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ORIGINAL ARTICLE

Emotional overeating questionnaire: a validation study in Italian adults with obesity, overweight or normal weight

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Abstract

Purpose This study aimed at testing the validity and reliability of the Emotional Overeating Questionnaire (EOQ) in a sample of Italian adults with obesity, overweight or normal weight.

Materials and methods Participants were 314 Italian adults (72.6% females, aged 18–76 years) with obesity (27.4%), overweight (21.3%), or normal weight (51.3%), who completed the EOQ and measures of binge eating, mental well-being, and mindful eating. Retesting was performed 4 weeks later in a randomly selected subsample of 60 participants. Factor structure of the EOQ was estimated by confirmatory factor analysis (CFA). Reliability was tested with McDonald's ω and ordinal α coefficients for internal consistency and Cohen's weighted Kappa coefficient (K_w) for test–retest reliability.

Results Based on CFA, the five negative emotional items formed one factor (EOQ-5) with good reliability ($\omega = 0.89$; ordinal $\alpha = 0.88$; $K_w = 0.71$), while the item referring to happiness was dropped. EOQ-5 scores were associated with higher binge eating, lower mental well-being, and lower mindful eating. A cut-off point of two identified individuals at risk for binge eating disorders with 75% sensitivity and 67% specificity. Negative emotional overeating was more frequent in women with obesity than women with normal weight and men with obesity.

Conclusions EOQ-5 is a valid and reliable tool for measuring the frequency of emotional overeating at the Italian community-level.

Level of evidence Level V, cross-sectional, descriptive study.

Keywords Emotional overeating · Obesity · Overweight · Normal-weight · Sex differences · Validation · Confirmatory factor analysis

Introduction

Emotional eating is the tendency to overeat in response to emotions [1] and has predominately been characterized by negative emotions (e.g., anger, sadness, or boredom), although sometimes it also includes positive emotions [2]. Eating in response to negative emotions has been associated with increased consumption of high-fat and high-sugar foods, higher body mass index (BMI) [3], poor psychological well-being, and psychological symptoms and diseases such as eating disorders, anxiety, depression, obsessive–compulsive behaviors, and psychoticism [4–8]. There is also evidence that negative emotional eating is a stronger predictor of overeating than other eating behaviors such as restraint or disinhibition [9]. Therefore, emotional eating warrants clinical attention because of its association with eating disorders, but it may also represent a risk eating behavior in relation to obesity and overweight. Given that prevalence rates of overweight and obesity continue to be a leading public health concern worldwide [10], there is a need to investigate and understand behaviors, such as emotional overeating, that play a role in disordered eating and weight gain [11]. However, the frequency and correlates of emotional overeating in community samples have received considerably less attention than in clinical samples.

The Emotional Overeating Questionnaire (EOQ) [12] is a brief 6-item self-report that measures the frequency

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of overeating behavior in response to five negative (i.e., anxiety, sadness, loneliness, tiredness, and anger) and one positive emotion (i.e., happiness). Frequency refers to how many days, over the prior 28 days, the participant reports the occurrence of an episode of overeating defined as "eating an unusually large amount of food, given the circumstances" [12, p. 142]. Advantages of the EOQ compared with other existing tools are that it refers to overeating in response to emotions instead of just eating and assesses the frequency of overeating. Frequency is the gold-standard response set when examining eating pathology [13, 14], and the EOQ differs in this way from other measures that assess the desire to eat [15, 16], the tendency to eat [2], or how much one eats [17, 18] when feeling certain emotions. Finally, the EOQ brief 6-item length may reduce the respondent burden of long questionnaires and simplify administration.

The EOQ has been developed and validated in patients with binge eating disorder (BED) and BMI ≥ 25 showing good factorial validity as a one-factor measure and good reliability with Cronbach's $\alpha = 0.85$ and intra-class correlation coefficient (ICC) = 0.73 for the 1-week test–retest [12]. Convergent validity was found with measures of binge episodes, eating disorder symptomatology, and depressive symptoms [12] as well as with overeating in a sample bariatric surgery patients [19]. However, the 6-item EOQ showed a different structure across clinical and non-clinical samples. Indeed, in the original study of patients with BED [12], one factor emerged from explorative factor analysis (EFA) with all items of negative and positive emotional overeating loading on the factor. In a sample of female, normal weight university students [20], one factor was extracted from the five negative emotional items. The measure had good reliability ($\alpha = 0.81$) and was positively associated with measures of disordered eating symptoms and loss of control over food intake. The item referring to happiness was excluded as its loading was under the threshold (< 0.40) established by the authors to retain an item within EFA.

To the best of our knowledge, no study has evaluated the factor structure of the EOQ in a non-clinical sample of females and males of different age and educational attainment and various levels of BMI. Accordingly, the principal aim of this study was to investigate the factor structure of the EOQ by means of confirmatory factor analysis (CFA) in a community sample of both sexes with a wide range for age, education, and BMI. We also aimed at investigating the reliability and convergent/discriminant validity of the best fitting factor model and its associations with demographic characteristics and BMI levels.

