as with current DSH among adolescents. On the other hand, maternal mood disorders predict current DSH, specifically in children.

## Discussion

This study provides the prevalence rates of DSH, its clinical correlates and association with maternal psychopathology with in children and adolescents from a community sample. The current and lifetime DSH prevalences were 0.6% and 1.8%, respectively, with no significant differences regarding age, gender or race. The chance of reporting a lifetime DSH episode was lower among the middle-class than the upper-class. Major depression, ADHD and ODD were associated with DSH independently of co-occurring psychiatric syndromes. Moreover, maternal anxiety disorder was strongly associated with lifetime DSH in children and with current DSH in adolescents. However, maternal mood disorder was associated with current DSH specifically in younger children.

Our lifetime DSH estimate was lower than that of a recent systematic review, which reported an international

**Table 2** Deliberate self-harm (DSH) prevalence in subpopulations and demographic bivariate associations stratified by age

| | 6 to 9 years (n=1,172) | | | | 10 to 14 years (n=1,336) | | | | Total sample (n=2,508) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Current DSH (last month) | | Lifetime DSH | | Current DSH (last month) | | Lifetime DSH | | Current DSH (last month) | | Lifetime DSH | |
| | % | Bivariate model OR (95%CI) | % | Bivariate model OR (95%CI) | % | Bivariate model OR (95%CI) | % | Bivariate model OR (95%CI) | % | Bivariate model OR (95%CI) | % | Bivariate model OR (95%CI) |
| Age | | 1.49 (0.77-2.86) | | 1.52 (0.86-2.67) | | 1.03 (0.77-1.38) | | 0.95 (0.75-1.19) | | 1.14 (0.95-1.37) | | 1.00 (0.86-1.17) |
| Gender | | | | | | | | | | | | |
| Male | 0.3 | 1 | 2.1 | 1 | 0.8 | 1 | 1.5 | 1 | 0.5 | 1 | 1.8 | 1 |
| Female | 1 | 3.82 (0.84-17.29) | 1.3 | 0.61 (0.23-1.63) | 1.2 | 1.48 (0.49-4.45) | 1.6 | 1.07 (0.46-2.50) | 1.1 | 2.05 (0.89-4.75) | 1.5 | 0.81 (0.46-1.43) |
| Socioeconomic Status | | | | | | | | | | | | |
| A/B (the wealthiest) | 1.5 | 1 | 4.7 | 1 | 0.8 | 1 | 2.7 | 1 | 1.1 | 1 | 3.6 | 1 |
| C | 0.4 | 0.28 (0.06-1.25) | 1 | 0.20 (0.08-0.48)* | 0.9 | 1.18 (0.25-5.44) | 1.1 | 0.42 (0.18-0.96)† | 0.7 | 0.62 (0.28-1.35) | 1.1 | 0.29 (0.18-0.47)* |
| D/E (the poorest) | 0.3 | 0.20 (0.02-1.95) | 1.5 | 0.31 (0.07-1.35) | 1.8 | 2.27 (0.32-16.05) | 1.8 | 0.67 (0.15-2.90) | 1.0 | 0.92 (0.23-3.63) | 1.6 | 0.45 (0.16-1.25) |
| Race | | | | | | | | | | | | |
| Majority (White) | 0.7 | 1 | 2 | 1 | 1.2 | 1 | 1.9 | 1 | 1.0 | 1 | 2.0 | 1 |
| Minority (Black, mixed-race, Asian, Native South American or unknown) | 0.6 | 0.85 (0.17-4.16) | 1.4 | 0.73 (0.28-1.88) | 0.6 | 0.50 (0.14-1.75) | 0.9 | 0.45 (0.16-1.29) | 0.6 | 0.61 (0.21-1.77) | 1.2 | 0.59 (0.28-1.22) |

* $p < 0.001$; † $p < 0.05$.

**Table 3** DSH prevalence and associations with current youth/maternal psychopathology in the total sample

| | Current DSH (last month) | | | | Lifetime DSH | | | |
|---|---|---|---|---|---|---|---|---|
| | % | Bivariate model OR (95%CI) | Multiple model 1 OR (95%CI) | Multiple model 2 OR (95%CI) | % | Bivariate model OR (95%CI) | Multiple model 1 OR (95%CI) | Multiple model 2 OR (95%CI) |
| Youth psychiatric diagnoses (n=2,508) | | | | | | | | |
| Anxiety disorder | 1.5 | 1.90 (0.61-5.89) | 1.79 (0.60-5.40) | 0.96 (0.19-4.76) | 3.0 | 1.93 (0.77-4.82) | 1.90 (0.73-4.91) | 1.41 (0.48-4.13) |
| Major depression | 12.7 | 25.75 (9.29-71.31)* | 25.89 (9.39-71.40)* | 16.30 (4.98-53.36)* | 14.4 | 12.26 (5.28-28.51)* | 15.53 (6.62-36.41)* | 9.03 (3.13-26.11)* |
| ADHD | 4.4 | 10.20 (4.52-23.03)* | 12.20 (5.70-26.11)* | 6.57 (3.11-13.89)* | 6.8 | 6.56 (3.42-12.59)* | 7.24 (3.64-14.40)* | 4.43 (2.12-9.24)* |
| Oppositional defiant | 6.2 | 11.85 (4.10-34.30)* | 14.39 (4.99-41.48)* | 4.89 (1.61-14.87)† | 7.8 | 6.30 (2.35-16.89)* | 6.91 (2.60-18.38)* | 2.97 (1.15-7.67)‡ |
| Conduct disorder | 5.2 | 7.16 (1.53-33.50)‡ | 8.76 (2.46-31.27)† | 1.06 (0.09-12.50) | 11.5 | 8.47 (2.84-25.28)* | 11.45 (4.00-32.78)* | 2.97 (0.56-15.76) |
| Any mental disorder | 3.2 | 19.57 (5.94 -64.52)* | 20.95 (6.40-68.57)* | - | 5.3 | 8.93 (4.30-18.54)* | 9.78 (4.50-21.27)* | - |
| Maternal psychiatric diagnoses (n=2,295) | | | | | | | | |
| Anxiety | 2.3 | 5.13 (2.01-13.09)† | 4.95 (1.94-12.58)† | 3.08 (1.20-7.87)‡ | 4.0 | 3.72 (1.83-7.57)* | 3.88 (1.92-7.85)* | 2.89 (1.37-6.08)† |
| Any mood | 2.0 | 3.44 (1.68-7.06)† | 3.37 (1.64-6.93)† | 1.94 (0.98-3.86) | 3.4 | 2.62 (1.43-4.81)† | 2.96 (1.57-5.59)† | 1.72 (0.91-3.25) |
| Psychotic syndrome§ | 2.0 | 2.84 (0.73-11.01) | 2.77 (0.80-9.57) | 1.08 (0.28-4.23) | 2.4 | 1.50 (0.43-5.25) | 1.71 (0.52-5.61) | 0.74 (0.20-2.73) |
| Any mental disorder‖ | 1.7 | 3.57 (1.40-9.11)† | 3.46 (1.39-8.62)‡ | - | 3.2 | 2.91 (1.43-5.91)† | 3.12 (1.53-6.36)† | - |

95%CI = 95% confidence interval; ADHD = attention-deficit/hyperactivity disorder; DSH = deliberate self-harm; OR = odds ratio.
Multiple model 1, controlled for age, gender, socioeconomic status and race; Multiple model 2, controlled for age, gender, socioeconomic status, race and other diagnoses.
Anxiety disorder includes generalized anxiety disorder, separation anxiety disorder and social anxiety. For children, any mental disorder includes disorders used in specific analysis and post-traumatic stress disorder, including obsessive-compulsive disorder, specific phobia, other depression, mania/bipolar disorder, other hyperactivity, psychosis or eating disorder. For mothers, any mental disorder encompasses any current anxiety, mood, substance abuse, psychotic or attention-deficit/hyperactivity disorders.
§ Psychotic syndrome data was missing in 11 cases, which were excluded from analysis using listwise deletion.
‖ In eight subjects this variable couldn't be computed because of missing psychotic syndrome (n=11) and ADHD (n=16) data.
*$p < 0.001$; †$p < 0.01$; ‡$p < 0.05$.

**Table 4** DSH prevalence and associations with current child psychopathology, stratified by age

| | Current DSH (last month) | | | | Lifetime DSH | | | |
|---|---|---|---|---|---|---|---|---|
| | % | Bivariate model OR (95%CI) | Multiple model 1 OR (95%CI) | Multiple model 2 OR (95%CI) | % | Bivariate model OR (95%CI) | Multiple model 1 OR (95%CI) | Multiple model 2 OR (95%CI) |
| 6 to 9y (n=1,172) | | | | | | | | |
| Anxiety disorder | 0.8 | 1.27 (0.19-8.44) | 1.26 (0.20-8.01) | 0.89 (0.03-25.61) | 2.0 | 1.13 (0.29-4.39) | 1.21 (0.32-4.60) | 0.96 (0.30-3.08) |
| Major depression | 13.9 | 40.31 (8.33-194.95)* | 92.28 (15.01-567.13)* | 67.02 (6.06-740.87)† | 16.5 | 12.99 (3.63-46.56)* | 18.48 (4.15-82.19)* | 11.80 (2.15-64.80)† |
| ADHD | 2.9 | 7.89 (1.69-36.70)‡ | 9.59 (1.94-47.29)† | 6.28 (1.38-28.58)‡ | 5.6 | 4.47 (1.48-13.54)‡ | 4.48 (1.38-14.54)‡ | 3.03 (0.76-12.11) |
| Oppositional defiant | 4.2 | 10.40 (2.18-49.69)† | 16.48 (3.06-88.88)† | 4.85 (0.95-24.63) | 4.7 | 3.07 (0.84-11.21) | 3.33 (0.89-12.53) | 1.77 (0.56-5.56) |
| Conduct disorder | 3.4 | 5.78 (0.65-51.49) | 21.18 (1.74-258.59)‡ | 2.70 (0.03-228.89) | 21.9 | 17.46 (3.65-83.57)* | 40.57 (8.35-197.04)* | 15.14 (1.03-221.51) |
| Any mental disorder | 2.4 | 18.11 (2.16-152.03)† | 22.52 (3.05-166.46)† | - | 4.5 | 4.73 (1.87-11.96)† | 5.21 (2.01-13.54)† | - |
| 10 to 14y (n=1,336) | | | | | | | | |
| Anxiety disorder | 2.0 | 2.20 (0.66-7.42) | 2.09 (0.63-6.94) | 1.02 (0.20-5.27) | 3.8 | 2.77 (0.89-8.64) | 2.65 (0.81-8.67) | 1.82 (0.41-8.15) |
| Major depression | 12.0 | 18.89 (4.51-79.24)* | 17.01 (4.04-71.62)* | 9.44 (1.05-85.20) | 13.1 | 12.11 (3.37-43.52)* | 12.98 (3.57-47.21)* | 7.13 (1.06-48.10)‡ |
| ADHD | 6.1 | 12.56 (4.01-39.30)* | 13.68 (4.44-42.15)* | 7.11 (2.21-22.86)† | 8.1 | 9.63 (4.29-21.64)* | 10.67 (4.70-24.25)* | 5.88 (2.45-14.07)* |
| Oppositional defiant | 8.9 | 14.47 (3.87-54.13)* | 13.72 (3.64-51.73)* | 4.66 (1.10-19.74)‡ | 12.1 | 12.36 (3.81-40.09)* | 12.57 (3.92-40.32)* | 5.42 (1.51-19.47)‡ |
| Conduct disorder | 6.1 | 7.17 (0.89-57.53) | 7.45 (1.17-47.44)‡ | 1.32 (0.05-32.53) | 6.1 | 4.47 (0.57-34.89) | 5.35 (0.88-32.53) | 0.92 (0.04-20.22) |
| Any mental disorder | 3.9 | 20.81 (4.68-92.44)* | 20.79 (4.54-95.23)* | - | 6.1 | 21.50 (6.49-71.19)* | 23.09 (6.41-83.23)* | - |

95%CI = 95% confidence interval; ADHD = attention-deficit/hyperactivity disorder; DSH = deliberate self-harm; OR = odds ratio.
Multiple model 1, controlled for age, gender, socioeconomic status and race; Multiple model 2, controlled for age, gender, socioeconomic status, race and other diagnoses. Anxiety disorder includes generalized anxiety disorder, separation anxiety disorder and social anxiety. Any mental disorder includes disorders used in specific analysis and post-traumatic stress disorder, including obsessive-compulsive disorder, specific phobia, other depression, mania/bipolar disorder, other hyperactivity, psychosis or eating disorder.
*$p < 0.001$; †$p < 0.01$; ‡$p < 0.05$.

**Table 5** Prevalence of DSH in subpopulations and associations with current maternal psychopathology, stratified by age

| | Current DSH (last month) | | | | Lifetime DSH | | | |
|---|---|---|---|---|---|---|---|---|
| | % | Bivariate model OR (95%CI) | Multiple model 1 OR (95%CI) | Multiple model 2 OR (95%CI) | % | Bivariate model OR (95%CI) | Multiple model 1 OR (95%CI) | Multiple model 2 OR (95%CI) |
| 6 to 9y (n=1,079) | | | | | | | | |
| Anxiety disorder | 1.4 | 3.59 (0.76-16.93) | 4.25 (0.94-19.16) | 2.50 (0.83-7.55) | 4.7 | 4.25 (1.43-12.67)* | 5.17 (1.76-15.17)† | 4.46 (1.24-16.03)* |
| Any mood disorder | 1.5 | 3.92 (0.79-19.43) | 4.83 (1.09-21.34)* | 2.96 (1.15-7.59)* | 3.8 | 2.75 (1.07-7.07)* | 3.81 (1.58-9.15)† | 1.54 (0.61-3.86) |
| Psychotic syndrome‡ | 0.7 | 1.26 (0.14-11.54) | 1.42 (0.15-13.57) | 0.51 (0.04-6.35) | 1.4 | 0.78 (0.16-3.91) | 1.02 (0.19-5.30) | 0.39 (0.06-2.47) |
| Any mental disorder§ | 1.0 | 2.34 (0.49-11.21) | 2.78 (0.63-12.33) | - | 3.7 | 3.23 (1.11-9.40)* | 4.25 (1.44-12.52)* | - |
| 10 to 14y (n=1,216) | | | | | | | | |
| Anxiety disorder | 2.9 | 5.77 (1.81-18.45)† | 5.73 (1.79-18.36)† | 3.66 (1.15-11.61)* | 3.5 | 3.38 (1.48-7.75)† | 3.35 (1.45-7.74)† | 2.17 (0.96-4.91) |
| Any mood disorder | 2.4 | 3.14 (1.04-9.48)* | 2.96 (0.95-9.26) | 1.56 (0.40-5.98) | 3.2 | 2.52 (1.04-6.09)* | 2.51 (1.00-6.31) | 1.74 (0.60-5.05) |
| Psychotic syndrome‡ | 3.5 | 4.08 (0.67-24.86) | 3.93 (0.77-20.19) | 1.57 (0.23-10.89) | 3.5 | 2.45 (0.42-14.16) | 2.50 (0.48-13.17) | 1.24 (0.18-8.32) |
| Any mental disorder§ | 2.3 | 4.24 (1.33-13.51)* | 4.20 (1.32-13.35)* | - | 2.9 | 2.67 (1.19-6.01)* | 2.66 (1.17-6.04)* | - |

95%CI = 95% confidence interval; ADHD = attention-deficit/hyperactivity disorder; DSH = deliberate self-harm; OR = odds ratio.
Multiple model 1, controlled for age, gender, socioeconomic status and race; Multiple model 2, controlled for age, gender, socioeconomic status, race and other diagnoses. Anxiety disorder includes generalized anxiety disorder, separation anxiety disorder and social anxiety; any mental disorder encompasses any current anxiety, mood, substance abuse, psychotic or attention-deficit/hyperactivity disorders.
‡ Psychotic syndrome data was missing in 11 cases, which were excluded from the analysis using listwise deletion.
§ In eight subjects this variable couldn't be computed because of missing psychotic syndrome (n=11) and ADHD (n=16) data.
* $p < 0.05$; † $p < 0.01$.

lifetime DSH prevalence of 12.2%.[13] It was also lower than rates in other LMIC countries, such as Mexico (3.1% lifetime),[15] China (2.9% lifetime),[16] and South Africa (3.2% in the past-month).[17] In Brazil, estimates of past-year suicide attempts in 12- to 14-year-olds and 15- to 18-year-olds in Greater São Paulo public schools were 6.7% and 10%, respectively.[22] Another study in the state of Sergipe reported a 6% suicide attempt prevalence in adolescents from 13 to 18 years old.[20] The differences between our findings and those of other studies might be related to: 1) our sample, which consisted of a mostly younger age-group; 2) different assessment methods (self-report vs. maternal report). However, like our study, U.S. community studies have reported a suicide attempt prevalence of 1.5% in children from 7 to 12 years old[24] and retrospectively estimated a DSH onset of less than 1% before 12 years of age, although this rate reached 4 to 5% in later adolescence,[10] which was higher than our population.

Although DSH is commonly reported as higher among young girls,[10,15,20,24-26] some authors have reported comparable rates across genders,[9,27] which is consistent with our findings. We found that middle class children have a lower risk than those of higher socioeconomic strata. Despite evidence that the socially disadvantaged are at greater risk of attempting suicide,[27] mixed results have been found in Brazil regarding this factor,[46,47] including a positive association with income inequality.[47] Previous research about neighborhood influence on antisocial behavior found that increased economic distance between a child and his/her neighbors was associated with increased antisocial behavior, not only for poor children growing up among wealthier neighbors but also for wealthier children growing up among poor neighbors.[48] Our study focused on public schools, and it is expected that only a small portion of wealthier students would be enrolled in them. This small number of upper-class individuals, besides being affected by social disintegration, could also have higher levels of psychopathology or cognitive problems. Additionally, it is possible that middle class children have stronger religious affiliations, resulting in more meaning in life, which has been found to be negatively associated with suicide rates in multinational studies. In fact, the higher suicide rates in wealthy nations seem to be associated with less religiosity and meaning in life.[49] Results in the literature regarding ethnicity are inconsistent: some studies have suggested a predominance of DSH in non-Caucasians[26,29,30]; while other suggest a predominance in Caucasians,[10,31,50] and others, like ours, found no racial differences.[24,32]

Very few community studies on DSH have reported clinical correlates and adjusted for the co-occurrence of psychiatric diagnoses. Mood disorders (particularly depression) have been consistently associated with DSH, while anxious and disruptive disorders have shown conflicting results. Gould et al.[24] found associations between adolescent suicide attempts and mood, anxiety and substance abuse/dependence, but not with disruptive disorder. Nock et al.[10] corroborated the association with mood disorders, but found mixed results regarding anxiety and impulse control disorders. In longitudinal studies, DSH incidence

during adolescence was independently associated with depression, anxiety, antisocial behavior and a high risk of substance use.[9,27] In a follow-up study of a clinical sample of individuals with ADHD who were initially assessed at 4 to 6 years old, it was found that they were at increased risk, relative to matched controls, for meeting depression criteria and attempting suicide by age 18.[34] Our results align with previous research indicating that developmental trajectories involving a high level of disruptiveness are more consistently associated with lifetime self-harm than those with a high-level of anxiousness.[51] It is also important to point out that suicidal behavior is a criterion of major depression, which could inflate statistics about its co-occurrence with DSH. Additionally, clinicians are more likely to ask about DSH in patients with other depression symptoms, and our results highlight the importance of actively inquiring about both internalizing and disruptive disorders, especially in children, who are less likely than adults to seek help in the year prior to the onset of suicidal behavior.[1]

Previous studies have found associations between a wide range of parental mental disorders (such as depression, anxiety, substance abuse and antisocial personality disorders) and increased risk of lifetime suicide attempts by offspring.[35] Our results align with those of other LMIC studies, which found parental anxiety as the only familial psychopathology independently associated with offspring lifetime suicide attempts.[36-38] However, reverse causation cannot be excluded: qualitative research indicates that parents can react with anxiety, shame, anger, guilt and depression after discovering DSH in their children.[52]

Some limitations warrant consideration. First, due to its cross-sectional design, it is impossible to determine the direction of the relationship between DSH and maternal psychopathology. Second, evaluating only children who are being enrolled at school by a biological parent overlooks high-risk cases, such as adopted children and those avoiding, or being kept from, school. Finally, parental reports of psychopathology may either overlook covered self-harm behaviors or be influenced by overanxious parents who tend to overestimate symptoms in their children. Nevertheless, this study has certain strengths that should also be noted. First, the inclusion of young children from a large community sample fills a gap in DSH assessment in school-age children. Second, the use of a structured clinical interview to assess psychopathology with both children and mothers allowed us to assess psychopathology in a structured way, which is lacking in the current literature. Finally, our analysis included covariation for both demographic factors and co-occurring psychopathology, investigating both univariate and independent associations between maternal psychopathology and DSH, which fills a gap in the LMIC literature.

We conclude that DSH is an important problem in children and adolescents. Diagnoses of depression, ADHD and ODD are consistently associated with DSH, as is having a mother with anxiety disorder. Our results are relevant for clinicians and policy makers, since they reinforce the importance of a more comprehensive evaluation of DSH in children with the aforementioned mental disorders and since DSH is closely associated with suicide. Future longitudinal studies will be important for investigating the role of DSH as a predictor of psychopathological trajectories, which can facilitate the development of interventions.

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## Disclosure

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## ORIGINAL ARTICLE

# Correlations between caregiver psychiatric symptoms and offspring psychopathology in a low-resource setting

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**Objective:** Associations between parental/caregiver depression and adverse child outcomes are well established and have been described through one or more mechanisms: child psychopathology following exposure to a depressed caregiver, child psychopathology exacerbating a caregiver's depression, and caregiver and offspring depression sharing the same etiology. Data from low and middle-income countries is scarce. We examined correlations between common symptoms of mental disorders in caregivers and their offspring's psychopathology in a Brazilian sample.
**Methods:** In this cross-sectional study, adult caregivers were screened for depression during routine home visits by community health workers as part of the Brazilian Family Health Strategy. Caregivers with suspected depression were assessed using the Zung Self-Rating Depression Scale and the Self-Reporting Questionnaire (SRQ-20). Children's symptoms were evaluated using the Strengths and Difficulties Questionnaire (SDQ).
**Results:** The sample included 68 primary caregivers and 110 children aged 6 to 15 years. Higher caregiver scores on the SRQ-20 correlated significantly with psychiatric symptoms in offspring.
**Conclusion:** These results substantiate our hypothesis that child psychopathology correlates with caregivers' psychiatric symptoms. This paper adds to the growing literature on community mental health assessment and can help guide future strategies for reducing the burden of common mental disorders in caregivers and children alike in low and middle-income countries.

**Keywords:** Depressive disorder; primary health care; child; caregivers; Brazil

## Introduction

Common mental disorders, defined as depressive, anxiety, and somatic disorders, are typically encountered in community and primary care settings.[1] Major depressive disorder (MDD) is the most important common mental disorder because of its burden, and is among the top 10 causes of years lived with disability worldwide.[2] To date, most studies of common mental disorders in parents/caregivers and offspring with emotional and behavioral problems have focused on parental depression. MDD is a complex familial disorder that often affects offspring via different mechanisms, including genetic contributions[3,4] and shared social environment.[5-7] Numerous studies have shown that school-aged children of depressed mothers have increased rates of internalizing[8-11] and externalizing behavior.[10,12,13] Multiple studies, all from high-income countries, have examined the bidirectional effects of caregiver and childhood depression, suggesting that children's symptoms may also exacerbate caregiver depression.[7,14-17] However, data from low- and middle-income countries (LMIC) are scarce. One Chilean study documented that a large proportion of children of depressed mothers attending primary care clinics had psychopathological symptom scores in the clinical range, with a predominance of internalizing symptoms.[18] Two small studies, one each from Brazil and Malaysia, examined how offspring psychopathology was associated with maternal stress,[19,20] but none examined how child psychopathology may exacerbate caregivers' psychiatric disorders.

Within this context, we sought to examine how caregivers' psychopathology correlates with symptoms in their offspring. Both symptomatic and asymptomatic children were included. Considering reciprocal associations of child-caregiver psychopathology, we hypothesized that the psychopathology of caregivers and their children would be strongly correlated. To our knowledge, this is the first such study conducted in a LMIC.

## Material and methods

### *Study design*

This descriptive cross-sectional study recruited participants screened for inclusion in a randomized control trial (RCT) designed to compare the effectiveness of interpersonal

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counseling facilitated by community health workers versus enhanced treatment-as-usual within the Brazilian Family-Health Strategy (Estratégia de Saúde da Família), Unidade Básica de Saúde Iaçapé, in Sapopemba, a district of São Paulo, Brazil. The Research Ethics Committee of Universidade Federal de São Paulo (UNIFESP) and the Municipal Health Council of the city of São Paulo approved the study protocol. The trial was registered in the Brazilian Clinical Trials registry with accession number RBR-5qhmb5 (http://www.ensaiosclinicos.gov.br/rg/RBR-5qhmb5/). The outcome data from the RCT are under analysis and not yet published. This cross-sectional study, in turn, was design to examine the correlation between caregiver and child psychopathology in a poor district of the city of São Paulo, Brazil, within a community-based health outreach program conducted as part of the Brazilian Family-Health Strategy, among a subset of individuals screened for inclusion in the RCT.

### *Sample*

Participants were recruited by community health workers during routine home visits between May 1, 2013, and April 30, 2015. All community health workers were employees of the Municipal Health Council of São Paulo, and received no monetary compensation to screen participants. Participation in the study was voluntary, and no financial compensation was offered. Written informed consent was obtained from adults, and written informed assent from children. All caregivers of children aged 6-15 who screened positive for depression were invited to participate in this study if they met the following criteria: 1) not currently in treatment with antidepressants or psychotherapy; and 2) no active suicidal ideation, current/previous episodes of mania or hypomania, current/previous psychotic symptoms, or alcohol or psychoactive substance use disorders. The sole inclusion criterion for children was age 6-15 years. Exclusion criteria for children were: 1) ongoing psychiatric treatment or psychotherapy; or 2) a previous diagnosis of psychosis, autism spectrum disorder, or intellectual disability. For caregivers with more than one child aged 6-15, all were included in the study.

### *Instruments*

Research psychologists collected standard demographic information and administered a battery of instruments.

#### Zung Self-Rating Depression Scale[21]

This scale is a 20-item self-report screening questionnaire covering affective, psychological, and somatic symptoms associated with depression. Total scores range from 20 to 80; we used a cutoff point of $\geqslant 45$ as the inclusion criterion, according to the validated Brazilian version.[22] Although the scale can be self-administered, due to the low literacy level of the sample, the community health workers were trained to conduct the Zung screening orally. It was then re-administered by research psychologists.

#### Mini-International Neuropsychiatric Interview (MINI)[23]

For individuals with Zung scores $> 45$, a diagnosis of depression was confirmed by the research psychologist using the MINI,[23] a short semi-structured diagnostic interview compatible with DSM-IV and ICD-10 criteria. We used the Brazilian version translated and validated in Portuguese[24] to diagnose current major depressive episode (MDE), dysthymia, generalized anxiety disorder, panic disorder, agoraphobia, social phobia, and posttraumatic stress disorder.

#### Self-Reporting Questionnaire (SRQ-20)[25]

The SRQ-20 was specifically developed by the World Health Organization to identify minor psychiatric morbidity in primary care settings and the community in developing countries. It comprises 20 dichotomous items covering common mental disorder symptoms: depression, anxiety, and somatization. We used a cutoff of $\geqslant 8$ for positivity, according to the validated Brazilian version.[26]

#### Clinical Global Impression Instrument (CGI)[27]

The CGI provides an overall score of the clinician's view of the patient's symptoms, behavior, and functioning, using a seven-point scale for a single question. It ranges from 1 (normal) to 7 (extremely severe symptoms).

#### World Health Organization Quality of Life instrument – Abbreviated version[28] (WHOQOL-BREF)

The WHOQOL-BREF comprises 26 items, which measure the following quality of life domains: physical health, psychological health, social relationships, and the environment. Scores range from 0 to 100, with higher scores representing greater well-being. We used the validated Brazilian version.[29]

#### WorldSAFE core questionnaire[30]

An instrument used to investigate intrafamilial violence and associated factors, developed by the WorldSAFE steering committee of the World Studies of Abuse in the Family Environment (copyrighted in 1998). A section of the questionnaire was administered to adult women and sought to identify marital violence in the past (history) or current (in the last year). Only female caregivers in a current relationship answered this questionnaire. Disqualifying/humiliating, threatening, abandoning, or adulterous acts are considered forms of psychological violence, and the presence of at least one of the above was categorized as positive. Beating, punching, and kicking were considered severe forms of physical violence. Similarly, the presence of at least one of these incidents was categorized as positive. We used the translated Brazilian version developed by Bordin & Paula in 1999.

#### ABIPEME (Brazilian Association of Market Survey Institutes) survey[31]

An instrument used to determine socioeconomic status (SES) in Brazil, it considers level of education of the head of the household and a short inventory of household assets

(e.g. automobile, color TV, refrigerator, vacuum cleaner). Points range from zero to 34 and are classified from A (highest score and SES) to E (lowest score and SES).

Strengths and Difficulties Questionnaire (SDQ)[32]

This is a screening questionnaire for behavioral problems in children, designed to be completed by the primary caregiver. It provides a total score from 0 to 40 to detect children with psychiatric symptoms. We used the Portuguese version of the SDQ for children aged 4-17 years and including impact supplements, which functions well in Brazil, all being scored in the standard manner.[32] We considered a cutoff score of $\geqslant$ 14 for symptomatic children, as used in previous studies in Brazil.[33] We divided children into three groups: asymptomatic (SDQ $<$ 14 and impact supplement score = 0); symptomatic without impact (SDQ $\geqslant$ 14 and impact supplement score = 0); and symptomatic with impact (SDQ $\geqslant$ 14 and impact supplement score $\geqslant$ 1).

*Statistical analyses*

Analyses were performed in SPSS and Mplus version 7.4.[34] Descriptive analyses included mean and standard deviations (SD) for continuous variables and frequencies for categorical or ordinal variables. P-values $\leqslant$ 0.05 were considered statistically significant.

Comparisons between the three groups of children (asymptomatic vs. symptomatic without impact vs. symptomatic with impact), stratified by the adult caregiver's clinical characteristics, were conducted using Mplus 7.4. For caregivers with more than one child included in the study, the caregiver score for ordinal variables was repeated. Differences in continuous variables were tested by comparing groups' means through the Wald chi-square test (Model Test function in Mplus). Bonferroni p-value correction ($p \leqslant 0.02$) was used for pairwise comparisons. Differences in categorical or ordinal dependent variables were tested using cross-tabulation and the chi-square test.

Linear regression was performed to test the association between caregivers' mental health outcomes (e.g., Zung score, SRQ-20 score) and children's characteristics, including SDQ score (i.e., symptomatic with impact, symptomatic without impact, and asymptomatic), age, and gender. Regression analyses were conducted using maximum likelihood with robust standard error (MLR) estimation to analyze continuous dependent variables (e.g., Zung score). Weighted least squares means and variance adjusted (WLSMV) was used to analyze ordinal variables (e.g., MINI diagnosis). As some caregivers participated in the study with more than one child, the analyses were performed controlling for intra-class (i.e., within-family) correlation.

## Results

Of the 261 caregivers interviewed and screened for the RCT, 70 met the criteria for inclusion. Of these, 68 (97%) caregivers with 110 children agreed to participate. Demographic and clinical characteristics of the adult caregivers are described in Table 1. Mean age was

**Table 1** Demographic and clinical characteristics of the caregivers

| | Caregivers (n=68) |
|---|---|
| Age (years), mean (SD) | 39.68 (10.82) |
| Gender (female) | 66 (97.10) |
| Primary caregiver | |
| Mother | 58 (85.29) |
| Father | 2 (2.94) |
| Grandmother | 5 (7.36) |
| Aunt | 3 (4.41) |
| Race/ethnicity | |
| Black | 5 (7.40) |
| White | 29 (42.60) |
| Biracial/multiracial | 31 (45.60) |
| Other | 3 (4.40) |
| Marital status | |
| Married/cohabitating | 45 (66.20) |
| Single | 11 (22.40) |
| Separated/divorced | 6 (8.90) |
| Widowed | 5 (7.40) |
| Number of children | |
| 1 | 38 (55.90) |
| 2 | 22 (32.40) |
| $\geqslant$ 3 | 8 (11.80) |
| Education | |
| Primary | 35 (51.50) |
| Secondary | 29 (42.60) |
| Higher | 4 (5.90) |
| Religion | |
| Catholic | 24 (35.30) |
| Protestant | 27 (39.70) |
| Other | 3 (4.40) |
| None | 14 (20.60) |
| ABIPEME socioeconomic class | |
| A1/A2 | 0 (0.00) |
| B1/B2 | 22 (32.40) |
| C1/C2 | 36 (52.90) |
| D | 6 (8.80) |
| E | 4 (5.90) |
| Monthly household income (US$),* mean (SD) | 723.99 (552.82) |
| Zung, mean (SD) | 52.79 (6.88) |
| SRQ-20, mean (SD) | 13.12 (3.83) |
| CGI, mean (SD) | 4.60 (0.74) |
| MINI, depressive disorder | 61 (89.70) |
| MDE, current | 57 (83.80) |
| MDE, recurrent | 25 (36.80) |
| MDE, single episode | 43 (63.20) |
| Dysthymia | 5 (7.40) |
| MDE + dysthymia | 1 (1.50) |
| MINI, comorbidity with depressive disorder | 41 (37.30) |
| Generalized anxiety disorder | 12 (10.90) |
| Panic disorder | 8 (7.30) |
| Agoraphobia | 17 (15.50) |
| Social phobia | 9 (8.20) |
| Posttraumatic stress disorder | 7 (6.40) |

Data presented as n (%), unless otherwise specified.
ABIPEME = Brazilian Association of Market Survey Institutes categorization of Brazilian socioeconomic class; CGI = Clinical Global Impression instrument; MDE = major depressive episode; MINI = Mini-International Neuropsychiatric Interview; SD = standard deviation; SRQ-20 = Self-Reporting Questionnaire; Zung = Zung Self-Rating Depression Scale.
* Conversion factor: R$ 1.00 = US$ 3.50, August 2015.

**Table 2** Demographic characteristics of children

| | Total (n=110) | Asymptomatic* (n=42) | Symptomatic without impact† (n=20) | Symptomatic with impact‡ (n=48) | Statistic | p-value |
|---|---|---|---|---|---|---|
| Age (years), mean (SD) | 9.81 (2.70) | 9.81 (2.73) | 10.60 (2.54) | 9.47 (2.70) | 2.85 | 0.24§ |
| Gender | | | | | | |
| Female | 53 (48.20) | 20 (47.60) | 13 (65.00) | 20 (41.70) | 0.40 | 0.53 |
| Male | 57 (51.80) | 22 (52.40) | 7 (35.00) | 28 (58.30) | | |
| Education | | | | | | |
| Not attending school | 3 (2.70) | 1 (2.40) | 1 (5.00) | 1 (2.10) | 0.52 | 0.47 |
| Grade 1-4 | 60 (54.50) | 23 (54.80) | 8 (40.00) | 29 (60.40) | | |
| Grade 5-9 | 47 (42.80) | 18 (42.80) | 11 (55.00) | 18 (37.50) | | |
| Number of siblings, mean (SD); median | 1.06 (1.02); 1 | 1.33 (0.94); 1 | 0.80 (1.21); 0 | 0.92 (0.93); 1 | 5.33 | 0.07* |

Data presented as n (%), unless otherwise specified.
SD = standard deviation.
* Asymptomatic = Strengths & Difficulties Questionnaire $< 14$.
† Symptomatic without impact = Strengths & Difficulties Questionnaire $\geqslant 14$, impact supplement score = 0.
‡ Symptomatic with impact = Strengths & Difficulties Questionnaire $\geqslant 14$, impact supplement score $\geqslant 1$.
§ Wald's chi-square test.

39.68±10.82 years, and most caregivers (97.10%) were female. Most were mothers (n=58; 85.29%), two were fathers, five were grandmothers, and three were aunts. The most prevalent ethnicity was biracial/multiracial (n=31, 45.60%), followed by white/European (n=29, 42.60%). Forty-five (66.20%) were married or cohabitating with a partner. On average, they had one or two children (88.30%), low educational attainment, were of Catholic (n=24, 35.30%) or Protestant (n=27, 39.70%) religion, and of socioeconomic class C (n=36, 52.90%), according to the ABIPEME Brazilian classification (lower-middle class to middle-middle class). The mean scores for all adult caregivers' questionnaires were: Zung, 52.79±6.88; SRQ-20, 13.12± 3.83; and CGI, 4.60±0.74. Sixty-one (89.70%) caregivers met criteria for depressive disorder, including current MDE or dysthymia. Seven caregivers screened positive for depression on the Zung scale, but were negative according to the MINI. These caregivers with subclinical depression were still included in the sample.

The mean age of children was 9.81±2.70 years; 53 (48.20%) were female, 60 (54.50%) were attending 1st to 4th grade, and 47 (42.80%) were attending 5th to 9th grade. The children (n=110) were divided into three groups: asymptomatic (n=42); symptomatic without impact (n=20); and symptomatic with impact (n=48). As shown in Table 2, these groups did not differ significantly in terms of age, gender, education level, or number of siblings.

Table 3 describes differences among the three groups of children, stratified by the adult caregiver's clinical characteristics. The mean scores for all adult caregivers' questionnaires were: Zung, 53.67±7.47; SRQ-20, 13.22± 3.89; CGI, 4.65±0.76; and WHOQOL-BREF, 41.66±11.66. According to the MINI, 92 (83.60%) children had a caregiver with a current MDE diagnosis and seven (6.40%) had a caregiver with dysthymia. In total, 97 (88.20%) children had a caregiver with a depressive disorder (current MDE or dysthymia). Forty-two (38.20%) children had caregivers with recurrent MDE and 50 (45.50%) had a caregiver with a single MDE. Forty-one of all 110 children (37.30%) had caregivers with depressive disorders and comorbidities such as dysthymia, generalized anxiety disorder, panic disorder, agoraphobia, social phobia, or posttraumatic stress disorder. About two-thirds of the children (n=69; 62.73%) had female caregivers cohabitating with a current partner (spouse or partner). Among these, 42 children (60.90%) had a caregiver who reported current marital psychological violence and four (5.80%) had a caregiver who reported current severe marital physical violence. Most children (n=100; 90.91%) had a female caregiver who acknowledged a previous history of marital violence as defined by WorldSAFE. Of these, 83 (83.00%) had a caregiver with past history of marital psychological violence, and 38 (38.00%) had a caregiver who reported a past history of severe marital physical violence.

As described in Table 3, there was a significant difference ($p = 0.01$) in the distribution of caregivers with recurrent MDE according to the level of offspring psychopathology; the group of symptomatic children with impact had a higher frequency of caregivers with recurrent MDE, compared to both other groups (symptomatic children with impact, 54.20%; asymptomatic children, 26.20%; symptomatic children without impact, 25.00%). The three groups of children also had a different distribution in their caregivers' WHOQOL-BREF social relationships and environment domains ($p = 0.02$ and $p = 0.05$). Pairwise comparisons (Bonferroni correction) showed a significant difference between the asymptomatic vs. symptomatic groups, with impact on both domains ($p = 0.01$ and $p = 0.02$). No significant differences were observed between asymptomatic vs. symptomatic without impact ($p = 0.06$ and $p = 0.47$) or symptomatic with vs. without impact ($p = 0.90$ and $p = 0.47$). Female caregivers reporting current physical violence also had a different distribution ($p = 0.02$), with higher frequency in symptomatic children with impact compared to both other groups (symptomatic with impact, 11.50%; asymptomatic, 3.30%; symptomatic without impact, 0.00%).

We conducted a regression analysis to test for association between caregivers' clinical outcomes and children's characteristics; the results are shown in Table 4. Caregivers with symptomatic children with impact on

**Table 3** Findings in the three children's groups, stratified by adult caregiver's clinical characteristics

| Caregivers (n=68) | Total children (n=110) | Asymptomatic* (n=42) | Symptomatic without impact† (n=20) | Symptomatic with impact‡ (n=48) | Statistic | p-value |
|---|---|---|---|---|---|---|
| Zung | 53.67 (7.47) | 53.48 (8.58) | 54.30 (7.33) | 53.58 (6.31) | 0.12 | 0.94§ |
| SRQ-20 | 13.22 (3.89) | 12.98 (4.12) | 12.40 (3.87) | 13.77 (3.57) | 2.31 | 0.31§ |
| CGI | 4.65 (0.76) | 4.71 (0.67) | 4.50 (1.16) | 4.67 (0.59) | 0.50 | 0.78§ |
| MINI, n (%) | | | | | | |
| Depressive disorder | 97 (88.20) | 35 (83.30) | 16 (80.00) | 46 (95.80) | 4.93 | 0.09 |
| MDE, current | 92 (83.60) | 34 (81.00) | 14 (70.00) | 44 (91.70) | 2.05 | 0.15 |
| MDE, recurrent | 42 (38.20) | 11 (26.20) | 5 (25.00) | 26 (54.20) | 9.23 | 0.01 |
| MDE, single episode | 50 (45.50) | 23 (54.80) | 9 (45.00) | 18 (37.50) | 2.69 | 0.26 |
| Dysthymia | 7 (6.40) | 3 (7.10) | 2 (10.00) | 2 (4.20) | 0.25 | 0.62 |
| MDE + dysthymia | 2 (1.80) | 2 (4.80) | 0 (0.00) | 0 (0.00) | 3.30 | 0.19 |
| Comorbidity with depressive disorder | 41 (37.30) | 17 (40.50) | 6 (30.00) | 18 (37.50) | 0.64 | 0.73 |
| Generalized anxiety disorder | 12 (10.90) | 5 (11.90) | 2 (10.00) | 5 (10.40) | 0.72 | 0.97 |
| Panic disorder | 8 (7.30) | 4 (9.50) | 0 (0.00) | 4 (8.30) | 0.10 | 0.75 |
| Agoraphobia | 17 (15.50) | 6 (14.30) | 3 (15.00) | 8 (16.70) | 0.20 | 0.66 |
| Social phobia | 9 (8.20) | 3 (7.10) | 1 (5.00) | 5 (10.40) | 0.52 | 0.47 |
| Posttraumatic stress disorder | 7 (6.40) | 4 (9.50) | 0 (0.00) | 3 (6.20) | 0.74 | 0.39 |
| WHOQOL-BREF | | | | | | |
| Total quality of life | 41.66 (11.66) | 43.81 (20.65) | 44.37 (12.60) | 38.66 (9.35) | 5.10 | 0.07§ |
| Physical | 46.17 (18.75) | 44.81 (20.65) | 52.32 (17.36) | 44.79 (16.75) | 2.00 | 0.37§ |
| Psychological | 35.80 (15.10) | 36.61 (14.93) | 42.29 (16.94) | 32.38 (13.16) | 4.64 | 0.10§ |
| Social relationships | 41.75 (18.73) | 48.02 (19.18) | 38.33 (18.33) | 37.77 (16.72) | **8.10** | **0.02**§ |
| Environment | 44.46 (13.40) | 48.07 (12.12) | 44.53 (14.85) | 41.28 (12.87) | **6.01** | **0.05**§ |
| WorldSAFE core questionnaire, n (%) | | | | | | |
| Marital violence section, n (children)‖ | 69 | 30 | 13 | 26 | | |
| Current psychological violence | 42 (60.90) | 17 (56.70) | 5 (38.50) | 20 (76.90) | 2.79 | 0.10 |
| Current physical violence | 4 (5.80) | 1 (3.30) | 0 (0.00) | 3 (11.50) | **5.51** | **0.02** |
| Marital violence section, n (children) | 100 | 39 | 18 | 43 | | |
| History of psychological violence | 83 (83.00) | 33 (84.60) | 12 (66.70) | 38 (88.40) | 0.25 | 0.62 |
| History of physical violence | 38 (38.00) | 16 (41.00) | 1 (5.60) | 21 (48.80) | 0.73 | 0.39 |

Data presented as mean (standard deviation), unless otherwise specified.
Bold type indicates statistical significance.
CGI = Clinical Global Impression instrument; MDE = major depressive episode; MINI = Mini-International Neuropsychiatric Interview; SRQ-20 = Self-Reporting Questionnaire; WHOQOL-BREF = World Health Organization Quality of Life instrument-Abbreviated version; Zung = Zung Self-Rating Depression Scale.
* Asymptomatic = Strengths & Difficulties Questionnaire $< 14$.
† Symptomatic without impact = Strengths & Difficulties Questionnaire $\geqslant 14$, impact supplement score = 0.
‡ Symptomatic with impact = Strengths & Difficulties Questionnaire $\geqslant 14$, impact supplement score $\geqslant 1$.
‖ Only among female caregivers in a relationship.
§ Wald chi-square test.

overall distress and impairment had higher SRQ-20 scores compared to the caregivers of asymptomatic children (Beta = 0.20; p = 0.04). Caregivers of more than one child had higher scores on the Zung Self-Rating Depression Scale (beta = 0.44; p = 0.00).

## Discussion

As originally hypothesized, caregiver SRQ-20 score correlated significantly with "symptomatic with impact" status (SDQ score $\geqslant 14$ and impact supplement score $\geqslant 1$) in children. This result is in line with previous studies conducted in high-resource countries showing that, overall, the severity of a mother's depression is associated with her children's psychopathology.[10,11,18,35] According to Fritsch et al.,[18] it is possible that the association between the severity of the mother's illness and children's symptoms is part of a vicious circle or bidirectional – mothers become more severely depressed because they have children with mental disorders, and children's symptoms worsen in the presence of a mother's depression. The results of our analysis substantiate prior findings on correlations of caregiver and offspring psychopathology. Nevertheless, our results do not address causal processes. The next step is to design studies that can assess potentially population-specific causal pathways.

We also found that children with a greater number of siblings had caregivers who were more severely depressed (Zung), suggesting higher distress and an exacerbation of caregivers' symptoms. Previously, a few studies have shown sibling similarity for depression and anxiety disorders,[36,37] but future research should assess number of siblings and shared influences.

Community assessments of parental depression and its impact on offspring in LMICs are underreported, with little prior research.[18-20] Studies from high-income countries have pointed to a higher risk of psychiatric disorders in children of low-income depressed mothers,[14,35] although we did not find a correlation with household income in our sample.

We observed that caregivers with symptomatic children with impact were more likely to have recurrent MDEs.

**Table 4** Regression analysis between adult caregivers' clinical characteristics and children's group and demographics

| Caregivers (n=68) | Asymptomatic* vs. Symptomatic without impact† | Asymptomatic* vs. Symptomatic with impact‡ | Gender | Age | Number of siblings | Education level | Family income |
|---|---|---|---|---|---|---|---|
| Zung (continuous) | | | | | | | |
| Beta | -0.01 | 0.04 | 0.23 | 0.17 | 0.44 | 0.04 | -0.17 |
| p-value | 0.94 | 0.69 | 0.24 | 0.16 | **< 0.001** | 0.74 | 0.17 |
| SRQ-20 (continuous) | | | | | | | |
| Beta | -0.02 | 0.20 | 0.01 | 0.12 | 0.09 | -0.03 | -0.16 |
| p-value | 0.07 | **0.04** | 0.89 | 0.28 | 0.63 | 0.75 | 0.19 |
| CGI (continuous) Beta | -0.18 | 0.15 | -0.05 | 0.13 | 0.27 | -0.03 | -0.06 |
| p-value | 0.22 | 0.22 | 0.57 | 0.46 | 0.28 | 0.18 | 0.75 |

CGI = Clinical Global Impression instrument; SRQ-20 = Self-Reporting Questionnaire; Zung = Zung Self-Rating Depression Scale.
* Asymptomatic = Strengths & Difficulties Questionnaire $< 14$.
† Symptomatic without impact = Strengths & Difficulties Questionnaire $\geqslant 14$, impact supplement score = 0.
‡ Symptomatic with impact = Strengths & Difficulties Questionnaire $\geqslant 14$, impact supplement score $\geqslant 1$.

Findings from longitudinal studies support the notion that children of mothers with more chronic depression have worse outcomes.[38] We also found that caregivers with symptomatic children with impact had worse quality of life in the social relationships and environment domains of WHOQOL-BREF; additionally, they were more likely to report current physical violence from partners.

We must acknowledge the limitations of the present study. First, inclusion criteria were based on depression symptoms from the Zung screening scale. As a result, seven caregivers did not meet criteria for depressive disorders by MINI; three of these had a diagnosis of generalized anxiety disorder and four had subclinical symptoms based on the MINI. The main reason for our broader inclusion criteria is that anxiety and somatization are very common in primary care, and frequently comorbid.[39] The SRQ-20 was used to evaluate depression, anxiety, and somatization, given the substantial syndromic overlap in primary care and significance of common mental disorders,[40] and showed significant correlation with child's symptoms. Second, this small sample may have been biased by recruitment criteria that initially focused on including dyads of symptomatic participants, both adults and children. Thus, we cannot generalize the high prevalence of symptoms found in our study population. Third, we could not investigate specific diagnoses and differences in externalizing and internalizing symptoms further in our sample of children, due to a substantial amount of missing data in the asymptomatic group; this, again, is attributable to our initial interest in including only symptomatic children. Finally, to assess child psychopathology, we relied on the SDQ, which is based on caregiver reports; we did not obtain any information from the children themselves, nor from a clinician.

Strengths of the study include our sample demographics, since most previous studies examined homogeneous, middle- and upper-middle income, predominantly white families.[12] Moreover, none of the adults or children included in our study were currently in treatment, as they were recruited for a future intervention study. In addition, our adult participants were not seeking treatment, but rather were actively screened by community health workers.

These results substantiate our bidirectional hypothesis that children's psychopathology impacts caregivers' psychiatric symptoms and vice-versa, and can help guide future strategies for actions and prevention efforts aimed at reducing the burden of common mental disorders in both caregivers and children. To the best of our knowledge, this is the first study to evaluate the correlation between caregiver psychiatric symptoms and child psychopathology in a LMIC. Our data add to the growing literature on community assessments conducted within LMICs.

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## Disclosure

The authors report no conflicts of interest.

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## ORIGINAL ARTICLE

# Maternal recognition of child mental health problems in two Brazilian cities

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**Objective:** To identify child behaviors and types of impairment that increase the likelihood of maternal recognition of emotional/behavioral problems (EBP) in children and adolescents.
**Methods:** Maternal-reported data were obtained from two subsamples of 11-to-16-year-olds derived from cross-sectional studies conducted in two Brazilian municipalities: Itaboraí, state of Rio de Janeiro (n=480), and Embu, state of São Paulo (n=217). The Itaboraí study involved a representative sample of 6-to-16-year-olds (n=1,248; response rate = 86.0%) selected from the Family Health Program registry, which covered 85.5% of the municipal population. The Embu study was based on a probabilistic sample of clusters of eligible households (women aged 15-49 years, child < 18 years), with one mother-child pair selected randomly per household (n=813; response rate = 82.4%). The outcome variable was mother's opinion of whether her child had EBP. Potential correlates included types of child behaviors (hyperactivity/conduct/emotional problems as isolated or combined conditions) and impairment, assessed using the Strengths and Difficulties Questionnaire (SDQ); child's age and gender; maternal education and anxiety/depression (assessed using the Self-Reporting Questionnaire [SRQ]).
**Results:** Multivariate regression models identified the following correlates of maternal perception of child EBP: comorbidity (co-occurring hyperactivity/conduct/emotional problems), emotional problems alone, and interference of problems with classroom learning and friendships.
**Conclusion:** Comorbidity of different problem types, emotional problems alone, and interference with classroom learning and friendships increase the likelihood of maternal recognition of EBP in children.

**Keywords:** Adolescents; child psychiatry; epidemiology; families; community mental health

## Introduction

There are almost 63 million people under age 20 in Brazil.[1] Of these, 8.3 million may have mental health problems, according to the prevalence of DSM-IV disorders (13.1%) found among schoolchildren in a study conducted in four of the five Brazilian regions (n=1,623; 6-16 years; response rate = 81.1%).[2] However, the vast majority of Brazilian children who need mental health assistance do not receive appropriate care, mainly due to provider or system barriers,[3] but also to poor maternal recognition of emotional/behavioral problems (EBP) in their children.[4] In many countries, primary health care is the main setting of mental health treatment for children, who rely on adults such as parents and teachers to identify their problems and initiate service use.[5]

In Brazil, the Unified Health System provides universal access to health services for the entire Brazilian population. However, child and adolescent mental health services are still scarce. Specialized public services (Psychosocial Community Care Centers for Children and Adolescents) exist to assist severe cases, but are insufficient in number and distributed unequally within the country.[6] Therefore, when parents decide to seek treatment or support for their children with mental health problems, primary care facilities rather than specialized services are the main source of help, particularly among more disadvantaged populations.

Parents are more likely to report intentions to seek help or use services when they recognize a problem in their children.[7,8] Therefore, parental perception of mental health problems in their children is the first of several stages toward children receiving appropriate care, followed by seeking support from primary care services, recognition within primary care, and referral to specialized health services.[5] Parental perception is thus critical to improving access to treatment and avoiding escalation and perpetuation of problems into adult life, which may compromise individuals' functioning and wellbeing, putting them at risk of unemployment and social exclusion.[9] However, parental perception of child problems is not only influenced by child psychopathology[7,10] and functional impairment but also by other factors, such as the child's age and gender, maternal education, and maternal depression.[11] With increasing age, children's own perception of their functioning becomes increasingly important as a motive

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for seeking help.[10] Help is more often sought for boys during childhood and for girls during adolescence,[12] which is consistent with the higher prevalence of hyperactivity and conduct problems in young boys and depression in adolescent girls.[13]

Within this context, the present study aims to identify specific child behavior profiles and types of impairment identified by mothers that increase the likelihood of maternal recognition of EBP in their children, taking into account other potential correlates.

## Methods

### *Study design and setting*

Cross-sectional studies were conducted in two low-income municipalities of Southeast Brazil, both located in the greater metropolitan area of state capitals: Itaboraí, state of Rio de Janeiro (population 218,008 in 2010,[14] located 40 km from the state capital Rio de Janeiro) and Embu, state of São Paulo (population 207,663 in 2000,[15] located 24.5 km from the state capital São Paulo).

### *Sampling*

The original Itaboraí study (2009-2010) included a sample of 6-to-16-year-olds (n=1,248; response rate = 86.0%) randomly selected from the Family Health Program (FHP) registry. The FHP, adopted as a nationwide policy in the 1990s, is a strategy for reorganizing primary care in order to increase public access to health care. According to official information from the Itaboraí municipal government, 85.5% of the population was covered by FHP units in 2010.[16] Each unit was composed of one or two teams, with each team including a physician, a nurse, and around six community health workers responsible for making home visits to registered families. In 2009, 44 FHP teams were active in Itaboraí, 31 of which (70.5%) were involved in the study. For each team, 45 to 48 eligible families (having at least one child aged 6-16 years) were randomly selected, depending on the number of community health workers in the team. The selection of teams was based on the location of units, which were stratified according to the level of neighborhood violence: low violence (7/7 teams, 100%), high violence (13/14 teams, 92.9%), and intermediate violence (11/23 teams, 47.8%).

In Itaboraí, a three-stage sampling plan was applied. The first stage was determined by the level of violence (low, intermediate, high) in each neighborhood served by an FHP unit; these three geographical areas were based on census units. In areas with low and high levels of violence, all units were invited to participate, with 7/7 (100.0%) and 13/14 (92.9%) acceptance respectively. In the intermediate-violence area, 11/23 (47.8%) units were randomly selected to enter the study. The second stage was to conduct a random selection of families among all eligible families registered with the participating FHP units in each of the three geographical areas (low: 454/3,859, intermediate: 307/2,041, high: 487/4,061). The third stage was to randomly select a child among all eligible children in each participating family, in each of the three geographical areas (low: 1/1.70, intermediate: 1/1.55, high: 1/1.62).

The sample size of the original Itaboraí study (n=1,276) was calculated on the basis of the minimum expected prevalence (7%) of its primary outcome (use of mental health services in the past 12 months by children with moderate/severe mental health problems), with an adopted relative precision of 20% (5.6-8.4%).[17]

The original Embu study (2001-2002) was conducted in a community in which the participant municipal health center was located. Based on census units, 24 clusters (geographic areas of maximum internal homogeneity and similar size) in the area were selected randomly. In these clusters, all eligible households were identified (residences in which a woman aged 15-49 years lived with at least one of her children $<$ 18 years), and one mother-child pair was selected randomly per household. From this initial selection (n=987), 813 mothers participated in the study (response rate = 82.4%).

In Embu, mothers from all eligible households located in the randomly selected clusters (24/60) were invited to participate in the study. The mean number of eligible children in the participant households was two. The sample size of the original Embu study (n=864) was calculated on the basis of the expected prevalence (10%) of its primary outcome (child exposed to severe physical punishment), with an adopted relative precision of 20% (8.0-12.0%).[17]

### *Participants*

The present study was restricted to 11-to-16-year-olds from Itaboraí (n=480) and Embu (n=217) for whom complete data on the variables of interest were available, based on reports by (biological, adoptive, or step) mothers. In Itaboraí, 201 of 681 11-to-16-year-olds were excluded because the informant was not the mother (n=157), because the child had severe mental retardation (n=4), or because of missing data (n=40). In Embu, 10 of 227 11-to-16-year-olds were excluded due to missing data; none had severe retardation, and the informant was the mother in all cases.