The EOQ has been used in several studies of different samples in different countries, showing various associations with psychological, clinical or sociodemographic characteristics. High EOQ scores were associated with BED and with eating-disorder symptoms, such as eating concern, shape concern, and weight concern, in adults with overweight/obesity seeking treatment for weight loss in primary care ($n = 129$) [21]; with eating disorders in obese bariatric surgery candidates ($n = 337$) [22], and with under-estimation of obesity status in patient with class II obesity ($n = 173$) [23]. In patients with BED seeking treatment for obesity ($n = 326$) high EOQ scores were associated with difficulties with emotion regulation and depression [24]. In Veterans with obesity ($n = 120$) emotional eating was associated with post-traumatic stress disorder [25]. Finally, in a community sample ($n = 330$), EOQ scores were higher in participants with food addiction compared with those who were not [26].

Association with demographic variables showed that EOQ scores were generally unrelated to sex, age, and BMI, although a study of patients with BED and obesity [24] found an association with sex. In the literature of emotional eating in community samples, the effects of age and education were non-significant [7, 18], while women reported more frequent emotional eating behavior than men [9, 15, 18] and negative emotional eating was associated with higher BMI [5, 9, 15].

Based on the literature, the following hypotheses were postulated for this study: (1) emotional overeating would be positively associated with binge eating [21, 22] and the EOQ would demonstrate good sensitivity and specificity in identifying people at risk for BED, (2) emotional overeating would be negatively associated with mental well-being due to its positive association with depression [12, 24], (3) emotional overeating would be associated with mindless eating due to difficulties in recognizing internal cues of hunger and satiety as suggested by Bruch [27] and found in patients with BED and obesity [24], (4) emotional overeating would be more frequent in females than males [9, 15, 18, 24], and not related to age or education [7, 18], and (5) emotional overeating would be more frequent in participants with obesity or overweight than those of normal weight [5, 9, 15].

Method

Participants and procedure

A total of 392 volunteer adults responded to an advertisement on community services pages of three Italian cities asking to complete an online questionnaire for a research on eating behavior. Once the participant reached the online questionnaire initial page, a detailed description of the research was provided with the researchers' names and e-mail addresses, information regarding the privacy and data treatment, and informed consent to participate that was given by clicking on the "yes, I consent to participate" button. Inclusion criteria were older than 18 years, native Italian-speaking, and not being diagnosed with any eating

disorder. The final sample included 314 participants (80.1% of the initial sample); 78 questionnaires were excluded using listwise deletion due to 5–7% missing items in any of the considered variables, after observing that missingness was completely at random and the number of deleted cases did not dramatically affect the statistical power. No sociodemographic differences were found between who completed and who did not complete the questionnaire. Women were 72.6%; the age range was 18–76 years, $M_{age} = 35.75$, SD = 13.61; 51% had a bachelor's degree or higher; BMI range was 18.51–66.10, $M_{BMI} = 27.13$, SD = 8.11. Participants were classified into three categories based on the world health organization standards: 27.4% ($n = 86$) had obesity (BMI ≥ 30 kg/m^2), 21.3% ($n = 67$) were of overweight (BMI 25–29.9 kg/m^2), and 51.3% ($n = 161$) were of normal weight (BMI 18.5–24.9 kg/m^2). It is noteworthy that, although all participants were self-selected volunteers, the prevalence of people with BMI ≥ 25 kg/m^2 in this study (49%) was almost representative of the Italian population (49.8%) [28]. Among the final sample, 70 participants were randomly selected and invited to answer the EOQ again after 4 weeks via an online survey to assess test–retest reliability of the EOQ. Sixty participants completed the retest with a response rate of 85.7%.

Measures

The EOQ [12] is a 6-item measure of the frequency, over the prior 28 days, of overeating in response to anxiety, sadness, loneliness, tiredness, anger, and happiness. Participants rate the frequency of overeating in response to each emotion on a 7-point scale (0 = no days, 1 = 1–5 days, 2 = 6–12 days, 3 = 13–15 days, 4 = 16–22 days, 5 = 23–27 days, and 6 = everyday). Responses to the six items are generally summed up to form a global emotional overeating score, with higher score indicating more frequent emotional overeating. For the purposes of this study, the EOQ was translated into Italian and backtranslated by two independent bilingual psychologists.

The binge eating scale (BES) [29], Italian version [30], is a 16-item measure of binge eating behavior that uses a 3- or 4-point response format. The questions are mainly based upon the amount of food consumed, the perceived control over eating behavior, and a feeling of guilt after overeating. Scores range from 0 to 46, with individuals scoring > 17 considered moderate to severe binge eaters and thus at risk for BED [29]. Cronbach's α in our sample was 0.91.

The 5-item world health organization well-being index (WHO-5) is a widely used 5-item measure of subjective psychological well-being. It is a sensitive and specific screening tool for depression and has been applied successfully across a wide range of study fields [31]. In this study Cronbach's α was 0.88.