### *Variables and instruments*

Both the Itaboraí and Embu studies collected information on the outcome variable (mother's opinion of whether her child had EBP) and potential correlates (different types of child behavior profiles and impairment, child's age and gender, and maternal education). Maternal opinion was assessed by the following question: "Do you think $<$name of index child$>$ has emotional or behavioral problems?" Maternal reports about their child's specific behavior profiles were then measured on the Strengths and Difficulties Questionnaire (SDQ), a widely used screening instrument with good psychometric properties.[18,19] The SDQ was developed by Goodman[18] and validated in Brazil by Fleitlich-Bilyk & Goodman.[20] The SDQ was used to identify children with clinical-level conduct problems, emotional problems, and hyperactivity, according to maternal reports (cutoff points defined clinical levels as

detailed at www.sdqinfo.com). The SDQ was also used to identify impairments arising from those problems (child distress and interference with home life, friendships, classroom learning, and leisure activities), and scored positive when mothers reported "quite a lot/a great deal" of impact on children's functioning (versus "only a little/not at all"). Data on maternal anxiety/depression was obtained, only in Embu, using the Self-Reporting Questionnaire (SRQ-20), a screening measure developed by the World Health Organization with a total score ranging from 0 to 20.[21] The SRQ-20 was validated for the Brazilian population with a cutoff point $> 7$.[22]

### *Procedures*

All interviews were conducted in the child's household (in Itaboraí) or at the local health center (in Embu). All questions were asked verbally. For both subsamples of 11-to-16-year-olds, all interviewees were mothers, the great majority of whom were biological mothers (Itaboraí: 98.1%, Embu: 99.1%). In both studies, the question on the mother's opinion about her child's EBPs was asked before completion of the SDQ.

### *Statistical analysis*

Chi-square tests identified significant differences between groups. A significance level of $p < 0.001$ was adopted due to the multiple tests conducted. All child and mother factors potentially associated with maternal recognition of child EBPs were entered into logistic regression models to estimate unadjusted and adjusted odds ratios (univariate and multivariate analysis respectively). Sampling weights applied to data analysis were calculated on the basis of the study sampling plan. In this paper, unweighted numbers of subjects are presented, but percentages are weighted to generate frequencies representative of the population of same-age children and adolescents living in Itaboraí and Embu.

### *Ethics approval*

The Research Ethics Committee of Universidade Federal de São Paulo approved the Itaboraí study (process number 0601/09) and the Embu study (process number 0740/02). Written informed consent was obtained from all participating mothers.

## Results

Table 1 reports the characteristics of children/adolescents and mothers in the Itaboraí and Embu samples. Table 2 shows the types of clinical-level mental health problems in each sample, occurring either alone or with other types (comorbidity). Clinical-level conduct problems were mostly comorbid in Itaboraí (71.4%) and in Embu (78.9%). Clinical-level hyperactivity was also mostly comorbid in Itaboraí (83.4%) and in Embu (72.2%). Clinical-level emotional problems occurred combined with conduct/hyperactivity problems in a slightly higher proportion than alone in Itaboraí (55.7% vs. 44.3%), but occurred mostly alone in Embu (78.6%) (Table 2).

Among children with conduct problems alone, some 50% in both samples were not perceived as having emotional/behavioral difficulties by their mothers (Table 3). This lack of maternal recognition of problems also applied to about 70% of children with emotional problems alone in both studies, and to the majority of children with hyperactivity alone in Itaboraí (83.4%) and in Embu (60.0%). In both studies, children with emotional problems alone and comorbidity were significantly more likely to be perceived by their mothers as having EBPs, compared to children with no mental health problems (Table 3). In Itaboraí, maternal recognition of problems was much more common among children with comorbidity than among children with emotional problems alone or hyperactivity alone ($p < 0.005$), but children with conduct problems alone and children with comorbidity were similarly recognized by mothers as "problematic." In Embu, no differences in maternal perception were found among the four categories of problems.

Univariate regression analysis showed the strength of association between each potential correlate and the study outcome (Table 4). It is interesting to note that the high effect size of all impairment components was drastically reduced in multivariate models (Table 5), confirming the existence of multiple associations within this group of variables. Multivariate regression models showed that, in both studies, comorbidity, clinical-level emotional problems alone, and problems' interference with classroom learning were independent correlates of mothers perceiving their children as "problematic," adjusting for other potential correlates (Table 5). These factors were significant correlates in the presence of maternal anxiety/depression (Embu model 2). Comorbidity was a stronger correlate than isolated conditions across both studies. In Itaboraí, conduct problems alone were more influential than emotional problems alone, but in Embu, the opposite was noted. In Itaboraí, male gender, child distress, and interference with leisure activities were also significant correlates (Table 5). In Embu model 2, interference with leisure activities was a significant correlate, but in the opposite direction, which may be explained by collinearity with "child distress" (of the five subjects positive for interference with leisure activities, four were positive for child distress). When excluding interference with leisure activities from the Embu models, interference with friendships remained non-significant in model 1 (odds ratio [OR] = 2.25; 95%CI 0.53-9.48) and lost significance in model 2 (OR = 2.92; 95%CI 0.61-14.04).

## Discussion

According to the Grand Challenges in Global Mental Health initiative, improvement of children's access to evidence-based care by trained health providers in low- and middle-income countries is one of the top five challenges to improve the lives of people living with mental, neurological, and substance-use disorders.[23] According to Patel et al.,[24] the

**Table 1** Characteristics of 11-to-16-year olds and mothers from two samples: Itaboraí, state of Rio de Janeiro (2009-2010), and Embu, state of São Paulo (2001-2002), Brazil*

| Sample characteristics | Itaboraí n=480 | Embu n=217 |
|---|---|---|
| Adolescents | | |
| Gender | | |
| Male | 237 (49.0) | 99 (45.6) |
| Female | 243 (51.0) | 118 (54.4) |
| Maternal reports of mental health problems (SDQ) | | |
| Conduct problems | | |
| Clinical | 163 (35.1) | 19 (8.8) |
| Borderline/normal | 317 (64.9) | 198 (91.2) |
| Emotional problems | | |
| Clinical | 224 (45.9) | 56 (25.8) |
| Borderline/normal | 256 (54.1) | 161 (74.2) |
| Hyperactivity | | |
| Clinical | 86 (17.8) | 18 (8.3) |
| Borderline/normal | 394 (82.2) | 199 (91.7) |
| Maternal reports of impairment components (SDQ) | | |
| Child distress | | |
| Quite a lot/a great deal | 54 (11.5) | 11 (5.1) |
| Only a little/not at all | 426 (88.5) | 206 (94.9) |
| Interference with home life | | |
| Quite a lot/a great deal | 45 (10.3) | 7 (3.2) |
| Only a little/not at all | 435 (89.7) | 210 (96.8) |
| Interference with friendships | | |
| Quite a lot/a great deal | 27 (6.1) | 7 (3.2) |
| Only a little/not at all | 453 (93.9) | 210 (96.8) |
| Interference with classroom learning | | |
| Quite a lot/a great deal | 76 (17.0) | 14 (6.5) |
| Only a little/not at all | 404 (83.0) | 203 (93.5) |
| Interference with leisure activities | | |
| Quite a lot/a great deal | 19 (3.8) | 5 (2.3) |
| Only a little/not at all | 461 (96.2) | 212 (97.7) |
| Any impairment | | |
| Yes | 113 (25.1) | 21 (9.7) |
| No | 367 (74.9) | 196 (90.3) |
| Mothers | | |
| Education (years) | | |
| 0-4 | 157 (31.3) | 78 (35.9) |
| 5 or more | 323 (68.7) | 139 (64.1) |
| Anxiety/depression (SRQ-20) | | |
| Yes ($>$ 7) | N/A† | 74 (34.1) |
| No (0-7) | N/A† | 143 (65.9) |
| Opinion about child's mental health status | | |
| Emotional/behavioral problems | 172 (36.3) | 44 (20.3) |
| No emotional/behavioral problems | 308 (63.7) | 173 (79.7) |

Data presented as n (%).
N/A = not applicable; SDQ = Strengths and Difficulties Questionnaire; SRQ-20 = Self-Reporting Questionnaire.
* Numbers of subjects are unweighted (refer to the sample) and all percentages are weighted, representing frequencies in the population of 11-to-16-year-olds from Itaboraí and Embu.
† Not applicable (variable not included in the Itaboraí study).

most viable strategy to address the treatment gap is through empowerment of existing human resources that are most intimately concerned with child care, including empowerment of parents.

In the present study, even when mothers reported child symptoms on the SDQ that indicated clinical-level conduct problems, emotional problems, or hyperactivity, mothers often did not perceive their child as having an EBP. This lack of maternal recognition is in accordance with a previous U.S. study, which found that, in a sample of children with mental disorders, only 39% of parents perceived their child to have a mental health problem.[11]

Nonetheless, in Itaboraí and Embu, children with conduct problems alone, emotional problems alone, and comorbidity were significantly more likely to be perceived by their mothers as having EBPs, compared to children with no problems. This is consistent with a previous study in the Netherlands[25] that found an association between parents perceiving their children as having EBPs and children's mental health problems indicated both by a screening questionnaire (Child Behavior Checklist/6-18) and by a diagnostic instrument (Diagnostic Interview Schedule for Children, IV).

In our investigation, multivariate models identified specific types of child behavior profiles and impairment that correlated independently with the mother's opinion of whether the child had any EBPs. The implications of these findings are discussed in turn.

**Table 2** Clinical-level mental health problems (SDQ) occurring alone or concomitantly in two samples of 11-to-16-year-olds: Itaboraí, state of Rio de Janeiro (2009-2010), and Embu, state of São Paulo (2001-2002), Brazil*

| Clinical-level problems (SDQ, mother's report) | Itaboraí n=480 | Embu n=217 |
|---|---|---|
| Conduct | | |
| Alone | 45 (28.6) | 4 (21.1) |
| Combined with hyperactivity/emotional | 118 (71.4) | 15 (78.9) |
| Any clinical-level conduct problems | 163 (100.0) | 19 (100.0) |
| Emotional | | |
| Alone | 101 (44.3) | 44 (78.6) |
| Combined with hyperactivity/conduct | 123 (55.7) | 12 (21.4) |
| Any clinical-level emotional problems | 224 (100.0) | 56 (100.0) |
| Hyperactivity | | |
| Alone | 11 (16.6) | 5 (27.8) |
| Combined with conduct/emotional | 75 (83.4) | 13 (72.2) |
| Any clinical-level hyperactivity | 86 (100.0) | 18 (100.0) |

Data presented as n (%).
SDQ = Strengths and Difficulties Questionnaire.
* Numbers of subjects are unweighted (refer to the sample) and all percentages are weighted, representing frequencies in the population of 11-to-16-year-olds from Itaboraí and Embu.

**Table 3** Mothers perceiving emotional/behavioral problems in their children, stratified maternal reporting of isolated vs. combined clinical-level problems (SDQ): rates in Itaboraí, state of Rio de Janeiro, and Embu, state of São Paulo, Brazil*

| Clinical-level problems (SDQ, mother's report) | Itaboraí | | Embu | |
|---|---|---|---|---|
| | Problems n=172 | No problems n=308 | Problems n=44 | No problems n=173 |
| None (reference category) | 21 (11.1) | 164 (88.9) | 16 (11.0) | 129 (89.0) |
| Conduct problems alone | 21 (50.3)† | 24 (49.7) | 2 (50.0) | 2 (50.0) |
| Emotional problems alone | 31 (30.5)† | 70 (69.5) | 13 (29.5)† | 31 (70.5) |
| Hyperactivity alone | 2 (16.6) | 9 (83.4) | 2 (40.0) | 3 (60.0) |
| Comorbidity‡ | 97 (70.7)† | 41 (29.3) | 11 (57.9)† | 8 (42.1) |

Data presented as n (%).
SDQ = Strengths and Difficulties Questionnaire.
* Numbers of subjects are unweighted (refer to the sample) and all percentages are weighted (refer to the population).
† $p < 0.001$ in chi-square tests with none as reference category.
‡ Co-occurrence of two or three problems (conduct, emotional, hyperactivity).

*Problem type*

Comorbidity was a stronger predictor of mothers perceiving their child as having an emotional/behavioral difficulty compared to isolated conditions, which is consistent with a recent Brazilian study examining the capacity of teachers to identify students in need of mental health evaluation/treatment.[26]

One interpretation of the finding that, in Itaboraí, conduct problems alone had a stronger association with mothers' perception of child EBPs compared to emotional problems alone might be that externalizing behaviors are particularly distressing for parents and, therefore, children with externalizing behaviors are more frequently perceived as "problematic" than children with internalizing problems.[27,28] Hankinson[28] examined thresholds for parents' perceptions of children's problems and subsequent help-seeking decisions based on children's behaviors presented in vignettes. Externalizing behaviors alone were rated by parents as more serious and representing a greater need for treatment than internalizing behaviors alone. As such, mothers may have a lower threshold for identifying externalizing symptoms as "problematic" than for internalizing symptoms, which may be less noticeable.[29] Furthermore, conduct problems alone in the Embu sample were not a significant correlate of mothers' perception of child EBPs, probably due to the low number of these problems observed.

*Impact of problems*

In both studies, children's problems interfering with classroom learning was associated with mothers' perceptions of their child having an emotional/behavioral problem, independently of the presence of child psychopathology identified by clinical-level SDQ scales, other types of impact, maternal anxiety/depression, or demographic variables. This is consistent with findings from a general-population sample of Dutch 4-to-18-year-olds in which academic problems were strongly associated with perceived mental health service need and utilization, independently of child internalizing and externalizing behaviors or family stress.[10] A review of influences on the help-seeking

**Table 4** Correlates of maternal opinion about child emotional/behavioral problems, identified by univariate logistic regression models, in two samples of 11-to-16-year-olds: Itaboraí, state of Rio de Janeiro, and Embu, state of São Paulo, Brazil*

| | Itaboraí n=480 | | Embu n=217 | |
|---|---|---|---|---|
| Sample characteristics | Unadjusted OR (95%CI) | p-value | Unadjusted OR (95%CI) | p-value |
| Adolescents | | | | |
| Age (years) | 1.02 (0.95-1.09) | 0.649 | 1.06 (0.91-1.23) | 0.442 |
| Gender (male vs. female) | **1.66 (1.21-2.29)** | **0.030** | 0.70 (0.43-1.13) | 0.133 |
| Clinical-level problems (SDQ, mother's report) | | | | |
| Conduct problems alone† | **8.13 (4.23-15.64)** | **< 0.001** | **8.06 (1.66-39.15)** | **0.012** |
| Emotional problems alone† | **3.53 (2.07-6.02)** | **< 0.001** | **3.38 (1.83-6.25)** | **< 0.001** |
| Hyperactivity alone† | 1.60 (0.38-6.79) | 0.510 | **5.38 (1.21-23.87)** | **0.029** |
| Comorbidity† | **19.45 (13.52-27.97)** | **< 0.001** | **11.09 (4.24-29.00)** | **< 0.001** |
| Impairment components (SDQ, mother's report) | | | | |
| Child distress‡ | **25.99 (11.21-60.24)** | **< 0.001** | **3.57 (1.28-9.97)** | **0.017** |
| Interference with home life‡ | **10.50 (5.13-21-51)** | **< 0.001** | **3.09 (1.04-9.18)** | **0.043** |
| Interference with friendships‡ | **23.45 (9.35-58.81)** | **< 0.001** | **5.67 (1.72-18.66)** | **0.006** |
| Interference with classroom learning‡ | **16.42 (9.67-27.86)** | **< 0.001** | **6.19 (2.98-12.84)** | **< 0.001** |
| Interference with leisure activities‡ | **20.92 (12.40-35.32)** | **< 0.001** | 0.98 (0.15-6.39) | 0.985 |
| Mothers | | | | |
| Education (0-4 years vs. > 4 years) | **1.32 (1.02-1.72)** | **0.037** | 1.02 (0.68-1.54) | 0.910 |
| Anxiety/depression (SRQ-20)§ | N/A‖ | | **3.33 (1.98-5.61)** | **< 0.001** |

Bold font indicates significant results.
95%CI = 95% confidence interval; N/A = not applicable; OR = odds ratio; SDQ = Strengths and Difficulties Questionnaire; SRQ-20 = Self-Reporting Questionnaire.
* Sampling weights applied to determine unadjusted OR and 95%CI.
† Compared to no problems on SDQ.
‡ Quite a lot/a great deal vs. only a little/not at all.
§ Yes (total score > 7) vs. no (total score 0-7).
‖ Not applicable (variable not measured in the Itaboraí study).

process concluded that school-related problems play an important role, influencing not only parental help-seeking but also problem recognition by general practitioners.[12] In the Itaboraí sample, interference with friendships was also interpreted by mothers as a red flag of child EBPs. This is in accordance with Brazilian cultural norms, which expect children to be very social. In Embu, interference with friendships was not a significant correlate of mothers' perception of child EBPs in model 1 and lost significance in model 2 when the variable "interference with leisure activities" was excluded from the model due to collinearity with "child distress." This lack of significance is probably due to the low number of subjects classified as having "quite a lot/a great deal" of interference with leisure activities in the Embu sample.

### *Child gender*

In the Itaboraí sample, mothers were more likely to perceive EBPs in their children when the child was a boy, independently of clinical-level problems and impairment. These results are in agreement with a Brazilian study that examined a probabilistic sample of schoolchildren (n= 1,721; grades 2-6) and identified female gender as a correlate of low mental health service utilization in the presence of psychiatric disorders and/or neurodevelopmental problems.[30] However, in Embu, gender was not a correlate of maternal perception of children's problems. This inconsistency in findings across sites might be explained by an association of gender with variables not measured in our study that may have differed between sites. For example, our study did not include correlates of antisocial behavior (e.g., alcohol/illicit drug use[31] and involvement with criminality[32]), which are predominant in males compared to females, and are signs of severity that may make mothers more likely to recognize their child as having EBPs. If alcohol/illicit drug use and involvement with criminality were more common in Itaboraí than in Embu, this could explain why male gender was associated with maternal recognition of children's problems in the former but not in the latter. This hypothesis is coherent with the fact that, in 2006, Itaboraí recorded a higher homicide rate among adolescents (6.0 deaths per 1,000 in the age range 12-18 years) compared to Embu (2.8 deaths per 1,000 in the same age range).[33]

### *Parental psychopathology*

Parental recognition of children's problems partly depends on levels of distress or burden experienced by the parents in raising their child.[12,34] Parental distress reduces the threshold for parents perceiving their children's behaviors as "problematic."[10,29,35,36] Also, high levels of stress reduce parental self-efficacy to cope with parenting demands and other daily challenges, making parents more likely to seek help from pediatric primary care services.[37] Because parental distress and below-average self-efficacy in high-stress environments are associated with perceiving children as having problems, it is reasonable to hypothesize that mothers with anxiety/depression would be more likely to perceive their sons/daughters as having EBPs.

**Table 5** Correlates of maternal opinion about child emotional/behavioral problems, identified by multivariate logistic regression models, in two samples of 11-to-16-year-olds: Itaboraí, state of Rio de Janeiro, and Embu, state of São Paulo, Brazil*

| | Itaboraí n=480 | | Embu n=217 | | | |
|---|---|---|---|---|---|---|
| | Model 1 | | Model 1 (excluding maternal anxiety/depression) | | Model 2 (including maternal anxiety/depression) | |
| **Sample characteristics** | **Adjusted OR (95%CI)** | **p-value** | **Adjusted OR (95%CI)** | **p-value** | **Adjusted OR (95%CI)** | **p-value** |
| Adolescents | | | | | | |
| Age (years) | 1.04 (0.96-1.13) | 0.320 | 1.04 (0.88-1.21) | 0.651 | 1.01 (0.86-1.19) | 0.884 |
| Gender (male vs. female) | **1.94 (1.39-2.71)** | **< 0.001** | 0.70 (0.42-1.19) | 0.176 | 0.70 (0.41-1.19) | 0.175 |
| Clinical-level problems (SDQ, mother's report) | | | | | | |
| Conduct problems alone† | **6.52 (3.39-12.53)** | **< 0.001** | 4.92 (0.96-25.14) | 0.055 | 4.97 (0.80-30.93) | 0.083 |
| Emotional problems alone† | **2.19 (1.29-3.71)** | **0.005** | **2.69 (1.49-4.85)** | **0.002** | **2.09 (1.10-3.99)** | **0.027** |
| Hyperactivity alone† | 1.35 (0.44-4.12) | 0.588 | 3.42 (0.62-18.69) | 0.149 | 2.10 (0.44-9.99) | 0.337 |
| Comorbidity† | **11.11 (7.18-17.17)** | **< 0.001** | **10.69 (3.56-32.12)** | **< 0.001** | **7.80 (2.45-24.90)** | **0.001** |
| Impairment components (SDQ, mother's report) | | | | | | |
| Child distress‡ | **13.08 (6.03-28.37)** | **< 0.001** | 1.18 (0.42-3.27) | 0.746 | 1.02 (0.40-2.62) | 0.969 |
| Interference with home life‡ | 0.93 (0.45-1.94) | 0.847 | 1.93 (0.56-6.61) | 0.282 | 1.96 (0.55-7.01) | 0.285 |
| Interference with friendships‡ | **4.20 (1.16-15.21)** | 0.030 | 4.50 (0.68-29.81) | 0.113 | **6.89 (1.16-40.79)** | **0.035** |
| Interference with classroom learning‡ | **4.65 (2.32-9.33)** | **< 0.001** | **3.31 (1.39-7.90)** | **0.009** | **3.81 (1.73-8.39)** | **0.002** |
| Interference with leisure activities‡ | **2.62 (1.26-5.45)** | 0.012 | 0.08 (0.01-1.05) | 0.054 | **0.06 (0.01-0.56)** | **0.015** |
| Mothers | | | | | | |
| Education (0-4 vs. > 4 years) | 1.06 (0.75-1.48) | 0.745 | 0.95 (0.57-1.57) | 0.818 | 0.66 (0.36-1.22) | 0.175 |
| Anxiety/depression (SRQ-20)§ | N/A‖ | | VEP¶ | | **2.84 (1.36-5.91)** | **0.007** |

Bold font indicates significant results.
95%CI = 95% confidence interval; N/A = not applicable; OR = odds ratio; SDQ = Strengths and Difficulties Questionnaire; SRQ-20 = Self-Reporting Questionnaire; VEP = variable excluded on purpose.
* Sampling weights applied to determine adjusted OR and 95% CI.
† Compared to no problems on SDQ.
‡ Quite a lot/a great deal vs. only a little/not at all.
§ Yes (total score >7) vs. no (total score 0-7).
‖ Not applicable (variable not measured in the Itaboraí study).
¶ Variable excluded from Embu model 1 on purpose to make it comparable to Itaboraí model 1.

*Conclusion*

In conclusion, this study contributed new evidence on isolated and combined types of child behavior profiles in relation to maternal perception of children's EBPs. It emphasized the strong role of comorbidity in increasing the likelihood of a mother's recognition of her child as "problematic." Our study also contributed new evidence on the specific types of impairment that are related to maternal perception of children's problems, highlighting the particular importance of impaired school performance and problem interference with friendships, instead of using only one measure of global functioning. Our findings are probably generalizable to other disadvantaged Brazilian populations living in similar socioeconomic contexts. However, the study has limitations, such as the small number of children with conduct problems alone in the Embu sample and with hyperactivity alone in both samples, which reduced statistical power to find significant associations between these isolated conditions and the study outcome. Other limitations include the absence of other relevant potential correlates (e.g., maternal beliefs/understanding about mental illness, signs of severity of child antisocial behavior such as alcohol/illicit drug use and criminality) and the lack of an independent assessment of whether the children actually had mental health problems, since only a screening instrument (SDQ) was completed by the mothers. Because the study outcome (mother's opinion of whether her child had EBPs) and main independent variables of interest (types of child behaviors and impairment) were measured on the basis of information provided by the same respondent, this data relationship may have influenced the study results. Nevertheless, while this last factor may be seen as a limitation, it also provides an interesting perspective on our results, because the mothers in this study did not always perceive their child as having problems even when they noticed symptoms (as reported on the SDQ).

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## Disclosure

The authors report no conflicts of interest.

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## ORIGINAL ARTICLE

# Dysfunctional eating behaviors, anxiety, and depression in Italian boys and girls: the role of mass media

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**Objective:** Extensive research has implicated identification with characters in mass media in the emergence of disordered eating behavior in adolescents. We explored the possible influence of the models offered by television (TV) on adolescents' body image, body uneasiness, eating-disordered behavior, depression, and anxiety.
**Methods:** Three hundred and one adolescents (aged 14-19) from southern Italy participated. They completed a questionnaire on media exposure and body dissatisfaction, the Eating Disorder Inventory-2, the Body Uneasiness Test, the Beck Depression Inventory, and the State-Trait Anxiety Inventory – Form Y.
**Results:** The main factors contributing to females' eating-disordered behaviors were their own desires to be similar to TV characters, the amount of reality and entertainment TV they watched, and the discrepancy between their perceptions of their bodies and those of TV characters. Friends' desire to be similar to TV characters contributed most to depression, anxiety, body uneasiness, and eating disorders for both males and females.
**Conclusion:** Our data confirm that extensive watching of reality and entertainment TV correlates with eating-disordered behavior among females. Moreover, the well-known negative effects of the media on adolescents' eating-disordered behaviors may also be indirectly transmitted by friends who share identification with TV characters.

**Keywords:** Adolescents; eating disorders; child psychiatry; women; gender differences

## Introduction

Adolescents constitute one-fifth of the world's population.[1] The World Health Organization calculated that over 50% of mental disorders begin in adolescence,[2,3] although they are often detected later in life.[4] A 2015 systematic review and meta-analysis on the worldwide prevalence of psychiatric disorders in children and adolescents indicated a pooled estimate of 13.4% of youth affected by any mental disorder, showing that around 241 million youngsters in the world are affected by a psychiatric disorder.[5] Moreover, among youngsters, psychiatric disorders account for 15-30% of the disability-adjusted life years lost during the first 30 years of life[6]; thus, it seems reasonable to both study and invest in research and intervention targeting the mental health of adolescents.[7]

Eating disorders (EDs) are among the most pernicious mental illnesses beginning in adolescence.[8,9] The mortality rate for anorexia nervosa (AN) is much higher than for other psychiatric disorders: the standardized mortality ratios are 5.86 for AN, 1.93 for bulimia nervosa (BN), and 1.92 for EDs not otherwise specified (EDNOS). Technology and mass media may be putting greater proportions of adolescents at risk of developing EDs, which can be exacerbated by idealistic body images presented in the media. In fact, it has been suggested that the glamorization of specific body shapes fomented by the fashion world, for which youngsters represent a core market, can account for the high prevalence of EDs in developed countries. Furthermore, media globalization is correlated to an increased prevalence of EDs in developing countries.[4] A recent longitudinal study[10] conducted with 2,287 participants found that, once dysfunctional ED behaviors start, they become extremely difficult to stop: adolescents with more severe symptomatology continued to belong to the pathological eating behaviors group at 10-year follow-up, indicating the importance of early detection and appropriate intervention.

Patients with AN, BN, and binge-eating disorder (BED) present with disturbed body image and eating and/or weight loss behaviors, leading to severe impairment of quality of life and to high personal and social costs.[11,12] There are also other nonspecific feeding and eating-related maladaptive behaviors, which do not meet all diagnostic criteria for a specific ED, that are very common in community samples, such as chronic dieting, fasting,

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bingeing, purging, and abuse of laxatives and/or diuretics. These symptomatic behaviors increase the risk of "subsequent development of a specific ED."[13] They also dangerously increase the risk of both physical pathological conditions, such as delayed puberty, digestive/urinary abnormalities, and mouth ulcers, and psychological conditions, such as depression, suicide attempts, anxiety, and substance abuse.[14-16] In a systematic review[12] of a large number of community-based studies, the authors highlighted the robust associations between ED prevalence and female sex, younger age cohort, and a history of abuse (particularly physical or sexual). In another review of the literature on the incidence, prevalence, and mortality rates of EDs,[17] AN was found to be on the rise among 15-to-19-year-old girls. BED has been found to be more common among males and older individuals than other EDs.[17]

In a study on the epidemiology of EDs in six European countries (Belgium, France, Germany, Italy, the Netherlands, and Spain), the lifetime prevalence of AN, BN, binge-ED, subthreshold binge-ED, and any binge eating was 0.48, 0.51, 1.12, 0.72, and 2.15%, respectively.[18] Lifetime prevalence was consistently three to eight times as high among women as men for all EDs, except subthreshold BED. Moreover, EDs showed high levels of comorbidity with other mental disorders.[18] Despite the high presence of comorbid disorders in this sample, which should theoretically increase the likelihood of seeking treatment, very few individuals sought contact with mental health services for psychological problems. Among other reasons, the ego-syntonic and reinforcing nature of symptoms in EDs (e.g., anxiolytic, anesthetic, or reward-inducing effects of fasting, bingeing, purging, and excessive exercise) may explain the low motivation of these patients to seek professional help.[19]

EDs comprise a variety of symptoms that severely impair physical, mental, and social aspects of everyday life, perhaps more so than other common psychiatric disorders.[20] EDs are associated with mood and anxiety problems, substance use, and impulse control disorders, contributing to overall impairment and decreased quality of life.[21]

In particular, adolescence represents a developmental period when weight-related teasing by peers and other environmental risk factors, such as the exposure to unattainable thinness ideals, can negatively affect boys' and girls' lives.[22] For these reasons, adolescence represents a critical target period for prevention programmes.[22,23]

It is well established that prolonged direct exposure to media pressure towards thinness, as well as indirect exposure through the media's effects on peers and significant others, represent important risk factors for body dissatisfaction and dysfunctional eating behaviors in adolescents and young adults.[24] Objectification theory[25] contends that women in Western culture are constantly objectified and that their bodies are used by others as a way of assessing their personal worth. Through socialization, women internalize the idea that their self-worth is largely based on the way other people view them. This, in turn, leads to their own continual comparisons of their body images to others.[25]

Interestingly, self-objectification has been found to play a role in depression, which is frequently comorbid with EDs. In a systematic review of research,[26] a hypothesized causal link between self-objectification and depression was tested. There was clear support for this causal link in the data from female participants, but mixed support for males, indicating a potentially more complex etiology of male EDs.[26] Self-objectification can also be derived from the media, in addition to perceived body idealization resulting from conversations with peers and friends.

In a study[27] focused on the relationship between drive for thinness, self-esteem, and media influence, women were found to be more significantly influenced than men by the media in terms of drive for thinness. Models in the media were perceived to have ideal bodies, which led to an internalization of the media message that affected the body image of the viewers, both male and female.[27]

Media effects may not be limited to North America, where most of the research has been conducted. The global access to mass media, including television (TV) and film, creates an international dilemma, as seen in a study of adolescents in Fiji whose body image was negatively affected by gaining access to social networks.[28] The desire for approval, which has been identified as a leading cause of EDs, can stem from comparisons made to characters and figures in the media.[29] The ideal of feminine beauty is portrayed as something impossible to attain, but important to work towards. The media presents unattainable ideals to adolescents (see, e.g., Miotto et al.[30]), but does not disseminate information regarding the dangers and prevalence of the EDs that come as negative consequences of striving for thinness. Nevertheless, the key element may be not mere exposure to media, but exposure without critical consideration: adolescents spend an average of 7 or more hours/day with media, which is more than they do on any other activity except sleeping.[31] Although adolescents have access to several media, TV remains predominant and, when a TV is in the bedroom, parents are less capable of monitoring adolescents' viewing habits[31] by co-viewing and discussing the characters' appearance or choices and behavior. Therefore, a passive, uncritical, and unquestioning stance may contribute to the strong impact these images have on adolescents' thoughts and feelings.

The objective of the present study was to evaluate the influence of models offered by the mass media (TV) on adolescents' perceptions of their own body image and on psychopathology. We hypothesized that: i) exposure to TV would correlate positively with susceptibility to distorted bodily perceptions, disordered eating behavior, anxiety, and depression; ii) the participants' distorted perception of their own bodies compared to those of TV characters would correlate positively with body uneasiness, disordered eating behavior, anxiety, and depression; and iii) participants' and their friends' desire to be similar to models of TV characters would correlate positively with disordered eating behavior.

## Methods

### *Study design and participants*

Three hundred and one male and female adolescents between the ages of 14 and 19, recruited from 13 high

school classes across southern Italy, participated in the study. The sample was made up of 148 females (49.17%, mean age 17.136, standard deviation [SD] = 1.3) and 153 males (50.83%, mean age 17.176, SD = 1.2), an almost equal distribution of sex and age.

### *Ethical considerations*

This study was carried out after approval by the ethics committee of Dipartimento di Psicologia dei Processi di Sviluppo e Socializzazione, Sapienza Università di Roma. Assessment was conducted during one session lasting around 1 hour, which took place in the participants' classrooms. The study was introduced to the participants and a set of questionnaires was administered under the supervision of a proctor capable of providing clarification. Administration was carried out in a manner that ensured anonymity. Before administering the test, the participants were asked to read and sign an informed consent form where the study and Italian Law 675/96, which guarantees the privacy of personal information, were explained. Parents signed the informed consent form for underage participants, whereas those who were of legal age signed the form themselves. The consent rate was 94%. Participants were not given any incentive to participate in the study, and their involvement was voluntary. To ensure the participants' anonymity, no names were identified on the questionnaires.

Respondents were asked to indicate the average daily time spent watching TV and the name and type of their favorite TV programs. In addition, participants specified the body type of their favorite TV character (both male and female), how similar to these characters they perceived themselves to be, and whether they or their friends would like to resemble these characters physically.

### *Instruments*

#### Eating Disorder Inventory-2 (EDI-2)

The EDI-2 is a self-report measure[32,33] used to assess ED psychopathology (i.e., attitudes and behaviors relevant to bulimia and AN) in both males and females over the age of 12. This second version contains 91 items and 11 subscales that measure: 1) drive for thinness; 2) bulimia; 3) body dissatisfaction; 4) ineffectiveness; 5) perfectionism; 6) interpersonal distrust; 7) interoceptive awareness; 8) maturity fears; 9) asceticism; 10) impulse regulation; and 11) social insecurity. Participants rated their level of dissatisfaction on a letter scale from A (never) to F (always), and were also asked to indicate their weight in kilograms and height in centimeters. This instrument has shown to be reliable for the assessment of EDs, with highly stable test-retest reliabilities over time. Previous research has shown significant test-retest correlations ranging from 0.81-0.89 in the ED group and from 0.74-0.95 in the group with other diagnoses, such as depression and obsessive-compulsive disorder.[34] In this study, Cronbach's alpha was 0.71.

#### Body Uneasiness Test (BUT)

The BUT is a 71-item self-report questionnaire divided into two parts.[35] BUT-A consists of 34 statements and measures weight phobia, body image concerns, avoidance, compulsive self-monitoring, detachment, and estrangement feelings towards one's own body (depersonalization). Sample items include: ''Eating in the presence of others causes anxiety''; ''I avoid mirrors''; and ''I compare my appearance with that of others.'' On the other hand, the 37-item BUT-B examines specific worries about particular body parts, features (e.g., odor), or functions (e.g., sweating). Response options for all items were based on a six-point scale, ranging from 0 (never) to 5 (always). BUT-A scores were averaged in a Global Severity Index (GSI) and five subscales: Weight Phobia (fear of being or becoming fat); Body Image Concerns (worries related to physical appearance); Avoidance (body image-related avoidance behavior); Compulsive Self-Monitoring (compulsive checking of physical appearance); and Depersonalization (detachment and estrangement feelings toward the body). BUT-B scores were combined in two measures (Positive Symptom Total and Positive Symptom Distress Index) and in eight subscales related to specific worries about particular body parts or functions. Higher scores indicate greater body uneasiness. Research on the validity of the BUT indicates that this questionnaire has satisfactory internal consistency (alpha $>$ 0.7) and strong test-retest reliability (correlation coefficients $>$ 0.7). It has been shown to be a valuable instrument for screening and clinical assessment of abnormal body image attitudes, AN (restrictive and binge-purging types), and BN (purging type).[35] In this study, Cronbach's alpha for this measure was 0.91.

#### Beck Depression Inventory (BDI-II)

The BDI-II is a 21-item self-report inventory used to measure characteristic attitudes and symptoms of depression, such as hopelessness, irritability, and feelings of guilt.[36,37] Participants are asked to indicate which statement best describes their feelings over the past 7 days. Each item has between four and six choices, ranging in intensity. Sample items include: ''I don't enjoy things the way I used to''; ''I feel the future is hopeless and that things cannot improve''; and ''I blame myself all the time for my faults.'' Scores are combined and compared to a key to determine the presence and severity of depression, ranging from ''normal ups and downs'' to ''extreme depression.'' Previous studies on the psychometric properties of the BDI-II have demonstrated high internal consistency, with alpha coefficients of 0.86 and 0.81 for psychiatric and non-psychiatric populations, respectively.[38] In this study, Cronbach's alpha for this measure was 0.82.

#### State-Trait Anxiety Inventory – Form Y (STAI-Y)

The STAI-Y is a self-report inventory that measures state and trait anxiety.[39,40] Form Y contains 20 items that assess state anxiety and 20 for trait anxiety. Sample state anxiety items include: ''I feel worried'' and ''I feel secure.'' Trait anxiety items include: ''I worry too much over

something that really doesn't matter" and "I am content." For the items on state anxiety, participants are asked to indicate whether the statement describes their current mood state. Responses are based on a four-point scale ranging from "not at all" to "extremely." For the items on trait anxiety, participants indicate whether the statement describes how they feel most of the time. Responses are based on a four-point scale ranging from "almost never" to "almost always." Previous research has demonstrated a high internal consistency, with alpha coefficients ranging from 0.86-0.95 and test-retest coefficients from 0.65-0.75 over a 2-month interval.[39] In this study, Cronbach's alpha was 0.84 for the trait scale, which was used in the regression analyses.

*Statistical analysis*

We conducted a series of initial analyses to determine the viability of pooling data from male and female participants into a single set of multiple-regression analyses, thus maximizing statistical power. First, we determined that the participants' gender was the strongest predictor of eating-disordered behavior and body uneasiness in our data. Furthermore, many of the interactive effects of gender and the other predictors were significant. Because we did not have the statistical power to enter all of these interactions into a single equation, we opted to compute separate regression equations for male and female participants.

## Results

Table 1 displays the standardized beta coefficients separately by gender. Male friends' desire to physically resemble TV characters was the only statistically significant factor contributing to the criterion measures. Notably, that variable emerged as a significant predictor of all four dependent variables: depression, anxiety, eating-disordered behavior, and body uneasiness.

As shown in the table, several significant predictors emerged in the regressions computed with data obtained from female participants. Consequently, the overall variance explained for females was greater than for males, especially for the more proximal criterion variables of eating-disordered behavior and body uneasiness. As in the results obtained for males, friends' desire to be similar to media characters emerged as a significant predictor of all four criterion variables, making this the most consistent predictor in the entire data set. However, some additional predictors were significant only for females, including some significant findings for females' own desire to be similar to media characters and the discrepancy they perceived between their own body image and that of the character. There results suggest that Italian female adolescents internalize media messages about the ideal body to some extent, which was not evident in the data obtained from males.

**Table 1** Multiple regression summary for males and females: standardized beta coefficients and significant *t* values

| Predictor variable | Males | Females (beta) |
|---|---|---|
| Depression | | |
| Hours watched | 0.127 | 0.384 |
| Idolization of characters | -0.558 | 0.957 |
| Desire to be similar | 1.221 | 0.751 |
| Friends' desire to be similar | 0.218/2.650† | 2.013 |
| Discrepancy from ideal | 0.111 | 0.539 |
| Cumulative $R^2$ | 0.07 | 0.05 |
| Anxiety | | |
| Hours watched | 0.072 | -0.046 |
| Idolization of characters | 0.079 | 0.032 |
| Desire to be similar | 0.010 | 0.121 |
| Friends' desire to be similar | 0.183/2.184* | 0.286/2.329† |
| Discrepancy from ideal | -0.009 | 0.949 |
| Cumulative $R^2$ | 0.04 | 0.11 |
| Eating disordered behavior | | |
| Hours watched | -0.046 | 0.004 |
| Idolization of characters | 0.032 | -0.083 |
| Desire to be similar | 0.121 | 0.211/2.611† |
| Friends' desire to be similar | 0.286/3.556† | 0.110 |
| Discrepancy from ideal | 0.005 | 0.310 |
| Cumulative $R^2$ | 0.12 | 0.19 |
| Body uneasiness | | |
| Hours watched | 0.022 | 0.036 |
| Idolization of characters | -0.048 | 0.031 |
| Desire to be similar | 0.143 | 0.214/2.726† |
| Friends' desire to be similar | 0.213/2.613† | 0.194/2.415* |
| Discrepancy from ideal | 0.117 | 0.332/4.292‡ |
| Cumulative $R^2$ | 0.09 | 0.24 |

*$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$.

## Discussion

Our results highlight the difference between male and female adolescents in terms of susceptibility to misperception of their body caused by the mass media. The stronger prediction of outcome for females corroborate previous findings,[27] showing that females were influenced by the media in terms of drive for thinness significantly more than males were. A higher prevalence of ED symptoms has been found in women as compared to men. Thus, women may be more susceptible than men to body misperceptions caused by the media.

Objectification theory states that, in Western culture, women are specifically objectified and their body is used to measure their self-worth. Through the perception that their self-worth is mainly based on how people view them, women subconsciously tend to compare their body image to others' more than men do.[25] According to objectification theory, women already have a stronger propensity to being swayed by the media and, in turn, viewing their body in a negative way as compared to the "ideal body" that is represented in TV or in other media. Our data indicate that women are much more susceptible to the mass media through direct comparisons. Men may have a different etiology in regards to the effect of mass media and ED behaviors, or may simply not be as sensitive to media influences as are females. One possible explanation is that females may be more sensitive to these issues than males because they watch more entertainment and image-focused TV.[41] With respect to TV viewing time, women of all ages spend more time watching TV than their male counterparts.[42] This could explain the more direct effect on dysfunctional EDs. On the other hand,

men spend more than twice as much time as women using gaming consoles, so one may infer that they are less directly influenced by TV watching.[43]

One interesting finding of our study is the very consistent strength of the vicarious influence of friends, specifically of friends' perceptions of media characters. This emerged as a significant predictor for both males and females, but stands out as the only significant predictor in our data set for males. While both males and females appear to be sensitive to the influences of friends, it is commonly held that females are more invested in relations than are males.[44] This does not preclude the possibility of boys being influenced very strongly by their friends in this particular way, especially in the Italian culture, where boys and men do interact socially to a considerable extent.[45]

Our findings should be viewed while taking certain limitations into consideration. First, the correlational nature of our data. Although we did obtain statistically significant correlations in our sample, we cannot determine whether the mass media caused the psychological problems or only contributed to them. Therefore, we are unsure whether the initial presence of depression and/or anxiety might have made the participants more susceptible to EDs or if instead those factors were a consequence of EDs. Second, all measures were self-reported and may thus have been affected by self-report bias. Also, we did not account for genetic factors. If any of the participants had a genetic predisposition toward ED behavior, exposure to the mass media may have had a stronger effect on them than on others without such predispositions.

Though not all of our hypotheses were confirmed, our data revealed interesting information about the differences in male and female susceptibility to the mass media. Although no direct causal relationships can be drawn from this study, our data show a relationship whereby women are more susceptible to ED behaviors, distorted perception of their own bodies, and depression through direct comparisons to the mass media. On the other hand, males are more susceptible to distorted perception of their body, state and trait anxiety, and depression using indirect comparisons to the mass media through their friends. We suggest that future studies should explore the etiology of EDs in men and the indirect influence of mass media characters.

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## Disclosure

The authors report no conflicts of interest.

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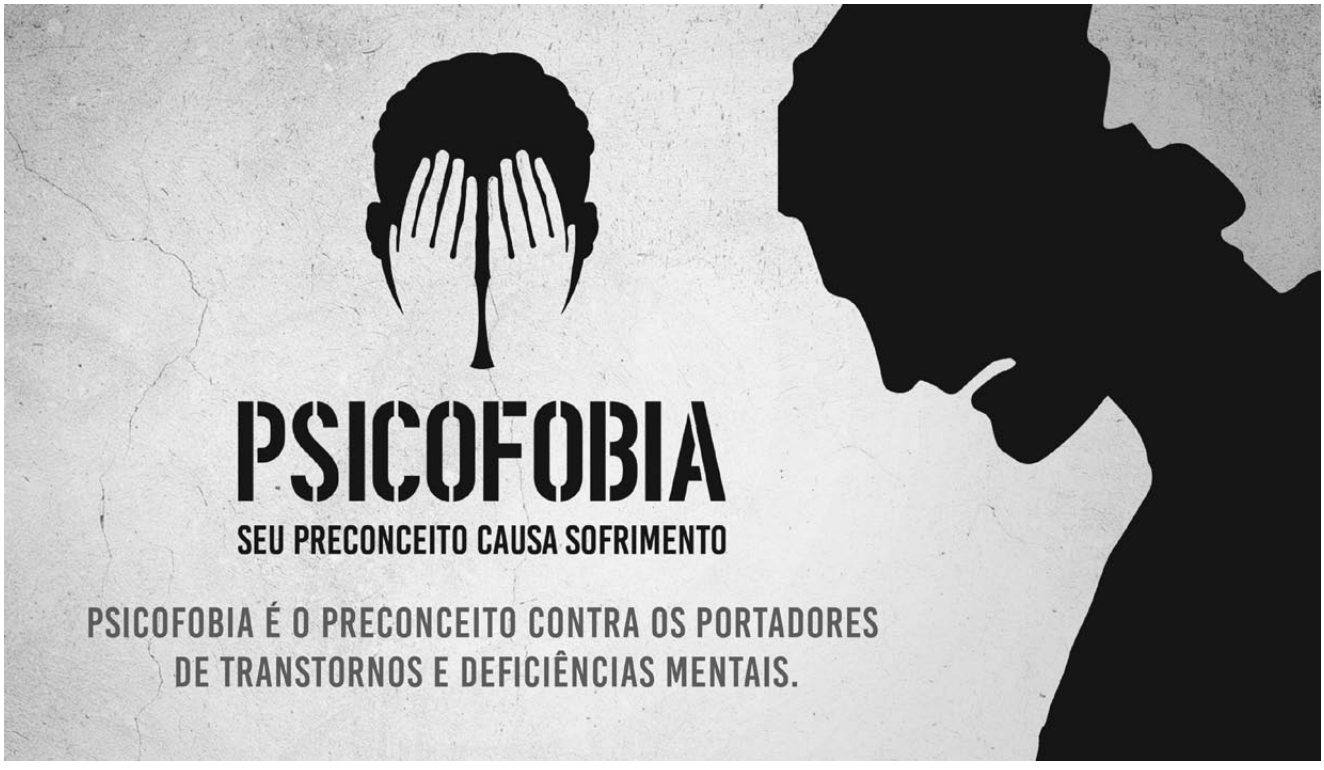

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## ORIGINAL ARTICLE

# Empathic skills and theory of mind in female adolescents with conduct disorder

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**Objective:** Most studies on conduct disorder (CD) have focused on male adolescents, disregarding analysis of this psychopathology in women. The purpose of this study was to identify differences in empathy and theory of mind (ToM) in a group of adolescent women with CD and a control group.
**Method:** Thirty-six adolescent women were selected from an initial sample of 239 adolescents (CD group = 18, control group = 18). Empathy and ToM were evaluated through objective instruments. Mean comparisons and multivariate analysis were performed to ascertain differences between cases and controls and to propose a prediction model based on clinical status.
**Results:** Significant differences in empathic abilities and ToM were found between the groups. The model that differentiated both groups was composed of eye-reading ability, perspective taking, and personal distress.
**Conclusion:** These findings are consistent with previous studies. Capacity to take the other's perspective and the recognition of emotions in the face are protective factors against CD in women.

**Keywords:** Conduct disorder; empathy; theory of mind; women; callous unemotional traits

## Introduction

Conduct disorder (CD) during childhood and adolescence is characterized by social norms violations such as theft, private property destruction, transgressions of other people's rights, physical and relational aggressions, extortion, and intimidation. The most recent description of this pathology has included a relevant clinical specifier termed callous-unemotional traits (CUT), which is associated with more serious conduct problems and worse response to treatment.[1] Adolescents with CD and CUT present limitations in prosocial emotional processing, serious difficulties in feeling guilt or remorse, and a significant decrease in their empathic abilities.[1] The prevalence of this disorder in children and adolescents is believed to range between 2% and 10%, with men being more frequently affected (male-to-female ratio 4:1). Male adolescents exhibit more aggressive behaviors, such as fighting, vandalism, and theft, while women more often seem to show relational aggressions that imply a deterioration of relationships with others, emotional manipulation, and a higher tendency to deceit, truancy, and prostitution.[1-3]

Several studies of CD have included samples of male adolescents or of both genders.[4,5] There is a dearth of research on this disorder exclusively in women. Currently, a few clinical differences have been established to distinguish the main features of CD in each gender[4-7]; however, knowledge about the differences between women with and without CD, particularly regarding empathy and social cognition processes, is scarce.

Recent studies have pointed out social cognition and empathy deficits in women with CD.[8,9] These studies have established that women with CD have a higher deficit of facial acknowledgement of happiness, sadness, and fear – emotions linked to empathic answers and prosocial behavior. Research has also described that these adolescents present slower emotional processing, which limits the decoding of such emotions and generates a delay in the empathic responses needed to understand and affectively bond with the emotional and mental states of others.[9-11] Previous findings, supported by clinical evidence, proposed the CUT specifier for CD subtypes that involve absence of guilt and lack of empathic concern for others.[12] According to this, women with CD and limitations in abilities related to the theory of mind (ToM) have important psychopathic traits and blunted prosocial responses, which involve a lack of concern for the negative consequences caused by their actions and low empathic concern.[11-13]

Hence, empirical evidence shows that deficits in emotional and empathic processing and in ToM abilities are predictive of antisocial conduct during childhood and adolescence. Specifically, empathy has been described as an inhibitory response to aggressive and antisocial conducts that may lead to prosocial behaviors, as it may have an impact over the abilities to feel (affective component) and understand (cognitive component) emotional and mental states and, therefore, to experience guilt or embarrassment when one's actions affect others negatively.[14] On the other hand, some studies suggest that deficits in empathy and, particularly, in ToM abilities in adolescents

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lead to difficulties in social adaptation, in interactions with peers, and in family and academic scenarios. In this line, children and adolescents who have difficulty "reading" the emotional states of others through eye-reading ability and difficulty understanding situations (whether affectively or cognitively) within context in their interactions with others are more likely to experience behavioral problems in their development.[15-18]

The purpose of this study was to identify and analyze possible differences in empathy and ToM between a group of female adolescents with CD and a control group. Based on empirical evidence, we hypothesize that there will be significant differences between the two groups, with the control group performing better on measures of empathy and ToM. Our second hypothesis states that women with CD might have lower empathy scores due to CUT compared to healthy controls, and, finally, that empathic dimensions and ToM variables will be predictive of CD in female adolescents.

## Method

### *Participants*

This study is part of a larger research project, "Theory of mind and empathy as predictors of conduct disorder in adolescence,"[17] conducted on a total sample of 239 adolescents (CD group = 157; no CD group = 82). Only 18 participants in the CD group were women. From this initial sample, 36 female adolescents aged 15 to 17 years were selected (18 with CF from Centro Juvenil Amigoniano, and 18 controls without CD from Instituto Técnico San Rafael). Only women who met DSM-IV-TR criteria for CD[19] were selected to compose the case group; then, the same number of controls was selected randomly.

The Conduct Disorder Module of the International Neuropsychiatric Interview (MINI)[20] was applied to the CD group. In the no-CD group, the DSM-IV-TR criteria were applied to ensure that a diagnosis of conduct disorder was not present. The clinical history of all participants was studied and subjects with evidence of psychosis, autism, neurological diseases, or any medical condition that might suggest another developmental, emotional, or behavioral disorder were excluded. Participation in the study was voluntary, and both the adolescents and their parents or legal guardians provided written informed consent.

### *Instruments*

#### Conduct disorder

Clinical interviewers used the DSM-IV-TR criteria for screening[19] and confirmed the diagnosis with the Conduct Disorder module of the MINI.[20] CUTs were explored using the same instrument. The MINI is a short structured diagnostic interview that explores the main psychiatric disorders in axis I of the DSM-IV[21] and the ICD-10.[22] Validity and reliability studies have compared the MINI to the Structured Clinical Interview for DSM, Psychiatric Patients (SCID-P)[23] for the DSM-III-R[24] and the Composite International Diagnostic Interview (CIDI). The results of these studies show that the MINI has acceptably high validity and reliability and can be administered in a shorter period of time (from 11.6 to 18.7 minutes; 15 minutes on average) than the aforementioned instruments.

#### Empathy

The Interpersonal Reactivity Index[25] was used for multidimensional assessment of empathy. This test evaluates four dimensions of empathy – two in the cognitive component (perspective taking and fantasy) and two in the affective component (empathic concern and personal distress) – and consists of 28 items, answered on a 5-point Likert scale ranging from "Does not describe me well" to "Describes me very well." The measure has four subscales, each made up of seven different items. These subscales are:

- Perspective taking: the tendency to spontaneously adopt the psychological point of view of others;
- Fantasy: taps respondents' tendencies to transpose themselves imaginatively into the feelings and actions of fictitious characters in books, movies, and plays;
- Empathic concern: assesses "other-oriented" feelings of sympathy and concern for unfortunate others;
- Personal distress: measures "self-oriented" feelings of personal anxiety and unease in tense interpersonal settings.

The internal consistency of the dimensions ranges from 0.68 to 0.79, and test-retest reliability varies from 0.61 to 0.81 during a period of 60 to 75 days.

#### Theory of mind

The Faux Pas Test, based on the procedure described by Stone et al.,[26,27] consists of 20 stories, of which half contain a social *faux pas* and the other half are control stories with a minor conflict that does not constitute a *faux pas*. There are also *faux pas* detection questions and memory questions that measure the comprehension of details in the story. For example, in one story, Mary says "I don't think I've met this little boy" to a child's mother; in fact, the child is a little girl. The speaker did not say this out of any malicious intent, but out of a mistaken belief. The *faux pas* in this case lies in the fact that it may unintentionally upset parents for their little girl to be thought of as a boy. In another story, Tim is in a restaurant and spills his coffee. He turns to the waiter and says, "I've spilt my coffee. Would you be able to mop it up?" In fact, the other person is not a waiter but simply another customer. Once again, there is no malice involved; the speaker was simply mistaken. However, the *faux pas* in this case arises because it is a bit rude to ask a bystander to clean up your mess.[26] The scoring system used was the one established by Stone et al.,[26] with test-retest markers of reliability of 0.83 and evaluator reliability of 0.76.

The Reading the Mind in the Eyes Test was used to measure emotion-reading ability and the attribution of mental states of others by including their beliefs and intentions.[28] The test consists of 36 pictures of different

actors' eyes. The pictures are presented one at a time in a fixed order. Each stimulus consists of four written words describing emotions, among which the participant has to choose that which best describes what the person is thinking or feeling. One point is awarded for every correct response; the maximum total score is 36. Scoring data were obtained from studies conducted in a general Latin American population.[29]

### *Procedure*

All adolescents were evaluated by clinical professionals affiliated with the Basic and Applied Neuroscience research group from Fundación Universitaria Luis Amigó. The clinical criteria for conduct disorder (DSM-IV-TR[18]) were applied to each adolescent. Those who did not meet the criteria were assigned to the control group, while those who met the criteria underwent the MINI[19] and were then classified in the CD group with CUT as appropriate. Then, empathy and ToM tests were administered to both groups. All assessments were performed in a single 60-minute session in a quiet and comfortable place.

### *Statistical analysis*

SPSS version 22 was used for data analyses. The hypothesis of normality was tested by the Shapiro-Wilk method for age variables and test scores (ToM and empathy). All variables were normally distributed. Measures of central tendency were described for age and test scores, which were also compared by the Student *t*-test. Then, a multivariate analysis of covariance (MANCOVA) was performed to determine whether the empathy and ToM test scores differed according to the independent variable clinical status (CD vs. no CD). Finally, a binomial logistic regression model was constructed to establish predictors of risk for or protection against CD in female adolescents.

## Results

The means and standard deviations of ToM and empathy scores are described in Table 1.

To determine whether empathy and ToM test scores differed between the CD and no-CD groups, MANCOVA was performed. CD diagnostic status (CD vs. no CD) was taken as a factor, while the Eye Test, the Faux Pas Test, and the empathy represented by the fantasy, empathic concern, perspective taking, and personal distress domains were the dependent variables.

According to Wilks's lambda statistic, MANCOVA showed that the dependent variables (empathy and ToM) were significantly affected by the independent variable, meaning that scores in the empathy and ToM test dimensions were affected by the diagnosis of CD ($F = 24.64$; $p < 0.000$). In a test of effects among subjects, the only variable that did not predict differences between the groups was the Faux Pas Test ($F = 2.69$; $p = 0.110$). The remaining dependent variables – Eye Test ($F = 52.09$; $p < 0.000$), perspective taking ($F = 43.16$; $p < 0.000$), and personal distress ($F = 16.89$; $p < 0.000$) – clearly differentiated the two groups.

A binomial logistic regression model (Table 2) was constructed to establish predictive factors according to the categorical variable clinical status (CD vs. no CD). Initially, the Introduce method was used and all variables that represented empathy and ToM measurements were included (fantasy, perspective taking, personal distress, empathic concern, Eye Test, and Faux Pas Test). Subsequently, the variables with a very high standard error or with a confidence interval including the null value were eliminated from the model. Only the variable Fantasy was thus eliminated from analysis. Then, a new regression model was applied using Wald's backwards elimination method, where the omnibus coefficient showed significant changes in the predictive test with the variables Eye Test, perspective taking, and personal distress ($\chi^2 = 43.34$; $p < 0.000$). Finally, with a more consistent filter, a model was applied again through the Introduce method, selecting the aforementioned variables. According to this model, the

**Table 1** Means and standard deviations of empathy and theory of mind variables for both groups

| | CD (n=18) | | No CD (n=18) | | | | |
|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | *t* | p-value | *d* |
| Age | 16.33 | 0.76 | 16.28 | 2.63 | -0.08 | 0.93 | |
| *Faux pas* | 91.72 | 29.99 | 92.17 | 31.36 | 0.04 | 0.96 | |
| Eye reading | 13.74 | 5.40 | 27.91 | 5.94 | 7.21 | 0.000* | 0.78 |
| Perspective taking | 14.44 | 5.04 | 25.17 | 4.74 | 6.57 | 0.000* | 0.75 |
| Fantasy | 22.17 | 5.56 | 23.56 | 4.66 | 0.81 | 0.42 | |
| Empathic concern | 16.83 | 3.58 | 24.78 | 4.03 | 6.24 | 0.000* | 0.73 |
| Personal distress | 15.33 | 3.83 | 21.39 | 4.93 | 4.11 | 0.000* | 0.58 |

*d* = effect size (Cohen's); SD = standard deviation.
* $p < 0.001$.