The mindful eating questionnaire, Italian version (MEQ-20) [32] is a 20-item short form of the MEQ [33] developed to measure mindful eating. It is formed by two subscales: Recognition when being hungry or full and Awareness of how food affects the senses. In this study, Cronbach's α was 0.76 for Recognition and 0.80 for Awareness.

Information was also collected on sex, age, educational level, and self-reported height and weight to calculate the BMI.

Data analyses

Skewness, kurtosis, mean and median values were preliminary calculated for each EOQ item. Descriptive statistics, including skewness and kurtosis, were also calculated for the summative score of all the psychological scales. At the item level, the EOQ was submitted to CFA to test for the original 6-item one-factor model [12] and an alternative one-factor model with only the five negative emotional items [20]. We used the robust unweighted least squares (RULS) method for ordinal-observed variables with polychoric correlations and asymptotic covariance matrices [34]. Goodness of fit was evaluated using the following criteria: ratio of the Satorra–Bentler scaled χ^2 to its degrees of freedom (S-B χ^2/df) ≤ 5 [35], standardized root mean-square residual (SRMR; cutoff < 0.08), non-normative (NNFI) and comparative (CFI) fit indices (cutoff ≥ 0.95) [36]. The Aikake Information Criterion (AIC) was also inspected, with lower values indicating a better fit [37]. Internal consistency was tested using McDonald's ω and ordinal α, and 4-week test–retest reliability was tested with Cohen's weighted Kappa coefficient to measure agreement in ordinal data with $K_w > 0.60$ good [38].

At the EOQ summative scale level, partial Spearman's rank correlations (r_s) with BES, WHO-5, and MEQ were calculated by BMI category controlling for the effect of sex, due to the non-normal distribution of the EOQ total score. Receiver Operating Characteristic (ROC) curve was calculated to estimate sensitivity and specificity of the EOQ score in relation to binge eating as measured with the BES using a cut-off > 17 [29].

For group differences we used ANOVA with Dunnett's T3 for multiple comparisons. To control for Type I error Welch's adjustment was used for independent groups with nonnormally distributed data and heterogeneous variances [39] (Levene statistic based on median was 4.17, $p = 0.001$).

Significance was set at $p \leq 0.05$. Effect size according to Cohen was r_s of 0.10 small, 0.30 medium, and 0.50 large; d of 0.20 small, 0.50 medium, and 0.80 large [40]. CFAs were performed with LISREL 8.80 and the other analyses with IBM-SPSS 25.

Results

Factor structure and reliability of the EOQ

Preliminary analyses showed that all EOQ items had frequency distributions that were positively skewed (values between 1.44 and 1.81) and leptokurtic (values between 1.60 and 2.77). Median values were between 0 and 1 showing floor effects. Skewness, kurtosis, and the mean and median values for each EOQ item are reported in Table 1. The model fit of the 6-item one-factor EOQ was nonoptimal (S-B $\chi^2_9 = 57.27$, $p < 0.001$; S-B $\chi^2/df = 6.36$; SRMR = 0.06; NNFI = 0.93; CFI = 0.96). The alternative 5-item one-factor model was tested, after removing the happiness item, which had a nonsignificant factor loading ($\lambda = 0.09$, $p = 0.11$) and small correlations with the other items ($r = -0.01$ to 0.27). The fit was good (S-B $\chi^2_5 = 20.62$, $p < 0.001$; S-B $\chi^2/df = 4.12$; SRMR = 0.03; NNFI = 0.97; CFI = 0.99), with all items loading highly on the latent factor ($\lambda = 0.67$–0.89, $p < 0.001$) and error variances in the 0.20–0.56 range (Fig. 1). The AIC-value (50.62) for the 5-item model was lower and thus better than that for the 6-item model (AIC = 93.27). The 5-item one-factor model had also a higher McDonald's coefficient ($\omega = 0.89$) compared to the 6-item one-factor model ($\omega = 0.84$).

The sum of the five items (EOQ-5) formed an index of negative emotional overeating (scores range 0–35), while the happiness item was dropped. Internal consistency was optimal also with the ordinal α coefficient ($\alpha = 0.88$), and test–retest reliability was good with $K_w = 0.71$.

In the EOQ-5, none of the participants returned a total score of zero, indicating that all of them had at least one episode of negative emotional overeating within the past 28 days. The frequency distribution of the EOQ-5 scale was moderately skewed and leptokurtic (Table 1).