**Table 2** Binary logistic regression model for clinical status according to empathy and theory of mind test scores

| | B | Standard error | Wald | p-value | Exp (B) | 95%CI |
|---|---|---|---|---|---|---|
| Perspective taking | -0.12 | 0.20 | 4,20 | 0.03 | 0.80 | 0.71-0.88 |
| Eye Test | -1.17 | 0.64 | 3.30 | 0.05 | 0.30 | 0.87-0.96 |

95%CI = 95% confidence interval.

empathy dimension perspective taking and the Eye Test were predictors of clinical status. The predictive capacity of this model was 62.4.

## Discussion

The purpose of this study was to analyze differences in empathy and ToM between a group of female adolescents with CD and a control group without CD. The adolescents with CD scored very low on the empathy test compared to the control group. Specifically, significant differences were found in the cognitive dimension perspective taking ($p < 0.001$; $d = 0.78$) and the affective dimensions empathic concern ($p < 0.001$; $d = 0.75$) and personal distress ($p < 0.001$; $d = 0.58$). These empathic abilities have been described as factors that inhibit the expression of aggressive and antisocial behaviors during childhood and adolescence,[8,14,29] and their adequate development generates affective and cognitive mechanisms that allow the subject to understand other people's emotions, to adopt their perspective, and to respond affectively toward their anguish. These results validate our first and second hypotheses about the mean differences between groups, the superior performance of the control group on measures of empathy and ToM, and the lower affective empathy scores in the CD group; all of the significant differences had a large size of effect as measured by Cohen's *d* statistic.

Differences in affective empathy scores between groups were also observed, specifically in the personal distress and empathic concern dimensions; this was attributable to the poor emotional response of adolescents in the CD group toward the negative experiences and needs of others, as well as to a deficit in identifying emotionally connected facial traits. Several studies support this finding and link it to CUTs.[3,8,30-33]

On the other hand, the Faux Pas Test showed no difference between groups. Both the CD and no-CD groups performed very similarly and within the expected response rate for the general population. This runs counter to our expectation that adolescents in the CD group would score lower than controls, as suggested by previous studies.[14,18] However, there is also evidence that the development of abilities in ToM does not guarantee social adaptation.[34] Some children and adults can consistently use their ToM abilities for antisocial purposes. For example, subjects with Machiavellian personality characteristics have a tendency to manipulate interpersonal situations to their benefit, and their abilities in ToM work as a psychological mechanism that can facilitate the achievement of such strategies in their relations with others.[34] Consistent with this, subjects with Machiavellian beliefs have also been found to exhibit a kind of affective coldness without empathic concern and take advantage of their ToM abilities as a social tool they use according to their own convenience.[35-37] This may partially explain why mean Faux Pas Test scores were similar in both groups of adolescents, and suggests the CUTs of adolescents with CD can be a contributing factor to the instrumental use of their ToM abilities. This operational use of mind-reading abilities should be further explored both in healthy controls and in subjects with CD.

According to our results, the ability to take the other's perspective and to "read" the other's emotional states would probably represent predictive factors involved in the inhibition of dissocial conducts. The cognitive dimension of empathy (perspective taking) plays a significant role in the generation of behaviors that constitute an empathic response toward others' anguish, based on the capacity to "read" their emotional states. Some authors corroborate this, and suggest the primacy of perspective taking and reading of emotions in others as mechanisms that allow the activation of an emotional system compatible only with help behaviors, inhibiting hostile responses and facilitating a regular social function.[38-40] Thus, the deficits in perspective taking and eye reading exhibited by the CD subjects would increase their likelihood of displaying antisocial behavior and worsening social relations,[41,42] as often happens in adolescents with CD. The empirical evidence regarding abilities for eye reading and empathy is consistent with our findings, and suggests a close connection between these abilities and facilitation of proper social functioning. The existing evidence also argues for differences in ToM and empathy between adolescents with and without CD, aside from their probable interdependence as predictive factors in regular empathic emotional development and prosocial behavior.[42]

The findings of this study will contribute to a better understanding of CD in women and its connection to the empathic and social cognition processes. They also point to a possible line of future research, namely, further investigation on the instrumental use of abilities in ToM and CD during childhood and adolescence. A deeper exploration of CUTs and their possible effects on social and moral cognition in children and adolescents with CD may also be warranted.

Finally, the limitations of this study must be discussed. First, the small sample size may have affected the statistical power to reveal significant associations among the variables of interest, which has a direct effect on the predictive effect demonstrated in the regression model. Second, the use of social cognition measurement instruments that have not been standardized for use in the Colombian context may have led to errors in interpretation of results.

## Disclosure

The authors report no conflicts of interest.

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## ORIGINAL ARTICLE

# Further evidence of psychological factors underlying choice of elective cesarean delivery by primigravidae

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**Objective:** Requests for elective cesarean delivery (ECD) have increased in Iran. While some sociodemographic and fear-related factors have been linked with this choice, psychological factors such as self-esteem, stress, and health beliefs are under-researched.
**Methods:** A total of 342 primigravidae (mean age = 25 years) completed questionnaires covering psychological dimensions such as self-esteem, perceived stress, marital relationship quality, perceived social support, and relevant health-related beliefs.
**Results:** Of the sample, 214 (62.6%) chose to undergo ECD rather than vaginal delivery (VD). This choice was associated with lower self-esteem, greater perceived stress, belief in higher susceptibility to problematic birth and barriers to an easy birth, along with lower perceived severity of ECD, fewer perceived benefits from VD, lower self-efficacy and a lower feeling of preparedness. No differences were found for marital relationship quality or perceived social support.
**Conclusions:** The pattern suggests that various psychological factors such as self-esteem, self-efficacy, and perceived stress underpin the decision by primigravidae to have an ECD.

**Keywords:** Elective cesarean delivery; vaginal delivery; psychological predictors; Health Belief Model; fear; stress

## Introduction

The obstetric dilemma[1] refers to the trade-off between a woman's relatively small pelvis and birth canal compared to fetal head and shoulder size. While a smaller pelvis and pelvic birth canal evolved as a result of bipedalism during the last four to five million years, the newborn's head dimensions have increased over the last 500,000 years due to rapid brain expansion.[2] This cephalopelvic disproportion is responsible for obstructed labor, which ranges from 3% to 6% worldwide.[3] Cesarean delivery (CD) has thus become a common option for dealing with cephalopelvic disproportion. Very recent evidence indicates that CDs are increasing worldwide[4] and, according to Mitteroecker et al.,[3,5] there is reason to believe that while increased rates of CD are a response to a cephalopelvic disproportion, they will also lead to further increases in this disproportion.

The grounds for performing a CD can be categorized as absolute, relative, or elective. Whereas in absolute and relative indications for CDs, the health of both mother and fetus are primary considerations (e.g., placenta previa, HIV infection, contracted pelvis, obesity and diabetes mellitus, breech presentation or previous cesarean section), for elective cesarean delivery (ECD; also called cesarean delivery on maternal request, or CDMR) the mother's desire, rather than a medical indication, is the chief factor.[6-9]

Worldwide, the CD rate is approximately 30-40% in public hospitals and 50-60% in private hospitals, with the highest rates (90%) found in private practice in Brazil.[10] The rate of ECDs in both developed and developing countries, such as Iran,[11,12] is increasing. In Iranian province of Hamadan, the CD rate is 47.5% in public hospitals and 79.1% in private hospitals.[13] These rates are much higher than the 10-15% rate recommended by the World Health Organization (WHO).[11]

While it is clear that CD is increasing worldwide, there is no uniform agreement regarding the reasons for, or consequences of, ECDs.[14]

In a review of the literature, Mylonas & Friese[15] identified three reasons for choosing ECD: a) the physical health profiles of the mother and fetus; b) legal aspects, and c) psychological factors. The physical health category involves factors such as advanced maternal age, fertility treatment, obesity, diabetes mellitus, previous pregnancies, and previous CDs.[16,17] Legal aspects include issues of responsibility (and financial consequences) in the event of injury to the mother or child. Both risk-oriented and

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risk-averse attitudes can be found among obstetricians. As for psychological factors, fear seems to be the most powerful influence underlying ECD.[18-20] More specifically, fear of complications, tokophobia,[17,21] dysfunctional beliefs about childbirth,[22,23] previous traumatic births, depression.[24] and other psychiatric and psychosomatic issues can lie behind a decision to undergo ECD. In a previous study,[25] we found that fear for the health and life of the fetus, fear of the process of labor and childbirth, and doubts about the competence and behavior of the maternity staff, along with fear of parenthood and family life were the strongest factors associated with seeking ECD. In short, both expectant mothers and perinatal health experts can list a number of reasons for choosing ECDs.

Evidence for the benefits of ECDs is mixed. On the one hand, several studies have reported that, compared to vaginal delivery (VD), hospitals stays are longer following ECDs, and the risk of hysterectomy due to post-partum bleeding and cardiac arrest is higher.[15] A large cohort study in Scotland indicated that children born by CD had a higher risk of asthma by age 5 (however, Black et al.[26] emphasized that this study counted both planned and unplanned CDs). Likewise, other studies[27] have reported higher rates of severe maternal health outcomes after E/CD and higher rates of postpartum depression for CD than for VD.[28]

On the other hand, there is evidence that, compared to VD, there is less abdominal and perineal pain during and three days after ECD, as well as fewer vaginal injuries and anesthesia-related emergencies (e.g. shock and bleeding).[15] More recently, Molina et al.[29] investigated the association between CDs and maternal and neonatal mortality across all 194 WHO member states and found that a CD rate of up to approximately 19% was associated with lower levels of maternal and neonatal mortality, which calls the 1985 WHO recommendation to restrict CD rates to a maximum of 10-15% into question[11] (for further discussion, see D'Alton & Hehir[30]). Likewise, Betran et al.[31] also observed that ECD rates above 9-16% were not associated with higher mortality outcomes. More importantly, two studies published in 2007 (Gamble et al.[32] and McCourt et al.[33]) pointed out that the psychosocial context of obstetric care had until then involved a power imbalance in favor of the physician and that the following factors had not been taken into account in the historical context of maternal decision-making: the influence of care offered, the interaction between the expecting mother and health care providers, the context of care, tokophobia, and the perceived inequality and inadequacy of care. The WHO's most recent statement (2015)[34] acknowledged that CD decisions should reflect women's individual care requirements rather than conform to predetermined limits. We also note that large cohort studies[4,29,31,35] have not taken into account emotional factors in decisions for ECD.

To address this imbalance, the present study focused on psychological reasons for ECDs. Specifically, we considered women's self-esteem, stress, and health-related beliefs based on the Health Belief Model (HBM). Briefly put, the HBM[36] seeks to explain the cognitive-emotional processes that underlie health-related behavior. Thus, we used HBM constructs applied to VD childbirth, such as the perceived susceptibility to poor/difficult VD, and the benefits of and barriers to VD. Due to limited previous research in this area, the following research question was formulated: Are there differences in self-esteem, perceived stress, marital relationship quality, and HBM scores between primigravidae opting for ECD and those opting for VD? That is, do women who choose ECD have lower self-esteem, higher perceived stress, lower marital relationship quality, and more negative health-related beliefs?

To answer these questions, a sample of primigravidae referred to public health care centers for routine prenatal care was assessed. We believe this study has the potential to shed more light on the psychological processes underlying the choice of ECD and might facilitate effective educational interventions and health care programs aimed at improving women's capacity to make informed decisions regarding ECDs and VDs.

The present data are part of larger study investigating Iranian women's attitudes to CD and VD. In a previous study,[25] we found that ECD was associated with advanced age, higher education level, higher family income, and unplanned pregnancy, as well as that women opting for ECD had higher fear scores in the following dimensions: labor and childbirth, life and well-being for themselves and for the fetus, becoming a parent and family life after delivery, their own competencies, and the competencies of the maternity ward staff. In this paper, we focus on previously unpublished evidence concerning the psychological factors underpinning decisions for ECD.

## Methods

### *Procedure*

This cross-sectional study was carried out among primigravidae referred to public health care centers for routine prenatal care in Hamadan, Iran. The health care centers of three of the four municipal areas of Hamadan were randomly selected. To select potential participants, stratified random sampling was used. Eligible participants were informed about the aims of the study and the voluntary basis of participation. Participants were informed that the data would be handled anonymously and provided written informed consent. Of the 470 individuals approached, 342 met the inclusion criteria (see below) and agreed to participate.

### *Sample*

As mentioned above, a total of 342 women (mean age = 25 years; standard deviation [SD] = 3.5) took part in the study.[25] The inclusion criteria were: 1) being at the end of the first trimester (gestational age between 13-15 weeks); 2) having no legal or medical indication for CD; 3) being willing and able to complete questionnaires covering sociodemographic, psychological, and pregnancy-related questions (see below); and 4) aged between 18 and 35 years. The exclusion criteria were: 1) not meeting any point of the inclusion criteria; 2) a history of or existing medical, psychiatric, or obstetric problems, including

congenital fetal anomaly; 3) a history of inherited disease in the mother's or father's family.

*Instruments*

Participants completed a set of questionnaires covering sociodemographic, psychological and pregnancy-related information.[25] The data used in the present study are from the psychological instruments, which are described below. Before these evaluations began, however, the participants reported whether they were opting for ECD or VD.

Self-esteem

Participants completed the Farsi version of the Rosenberg Self-Esteem Scale (RSES), translated and validated by Shapurian et al.[37] The RSES consists of 10 items and is used as a one-dimensional measure of global self-esteem (cognitive and affective components), general self-worth, and positive self-esteem. Answers are given on four-point Likert scales ranging from 0 (= strongly disagree) to 3 (= strongly agree), with higher total scores reflecting higher self-esteem. Scores between 15 and 25 points are within the normal range; scores below 15 points are associated with lower self-esteem.

Perceived stress

To assess perceived stress, the Farsi version of the Perceived Stress Scale (PSS[38]), translated and validated by Maroufizadeh et al.,[39] was used. The PSS is a measure of the degree to which situations in one's life are appraised as stressful. The 10 items are intended to measure how unpredictable, uncontrollable, and overloaded respondents find their lives. Answers are given on 5-point Likert scales ranging from 'never' to 'very often' (reverse scoring was used for some items). Higher total scores reflect greater subjectively perceived stress.

Marital relationship quality

The Farsi version of the Revised Dyadic Adjustment Scale (RDAS[40]), translated and validated by Isanezhad et al.,[41] was used to assess marital satisfaction. The RDAS consists of 14 items, with answers given on a 6-point Likert scale ranging from 0 (= not at all) to 5 (= completely true). Higher total scores reflect greater satisfaction.

Perceived social support

To assess perceived social support, we used the Farsi version of the Multidimensional Scale of Perceived Social Support (MDSPSS[42]), translated and validated by Bagehrian-Sararoudi et al.[43] It consists of twelve questions that assess perceived support from family, friends, and significant others. Answers are given on a 7-point Likert scale ranging from 1 (= strongly disagree) to 7 (= very strongly agree). Higher total scores reflect stronger perceptions of social support.

Health Belief Model (HBM)

To assess the participants' health beliefs, the Farsi version of the HBM questionnaire,[36] translated and validated by Assari,[44] was administered. The questionnaire includes 43 questions on the following topics: perceived susceptibility to poor or difficult VD (5 items), perceived severity of complications associated with VD (7 items), perceived benefits of VD (spontaneous VD; 7 items), perceived barriers to successful VD (8 items), self-efficacy for VD (10 items), and feelings of preparedness for VD (6 items). The answers are given on a 5-point Likert scale, end-anchored by 1 (= strongly disagree) and 5 (= strongly agree).

*Statistical analysis*

Preliminary calculations: to determine whether planned or unplanned pregnancies had an influence on the pattern of results, a series of *t*-tests were performed. It was observed that planned or unplanned pregnancy had no systematic effect on the results (all $t$ values $< 1.2$ and p values $> 0.25$).

The participants were divided into two groups according to delivery type. The psychological and HBM-related data were compared between groups using chi-square and *t*-tests. To predict which psychological and HBM-related dimensions best predicted ECD, a binary logistic regression analysis was performed with the psychological factors (self-esteem, perceived stress, quality of marital relationship, perceived social support) and health-related belief dimensions as independent factors, and the choice of delivery method (ECD vs. VD) as the dependent variable. The significance level was set at 0.05 for all tests. All statistical analyses were performed with SPSS version 23.0.

## Results

*General characteristics of the primigravidae*

The mean participant age was 25 years (range 18-34 years); 224 (65.5%) had planned pregnancies, and 214 (62.6%) requested ECD on non-medical grounds in the course of a normal pregnancy. Participants opting for ECD were 1.86 years older than participants opting for VD (ECD: n=214; mean = 25.88 years, SD = 3.62; range: 18-34 years; VD: n=128; mean = 24.02 years, SD = 2.87; range: 18-32 years; $t_{340} = 4.96$, p = 0.01, $d = 0.47$).

*Psychological factors*

Table 1 shows all statistical indices (descriptive and inferential statistics). Compared to VD, participants opting for ECD had lower self-esteem scores and higher perceived stress scores, whereas no significant mean differences were found for marital relationship quality or perceived social support.

*Health Belief Model (HBM)*

Table 1 also reports all statistical indices related to the HBM constructs. Compared to VD, participants opting for

ECD had higher scores for susceptibility to poor or difficult VD and barriers to a successful VD (i.e., lower confidence in VD) and lower scores for severity of complications of ECD, the benefits associated with VD, preparedness for VD, and self-efficacy in coping with VD.

*Predicting elective cesarean delivery (ECD)*

To predict the choice of ECD, a binary logistic regression analysis was performed. All statistical indices are shown in Table 2. ECD was predicted by higher perceived susceptibility to a poor or difficult VD, greater barriers to a successful VD, and lower self-efficacy, while severity of complications, benefits and preparedness were excluded from the equation.

## Discussion

A total of 214 (62.3%) of the 342 primigravidae opted for ECD in the absence of medical indications. The key finding of the present study was that those opting for ECD reported higher levels of perceived stress and had lower self-esteem.

The research question involved differences in self-esteem, perceived stress, marital relationship quality and HBM dimensions between primigravidae opting for either ECD or VD, i.e., do women opting for ECD also have lower self-esteem, higher perceived stress, a poorer marital relationship quality, and lower HBM scores than women opting for VD? The answer was not clear-cut. Whereas those opting for ECD also had lower self-esteem and higher perceived stress, no differences were found regarding marital relationship quality or social support.

Regarding marital relationship quality and social support, the present findings are at odds with previously published evidence. For example, one study found that women reporting greater tokophobia also showed a greater response when midwives were very supportive.[45] Leone et al.[46] reported that the odds of ECD were inversely related to the frequency with which women exchanged reproductive health information with friends and family. Saisto et al.[47] reported that lower marital satisfaction was associated with increased fear of VD. In contrast, we found that perceived social support and marital relationship quality were unrelated to the decision for or against ECD by primigravidae. The data available to us in this study shed no further light on why marital relationship quality was unrelated to ECD,

**Table 1** Relationship between psychological characteristics and mean scores on Health Belief Model constructs vs. choice of mode of delivery

| | Elective cesarean delivery (n=214) | Vaginal delivery (n=128) | *t*-test | *d* |
|---|---|---|---|---|
| Psychological characteristics | | | | |
| Age (years) | 25.88 (3.62) | 24.02 (2.87) | | |
| Self-esteem | 25.88 (1.78) | 26.30 (1.75) | $t_{340} = 2.09$* | 0.24 |
| Perceived stress | 25.60 (5.73) | 20.88 (3.23) | $t_{340} = 9.78$† | 1.05 |
| Quality of marital relationship | 47.40 (3.89) | 47.70 (3.79) | $t_{340} = 0.63$ | 0.08 |
| Social support | 53.96 (9.60) | 53.50 (9.06) | $t_{340} = 0.44$ | 0.05 |
| Beliefs | | | | |
| Susceptibility | 16.25 (2.66) | 14.99 (2.44) | 4.47† | 0.50 |
| Severity | 24.85 (3.89) | 26.13 (3.66) | 3.00* | 0.34 |
| Benefits | 27.24 (3.60) | 28.56 (3.55) | 3.29‡ | 0.37 |
| Barrier | 28.37 (3.95) | 25.50 (4.62) | 6.17† | 0.67 |
| Self-efficacy | 20.28 (3.45) | 21.73 (3.50) | 3.75* | 0.42 |
| Cue to action | 35.12 (3.73) | 36.27 (3.51) | 2.82* | 0.32 |
| Total beliefs | 152.10 (9.83) | 153.10 (9.92) | 0.91 | 0.10 |

Data presented as mean (standard deviation).
* $p < 0.05$; † $p < 0.001$; ‡ $p < 0.01$.

**Table 2** Logistic regression analysis of psychological dimensions and Health Belief Model constructs for choice of elective cesarean delivery

| Variables | B | SE | Wald | OR | 95%CI |
|---|---|---|---|---|---|
| Perceived stress | -0.01 | 0.06 | 0.05 | 0.99 | 0.88-1.11 |
| Self-esteem | 0.002 | 0.11 | 0.000 | 1.00 | 0.81-1.24 |
| Beliefs | | | | | |
| Susceptibility | 0.13 | 0.05 | 5.57* | 1.13 | 1.02-1.26 |
| Seriousness | -0.02 | 0.04 | 0.26 | 0.98 | 0.91-1.06 |
| Benefits | -0.03 | 0.04 | 0.56 | 0.97 | 0.89-1.10 |
| Barrier | 0.14 | 0.03 | 17.11† | 1.15 | 1.08-1.23 |
| Self-efficacy | -0.08 | 0.04 | 5.23* | 1.11 | 0.99-1.19 |
| Cue to action | 0.02 | 0.05 | 0.18 | 1.02 | 0.93-1.12 |
| Constant | -15.56 | 4.808 | 10.48† | 0.000 | |

95%CI = 95% confidence interval; B = coefficient; OR = odds ratio; SE = standard error.
* $p < 0.01$; † $p < 0.001$.

unlike the findings of Saisto et al.[47] We found that self-esteem, stress and health beliefs were unrelated to marital relationship quality. In this context, it is worth noting that in a qualitative study in Argentina,[48] where the CD rate is approximately 30%, it was observed that most expectant mothers at both public and private hospitals preferred VD due to cultural, personal, and social factors. VD was viewed as normal, healthy, and a natural rite of passage from womanhood to motherhood. The pain associated with VD was viewed positively. In contrast, women viewed CD as a medical decision and often deferred to medical staff to make this decision on medical grounds. In the present study, and for Iranian primigravidae in general, we have no estimate of the extent to which VD would be seen as a normal, healthy, and a natural rite of passage from womanhood to motherhood; to the best of our knowledge nothing has yet been published on this question.

A further finding of the present study was that lower self-esteem was associated with a greater likelihood of ECD. Research on this topic is limited and has mainly focused on self-esteem levels after discharge following CD. Salomonsson et al.[49] reported that higher self-esteem and higher self-efficacy scores were associated with choosing VD over ECD. Loto et al.[50] reported lower self-esteem scores both prior to and after discharge in women who had CDs than in women who had VDs. We cannot say on the basis of the present study why there was an association between low self-esteem and ECD, although we may speculate that primigravidae opting for ECD at the end of the first trimester, that is, 25 to 27 weeks before their due date, might have low confidence in their ability to cope with the difficulties of childbirth.

To the best of our knowledge, this is the first study showing an association between ECD and higher perceived stress scores. Generally speaking, higher stress scores reflect a subjective appraisal of being less able or unable to cope with a situation; in other words, higher stress scores generally reflect the belief that the situations an individual faces exceed their skills and competencies. The reasons for the higher stress scores in primigravidae opting for an ECD in the present dataset remain unclear. One might plausibly speculate that these higher stress scores were related to lower self-esteem in a sort of reciprocal influence. Given our current lack of understanding of the mechanisms underlying the association between stress and ECD, future studies should more closely examine this issue.

Regarding the HBM scores, the overall pattern showed that dysfunctional beliefs about VD tended to result in a decision for ECD, as shown in Tables 1 and 2. In our view, the overall pattern of HBM scores reflects higher stress, lower self-esteem, more dysfunctional beliefs about childbirth[22,23] and fear of pregnancy and birth-related issues, as has been reported extensively in prior studies.[13,15,17,21] Our conclusion is that psychological issues rather than convenience/scheduling issues[51] or legal/medical indications[15] were the main factors for ECD. Accordingly, we propose that pre-birth information and counselling could help primigravidae weigh the risks and benefits of both ECD and VD.

Despite the novelty of the findings, several limitations warn against overgeneralization of the results. First, although the centers and the participants were randomly selected to limit possible sampling biases, the data were gathered in a single city, which could limit the generalizability of the findings. Second, the pattern of results could reflect the influence of further latent, but unassessed, variables that might have biased two or more dimensions in the same or opposite directions. This could be especially important with respect to physical activity, since Poyatos-Leon et al.[52] observed that regular physical activity during pregnancy reduced the odds of CD. Third, while we assessed the choice of delivery and psychological status at the end of the first trimester, we do not know whether or to what extent psychological status or choice of delivery method changed over time. In this respect, it would have been interesting to know whether further counselling, for example, during the second and third trimesters could have influenced the choice by impacting fear, stress, and self-esteem.

In conclusion, the pattern of results suggests that psychological factors related to low self-esteem, higher stress levels, tokophobia issues and dysfunctional beliefs about ECD and VD were associated with choosing ECD, while social support and marital relationship quality were not associated with a delivery method. Taking into account the sociodemographic and fear-related characteristics of primigravidae opting for ECD,[13,25] we suggest that the psychosocial context of pregnant women should be taken into consideration in programs for reducing ECDs.[32,33] As our findings show, primigravidae did not opt for ECD out of convenience or scheduling, as has been suggested in the US media,[51] but in response to more fundamental psychological needs.

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## Disclosure

The authors report no conflicts of interest.

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## ORIGINAL ARTICLE

# Predictors of length of stay in an acute psychiatric inpatient facility in a general hospital: a prospective study

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**Objective:** There have been significant reductions in numbers of psychiatric beds and length of stay (LOS) worldwide, making LOS in psychiatric beds an interesting outcome. The objective of this study was to find factors measurable on admission that would predict LOS in the acute psychiatric setting.
**Methods:** This was a prospective, observational study.
**Results:** Overall, 385 subjects were included. The median LOS was 25 days. In the final model, six variables explained 14.6% of the variation in LOS: not having own income, psychiatric admissions in the preceding 2 years, high Clinical Global Impression and Brief Psychiatric Rating Scale scores, diagnosis of schizophrenia, and history of attempted suicide. All variables were associated with longer LOS, apart from history of attempted suicide.
**Conclusions:** Identifying patients who will need to stay longer in psychiatric beds remains a challenge. Improving knowledge about determinants of LOS could lead to improvements in the quality of care in hospital psychiatry.

**Keywords:** Outcome studies; inpatient psychiatry; chronic psychiatric illness; administration; other delivery issues

## Introduction

In the last few decades, changes in how we understand mental illness, advances and improvement in availability of biological psychiatric treatments, greater political interest in mental health, and the emphasis on the costs of medical care have resulted in several modifications to how psychiatric hospital care is provided. Neuroleptic drugs, introduced in the 1950s, were the first effective treatment for psychotic disorders, and enabled some long-stay hospital patients to be discharged.[1,2] Movements for deinstitutionalization of mental health advocate greater emphasis on community-based services for people with mental illness.[3] For hospital psychiatry, this means shifting from long-stay (months, years) admissions in asylum institutions to provision of acute care in short-stay psychiatric beds in general hospitals.[4-6] Today, acute inpatient psychiatric care makes up a relatively small proportion of mental health care in a community-based system of care which tends to be based on the medical model: making a diagnosis and treating acute or dangerous symptoms. Acute psychiatric care now focuses on stabilization, safety, and rapid discharge.[7] Economic pressures also mean that it is important to reduce the cost of treatment, which includes reducing the length of hospital stay as much as possible.[6]

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There is a worldwide trend towards closure of psychiatric beds, and, in many countries, the total number of psychiatric beds is steadily decreasing. In the United States, for example, there were around 525,000 psychiatric beds in 1970 but fewer than 212,000 by 2002.[8] In Brazil, there were around 87,134 psychiatric beds in 1994.[9] By 2011, this figure had fallen to 32,284.[10] Consequently, the pressure to reduce inpatient stays increased, and is now shifting to emergency departments as well.[11] Nevertheless, length of stay (LOS) continues to be longer overall for mental disorders than for other conditions: in the U.S., the mean LOS for psychiatric admissions is 8.2 days, compared with 4.6 days for all diagnoses.[12]

In this context, LOS in inpatient psychiatric services has become an interesting outcome for patients, care providers, and health insurance payers. The ability to identify determinants of LOS at admission – and, thus, identify patients who are likely to need a longer stay early on – may help treatment planning. Previous studies using various methodological approaches have shown that gender, age, psychiatric diagnosis, history of hospitalization, level of functioning, severity of disease, hospital characteristics, and type of insurance are all associated with LOS,[2,13-20] but the results were only modest in terms of prediction of LOS. This suggests that there are other factors related to LOS which have not yet been explored. Moreover, high-income countries have been the main source of evidence on determinants of LOS in the international literature; there is a lack of information about which variables are important in less wealthy countries.

Within this context, the main objective of this study was to identify factors measurable at admission that would

predict LOS in an acute psychiatric facility, including factors that were not identified as predictors in previous studies. The intention was to develop a comprehensive, multivariable model including variables identified in previous studies and variables not previously investigated, namely: having one's own income, 2-year history of psychiatric admissions, total Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impression (CGI) scores, cause of admission, age at diagnosis, time since diagnosis, and history of suicide attempts. The secondary objective was to evaluate LOS and its determinants in a middle-income country.

We hypothesized that LOS would be longer for patients without their own income, who had been admitted to hospital for psychiatric reasons in the preceding 2 years, been admitted for risk of aggression, been diagnosed at an earlier age, and had a longer history of illness or a history of suicide attempts.

## Methods

### *Study design and setting*

This prospective, observational study was conducted in the inpatient psychiatric unit of a general, university-affiliated, tertiary hospital in southern Brazil (Hospital de Clínicas de Porto Alegre, HCPA). The facility was a 36-bed acute psychiatric inpatient unit, with 26 beds intended for patients admitted through public Unified Health System and 10 beds intended for private patients. Patients may be admitted as psychiatric emergencies, transferred from another department within the hospital, or referred from other psychiatric services. The unit is staffed by 10 medical teams.

### *Participants*

The sample consisted of all patients aged 18 years or older who were admitted to a psychiatric bed at the study facility between June 2011 and December 2013, except those who met one or more of the following non-inclusion criteria:

1) Patients admitted to specific treatment programs offered by the facility, namely patients with (a) a substance-related disorder as the main diagnosis and/or detoxification as a main cause of admission; or (b) anorexia as the main cause of admission;
2) Persistent and severe agitation during the first 72 hours of admission, which severely interfered with data collection; this was operationalized as need for mechanical restraint and/or sedation during most of the day;
3) Patients with a severe cognitive impairment which prevented collection of the required information, unless an adult caregiver was able to provide it;
4) Patient refusal to participate.

We also did not consider very short admissions, defined as LOS $< 7$ days. Other exclusion criteria were (a) death during stay, regardless of cause, and (b) failure to obtain a complete set of data. To avoid dependence between the variables, only one admission per individual (namely, the first) was included. Figure 1 provides a detailed flow diagram of the participant selection procedure. To assess the risk of selection biases, we compared excluded and included patients in terms of age, gender, type of insurance, and LOS.

### *Measures*

Structured protocols were used to collect data. All data were collected within 72 hours of admission by a trained research team. Researchers were not involved in patient care.

Selection of candidate predictor variables was based on previous findings or on clinical relevance.

Independent variables included as possible predictors were:

1) Sociodemographic variables: age, gender, ethnicity (Caucasian vs. non-Caucasian), relationship status (with vs. without a partner), educational level (completed vs. did not complete high school), area of residence (metropolitan area vs. outside metropolitan area), type of insurance (public vs. private), and income (with vs. without own income).
2) Psychiatric history: lifetime history of psychiatric hospital stays and history of psychiatric hospital stays in the preceding 2 years, previous suicide attempts, age at first diagnosis, and time since first diagnosis.
3) Current episode: main cause of admission, main diagnosis at admission according to ICD-10,[21] and scores on CGI,[22] BPRS,[23] and Global Assessment of Functioning (GAF).[24]

Severity of illness was assessed using the CGI (0 = not ill to 6 = extremely ill) and was treated as a continuous variable. The GAF is used to assess psychosocial functioning in daily life (e.g., work, social interactions, relationships); scores range between 0 (poor functioning) and 100 (very good functioning). The BPRS is an 18-item scale used to measure general psychiatric symptoms. These three scales were administered during patient interviews. All other data were collected directly from the patient where possible; in other cases, relatives were requested to provide the information, and if no relative was available, the medical team assistant was consulted. If these three strategies failed, we sought to obtain the information from electronic records. In a previous analysis, medical team was evaluated as predictor because of its potential confounder role in LOS.

The outcome of interest, LOS, was treated as a continuous variable. In the case of patients transferred from other departments within the hospital, only days in the psychiatric unit were counted.

### *Ethical considerations*

The HCPA Ethics Committee approved this study with protocol #10-265. All eligible patients were invited to participate. If a patient's capacity to consent was compromised by psychotic symptoms or intellectual disability, a relative or guardian was contacted to confirm participation. All participants – and, when applicable, a relative or guardian – were informed about the study and provided written informed consent.

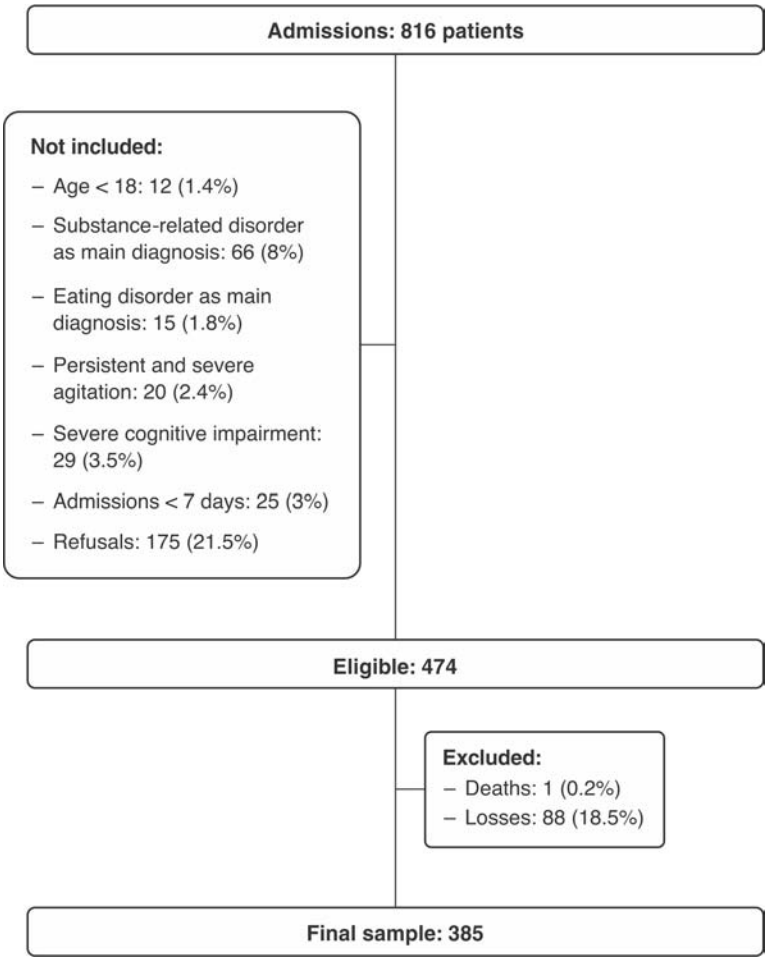


**Figure 1** Flowchart of participant selection procedure.

*Statistical analysis*

Statistical analyses were performed in SPSS for Windows version 21.1. The normality of the distribution of variables was measured using the Kolmogorov-Smirnov test. Comparisons between included and excluded patients were conducted using the Mann-Whitney *U* test for non-parametric continuous variables and the independent-samples *t*-test for parametric continuous variables. The chi-square test was used for frequency comparisons.

Predictors of LOS were evaluated using a non-hierarchical, stepwise linear regression model. LOS was treated as a continuous variable; however, as linearity is a prerequisite for linear regression and the raw LOS data were not normally distributed, we used the natural logarithm (ln) of LOS, which was normally distributed according to the Kolmogorov-Smirnov test, as the dependent variable. First, candidate variables were tested individually in a bivariate model; only variables with a coefficient of determination ($R^2$) $> 0.01$ (i.e., at least 1% of the variance in the outcome is explained by the variable) and a p-value $< 0.1$ on the bivariate model were included in the multivariable model. Further multivariable analyses were performed; variables were removed one by one according to their collinearity (mainly measured by variance inflation factor [VIF]) and p-value until a final model was reached. The significance level for the final model was set at 0.05. We used graphical residual analysis to verify the assumptions of linearity and homoscedasticity.

*Preliminary analysis*

Before carrying out linear regression analysis, we tested whether medical team was a predictor of LOS, to allow control for the potential influence of characteristics of the medical team responsible for each patient's care on LOS. All possible interactions between variables were pretested. Considering the possibility of a nonlinear relation between variables and LOS, quadratic terms of all variables were also tested as predictors of LOS in bivariate analysis. Since these quadratic terms were not better than the original variables in any of the cases, we chose to keep the original variables alone.

## Results

During the study period, 816 patients were admitted, of whom 474 (58.08%) met the inclusion criteria. One

patient died during the stay and data for a further 88 were incomplete; these patients were excluded from analyses, giving a final sample of 385 patients.

### *Comparison of excluded and included patients*

Group comparisons indicated that excluded and included patients were similar in terms of age, type of insurance, and LOS; however, the proportion of women was higher in the excluded group (64.88% vs. 49.5%).

### *Length of stay and demographic variables*

LOS ranged from 7 to 199 days and was not normally distributed (mean = 30.02, standard deviation = 20.81, Shapiro-Wilk W = 0.74, $p < 0.01$). The mean age was 43.48 years (range 18 to 89 years); 8.8% of the sample was aged $> 65$. The median LOS was 25 days (interquartile range [IQR] 16 to 36.5 days). The characteristics of the sample are shown in Table 1.

### *Clinical characteristics*

The clinical characteristics of the sample are shown in Table 2. Most patients (66.8%) had a history of at least one previous hospital stay, and 177 (46%) had been hospitalized at least once in the preceding 2 years. Fifty-four percent of patients had attempted suicide at least once, and the main reason for admission was suicide risk (44.2%), followed by risk of aggression towards others (23.9%). Mood disorders were the most common diagnosis (60.3%), followed by schizophrenia and related disorders (28.8%). Together, these two classes accounted for 89.1% of primary diagnoses in this sample.

### *Multivariable linear regression model: predictors of length of stay*

Because LOS was not normally distributed, we used ln(LOS) as the dependent variable (mean = 3.23, standard deviation = 0.58; Kolmogorov-Smirnov D = 0.039, p = 0.198). The identity of the medical team did not influence LOS. None of the quadratic terms or interactions were included in the model, because they did not add any predictive power to the original variables.

The step-by-step modeling process is summarized in Table 3. In bivariate analysis (step 0), each variable was tested as the sole predictor of the dependent variable. The only demographic variable to predict LOS in a bivariate model was without own income. History of previous hospital stay, history of hospital stays in the preceding 2 years, history of suicide attempts, suicide risk or risk of aggression as main reason for admission, CGI, GAF, and BPRS scores, and diagnosis of mood disorder or schizophrenia and related disorders all met the criteria for inclusion in the multivariable model. All these variables were related to longer LOS, apart from history of suicide attempts, admission due to suicide risk, and diagnosis of mood disorder.

Age at first diagnosis and time since first diagnosis were related to LOS, but were not included in the multivariable model because of their very low $R^2$ values. In the multivariable analysis, the variables elected in step 0 were inserted together as independent variables, and the variables with the greatest collinearity, as measured with the VIF, were subsequently removed one by one until collinearity was eliminated (i.e., all VIF values were $< 2$), which was achieved in step 4. From step 5 onwards, variables were removed one by one in descending order of p-value.

The final model was achieved after six steps. This model contained six variables, which explained 14.6% of variance (F-test: 11.982; sig 0.000, gl 278) in ln(LOS): not having one's own income, history of at least one psychiatric

**Table 1** Sociodemographic characteristics of included patients on admission

| Variable | |
|---|---|
| Length of stay, median (IQR) | 25 (16-36.5) |
| Age, mean (SD) | 43.48 (15.0) |
| Male gender | 195 (50.6) |
| Public health system users | 283 (73.5) |
| Caucasian ethnicity | 317 (82.3) |
| Area of residence: metropolitan | 287 (74.5) |
| Educational level | |
| Lower than middle school | 139 (36.1) |
| Middle school | 77 (20.0) |
| High school | 122 (29.1) |
| Higher education | 57 (14.8) |
| Employment status | |
| Employed | 93 (24.2) |
| Without own income | 125 (32.5) |
| On sickness benefit/allowance | 74 (19.2) |
| Retired | 39 (10.1) |
| Disability allowance | 54 (14.0) |
| Relationship status: without partner | 262 (68.1) |

Data presented as n (%), unless otherwise specified.
IQR = interquartile range; SD = standard deviation.

**Table 2** Clinical characteristics of patients included in the final sample (n=385)

| Clinical characteristics | |
|---|---|
| Previous psychiatric admission | 257 (66.8) |
| History of hospital stays in the last 2 years (yes) | 177 (46.0) |
| Number of previous psychiatric hospital stays, median (IQR) | 3 (2-7)* |
| Previous suicide attempt | 210 (54.5) |
| Number of previous suicide attempts, median (IQR) | 2 (1-3)† |
| Age in years at first diagnosis, median (IQR) | 29 (20-40) |
| Time in years since first diagnosis, median (IQR) | 8 (2-20) |
| Reason for admission | |
| Suicide risk | 170 (44.2) |
| Risk of aggression | 92 (23.9) |
| Worsening of symptoms | 76 (19.7) |
| Diagnostic uncertainty | 23 (6.0) |
| Risk of moral exposure | 20 (5.2) |
| Other | 4 (1.0) |
| Main diagnosis (ICD-10) | |
| (F00-F09) Organic, including symptomatic, mental disorders | 8 (2.1) |
| (F20-F29) Schizophrenia, schizotypal, and delusional disorders | 111 (28.8) |
| (F30-F39) Mood (affective) disorders | 232 (60.3) |
| (F40-F48) Neurotic, stress-related, and somatoform disorders | 13 (3.4) |
| (F60-F69) Disorders of adult personality and behavior | 8 (2.1) |
| (F70-F79) Mental retardation | 4 (1.0) |
| Others | 5 (1.3) |
| CGI score, median (IQR)‡ | 6 (5-6) |
| BPRS score, median (IQR) | 23 (16-32) |
| GAF score, median (IQR) | 30 (20-40) |

Data presented as n (%), unless otherwise specified.
BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impression; GAF = Global Assessment Functioning; IQR = interquartile range; SD = standard deviation.
* Considering only the subsample with a history of hospital stays.
† Considering only the subsample with a history of suicide attempts.
‡ CGI was treated as a continuous variable.

hospital stay in the preceding 2 years, CGI score, BPRS score, diagnosis of schizophrenia and related disorders according to ICD-10 criteria, and history of suicide attempts.

## Discussion

Our study demonstrates that LOS in acute psychiatry beds is predicted by variables not mentioned in previous research, namely not having one's own income, history of psychiatric hospital stay in the preceding 2 years, total BPRS score, and history of suicide attempts. We also corroborated previous reports that CGI score and a diagnosis of schizophrenia predict LOS in a psychiatric bed. Together, these six independent variables accounted for 14.6% of the variance in ln(LOS).

### *Sociodemographic factors*

Neither gender, age, nor relationship status were related to LOS in our sample, which contrasts with findings from larger samples. LOS was found to be positively associated with female gender[18] and older age[13,14] in studies with more than 3,118 participants.[18] The small number of elderly people in the sample (8.8%) may explain why age was not related to LOS in our sample. Type of insurance was not associated with LOS in this sample, which conflicts somewhat with evidence that hospital type (general hospital vs. psychiatric hospital) and type of insurance are related to LOS for persons with serious mental illness.[17,20] It is likely that this association was not detectable in this sample because the different groups of patients shared the same facility and treating teams. The only sociodemographic factor associated with LOS in our sample was not having one's own income. Patients without an income probably stay longer in a psychiatric bed because of social difficulties related to discharge. This finding demonstrates a need to pay attention to the finances of severely ill patients.

### *Psychiatric history*

Some previous studies found a highly significant relationship between having had a previous hospital stay and LOS.[14,15,18] In bivariate analyses, both lifetime and 2-year history of psychiatric hospital stays were related to LOS, but in the final multivariable model, only 2-year history of psychiatric admissions was retained. Our study suggests that having been treated in a psychiatric inpatient admission in the last 2 years is a more important determinant of LOS than lifetime history of psychiatric hospital stays. A history of attempted suicide was very common in our sample (54.5%), and was negatively associated with LOS. Contrary to our hypothesis, admission based on risk of aggression was not related to LOS in the final model.

**Table 3** Linear regression analysis of natural logarithm of length of stay (LOS): steps from bivariate model to final multiple model

| | Bivariate analysis | | Multivariate analysis | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Step 0 | | Step 1 | Step 2 | Step 3 | Step 4 | Step 5 | Step 6 |
| | β standardized (p-value) | Adjusted R2 | β standardized | β standardized | β standardized | β standardized | β standardized | β standardized |
| Age, years | -0.016 (0.749) | < 0.01 | | | | | | |
| Female gender | 0.011 (0.833) | < 0.01 | | | | | | |
| Caucasian ethnicity | 0.040 (0.437) | < 0.01 | | | | | | |
| Area of residence: non-metropolitan | -0.023 (0.658) | < 0.01 | | | | | | |
| Educational level: did not complete high school* | 0.07 (0.172) | < 0.01 | | | | | | |
| Without own income† | **0.175 (0.001)** | 0.028‡ | **0.114 (0.021)** | **0.112 (0.022)** | **0.110 (0.024)** | **0.109 (0.025)** | **0.110 (0.022)** | **0.111 (0.021)** |
| Relationship status: without partner | 0.014 (0.782) | < 0.01 | | | | | | |
| Public health system user | 0.083 (0.105) | < 0.01 | | | | | | |
| Lifetime history of psychiatric admission | **0.182 (0.001)** | 0.03‡ | 0.035 (0.576) | 0.036 (0.558) | 0.040 (0.515) | 0.041 (0.508) | | |
| Psychiatric admission in the preceding 2 years | **0.160 (0.002)** | 0.023‡ | 0.081 (0.174) | 0.081 (0.175) | 0.078 (0.186) | 0.078 (0.187) | **0.100 (0.039)** | **0.104 (0.033)** |
| History of suicide attempt | **-0.124 (0.015)** | 0.013‡ | -0.079 (0.137) | -0.081 (0.125) | -0.080 (0.129) | -0.079 (0.131) | -0.075 (0.150) | **-0.096 (0.05)** |
| Age at first diagnosis | -0.098 (0.055)‡ | < 0.01 | | | | | | |
| Time since first diagnosis | 0.098 (0.054)‡ | < 0.01 | | | | | | |
| Cause of admission | | | | | | | | |
| Suicide risk | **-0.181 (< 0.001)** | 0.03‡ | -0.058 (0.357) | -0.061 (0.323) | -0.057 (0.350) | -0.062 (0.266) | -0.069 (0.204) | |
| Risk of aggression | **0.115 (0.024)** | 0.011‡ | 0.017 (0.761) | 0.015 (0.789) | 0.010 (0.858) | | | |
| Worsening of symptoms | 0.061 (0.235) | < 0.01 | | | | | | |
| Diagnostic uncertainty | 0.059 (0.246) | < 0.01 | | | | | | |
| Risk of moral exposure | 0.075 (0.142) | < 0.01 | | | | | | |
| CGI | **0.286 (< 0.001)** | 0.08‡ | **0.202 (0.007)** | **0.186 (0.002)** | **0.188 (0.001)** | **0.188 (0.652)** | **0.192 (0.001)** | **0.188 (0.001)** |
| BPRS | **0.286 (< 0.001)** | 0.079‡ | 0.098 (0.114) | 0.094 (0.123) | 0.093 (0.126) | 0.094 (0.612) | 0.095 (0.117) | 0.102 (0.088) |
| GAF | **-0.194 (< 0.001)** | 0.035‡ | 0.025 (0.724) | | | | | |
| Main diagnosis (ICD-10) | | | | | | | | |
| (F00-F09) Organic, including symptomatic, mental disorders | 0.091 (0.077) | < 0.01 | | | | | | |
| (F20-F29) Schizophrenia, schizotypal, and delusional disorders | **0.231 (< 0.001)** | 0.051‡ | **0.136 (0.085)** | **0.140 (0.075)** | **0.103 (0.054)** | **0.104 (0.792)** | **0.106 (0.046)** | **0.126 (0.013)** |
| (F30-F39) Mood (affective) disorders | **-0.168 (0.001)** | 0.026‡ | 0.046 (0.566) | 0.050 (0.524) | | | | |
| (F40-F48) Neurotic, stress-related, and somatoform disorders | **-0.109 (0.034)** | < 0.01 | | | | | | |
| (F60-F69) Disorders of adult personality and behavior | -0.048 (0.352) | < 0.01 | | | | | | |
| Intercept | | | 2.313 | 2.4 | 2.441 | 2.446 | 2.453 | 2.424 |
| $R^2$ | | | 0.14 | 0.143 | 0.144 | 0.147 | 0.148 | 0.146 |

LOS = length of stay; CGI = Clinical Global Impression; BPRS = Brief Psychiatric Rating Scale; GAF = Global Assessment Functioning.
Significant results shown in bold.
* Educational level was dummy-coded as a binary variable. with completion of high school or more as the reference category.
† Income was dummy-coded as a binary variable, with having own income as the reference category.
‡ $R^2 > 0.01$.

*Current episode*

In this sample, total BPRS score was positively associated with LOS, even in the multivariable model. Hopko et al. demonstrated that data from the BPRS subscales could be used to identify up to 80% of patients who required extended hospital care.[15] In our sample, total BPRS score was associated with LOS independently of diagnosis. In the bivariate models (Step 0), CGI score was the single variable which accounted for most variance in ln(LOS) ($R^2$ = 0.08). Even when other variables were added to the model, CGI remained positively associated with LOS, which is consistent with the findings of Warnke et al.[16] This is particularly important, as the CGI scale is quick and easy to administer and is in very widespread use.

Reason for admission was not a determinant of LOS in the multivariable final model, rejecting our hypothesis that patients admitted for risk of aggression would need longer hospitalization. In our study, diagnoses of mood disorders or schizophrenia and related disorders (using ICD-10 criteria) were associated with LOS in bivariate models; diagnoses of mood disorders were negatively associated with LOS. In the multivariable final model, schizophrenia and related disorders remained positively associated with LOS. Several studies have reported that a diagnosis of schizophrenia is positively associated with LOS.[14,16,18,25] Our findings confirm that patient with schizophrenia have longer stays as psychiatric inpatients than patients with other mental disorders. This may reflect the combination of complex, hard-to-treat acute symptoms and social withdrawal which characterize schizophrenia, and can prevent achievement of rapid discharge.

*Length of stay*

The median LOS was 25 days, a figure very similar to the median 22-day stay reported for a Swiss sample.[16] However, LOS varies widely between studies. A previous Brazilian study reported a mean LOS of 20 days.[26] A large U.S. study of more than 45,000 subjects reported a mean length of psychiatric hospital stay was 10.0 days,[20] while in an Australian sample, the median LOS was 12 days.[2] In contrast, the mean LOS in a Japanese sample was 49 days,[27] and in a Chinese sample, 45 days.[25] We hypothesize that the marked difference between LOS in different countries can be attributable to differences in the range of treatment options available in the community in different places, as well as to cultural aspects regarding style of psychiatric care delivery. There is still some doubt as to whether short admissions should be recommended (because they help prevent patients from becoming institutionalized) or whether they are harmful (because they do not allow the causes and symptoms of illness to be fully addressed). This issue is further complicated by the existence of a group of patients who have short but frequent admissions, also known as revolving-door patients. A recent Cochrane review which compared stays of less than vs. more than 28 days in patients with severe mental illness concluded that there were no benefits from longer hospital stays in terms of readmission and other outcomes, and that short stays were associated with better social functioning.[28] Especially because of the restricted number of psychiatric beds nowadays, rapid discharge means greater availability of such beds, which, in turn, means an opportunity to provide care to another patient. On the other hand, very short hospital stays may reduce the opportunity for a comprehensive investigation and make it more difficult to address the psychosocial aspects of a patient's illness, thus compromising the chances of sustained recovery.[6] For some patients, a short stay is not sufficient to stabilize their symptoms and may not be long enough to even begin to treat serious illnesses; in these cases, a longer stay would reduce the odds of rapid readmission, homelessness, and criminalization.[1] Therefore, any policy meant to reduce the duration of inpatient treatment should be carefully evaluated to ensure that potential negative consequences for patients are avoided.[29]

This study has several strengths. First, we found four predictors of LOS which have not been mentioned in previous international studies, namely being without an income, history of psychiatric admissions in the preceding 2 years, total BPRS score, and history of suicide attempts. Second, this was a prospective study based on primary data rather than hospital records; hence, data were accurate and clinically detailed. Third, we performed a comprehensive analysis including several categories of predictors – demographic variables, psychiatric history variables, current episode variables – in a single model. Fourth, the sample encompassed a wide range of diagnoses. Fifth, in contrast to most of the published evidence in this area, our study was conducted in a middle-income economy, thus providing data about LOS produced in a population outside high-income countries.

The sample size was small compared with other investigations into potential determinants of LOS. This probably explains why we failed to find relationships between LOS and age, gender, and relationship status. It is possible that, in a larger sample from this population, we might detect a negative association between LOS and age at diagnosis or a positive association between LOS and duration of illness. The common weaknesses of large-sample studies are, however, that they tend to be retrospective and based only on data from hospital records. About 6% of patients admitted during the study period were not included in the study because they exhibited severe, persistent agitation or a severe cognitive impairment; we are therefore unable to comment on predictors of LOS in these patient groups. Our analysis of LOS also excluded very short admissions. Our rate of loss was 18.5% among eligible patients. There were more female than male patients with missing data; however, as included and excluded patients were similar with respect to LOS, age, and type of insurance, it is unlikely that their exclusion biased the findings significantly. Generalization of these findings to other settings can be compromised by the fact that policies regarding hospitalization vary widely across settings, depending on culture, local legislation, and even hospital type (psychiatric bed in a general hospital vs. dedicated psychiatric hospital).

Six independent variables accounted for 14.6% of the variance in ln(LOS), indicating that a small proportion

of the variance in LOS can be predicted from patient characteristics which are measurable on admission. This finding is consistent with other studies,[14,18] and suggests that prediction of LOS is far from straightforward, with multiple factors being involved.[15,30]

Identifying patients who will need to stay longer in a psychiatric bed remains a challenge. It is likely that LOS is influenced more by the process of psychiatric treatment and by factors which emerge after admission, such as comorbidity and psychosocial impairments,[29,31] than by simple patient characteristics. Nevertheless, our findings suggest that patients without an income, with a recent history (previous 2 years) of psychiatric admissions, with high CGI or BPRS scores, or with a diagnosis of schizophrenia or related disorders based on ICD-10 criteria may benefit from early identification and careful discharge planning. LOS remains an under-investigated variable, and better understanding of the factors which influence it might lead to improvements in the quality of care in hospital psychiatry.

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## Disclosure

The authors report no conflicts of interest.

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## ORIGINAL ARTICLE

# Clinical improvement in patients with borderline personality disorder after treatment with repetitive transcranial magnetic stimulation: preliminary results

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**Objective:** Current treatment of borderline personality disorder (BPD) consists of psychotherapy and pharmacological interventions. However, the use of repetitive transcranial magnetic stimulation (rTMS) could be beneficial to improve some BPD symptoms. The objective of this study was to evaluate clinical improvement in patients with BPD after application of rTMS over the right or left dorsolateral prefrontal cortex (DLPFC).
**Method:** Twenty-nine patients with BPD from the National Institute of Psychiatry, Mexico, were randomized in two groups to receive 15 sessions of rTMS applied over the right (1 Hz, n=15) or left (5 Hz, n=14) DLPFC. Improvement was measured by the Clinical Global Impression Scale for BPD (CGI-BPD), Borderline Evaluation of Severity Over Time (BEST), Beck Depression Inventory (BDI), Hamilton Anxiety Rating Scale (HAM-A), and Barratt Impulsiveness Scale (BIS).
**Results:** Intragroup comparison showed significant ($p < 0.05$) reductions in every psychopathologic domain of the CGI-BPD and in the total scores of all scales in both groups.
**Conclusions:** Both protocols produced global improvement in severity and symptoms of BPD, particularly in impulsiveness, affective instability, and anger. Further studies are warranted to explore the therapeutic effect of rTMS in BPD.
**Clinical trial registration:** NCT02273674.