Table 1 Descriptive statistics of responses at the EOQ by emotion and at the other scales ($n = 314$)

	Mean	SD	Median	Skewness	Kurtosis
EOQ Anxiety	1.28	1.4	1.00	1.44	1.66
EOQ Sadness	1.20	1.514	1.00	1.53	1.79
EOQ Loneliness	1.04	1.50	0.50	1.77	2.57
EOQ Tiredness	1.06	1.51	0.00	1.65	2.06
EOQ Anger	0.96	1.45	0.00	1.81	2.77
EOQ Happiness	1.24	1.5	1.00	1.46	1.60
EOQ-5	5.53	6.10	2.00	1.68	2.29
BES	10.16	9.14	7.00	1.02	0.53
MEQ-Recognition	25.17	5.46	25.00	−0.03	−0.06
MEQ-Awareness	30.57	6.27	30.00	−0.02	−0.03
WHO-5	11.80	5.45	12.00	0.06	−0.49

EOQ emotional overeating questionnaire, *EOQ-5* emotional overeating questionnaire based on five negative emotions, *BES* binge eating scale, *MEQ* mindful eating questionnaire, *WHO-5* WHO well-being index

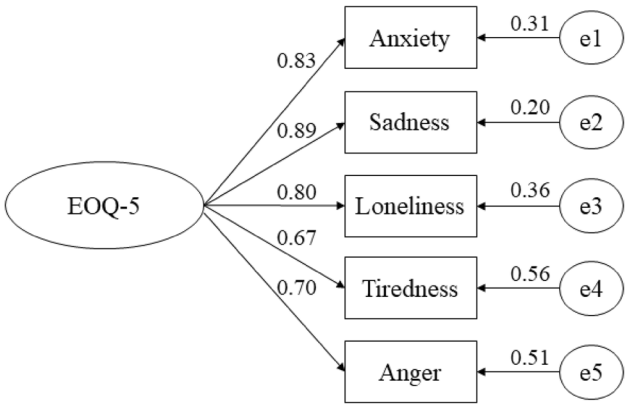

Fig. 1 Measurement model of EOQ-5 with standardized parameters

Correlations with other measures and sensitivity/specificity

Preliminary analyses showed that the BES, the WHO-5, and the MEQ scales were close to normally distributed (Table 1). As shown in Table 2, controlling for the effect of sex, EOQ-5 was associated with BES among all BMI groups with significant and strong positive correlations. A BES cut-off > 17 identified 76 (24.2%) participants who were at risk for BED and 238 (75.8%) who were not. The median value of the EOQ-5 scale in the whole sample was 2 and a value > 2 provided the best compromise between sensitivity (75%) and specificity (67%) in discriminating participants who were at risk for BED from those who were not, based on the BES cut-off.

EOQ-5 significantly and negatively correlated with WHO-5 with large, medium, or small effect sizes among participants with obesity, overweight and normal weight, respectively.

Correlations were significant, negative and strong with MEQ-Recognition among participants with obesity, and moderate among both overweight and normal-weight participants. Correlations with MEQ-Awareness were small to negligible among all BMI groups.

Associations with demographic characteristics and BMI

The EOQ-5 was not significantly associated with age ($r_s = 0.05$, $p = 0.38$) or education [Welch's $F(2145.79) = 0.59$, $p = 0.53$]. ANOVAs were run for sex differences separately among each BMI category and for BMI differences separately among women and men using post hoc tests when

Table 2 Spearman's partial (controlling for sex) correlations between EOQ-5 and the other measures according to BMI

	Total sample ($n=314$)	With obesity ($n=86$)	Overweight ($n=67$)	Normal weight ($n=161$)
	EOQ-5	EOQ-5	EOQ-5	EOQ-5
BES	0.52**	0.61**	0.44**	0.46**
MEQ Recognition	−0.44**	−0.51**	−0.33**	−0.34**
MEQ Awareness	−0.10	−0.22*	−0.02	−0.02
WHO-5	−0.31**	−0.49**	−0.28*	−0.37**

EOQ-5 emotional overeating questionnaire based on five negative emotions, *BMI* body mass index, *BES* binge eating scale, *MEQ* mindful eating questionnaire, *WHO-5* WHO well-being index

*$p<0.05$

**$p<0.001$

appropriate. Table 3 shows descriptive statistics and main effects of sex and BMI in the subgroups. Women scored higher than men among participants with obesity ($p=0.04$, Cohen's $d=0.46$) and with overweight ($p=0.02$, Cohen' $d=0.57$), with almost medium effect sizes, while no sex differences were found among participants of normal weight. Among women, those with obesity scored higher than women of normal weight ($p<0.001$, Cohen's $d=0.72$) with medium effect size, while women with overweight did not differ from both the other groups of women. Among men there were no differences in EOQ-5 according to BMI.

Discussion

In the present study we found the negative emotions of the 5-item EOQ to be a reliable single factor of emotional eating with adequate internal consistency and test–retest reliability. EOQ-5 scores were associated with higher binge eating, lower mental well-being, and lower mindful eating. A cut-off score of 2 identified individuals at risk for binge eating disorders with 75% sensitivity and 67% specificity. Negative emotional overeating was more frequent in women with obesity than women with normal weight and men with obesity.

The EOQ one-factor structure was consistent with a previous non-clinical female student sample [20], but unlike the original EOQ two-factor structure found in a clinical sample of patients with BED [12]. This may have been due to different emotional overeating patterns between patients with BED and non-clinical participants [41].

In our community sample, although participants who reported a diagnosis of eating disorder were excluded, overeating in response to negative emotions was associated with the habit of consuming a large amount of food and losing control over food intake, independent of sex and BMI. This result was in line with previous studies where emotional eating was associated with disordered eating behaviors such as binge eating [16, 21, 22, 42]. Emotional overeating might represent a risk eating behavior, as a cutoff score greater than two on the EOQ-5 scale identified people who might be at risk for BED in the present study.

In this study, negative emotional overeating was associated with poor perceived mental well-being and this association was the strongest among participants with obesity. This result was in line with previous studies of patients with BED [12, 24]. Finally, negative emotional overeating was associated with poor recognition of hunger and satiety. This might be explained by the difficulties in

Table 3 Comparisons of EOQ-5 scores by sex and BMI

	EOQ-5		
	Women	Men	Effect of sex
With obesity	8.69 (7.80)	5.28 (5.70)	$F(1.35.84)=4.32$*
Overweight	6.03 (6.54)	2.97 (3.55)	$F(1.53.39)=5.80$*
Normal weight	4.36 (4.79)	5.50 (6.04)	$F(1.48.37)=1.09$
Effect of BMI	$F(2.77.16)=8.93$**	$F(2.41.06)=2.84$	

Values are mean (standard deviation). Participants were $n=86$ (68 women and 18 men) with obesity. $n=67$ (35 women and 32 men) overweight. and $n=161$ (125 women and 36 men) normal weight

F value refers to Welch's test

EOQ-5 emotional overeating questionnaire based on five negative emotions, *BMI* body mass index

*$p<0.05$

**$p\leq0.001$

emotion regulation that characterize people who overeat in response to emotional cues instead of eating in response to hunger sensations [24, 27].

The EOQ-5 was not associated with age or education as has been reported in previous studies [7, 18]. Also consistent with non-clinical samples was that we found women to report more frequent emotional overeating behavior than men [9, 15, 18, 24]. In the literature, negative emotional eating was generally associated with higher BMI [5, 9, 15], while in our study EO was associated with higher BMI only among women.

In studies of patients with BED using the EOQ [12, 43], neither sex differences nor associations with BMI were found. This might indicate that within BED, other mechanisms than emotional overeating may play a role in weight regulation. However, in those studies, the constrained BMI range (all participants had a BMI ≥ 25) may have limited the observation of different emotional overeating frequencies according to BMI.

The present study has several limitations. First, it used a cross-sectional design that did not allow causal inferences. Second, it used a sample of convenience which limited the generalizability of findings. Indeed, women and more educated people were over-represented, as they are usually more likely to participate in surveys [44]. Third, BMI relied on self-reported height and weight and a large body of literature demonstrates that people systematically overestimate their height and underestimate their weight [e.g., 45, 46], although high correlations were also found between self-reported weight and height and objective measurements [46]. Finally, since the single item referring to happiness was discarded, future studies should develop a brief multi-item measure of the frequency of positive emotional overeating and investigate its relationship with the EOQ-5.

In conclusion, the results of our psychometric analyses support the use of the EOQ-5 as a brief, valid and reliable tool to measure the frequency of overeating behavior in response to negative emotions in Italian non-clinical adults. The findings of this study suggest that, in an adult community sample, emotional overeating in response to negative or positive emotions, as measured by the original EOQ [12], refers to two unrelated dimensions. Although the present study needs replication, it may help gain some insights into emotional overeating behavior, which might be a risk factor for overweight, obesity, BED, and reduced mental wellbeing.

In clinical contexts, the EOQ-5 could be used to test for improvements of eating behavior after treatments since emotional overeating is a learned behavior that can be modified with practice [3]. The associations found in this study between emotional overeating and mindful eating suggest that mindfulness-based eating interventions could effectively apply to emotional eaters, as it was found in 63% of the studies reviewed by O'Reilly et al. [47] as well as in a more recent study [48].

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Data availability The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the University of Bologna Bioethical Committee, which approved the study protocol, and with the 1964 Helsinki declaration and its later amendments.

Informed consent Informed consent was obtained from all participants included in the study.