**Keywords:** Borderline personality disorder; neurophysiology; neurosciences; psychosocial factors

## Introduction

Borderline personality disorder (BPD) is one of the most common personality disorders in clinical practice. It affects 1[1] to 5.9%[2] of the general population and accounts for 10% of outpatient psychiatry visits and more than 20% of the psychiatric inpatient population,[1,2] generating a huge demand for health services.[2] BPD prevalence is similar in both genders,[2] although diagnosis is more common in women. The disorder is characterized by persistent patterns of affective instability, problematic relationships, and marked impulsiveness,[2] which manifests as self-injurious behavior, substance abuse, suicidality,[2-4] and other high-risk behaviors. Comorbidity with disorders such as depression, anxiety, and posttraumatic stress disorder (PTSD) is common.[2]

Neuroimaging and neuropsychological studies[1,5] have shown that the clinical manifestations of BPD are related to changes in the frontolimbic network,[2,3] including amygdala hyperactivity and hypofunctionality in prefrontal structures[6] such as the orbitofrontal cortex (OFC), the ventromedial prefrontal cortex (VMPFC), and the dorsolateral (DLPFC) cortex.[7-9] Particularly, the DLPFC plays a key role in regulating top-down emotional control and impulsiveness.[9,10] These findings become relevant when considering that the current lines of treatment are psychotherapy (maintenance treatment) and pharmacological interventions (which are used during exacerbations of symptoms).[2]

Nevertheless, the use of neuromodulation, such as repetitive transcranial magnetic stimulation (rTMS),[11,12] could be beneficial to improve some symptoms of BPD and to normalize the cortical dysfunction associated with these manifestations.[13] This technique uses electromagnetic induction[14] to stimulate the cerebral cortex focally and noninvasively, with few side effects,[15,16] and is relatively pain free. The neuromodulatory action of rTMS involves excitatory and inhibitory neuronal processes and plastic changes.[16,17]

At present, rTMS has been approved for the treatment of depression in several countries; it is accepted as an evidence-based treatment option by the American

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Psychiatric Association (APA), the Canadian Network for Mood and Anxiety Treatments (CANMAT), and the World Federation of Societies of Biological Psychiatry (WFSBP).[11,12,18] The most frequent protocols are those using high frequencies ($>$ 1 Hz to a maximum of 20 Hz) over the left DLPFC[16,18-21] or low frequencies ($\leqslant$ 1 Hz) over the right one.[16,18] Effects have also been demonstrated in psychiatric disorders that share features with BPD, such as impulse control deficit[22,23] and anxiety symptoms.[18,22]

Studies have explored the therapeutic potential of rTMS in BPD using high-frequency protocols (10 Hz) on the right[13] and left[9] DLPFCs, although evidence shows that use of frequencies in the inhibitory ($\leqslant$ 1 Hz) or 5-Hz ranges can provide clinical benefits with greater tolerability and reduced risk of adverse events.[11,21,24] Thus, the aim of this study was to evaluate clinical improvement in patients with BPD after treatment with high-frequency (5 Hz) or low-frequency (1 Hz) rTMS of the left or right DLPFC, respectively.

## Material and methods

### *Participants*

Twenty-nine patients with BPD, of both genders (27 women), all right-handed, with an age range of 18-45 years (mean 30.2 years, standard deviation [SD] = 7.6), participated in a randomized clinical trial that was conducted over 12 months. Outpatients from the BPD Clinic of the Ramon de la Fuente Muñiz National Institute of Psychiatry (INPRF) in Mexico City, with a DSM-IV-TR[25] diagnosis of BPD and a score $>$ 8 on the Spanish version of the Borderline Diagnostic Interview Revised (DIB-R),[26-28] were included.

Subjects with intracranial metallic objects and medical devices contraindicated in transcranial magnetic stimulation (TMS) were excluded, as were subjects with epilepsy, history of seizures, substance dependence, suicidal ideation, psychotic symptoms, bipolar affective disorder, current major depressive episode, and other comorbid psychiatric disorders, except generalized anxiety disorder. To reduce the risk of inducing seizures by rTMS, subjects with epileptiform activity on an electroencephalogram were also excluded. A safety questionnaire was applied in accordance with international guidelines.[11,24]

All participants received a complete description of the study and provided informed consent. This study was conducted in compliance with the Declaration of Helsinki, was approved by the INPRF Research Ethics Committee, and was registered in the U.S. National Institutes of Health ClinicalTrials.gov platform (www.clinicaltrials.gov) with accession number NCT02273674.

### *Clinical evaluation of participants*

Six clinical tests were administered to assess BPD, anxiety and depressive symptoms, and impulsiveness. To determine the severity of BPD symptoms and their changes over time, the Clinical Global Impression Scale for BPD (CGI-BPD)[29] and the Spanish version of the Borderline Evaluation of Severity Over Time (BEST)[30] were applied. The CGI-BPD is an adaptation of the Clinical Global Impression scale (CGI) that was designed with the objective of evaluating both the severity and the subsequent change in response to an intervention in patients diagnosed with BPD. The CGI consists of 10 Likert-type items scored on a scale of 1 to 7, which evaluate nine psychopathological domains of BPD, and an additional overall score.

CGI-BPD consists of two formats to assess current severity and change over time. The instrument has demonstrated adequate validity, reliability, and sensitivity to change.[29] BEST, in turn, is a self-administered instrument designed to evaluate the severity and change over time of typical thoughts, emotions, and behaviors in BPD. This scale has also demonstrated adequate sensitivity to change, high internal consistency, and discriminant validity.[30]

The Barratt Impulsiveness Scale (BIS) was used to assess impulsiveness. It is self-administered and was validated in Spanish by Oquendo et al.[31] The BIS consists of 30 items grouped into three impulsiveness subscales: cognitive, motor, and unplanned. This test has a high internal consistency.[31]

The presence, severity, and change over time of anxiety and depressive symptoms were evaluated by the Hamilton Anxiety Rating Scale (HAM-A) and a 21-item version of the Beck Depression Inventory (BDI), respectively. Clinimetric tests were applied by an experienced psychiatrist, before and after 15 rTMS sessions, in order to evaluate changes in BPD, anxiety and depressive symptoms, and impulsiveness.

### *Repetitive transcranial magnetic stimulation procedure*

Participants were randomly assigned to receive one of two different rTMS protocols (5 Hz or 1 Hz), which generated two treatment groups. In both protocols, rTMS pulses were administered at an intensity equal to 100% of each patient's motor threshold using a Dantec MagPro rapid magnetic stimulator and a 50 mm Dantec MC-B70 butterfly (figure-eight) coil with 150° angulation.

The resting motor threshold (RMT) was determined at the start of each session, using the visual inspection method as described by Fitzgerald, in which the abductor pollicis brevis muscle (APBM) motor response is evaluated. Stimulation site was defined as 5 cm above the maximum stimulation point at the APBM region, according to descriptions in previous clinical guidelines for locating the DLPFC.[11,19]

In the 1 Hz group (n=15, 14 women), rTMS was applied to the right DLPFC (one 15-minute train, 1 pulse per second continuously, for a total of 900 pulses per session). In the 5 Hz group (n=14, 13 women), rTMS was applied to the left DLPFC (30 trains of 10 seconds each, with a 10-second interval between each train, for a total of 1,500 pulses per session). Both rTMS protocols consisted of one daily session from Monday through Friday for 3 weeks (15 sessions total).

### *Statistical analysis*

SPSS version 17 for Windows was used for statistical analysis. Comparison between age groups was performed

using the nonparametric Mann-Whitney *U* test, while gender distributions were compared by Fisher's exact test. To analyze changes in clinimetric test scores, the Mann-Whitney *U* was used to compare differences between groups, while the Wilcoxon test was used to evaluate the effect of rTMS within each group. Cohen's *d* was calculated in Microsoft Excel to analyze the effect size of rTMS on BPD symptoms.

## Results

Both treatment groups were relatively homogeneous in terms of age, sex, and baseline symptoms, since there were no statistically significant differences in these variables (Table 1). After application of the rTMS protocols, both groups showed significant reductions in total scores of all instruments (Table 2, Figures 1 and 2).

### *Borderline personality disorder symptoms and repetitive transcranial magnetic stimulation*

The change in the patients' symptoms, evaluated through the CGI-BPD, was obtained considering the score of each of the first nine BPD psychopathological domains, which assess current severity. The total score was also obtained by adding the scores of each of these nine domains. The Wilcoxon test was used for statistical analysis in both groups, and showed a significant reduction in CGI-BPD total score from baseline after rTMS ($z = 3.3$ in both groups, $p = 0.001$ for both groups), with a percent change of 29.4 and 28.7% for groups 1 and 5 Hz, respectively (Figure 1A), and an effect size of $d = 2.58$ for the 1 Hz group and $d = 2.02$ for the 5 Hz group.

Table 2 shows significant differences before and after rTMS, with effect sizes (obtained by the Wilcoxon test and Cohen's *d* respectively), for the nine CGI-BPD domains in each treatment group. It can be noted that both groups showed significant score reductions in all domains, particularly abandonment, impulsiveness, emotional instability, and anger, in which highly significant reductions ($p < 0.005$) were observed in both the 1 Hz and 5 Hz groups. In all CGI-BPD domains, Cohen's *d* effect size was $> 0.7$ (Table 2). However, no significant differences (Mann-Whitney *U*) in total score at baseline ($U = 91.0$, $p > 0.05$) or after rTMS ($U = 93.5$, $p > 0.05$) were found between the two groups (Figure 1), nor were there significant between-group differences in individual CGI-BPD domain scores (1 Hz vs. 5 Hz groups Pre rTMS or 1 Hz vs. 5 Hz groups Post rTMS, Table 2).

Total BEST scale scores in both the 1 Hz and 5 Hz groups also reduced significantly after rTMS ($41.0 \pm 14.5$ vs. $30.7 \pm 12.0$, $z = 2.3$, $p = 0.001$; $42.8 \pm 9.7$ vs. $26.8 \pm 11.8$, $z = -2.94$, $p = 0.003$ for 1 and 5 Hz, respectively). This represented 20.4% and 36.9% reductions from baseline for the 1 Hz and 5 Hz groups, with effect sizes of 0.8 and 1.54, respectively. No significant between-group

**Table 1** Statistical analysis of sociodemographic variables (age, sex) and baseline clinical test scores in the two treatment groups

| | Groups | | | |
|---|---|---|---|---|
| | 1 Hz (n=15) | 5 Hz (n=14) | Statistic | p-value |
| Age | 29.6±7.8 | 30.9±7.6 | $U = 76.5$ | 0.32 |
| Sex, male/female (% female) | 1/14 (93) | 1/13 (92) | Fisher's exact test | 0.9 |
| BDI | 30.9±15.6 | 31.9±14.6 | $U = 97.5$ | 0.982 |
| HAM-A | 20.2±6.8 | 15.5±6.4 | $U = 33$ | 0.120 |
| CGI-BPD | 41.1±4.7 | 40.2±6.0 | $U = 91.0$ | 0.747 |
| BEST | 41.0±14.5 | 42.8±9.7 | $U = 65.0$ | 0.510 |
| Barratt Impulsiveness Scale | 70.2±12.0 | 73.1±14.2 | $U = 94.0$ | 0.631 |

Data presented as mean ± standard deviation, unless otherwise specified.
BDI = Beck Depression Inventory; BEST = Borderline Evaluation of Severity Over Time; CGI-BPD = Clinical Global Impression Scale for Borderline Personality Disorder; HAM-A = Hamilton Anxiety Rating Scale.

**Table 2** Significant differences and effect sizes obtained by comparing values of the nine CGI-BPD domains, in each treatment group, before and after rTMS (Wilcoxon test and Cohen's *d*)

| | 1 Hz | | | | | 5 Hz | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Pre rTMS | | Post rTMS | | Cohen's *d* | Pre rTMS | | Post rTMS | | Cohen's *d* |
| | Mean | SD | Mean | SD | | Mean | SD | Mean | SD | |
| Abandonment | 4.2 | 0.8 | 3.0* | 1.0 | 1.37 | 4.0 | 0.9 | 2.9* | 0.5 | 1.57 |
| Unstable relationships | 4.2 | 0.8 | 3.1† | 0.8 | 1.42 | 4.5 | 0.7 | 3.1* | 0.9 | 1.8 |
| Identity | 3.7 | 0.6 | 3.1‡ | 0.9 | 0.81 | 3.7 | 1.0 | 2.9† | 1.0 | 0.83 |
| Impulsiveness | 4.4 | 0.5 | 2.6* | 0.8 | 2.79 | 4.0 | 0.8 | 2.6* | 1.1 | 1.51 |
| Suicide | 3.2 | 1.3 | 1.8† | 0.7 | 1.39 | 3.1 | 0.9 | 1.9* | 0.8 | 1.46 |
| Affective instability | 4.3 | 0.6 | 2.9* | 0.7 | 2.22 | 4.4 | 0.6 | 2.9* | 1.0 | 1.89 |
| Empty | 4.1 | 1.1 | 2.9* | 0.9 | 1.24 | 4.2 | 1.0 | 3.1† | 0.9 | 1.20 |
| Angry | 4.2 | 0.7 | 2.6* | 0.6 | 2.54 | 3.9 | 0.8 | 2.6* | 0.8 | 1.69 |
| Paranoid ideation | 4.4 | 0.8 | 3.4† | 1.1 | 1.08 | 4.0 | 1.4 | 3.1‡ | 1.1 | 0.74 |

CGI-BPD = Clinical Global Impression Scale for Borderline Personality Disorder; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation.
* $p < 0.005$; † $p < 0.01$; ‡ $p < 0.05$.

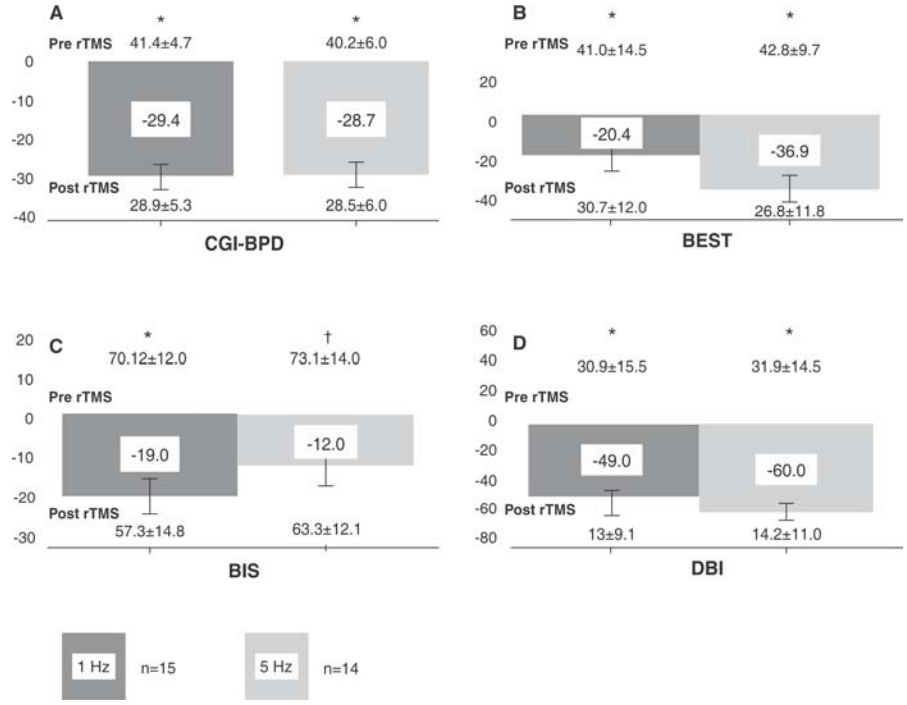


**Figure 1** Percent change in total Clinical Global Impression Scale for Borderline Personality Disorder (CGI-BPD), Borderline Evaluation of Severity Over Time (BEST), Barratt Impulsiveness Scale (BIS), and Beck Depression Inventory (BDI) scores after repetitive transcranial magnetic stimulation (rTMS). Both groups showed reductions in total score of all instruments (Wilcoxon test). Central squares show percent change. Data presented as mean ± standard deviation. * $p < 0.005$; † $p < 0.05$.

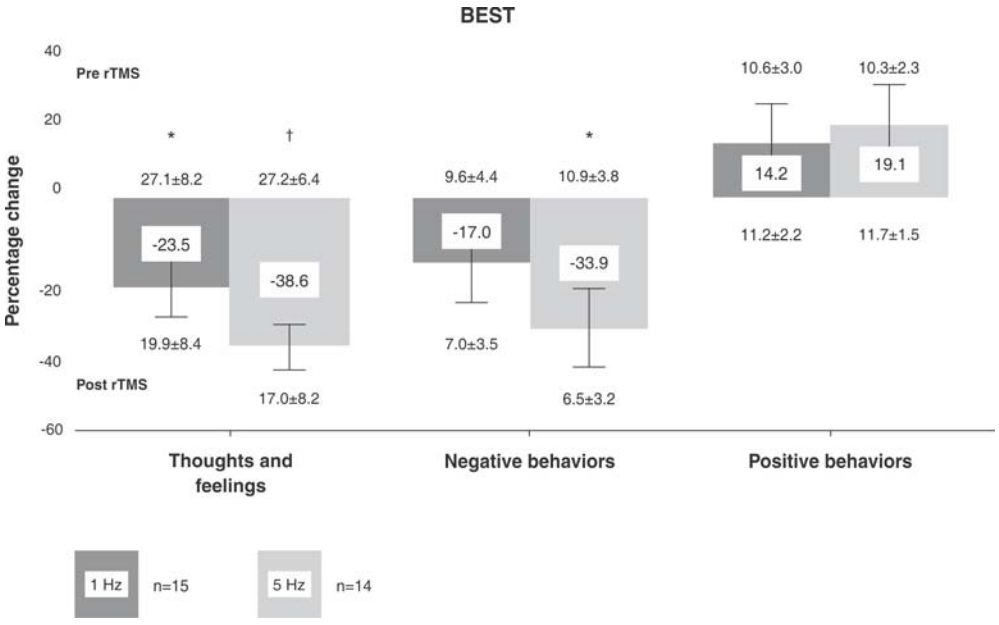


**Figure 2** Changes in Borderline Evaluation of Severity Over Time (BEST) dimensions. Data presented as mean ± standard deviation. * $p < 0.005$; † $p < 0.05$.

differences in BEST total score were found, whether at baseline ($U = 65.0$, $p > 0.05$) or after rTMS ($U = 56.0$, $p > 0.05$) (Figure 1B).

Regarding individual BEST scale dimensions, significant reductions were observed in both groups for Thoughts and Feelings (1 Hz = 27.1±8.2 vs. 19.9±8.4,

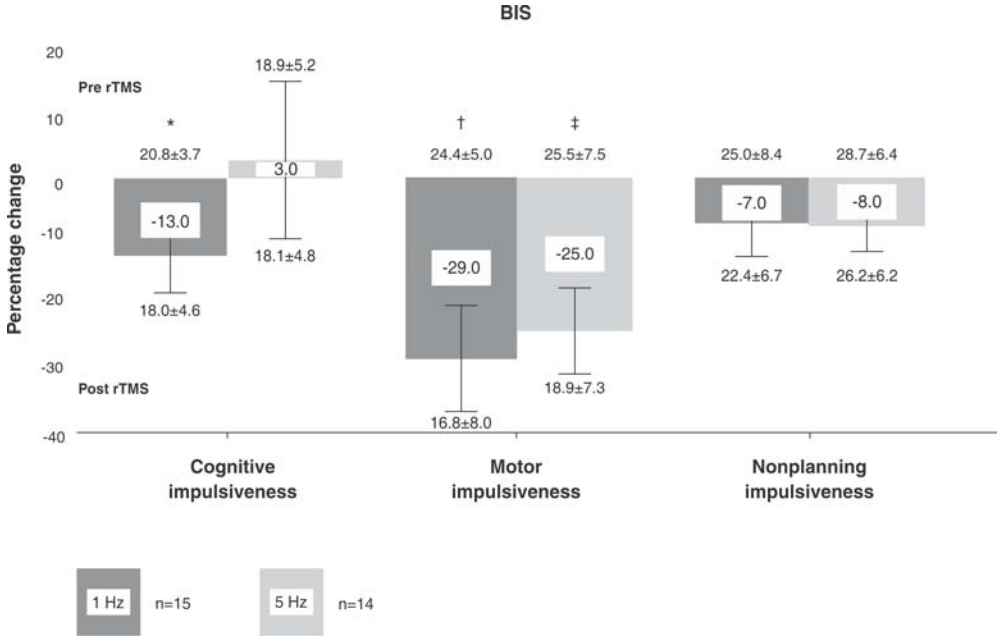


**Figure 3** Changes in Barratt Impulsiveness (BIS) dimensions. Data presented as mean ± standard deviation. * $p < 0.005$; † $p < 0.01$; ‡ $p < 0.05$.

z = 2.3, p = 0.021, Cohen's *d* = 0.90; 5 Hz = 27.2±6.4 vs. 17.0±8.2, z = 2.9, p = 0.003, Cohen's *d* = 1.44), representing a percent change of 23.5% for the 1 Hz group and 38.6% for the 5 Hz group, and in Negative Behaviors, with a 17% reduction for the 1 Hz group (9.6±4.4 vs. 7.0±3.5, z = 1.3, $p > 0.05$, Cohen's *d* = 0.68) and a 33.9% reduction for the 5 Hz group (10.9±3.8 vs. 6.5±3.2, z = 2.4, p = 0.014, Cohen's *d* = 1.3). In the Positive Behaviors dimension, no significant changes were observed in either 1 Hz group (10.6±3.0 vs. 11.2±2.2, z = -0.8, p = 0.39) or the 5 Hz groups (10.3±2.3 vs. 11.7±1.5, z = 1.4, p = 0.14). There were no significant between-group differences in individual BEST dimension scores at baseline or after rTMS (Figure 2A).

*Impulsiveness*

Comparison of baseline and post-treatment BIS scores showed significant reductions in total scores in the 1 Hz group (70.2±12.0 vs. 57.3±14.8, z = 3.2, p = 0.001, Cohen's *d* = 0.99) and the 5 Hz group (73.1±14 vs. 63.3±12.1, z = 2.3, p = 0.017, Cohen's *d* = 0.78), with change percentages of 18.96% and 11.83% respectively. No between-groups differences in impulsiveness scores were observed at baseline ($U = 94.0$, $p > 0.05$) or after magnetic stimulation sessions ($U = 87.0$, $p > 0.05$) (Figure 1C).

Analysis of changes in BIS dimension scores showed significant reductions for both groups in motor impulsiveness (1 Hz, 24.4±5.0 vs. 16.8±8, z = 2.7 p = 0.007, Cohen's *d* = 1.18, 29% change; 5 Hz, 25.5±7.5 vs. 18.9± 7.3, z = 2.8 p = 0.004, Cohen's *d* = 0.93, 25% change). Additionally, the 1 Hz group showed a significant reduction in cognitive impulsiveness dimension score (20.8±3.7 vs. 18.0±4.6, z = 2.0 p = 0.037, Cohen's *d* = 0.69, 13% reduction compared to baseline). There were no significant changes in the Nonplanning impulsiveness dimension. No significant differences were found on between-group comparison (Figure 3).

*Anxiety and depressive symptoms*

BDI scores reduced significantly from baseline after rTMS in both the 1 Hz group (30.9±15.5 vs. 13±9.1, z = -3.1, p = 0.002, Cohen's *d* = 1.46, percent change 49%) and the 5 Hz group (31.9±14.5 vs. 14.2±11.0, z = -3.3, p = 0.001, Cohen's *d* = 1.43, percent change 60%). No between-group differences were found at baseline ($U = 97.5$, $p > 0.05$) or after rTMS ($U = 96.5$, $p > 0.05$) (Figure 1D).

Similarly, HAM-A scores reduced after rTMS treatment in both groups (1 Hz, 20.2±6.8 vs. 8±4.7, z = -2.8, p = 0.005, Cohen's *d* = 2.16, percent change 60.3%; 5 Hz, 15.5±6.4 vs. 6.4±3.5, z = -2.9, p = 0.003, Cohen's *d* = 1.83, percent change 58.7%). Again, no between-groups differences at baseline ($U = 33$, $p > 0.05$) or after rTMS ($U = 43$, $p > 0.05$) were found.

## Discussion

This is the first study to explore the effect of rTMS, using 5 Hz frequencies on the left DLPFC and 1 Hz on the right DLPFC, on clinical improvement in patients with BPD. Previous studies have demonstrated the effectiveness of these protocols in treating depressive symptoms,[16,19] besides reducing discomfort and inducing seizure risk.[11,21,24]

Although imaging studies and the pathophysiology of BPD suggest dysfunction in the frontolimbic network, including the anterior cingulate cortex (ACC), the orbitofrontal and dorsolateral prefrontal cortex, the hippocampus, and

the amygdala,[2] limitations in access due to the design of TMS coils make stimulation of these structures more difficult. For instance, stimulation of the ACC or amygdala requires different coil designs, such as a double-cone angulated coil, Hesed-coil (H-coil), C-core coil, or circular crown-coil.[18,24] Furthermore, considering the physical discomfort observed during stimulation of other regions (orbitofrontal cortex and frontal pole) using a figure-eight coil, through a pilot study carried out by our research group in healthy volunteers, we decided to use the same anatomical targets reported in previous studies in both BPD and depression.[9,11,13,18]

Unlike in previous reports and treatment guidelines for conditions such as depression, where treatment is suggested to last 2 to 6 weeks of treatment,[18] reports on the application of rTMS in BPD have used only 10-session, 2-week protocols.[9,13] In this context, we decided to extend the number of sessions by 50% (15 sessions in 3 weeks), within parameters that have been demonstrated to elicit responses in the left[19] and right[16] DLPFC.

It is important to mention that, although it can be considered a soft stimulation parameter, the use of 900 pulses per session is greater than that reported in previous studies for conditions such as depression and PTSD, where a clinical effect has been reported even with protocols administering 120-1,200 pulses per session.[18]

Our results showed that both stimulation protocols were effective in reducing BPD symptom severity and several symptoms in particular, such as fear of abandonment, impulsivity, emotional instability, and anger. This may have a positive impact on reduction of self-harm and suicidal behavior, as well as improve family and interpersonal relationships through better social functioning.

After application of an inhibitory frequency (1 Hz) over the right DLPFC, we observed scores reductions in every clinimetric scale, particularly in BIS, with a significant decrease in the cognitive impulsiveness subscale. This result is similar to that reported by the Cailhol group,[13] by stimulating the same cortex, but with an excitatory frequency (10 Hz) on the right DLPFC.

Furthermore, using a lower excitatory frequency (5 Hz) on the left DLPFC, we obtained results similar to those reported by Arbabi et al. in a case report, where the same region was stimulated at 10 Hz.[9] In both studies, reductions in depressive affective symptoms and impulsiveness level were observed.

The effect of rTMS is influenced by variables such as frequency and number of pulses.[32] Even if the number of pulses in each rTMS session (1,500) was the same in both protocols; our study was performed in 15 sessions (22,500 total pulses) instead of the 10 sessions (15,000 total pulses) applied in Arbabi's case,[9] resulting in a larger amount of total pulses.

It is reasonable to assume that the significant improvement in every BPD psychopathological domain observed in our results is related to this larger amount of total pulses applied, as Arbabi et al.[9] only found changes in identity, impulsiveness, emotional instability and anger domains.

Evidence supports an association between BPD symptoms (specifically, impulsiveness and affective instability) with a deficit in top-down regulation of emotional processing, due to lower modulation of cortical structures (particularly the DLPFC) over subcortical structures (such as the amygdala).[10] It has also been reported that severity of self-harm in these patients is associated with level of impulsivity, anger, and somatic anxiety.[4] These data are consistent with findings of DLPFC functional disturbances in patients with BPD[2,7,33] and microstructural damage to the uncinate fasciculus white matter (WM),[3] the largest WM tract interconnecting the amygdala with prefrontal structures.[34]

Given this background, one could infer that using inhibitory frequencies ($\leqslant$ 1 Hz) on frontal structures would have a potentiating effect on BPD symptoms by further reducing DLPFC top-down regulation on the amygdala. However, our results after stimulation of the right DLPFC with 1 Hz suggest otherwise. Although we have no references to explain this effect on BPD symptoms, the use of inhibitory frequencies in other entities (i.e., attention-deficit hyperactivity disorder,[35] Tourette's syndrome,[23] posttraumatic stress[18]), which share impulse control failure and anxiety symptoms with BPD, suggest that this beneficial effect of rTMS may be attributable to improvement in functional deficits in the frontostriatal circuitry that appear to be associated with impulsivity[36] and affective instability in BPD.[3]

Moreover, the effect of excitatory frequencies on the left DLPFC can be interpreted in light of the Valencia Asymmetry Hypothesis,[37] which proposes that emotions associated with anxiety are processed predominantly by the right hemisphere, while the left hemisphere processes emotions related to approach behaviors and positive mood states.[10] Thus, 5 Hz rTMS applied over the left DLPFC could help increase top-down regulation of the amygdala, improving aspects such as impulsivity and affective instability.