References

1. van Strien T, Ouwens MA (2007) Effects of distress, alexithymia and impulsivity on eating. Eat Behav 8:251–257. https://doi.org/10.1016/j.eatbeh.2006.06.004
2. Sultson H, Kukk K, Akkermann K (2017) Positive and negative emotional eating have different associations with overeating and binge eating: construction and validation of the positive-negative emotional eating scale. Appetite 116:423–430. https://doi.org/10.1016/j.appet.2017.05.035
3. Frayn M, Knäuper B (2018) Emotional eating and weight in adults: a review. Curr Psychol 37:924–933. https://doi.org/10.1007/s12144-017-9577-9
4. Lindeman M, Stark K (2001) Emotional eating and eating disorder psychopathology. Eat Disord 9:251–259. https://doi.org/10.1080/10640260127552
5. Konttinen H, Männistö S, Sarlio-Lähteenkorva S, Silventoinen K, Haukkala A (2010) Emotional eating, depressive symptoms and self-reported food consumption. A population-based study. Appetite 54:473–479. https://doi.org/10.1016/j.appet.2010.01.014
6. Poínhos R, Oliveira BM, Correia F (2018) Psychopathological correlates of eating behavior among Portuguese undergraduate students. Nutrition 48:33–39. https://doi.org/10.1016/j.nut.2017.10.009
7. Bourdier L, Orri M, Carre A et al (2018) Are emotionally driven and addictive-like eating behaviors the missing links between psychological distress and greater body weight? Appetite 120:536–546. https://doi.org/10.1016/j.appet.2017.10.013
8. Braden A, Musher-Eizenman D, Watford T, Emley E (2018) Eating when depressed, anxious, bored, or happy: are emotional eating types associated with unique psychological and physical health correlates? Appetite 125:410–417. https://doi.org/10.1016/j.appet.2018.02.022
9. Gibson EL (2012) The psychobiology of comfort eating: implications for neuropharmacological interventions. Behav Pharmacol 23:442–460. https://doi.org/10.1097/FBP.0b013e328357bd4e
10. Williams EP, Mesidor M, Winters K, Dubbert PM, Wyatt SB (2015) Overweight and obesity: prevalence, consequences, and

causes of a growing public health problem. Curr Obes Rep 4:363–370. https://doi.org/10.1097/00000441-200604000-00002
11. Grace C (2011) A review of one-to-one dietetic obesity management in adults. J Hum Nutr Diet 24:13–22. https://doi.org/10.1111/j.1365-277X.2010.01137.x
12. Masheb RM, Grilo CM (2006) Emotional overeating and its associations with eating disorder psychopathology among overweight patients with binge eating disorder. Int J Eat Disord 39:141–146. https://doi.org/10.1002/eat.20221
13. Celio AA, Wilfley DE, Crow SJ, Mitchell J, Walsh BT (2004) A comparison of the binge eating scale, questionnaire for eating and weight patterns-revised, and eating disorder examination questionnaire with instructions with the eating disorder examination in the assessment of binge eating disorder and its symptoms. Int J Eat Disord 36:434–444. https://doi.org/10.1002/eat.20057
14. Fairburn CG, Cooper Z, O'Connor M (2014) The eating disorder examination, 17th ed. The centre for research on eating disorders at Oxford http://www.credo-oxford.com/pdfs/EDE_17.0D.pdf. Accessed 4 April 2019
15. van Strien T, Frijters JE, Bergers GP, Defares PB (1986) The dutch eating behavior questionnaire (DEBQ) for assessment of restrained, emotional, and external eating behavior. Int J Eat Disord 5:295–315. https://doi.org/10.1002/1098-108X(198602)5:2%3c295:AID-EAT2260050209%3e3.0.CO;2-T
16. Arnow B, Kenardy J, Agras WS (1995) The emotional eating scale: the development of a measure to assess coping with negative affect by eating. Int J Eat Disord 18:79–90. https://doi.org/10.1002/1098-108X(199507)18:1%3c79:AID-EAT2260180109%3e3.0.CO;2-V
17. Geliebter A, Aversa A (2003) Emotional eating in overweight, normal weight, and underweight individuals. Eat Behav 3:341–347. https://doi.org/10.1016/S1471-0153(02)00100-9
18. Meule A, Reichenberger J, Blechert J (2018) Development and preliminary validation of the salzburg emotional eating scale. Front Psychol 9:88. https://doi.org/10.1016/j.appet.2017.10.003
19. Weineland S, Alfonsson S, Dahl J, Ghaderi A (2012) Development and validation of a new questionnaire measuring eating disordered behaviours post bariatric surgery. Clin Obesity 2:160–167. https://doi.org/10.1111/cob.12005
20. Constant A, Gautier Y, Coquery N et al (2018) Emotional overeating is common and negatively associated with alcohol use in normal-weight female university students. Appetite 129:186–191. https://doi.org/10.1016/j.appet.2018.07.012
21. Wiedemann AA, Ivezaj V, Barnes RD (2018) Characterizing emotional overeating among patients with and without binge-eating disorder in primary care. Gen Hosp Psychiatry 55:38–43. https://doi.org/10.1016/j.genhosppsych.2018.09.003
22. Hrabosky JI, White MA, Masheb RM et al (2008) Psychometric evaluation of the eating disorder examination-questionnaire for bariatric surgery candidates. Obesity 16:763–769. https://doi.org/10.1038/oby.2008.3
23. Jones M, Grilo CM, Masheb RM, White MA (2010) Psychological and behavioral correlates of excess weight: misperception of obese status among persons with Class II obesity. Int J Eat Disord 43:628–632. https://doi.org/10.1002/eat.20746
24. Gianini LM, White MA, Masheb RM (2013) Eating pathology, emotion regulation, and emotional overeating in obese adults with binge eating disorder. Eat Behav 14:309–313. https://doi.org/10.1016/j.eatbeh.2013.05.008
25. Dorflinger LM, Masheb RM (2018) PTSD is associated with emotional eating among veterans seeking treatment for overweight/obesity. Eat Behav 31:8–11. https://doi.org/10.1016/j.beh.2018.07.005
26. Brunault P, Courtois R, Gearhardt AN et al (2017) Validation of the French version of the DSM-5 Yale food addiction scale in a nonclinical sample. Canadian J Psychiatry 62:199–210. https://doi.org/10.1177/0706743716673320
27. Bruch H (1961) Social and emotional factors in diet changes. J Am Dent Assoc 63:461–465. https://doi.org/10.14219/jada.archive.1961.0243
28. Ng M, Fleming T, Robinson M et al (2014) Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 384:766–781. https://doi.org/10.1016/S0140-6736(14)60460-8
29. Gormally J, Black S, Daston S, Rardin D (1982) The assessment of binge eating severity among obese persons. Addict Behav 7:47–55. https://doi.org/10.1016/0306-4603(82)90024-7
30. Imperatori C, Innamorati M, Lamis DA et al (2016) Factor structure of the Binge Eating Scale in a large sample of obese and overweight patients attending low energy diet therapy. Eur Eat Disorders Rev 24:174–178. https://doi.org/10.1002/erv.2384
31. Topp CW, Østergaard SD, Søndergaard S, Bech P (2015) The WHO-5 well-being index: a systematic review of the literature. Psychother Psychosom 84:167–176. https://doi.org/10.1159/000376585
32. Clementi C, Casu G, Gremigni P (2017) An abbreviated version of the Mindful Eating Questionnaire. J Nutr Educ Behav 49:352–356. https://doi.org/10.1016/j.jneb.2017.01.016
33. Framson C, Kristal AR, Schenk JM et al (2009) Development and validation of the mindful eating questionnaire. J Am Diet Assoc 109:1439–1444. https://doi.org/10.1016/j.jada.2009.05.006
34. Morata-Ramírez MA, Holgado-Tello FP (2013) Construct validity of Likert scales through confirmatory factor analysis: a simulation study comparing different methods of estimation based on Pearson and polychoric correlations. Int J Soc Sci Stud 1:54–61. https://doi.org/10.11114/ijsss.v1i1.27
35. Wheaton B, Muthen B, Alwin DF, Summers GF (1977) Assessing reliability and stability in panel models. Sociol Methodol 8:84–136. https://doi.org/10.2307/270754
36. Hu L, Bentler PM (1999) Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. Struct Equ Modeling 6:1–55. https://doi.org/10.1080/10705519909540118
37. Kline R (2011) Principles and practice of structural equation modeling, 3rd edn. Guilford, New York
38. Altman DG (1991) Practical statistics for medical research, 1st edn. Chapman & Hall, London
39. Cribbie RA, Wilcox RR, Bewell C, Keselman HJ (2007) Tests for treatment group equality when data are nonnormal and heteroscedastic. J Mod Appl Stat Methods 6:117–132. https://doi.org/10.22237/jmasm/1177992660
40. Cohen J (1992) A power primer. Psychol Bull 112:155–159 **(PMID:19565683)**
41. Nolan LJ, Halperin LB, Geliebter A (2010) Emotional appetite questionnaire. construct validity and relationship with BMI. Appetite 54:314–319. https://doi.org/10.1016/j.appet.2009.12.004
42. Duarte C, Pinto-Gouveia J (2015) Returning to emotional eating: the emotional eating scale psychometric properties and associations with body image flexibility and binge eating. Eat Weight Disord 20:497–504. https://doi.org/10.1007/s40519-015-0186-z
43. Udo T, McKee SA, White MA et al (2013) Sex differences in biopsychosocial correlates of binge eating disorder: a study of treatment-seeking obese adults in primary care setting. Gen Hosp Psychiatry 35:587–591. https://doi.org/10.1016/j.genhosppsych.2013.07.010
44. Angus VC, Entwistle VA, Emslie MJ, Walker KA, Andrew JE (2003) The requirement for prior consent to participate on survey response rates: a population-based survey in Grampian. BMC Health Serv Res 3:21. https://doi.org/10.1186/1472-6963-3-21

45. Niedhammer I, Bugel I, Bonenfant S, Goldberg M, Leclerc A (2000) Validity of self-reported weight and height in the French GAZEL cohort. Int J Obesity 24:1111–1118. https://doi.org/10.1038/sj.ijo.0801375
46. Kuczmarski MF, Kuczmarski RJ, Najjar M (2001) Effects of age on validity of self-reported height, weight, and body mass index: findings from the Third National Health and Nutrition Examination Survey, 1988–1994. J Am Diet Assoc 101:28–34. https://doi.org/10.1016/S0002-8223(01)00008-6
47. O'Reilly GA, Cook L, Spruijt-Metz D, Black DS (2014) Mindfulness-based interventions for obesity-related eating behaviours: a literature review. Obes Rev 15:453–461. https://doi.org/10.1111/obr.12156
48. Lattimore P (2019) Mindfulness-based emotional eating awareness training: taking the emotional out of eating. Eat Weight Disord St. https://doi.org/10.1007/s40519-019-00667-y