Interestingly, both forms of stimulation (1 Hz and 5 Hz) produced global improvement in BPD symptom severity, particularly in impulsiveness, affective instability, and anger. In these sense, the role of laterality and frequency of rTMS have been controversial technical aspects; for example, in previous studies of rTMS in BPD, the authors described improvement of the symptoms with the use of high-frequency protocols, independently of rTMS laterality. Fitzgerald[21] reported absence of a differential effect between right or left rTMS at low frequencies over the DLPFC for depression treatment, while Speer et al. reported that high frequencies (20 Hz) and low frequencies (1 Hz), when applied to the left DLPFC at 110% of RMT, had the same antidepressant effect.[38] Similarly, there are reports of clinical response to right or left rTMS in PTSD.[20]

However, different guidelines recommend the use of protocols with high frequencies over the left DLPFC for treatment of depression[18,24] and PTSD.[20] Speer et al.[39,40] evaluated the clinical and metabolic effect of protocols with high- and low-frequency rTMS over the left DLPFC through the use of positron emission tomography (PET) to measure changes in absolute regional cerebral blood flow. They reported that only high frequencies (20 Hz) were associated with increased global blood flow in the left prefrontal cortex, left cingulate gyrus, and left amygdala, as well as bilateral insula, basal ganglia, uncus,

hippocampus, parahippocampus, thalamus, and cerebellum; with low frequencies (1 Hz), the authors found decreases in blood flow in the right prefrontal cortex, left medial temporal cortex, left basal ganglia, and left amygdala.[39] In a second study,[40] the same authors showed that improvement with the use of high-frequency rTMS (20 Hz) was associated with hypoperfusion on baseline PET. In this sense, these papers showed differential effects of high vs. low frequencies in metabolic response to rTMS over the left DLPFC, although clinical response was reported with both protocols of rTMS.[40]

Among the limitations of this preliminary report, we must consider that the sample size was small, there was no sham group, and we did not use neurophysiology or neuroimaging techniques which might have revealed anatomical and functional changes associated with the clinical benefits of our rTMS protocols. Despite published studies on BPD and rTMS, we did not consider inclusion of a sham group essential, because ours is an exploratory study about the potential therapeutic effect of rTMS in the treatment of BPD. A report by Cailhol et al.[13] reported comparative results between five patients who received active treatment with rTMS and five sham subjects, and although they did not find significant differences between the two groups in clinical scales, cognitive improvement was reported in the active group. Therefore, differences in active vs. sham treatment have not been demonstrated yet. It is essential that future studies include sham groups, as partial responses to sham treatment have been found in other conditions, such as depression.

Despite the limitations mentioned above, our results support the use of rTMS as a supplemental treatment for BPD. Considering that BPD is the most common personality disorder in clinical practice, further studies are warranted to explore the potential therapeutic effect of rTMS in this condition.

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## Disclosure

The authors report no conflicts of interest.

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SPECIAL ARTICLE

# Depression and psychodynamic psychotherapy

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Depression is a complex condition, and its classical biological/psychosocial distinction is fading. Current guidelines are increasingly advocating psychotherapy as a treatment option. Psychodynamic psychotherapy models encompass a heterogeneous group of interventions derived from early psychoanalytic conceptualizations. Growing literature is raising awareness in the scientific community about the importance of these treatment options, as well as their favorable impact on post-treatment outcomes and relapse prevention. Considering the shifting paradigm regarding treatment of depressive disorder, the authors aim to provide a brief overview of the definition and theoretical basis of psychodynamic psychotherapy, as well as evaluate current evidence for its effectiveness.

**Keywords:** Depressive disorder; mood disorders, unipolar; psychotherapy; psychoanalysis and psychodynamic therapies

## Introduction

Depression is considered a frequent and complex condition. According to the World Health Organization, it is expected to be the third leading cause of disability worldwide by 2020.[1] The lifetime prevalence of major depressive disorder (MDD) is estimated at around 2-20%. The Global Burden of Disease Study 2010[2] revealed it as the second most prevalent cause of illness-induced disability, affecting people of all ages and social status, and a major impact factor in social, professional, and interpersonal functioning. Mathers et al.[3] predicted MDD as the leading worldwide cause of disease burden in high-income countries by the year 2030. The decrement in health associated with depression is described as significantly greater than that associated with other chronic diseases.[4] More than 60% of patients with MDD have a clinically significant impairment in their quality of life.[5]

Common features of all depressive disorders include the presence of sad or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function.[6] Overall, depression is characterized by a general feeling of sadness, anhedonia, avolition, worthlessness, and hopelessness. Cognitive and neurovegetative symptoms, such as difficulty in concentrating, memory alterations, anorexia, and sleep disturbances, are also present.

Various known risk factors for depression have been recorded in the literature: female gender, older age, poorer coping abilities, physical morbidity, impaired level of functioning, reduced cognition, and bereavement. Depression has been associated with an increased risk of mortality and poorer treatment outcomes in physical disorders.[7]

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Although not fully understood, psychological, social and biological processes are thought to overdetermine the etiology of depression; comorbid psychiatric diagnoses (e.g., anxiety and various personality disorders) are common in depressed people.[8]

The classical biological/psychosocial distinction, which separates psychotherapy from pharmacotherapy as treatment options for depression, is fading out. Growing evidence from the neuroscientific literature supports similar (and different) changes in brain functioning with these approaches, concluding that both psychotherapy and pharmacotherapy are biological treatments, and that there is no legitimate ideological justification for the decline of the former.[9]

Understandably, current treatment guidelines[10,11] for depressive disorders are increasingly advocating psychotherapy as a treatment option, alone or in combination with antidepressant medications.

Considering this shifting paradigm regarding treatment of depressive disorder, the authors aim to evaluate current evidence for the effectiveness of psychodynamic psychotherapy (PDP) in depression. A brief clarification of the definition of PDP and its theoretical basis for understanding depression are also presented.

## Methods

A narrative review was performed, including recent and current published papers on PDP and its role as a treatment modality in depressive disorders. Recent empirical studies were also included in order to integrate authors' critical perspectives, supported by classical and contemporary literature.

## Results

### *Defining psychodynamic psychotherapy*

PDP models are derived from early psychoanalytic conceptualizations, including ego psychology, object-relations

theory, self-psychology, and attachment theory. Treatment goals or focus and setting changes have been reconsidered by contemporary authors. Gabbard[12] described PDP's basic principles as: much of mental life is unconscious; childhood experiences, in concert with genetic factors, shape the adult; the patient's transference to the therapist is a primary source of understanding; the therapist's countertransference provides valuable understanding about what the patient induces in others; the patient's resistance to the therapeutic process is a major focus of therapy; symptoms and behaviors serve multiple functions, and are determined by complex and often unconscious forces; finally, the psychodynamic therapist assists the patient in achieving a sense of authenticity and uniqueness.

PDP operates on an interpretive-supportive continuum. Interpretive interventions enhance the patient's insight about repetitive conflicts sustaining his or her problems. The prototypic insight-enhancing intervention is an interpretation by which unconscious wishes, impulses, or defense mechanisms are made conscious. Supportive interventions aim to strengthen abilities ("ego functions") that are temporarily not accessible to a patient due to acute stress or that have not been sufficiently developed. Thus, supportive interventions maintain or build ego functions. Supportive interventions include, for example, fostering a therapeutic alliance, setting goals, or strengthening ego functions such as reality testing or impulse control. The use of more supportive or more interpretive (insight-enhancing) interventions depends on the patient's needs.[13]

### *Common factors of psychotherapy and specific features of the psychodynamic approach*

Common factors are currently understood as a set of common elements that collectively shape a theoretical model about the mechanisms of change during psychotherapy. A recent meta-analysis[14] has shed light on strong evidence regarding factors such as therapeutic alliance, empathy, expectations, cultural adaptation, and therapist differences in terms of their importance for psychotherapeutic treatments in theory, research, and practice.

Overall, the influence of common factors in psychotherapies has been estimated at 30% when consider ing the variation in depression outcomes. Nonetheless, other factors, including specific techniques, expectancy, the placebo effect, and extratherapeutic effects, have also been studied.[15]

Zuroff & Blatt[16] have concluded that the nature of the psychotherapeutic relationship, reflecting interconnected aspects of mind and brain operating together in an interpersonal context, predicts outcome more robustly than any specific treatment approach *per se*.

Regarding common factors in PDP, Luyten et al.[15] mentioned the important differences between psychodynamic and other treatments. Comparatively to cognitive-behavioral therapists, psychodynamic therapists tend to place stronger emphasis on certain aspects, namely: affect and emotional expression; exploration of patients' tendency to avoid topics; identification of recurring behavioral patterns, feelings, experiences, and relationships; the past and its influence on the present; interpersonal experiences; the therapeutic relationship; and exploration of wishes, dreams, and fantasies. Along with these features, specific characteristics of a psychodynamic-oriented treatment have been described: a focus on the patient's internal world; a developmental perspective; and a person-centered approach.

### *Depression from the psychodynamic perspective*

Psychodynamic understandings of depressive disorders were first described by Freud, Abraham, and Klein. Freud explored the individual's reactions to an actual loss or disappointment associated to a loved person, or to a loss of an ideal. Plainly, he tried to explain why some people react with a mourning affect (surpassed after a period of time) and others succumb into melancholy (depression, as we now call it). Mourning is the reaction to the loss of a loved one or the loss of an abstraction, which has taken the place of something (a country, freedom, or an ideal, for example), and although it involves significant disruptions from one's normal attitude towards life, it should not be regarded as pathological. Thus, mourning occurs following loss of an external object. Melancholy, on the other hand, arises from the loss of the object's love and is an unconscious process where a remarkable decrease in self-esteem is observed. Culpability is also a feature clearly present in melancholic processes, as the loss of the object comes with feelings of guilt, stressing the ambivalent feelings towards the lost object; not only because the individual knows that he or she attacked (in fantasy or in reality) the lost object, but mostly because he or she desired that very loss (due to the object's unsatisfactory presence and love). Freud clearly outlined the symptoms of melancholy: "... a profoundly painful dejection, cessation of interest in the outside world, loss of capacity to love, inhibition of all activity, and lowering of the self-regarding feelings to a degree that finds utterance in self-reproaches and self-revilings and culminates in delusional expectations of punishment."[17] These features seem to resemble the current DSM definition of depression.

Abraham proposed a specific model for the melancholic process,[18] consisting of a series of explanatory events: after an initial frustration (loss of an object), the subject reacts with externalization of the introjected object and its destruction, thus to an early anal-sadistic stage. Identification with the object - (primary) narcissism - results in its introjection, thus explaining the sadistic vengeance against the object as part of the subject's ego; one's self-destruction often manifested as suicidal thoughts. Ambivalence plays a key role, as the subject struggles with his own survival and destruction.

Klein later elucidated the importance of the establishment of an internal world in which the lost external object is "reinstated." Thus, in melancholy, there is a regression to an earlier failure to integrate good and bad partial objects into whole objects in the inner world. The depressive individual believes himself omnipotently responsible for the loss, due to his inherent destructiveness, which has not been integrated with loving feelings. Klein argues that pining, mourning, guilt, reparation, possibly delusional

thinking, omnipotence, denial, and idealization characterize depression.[19]

More recently, Luyten & Blatt[15] commented on these works as "still clinically relevant" but "often over specified, lacking theoretical precision, and too broad to be empirically tested." However, these authors stated that unconscious motives and processes still play an important role in recent psychodynamic theories of depression.

### *Evidence for psychotherapy as a treatment for depressive disorders*

A meta-analysis of direct comparisons found psychotherapy about as effective as pharmacotherapies for depressive disorders.[20] In another meta-analysis, Cuijpers et al.[21] included 92 different randomized controlled trials (RCTs) and demonstrated the efficacy of psychotherapy in comparison with pharmacotherapy – equal in the short-term and superior in the long-term, regarding relapse prevention. Different forms of psychotherapy have been compared, with no clear differences observed or, when so, with certain methodological specificities pointed out.[22] Nevertheless, the effectiveness of many well-recognized interventions has been regarded as possibly overestimated, considering that most evidence is based on symptom reduction.[23] A comprehensive meta-analysis[24] has highlighted the effectiveness of Interpersonal Psychotherapy (which has its structure and theoretical roots in PDP) in depression, as compared to other psychotherapies and vs. combined treatment, as well its role in preventing onset or relapse after successful treatment.

Extensive literature supports the efficacy of psychotherapy as an established treatment for MDD, stating its effectiveness and comparableness to that of antidepressant medications. The significance of these findings and possibility of publication bias have also been object of attention from the scientific community. A recent analysis stated an excess of significant findings relative to what would be expected for studies of psychotherapy's effectiveness for MDD.[25]

On this subject, Driessen et al.[26] found clear indications of study publication bias among U.S. National Institute of Health-funded clinical trials that examined the efficacy of psychological treatment for MDD, ascertained through direct empirical assessment. Through these data, the authors concluded that psychological treatment, like pharmacologic treatment, may not be as efficacious as the published literature would indicate.

Cuijpers et al.[27] published a meta-analysis on the effects of psychotherapies on remission, recovery, and improvement of MDD in adults. The response rate for the analyzed psychotherapies was 48% (vs. 19% in control conditions), and there was no significant difference between types of psychotherapy.

### *Evidence for psychodynamic psychotherapy as a treatment for depressive disorders*

Shedler[28] presented five independent meta-analyses showing that the benefits of PDP not only endure, but also increase with time (including after treatment end). Patients reported significant symptom reductions, which held up over time, and increased mental capacities, which allowed them to continue maturing over the years. Additionally, Shedler presented several studies demonstrating that it is the psychodynamic process that predicts successful outcome in cognitive therapy, rather than the pure cognitive aspects of treatment – i.e., non-psychodynamic psychotherapies may be effective because the more skilled practitioners utilize techniques that have long been central to psychodynamic theory and practice.

Leichsenring et al.[22] conducted an empiric review of supported methods of PDP in depression and suggesting a unified protocol for the psychodynamic treatment of depressive disorders. The authors found a twofold risk for poor outcome in depression when patients were diagnosed with a comorbid personality disorder. However, several studies were found to have methodological limitations, such as taking a personality disorder diagnosis in account as a primary object of treatment, sample size differences, and divergent results, largely depending on the personality cluster identified. The findings of these authors contradict repeated claims that PDP is not empirically supported.

A subsequent systematic review by Leichsenring[29] identified and included a total of 47 RCTs providing evidence for PDP in specific mental disorders; it stated the efficacy of PDP compared to cognitive-behavioral therapy (CBT) (but not to other forms of psychotherapy) in MDD, and concluded that several RCTs provide evidence for the efficacy of PDP in depressive disorders (including comparisons with control groups, waiting-list condition at the end of treatment, group therapy, pharmacotherapy, and brief supportive therapy).

Varying results have also been observed according to treatment duration – specifically, short-term (STPDP) vs. long-term psychodynamic psychotherapy (LTPDP) as applied in patients with depressive disorders. One recent meta-analysis[30] evaluated the efficacy of a specific STPDP (experiential dynamic therapy) within multiple psychiatric disorders, and found the largest effect on depressive symptoms. A meta-analysis from the Cochrane Collaboration[31] studied the effects of STPDP for common mental disorders across several studies, including 23 RCTs. It showed significantly greater improvement in the treatment groups as compared to controls, with most improvement maintained on medium- and long-term follow up.

Another meta-analysis by Leichsenring et al.[32] examined the comparative efficacy of LTPDP in complex mental disorders in RCTs fulfilling specific inclusion criteria (therapy lasting for at least a year or 50 sessions; active comparison conditions; prospective design; reliable and valid outcome measures; treatments terminated). It concluded that LTPDP is superior to less intensive forms of psychotherapy in complex mental disorders.

More recently, Driessen et al.[33] published a meta-analysis of 54 studies highlighting STPDP outcomes in symptom reduction and function improvement during treatment. They found either maintained or further improved gains at follow-up, and stated that the efficacy of STPDP compared to control conditions and outcomes on depression did not differ from that of other psychotherapies.

A recent review[34] provided evidence towards maintained effects with both modalities as a treatment option for depression, emphasizing their moderate (rather than large) effects. PDP is noted as a preferred alternative to pharmacotherapy in depressive disorders; nevertheless, the authors highlight the high frequency of studies involving psychotherapy in combination with medication – or adding to the effectiveness of medication. In comparison with CBT, PDP is described as neither largely nor reliably different. No single type of PDP was found particularly efficacious within its different forms. Regarding LTPDP, its cost-effectiveness and early stage are mentioned when describing its value, especially in more complex and chronic cases of depression.

## Discussion

An extensive, growing body of literature confirms that the classical divergence in treatment approaches for depressive disorders is fading. Psychotherapy has been found as efficacious as pharmacotherapy, with different results regarding its superiority in short-term and long-term relapse prevention.[20,23] Moreover, a systematic review has elucidated the potential benefits of a change in intervention design in depression, switching the paradigm from a symptom-oriented one to more rehabilitation- and functioning-oriented therapies.[23] These results are in agreement with Westen et al,[35] who presented evidence that treatments focusing on isolated symptoms or behaviors (rather than personality, emotional, and interpersonal patterns) are not effective in sustaining even narrowly defined changes.

The large number of publications in this topic has drawn the attention of the scientific community, prompting systematic analyses with increasing complexity and the creation of specific protocols for psychotherapeutic intervention, bearing in mind the importance of structured interventions by qualified clinical staff.

Although it would stray from the primary scope of this review, it is worth highlighting the growing number and relevance of published neuroscientific literature that reports neuroimaging and neurochemical changes exerted by psychotherapeutic interventions,[9] specifically PDP.[36]

The effectiveness of PDP has been found difficult to isolate due to its limitations as a measurable intervention, which has led to the proposition of unified protocols both to facilitate training and to improve the status of evidence.[22] The quality of PDP trials published from 1974 to 2010 was assessed in a review paper[37] which concluded that the existing RCTs of PDP mostly show superiority of PDP to an inactive comparator. Studies concerning longer-term treatments are scarce but highly relevant, as they focus on important individual aspects like chronic mood problems, which often result from a combination of depression, anxiety, and significant personality and relational problems.[15]

While these aspects are simple to clarify, few studies have taken them into account. Further RCTs could provide new evidence on the effectiveness of PDP, as well as facilitate its clear integration among the range of standard treatment options to consider for depressive disorders. One important related aspect refers to the training of future therapists in PDPs: institutes are mostly small and independent, and lack the necessary resources to conduct expensive or large-scale studies.

This narrative review presents certain limitations. Only recent published studies or systematic reviews were included. Due to practical reasons, only English-language publications were included, which may have left out important published findings. Publication bias may also be a factor, perhaps resulting in studies or systematic reviews that only showed positive or equal results for PDP treatments. However, we emphasize the importance of gathering and comparing recent findings and systematic reviews with classical published works in the field of PDP.

In conclusion, despite its controversial history, PDP's influence in the psychiatric panorama is definitely increasing. The effectiveness of PDP has been demonstrated in various studies which have compared it with other treatment modalities. In recent years, the body of empirical evidence supporting said effectiveness has grown, and, more recently, meta-analyses have confirmed the role of PDP in the treatment of depressive disorders.

Many advances have been made in to enable high-quality scientific research in this complex, layered field. Nonetheless, contemporary authors continue to claim the importance of early conceptualizations of the psychodynamic perspective toward depression and depressive disorders.

## Disclosure

The authors report no conflicts of interest.

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## LETTERS TO THE EDITORS

# Maintenance use of ketamine for treatment-resistant depression: an open-label pilot study

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Singh et al.[1] reported that two or three weekly 40 min i.v. infusions of ketamine (0.5 mg/kg) are safe and effective for maintaining an acute response to ketamine during one month of treatment for resistant depression (TRD).

We present herein the results of an open label pilot study of 8 TRD patients who received 40 min infusions of ketamine (0.5 mg/kg) for 7 weeks after a positive acute response to three ketamine infusions. We employed a maintenance protocol at a lower frequency as follows: three initial infusions every other day for a week, an infusion 7 days after the last initial infusion and infusions every two weeks thereafter. This lower frequency was based on the 18-day median time to loss of response reported by Murrough et al.[2]

In this study, those who did not respond adequately to appropriate courses of at least two antidepressants were considered TRD patients. The subjects were two men and six women, aged 25-53 years, diagnosed with major depressive disorder. They had no unstable clinical diseases and they were not acutely psychotic. Three patients had a comorbid diagnosis of generalized anxiety disorder, one of whom also had a diagnosis of fibromyalgia. Two of the individuals had been hospitalized once after attempting suicide. The mean duration of illness in this sample was 16 years. At the time of the study, four of the patients were in polytherapy, three were in monotherapy and one had chosen to discontinue antidepressants because he considered them ineffective.

They signed an informed consent form and completed a Beck Depression Inventory (BDI) three times: pretreatment (mean BDI scores = 33.75), 3 days after the initial infusions (mean BDI scores = 10.25) and on day 60 (mean BDI sores = 10.75). All eight patients sustained the response until day 60.

During the infusions all of the patients had some degree of dissociative symptoms, ranging from a feeling of lightheadedness to feelings of being outside the body or in another dimension. These symptoms began after 15 to 20 min of infusion and quickly reduced in intensity after the end of the infusions. All the patients could be discharged with no complications 30 min after the end of the infusions. Like Singh et al.,[1] we also observed that the dissociative symptoms decreased with repeated doses. Two patients complained of nausea, which was successfully treated with intravenous ondansetron. Despite this, seven of the patients described the infusion experience as pleasant and only one as unpleasant. No delusions or hallucinations were reported during the study. There were no clinical emergencies.

Thus, the use of multiple infusions of ketamine to maintain its acute effects might be an effective and well-tolerated treatment approach for TRD patients. An infusion every two weeks appears to suffice. This may represent a simple, quick way to bring longer term benefits for TRD patients with an acute ketamine response. Hence, this may be an alternative as we await eventual FDA approval of intranasal esketamine or new drugs targeting the glutamatergic system.[3] However, controlled studies with larger samples are required to replicate our findings.

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### Disclosure

The authors report no conflicts of interest.

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# Skin picking disorder comorbid with ADHD successfully treated with methylphenidate

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Skin picking disorder (SPD) is characterized by repetitive picking and scratching of the skin, leading to tissue damage and substantial distress.[1] The few pharmacological studies on SPD treatment have yielded conflicting results[2] and more pharmacological evidence is needed to guide clinicians.

Attention deficit hyperactivity disorder (ADHD) is characterized by symptoms that express varying levels of inattention, hyperactivity and impulsivity. Case reports of ADHD treatment with psychostimulants suggest they can also act on comorbid disorders with impulsive features (kleptomania, pathological gambling and bulimia nervosa).[3] Erdogan et al.[4] reported that SPD patients had a high prevalence of comorbid ADHD, but this has not been investigated in other studies. The only case report of ADHD comorbid with SPD, by Lane et al.,[1] described

**Table 1** Scores for depression, anxiety, impulsivity, inattention and hyperactivity questionnaires during treatment

| | No medication | MPH SODAS 20mg | MPH SODAS 30mg |
|---|---|---|---|
| BDI | 8 | 2 | 0 |
| ASRS D | 8 | 1 | 1 |
| ASRS HI | 3 | 0 | 0 |
| BIS AT | 22 | 22 | 21 |
| BIS PLAN | 36 | 35 | 29 |
| BIS MOT | 24 | 24 | 22 |
| BIS TOT | 84 | 81 | 72 |
| STAI T | 55 | 55 | 55 |
| STAI S | 62 | 62 | 60 |

ASRS D = Adult Self Report Scale – Inattention Symptoms; ASRS HI = Adult Self Report Scale – Hyperactivity and Impulsivity Symptoms; BDI = Beck Depression Inventory; BIS AT = Barratt Impulsiveness Scale – Attentional Subscale; BIS MOT = Barratt Impulsiveness Scale Motor Subscale; BIS PLAN = Barratt Impulsiveness Scale – Planning Subscale; BIS TOT = Barratt Impulsiveness Scale – Total Score; STAI S = State-Trait Anxiety Inventory – State Score; STAI T = State-Trait Anxiety Inventory – Trait Score.

a 9-year-old boy with a full-scale IQ of 77 who only experienced improvement when a behavioral intervention was associated with ongoing psychostimulant treatment. There are no case reports describing methylphenidate treatment in ADHD adults comorbid with SPD. Likewise, there are no reports in the literature of worsening SPD symptoms due to psychostimulant treatment in patients without ADHD.

We present the case of a 26-year-old college student who sought care because she could not control her scratching behavior. The patient reported starting the excoriation because she felt recurring insect bites on her skin. However, she described the itching as rapidly fading and that she continues excoriating without it. She only became aware of her behavior as she felt pain or bled. Most lesions were located on her thighs and legs. She was ashamed of her injuries and hid them by avoiding short clothes. Her dermatologist had already tried unsuccessfully to treat her SPD with fluoxetine and sertraline. Although she did not spontaneously self-report inattention and impulsivity symptoms, her family and friends frequently complained about them. The patient met DSM-5 criteria for both SPD and ADHD, and her husband and mother confirmed symptoms at clinically significant levels. We decided to treat ADHD first because of family and educational impairments and, after 1 month on 20 mg/day methylphenidate SODAS, she reported being able to focus on what she was feeling and that this aided her in inhibiting the impulse to scratch herself. She also stopped mentioning the itching sensation in her skin. After increasing MPH to 30 mg/day, she experienced further symptomatic improvement, and said that "did not even remember the injuries."

Table 1 presents self-report questionnaires measuring depression, anxiety, impulsivity traits and ADHD symptoms at baseline and when using 20 and 30 mg of MPH. These scores show that changes in inattention were most consistent with SPD decrease. During follow up assessments, the patient reported that her mood improved as her academic performance and social relations became less impacted by her ADHD. Although her Beck Depression Inventory scores decreased during treatment, her initial scores were already below the cutoff for clinical depression. The patient suspended medication by herself twice after the third month and resumed excoriating her skin, which again remitted with therapy.

Given the low efficiency of available pharmacologic agents for treating SPD (N-acetylcysteine, SSRIs), MPH might be an option for a subset of SPD patients. Since SPD can be defined as a repetitive behavior disorder due to impulsivity and inhibitory control deficits, and considering that the patient in this case report noticed that her scratching behavior was associated with mind wandering (inattention), we can suggest some hypothesis why the ADHD treatment helped improve SPD symptoms. Methylphenidate acts by inhibiting dopamine and noradrenaline reuptake, mainly in the *striatum* body, prefrontal cortex and *nucleus accumbens*. Thus, it can be posited that its action on prefrontal cortex could have helped reduce impulsivity, whereas its action on *striatum* body could have increased the attentional state. Thus, we suggest that increased attention span and decreased impulsivity could be mechanisms that, when achieved jointly, could decrease SPD symptoms. Further studies are needed to address whether methylphenidate benefits SPD individuals who do not have ADHD by improving cognitive functions (e.g. inattention or inhibitory control).

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# Is the regulation of Z-drugs in Brazil in line with scientific research and international standards?

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Z-drugs (i.e., zopiclone, zaleplon and zolpidem) first appeared on the market as a substitute for benzodiazepines (BZDs), purportedly having a lower risk of addiction due to improved pharmacokinetics. However, recent research has shown they may be similar to BZDs in terms of cognitive, behavioral and psychomotor performance[1]; risk of dependence[2]; and mortality.[3] Nevertheless, this scientific knowledge has not seemed to influence the rate of Zolpidem consumption, especially in developing countries,[4] where regulatory measures may be more vulnerable to the influence of the pharmaceutical industry. In light of this research, the Food and Drug Administration (FDA) released two Drug Safety Communications (DSCs) in 2013 regarding products containing Zolpidem, describing the risk of next-day impairment and recommending lower starting doses, particularly for women.[5]

Following this FDA action, a number of studies reported reductions in the prescribed dose,[6] reducing the risks of adverse effects. However, other research has shown that more than 70% of general practitioners do not recognize or even evaluate the side effects of these hypnotics,[7] and that the beliefs of clinicians and patients about the drugs' safety do not seem to keep pace with advances in research, producing a gap between scientific evidence and clinical practice. Education, backed by legislation, about the effects of the chronic use of these medications is extremely important to ensure appropriate prescription and reduce misuse. In Brazil, the regulations for prescribing Z-drugs are weak: The risk of dependence is explicitly stated on the leaflet accompanying Zolpidem although it is not classified under the same regulations as BZDs. A standard prescription is used rather than the specific blue one required for BZDs, and their packaging presents neither the customary black stripe found on the most strictly controlled medications nor the words "the abuse of this medicine can cause dependence," as can be found on BZDs. The packaging features only a red stripe, typical of medications such as antiepileptics or antidepressants, which may lead consumers to believe the medicine has a different status than BZDs and carries little or no dependence risk or other negative effects.

This lack of control and medical guidance could potentially contribute to dependence problems or other consequences. Although there is still a lack of evidence about the effect size for outcomes such as dementia, infections or cancer, as well as the heterogeneity of risk among different Z-drugs, there is mounting evidence that Z-drugs are similar to BZDs, at least with respect to motor vehicle accidents, falls and fractures.[8] Therefore, it is urgently necessary to disseminate information about the similarities between BZDs and Z-drugs, since they have been shown to cause similar adverse effects and dose escalation[1] due to tolerance, and thereby challenge the belief among professionals and patients that Z-drugs present less risk.[7] In addition, further research into the influence of regulation on the consumption of hypnotics is required. Policy makers must be made more aware of Z-drugs' potential for dependence and be encouraged to adopt measures such as those of the FDA, bringing regulations in line with those of BZDs in order to increase patient and physician knowledge about this issue and reduce potential harm.

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# Zika virus infection and psychosis

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We read the publication on ''Zika virus infection followed by a first episode of psychosis'' with great interest.[1] Corrêa-Oliveira et al. noted that ''to the best of our knowledge, this is the first report in which psychiatric symptoms were the only complication of acute ZIKV infection''[1] and concluded that ''Neuroimmune mechanisms leading to psychosis during acute CNS stress is an open and prolific field for research.''[1] In fact, a wide clinical spectrum of Zika virus infection has been reported, and psychological problems are possible.[2,3] Neuropsychiatric problems as the only clinical presentation in acute Zika virus disease is not a new finding. At least, psychotic features in acute Zika virus infection have already been observed in cases in which meningoencephalitis was later proved.[4] In the Zika virus infection with meningoencephalitis, spatial delusions with visual and kinesthetic hallucinations are observable.[5]

## Disclosure

The authors report no conflicts of interest.

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