INVITED REVIEW

Objective Diagnosis of Circadian Rhythm Disorders

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Summary: Circadian sleep–wake disorders are common. Because they represent conflict between the timing of the patient's endogenous rhythms and desired timing of sleep, the presenting complaints may include both difficulty of sleep initiation or maintenance and undesired or unplanned daytime or early evening sleepiness. Therefore, circadian disorders may be misdiagnosed as either a primary insomnia or a hypersomnia disorder, depending on which complaint is more troublesome for the patient. Objective information about sleep and wake patterns over long periods is crucial for accurate diagnosis. Actigraphy provides long-term information about the rest/activity pattern about an individual. However, caution should be applied in interpretation of the results because the information provided only includes information of movements, and activity is only an indirect circadian phase marker. Timing of light and melatonin therapy is critical for successful treatment of circadian rhythm disorders. Therefore, results of actigraphy are useful and should be used in conjunction with additional measurements, including 24 hours sleep–wake history, sleep log, and melatonin measurements.

Key Words: Circadian rhythm disorders, Actigraphy.

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Circadian rhythms are among the two key processes that regulate the timing and continuity of sleep and wakefulness. Directed by the suprachiasmatic nucleus, the circadian system influences a wide variety of functions, including metabolism, hormone release, sleep–wake propensity, and activity.

CIRCADIAN RHYTHM DISORDERS

Circadian rhythm sleep–wake disorders (CRSWDs) are characterized by a misalignment between the desired timing of sleep and the ability to fall asleep and remain asleep. Although circadian rhythm disorders usually manifest as extremely early or late sleep times, they may also frequently present as insomnia and/or excessive daytime sleepiness. When a patient is attempting to sleep at a conventional clock time instead of aligning sleep according to his or her underlying circadian rhythm of sleep–wake propensity, they would experience difficulty initiating or maintaining sleep. Conversely, when that patient tries to stay awake and remain alert during the endogenous sleep phase of their circadian cycle, he or she will experience excessive daytime sleepiness, as commonly seen with night-shift workers or patients with delayed sleep–wake phase disorder. Regardless of type, circadian rhythm sleep disorders can cause a major impairment of work, school, and social activities, lead to disruptions of social and family life, and increase the risk of developing many other medical complaints and disorders.

Although prevalence in the population remains unknown,[1] some estimates hold that up to 3% of the adult population suffers from a CRSWD,[2] with a higher prevalence (7%–16%) in adolescents and young adults.[1]

Despite their high prevalence, CRSWDs are commonly misdiagnosed as a primary insomnia disorder or, in some situations, a hypersomnia disorder because of insufficient history taking. In these cases, hypnotic treatments for insomnia or wake promoting treatments for hypersomnia symptoms are often unsuccessful and expensive and sometimes harmful or lead to delay in accurate diagnosis and effective treatment when there is an underlying CRSWDed. The diagnosis of CRSWD is based on a careful sleep history. Although these disorders are presumed to their name implies that they result from an abnormality of the circadian timing system, current diagnostic criteria do not require assessment of circadian rhythms in the diagnosis of a CRSWD. However, measurable and/or objective evidence is needed to better assess the sleep–wake pattern to support an accurate diagnosis and tailoring of the timing of administration of appropriate light therapy and melatonin or other medication or behavioral treatment options.

Currently, multiple instruments including sleep logs and sleep diaries are used in the diagnostic process and standardized questionnaires about chronotype (Morningness-Eveningness Questionnaires, Munich Chronotype Questionnaire).[3,4] Plasma melatonin and salivary dim light melatonin onset (DLMO) measurements and core body temperature are used in research applications and aid diagnostic precision of CRSWDs[5,6] but have remained of limited utility in usual clinical practice settings because of their labor intensiveness, expense, and special resources and settings that are required for accurate measurement, so these are typically not used for routine clinic use, although home sampling of DLMO may be considered (see further discussion in the Circadian Rhythm Disorder Assessment—DLMO section). Urinary 6-sulfatoxymelatonin may be useful in very specific clinical situations such as non–24-hour sleep–wake disorder.[7] Polysomnography, although a gold standard for assessment of sleep duration and quality, does not provide information about circadian phase and is not routinely used with CRSWD patients unless a comorbid sleep disorder is suspected. Actigraphy is an objective measure that is useful in clinical practice for assessment of multiday sleep–wake patterns to aid diagnosis of CRSWDs.

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ACTIGRAPHY

Actigraphy is helpful for the diagnosis and management of insomnia, circadian rhythm disorders, and excessive daytime sleepiness because it provides objective data regarding longitudinal sleep–wake patterns in the patient's usual home and work environment. Actigraphy, in addition to a sleep log, is particularly helpful for the evaluation and treatment of CRSWDs.[1,8] An actigraph is a small, lightweight wrist (or ankle)-worn computerized accelerometer with the ability to measure rest–activity patterns continuously over long periods (several days or as long as weeks to months).[10,11] After at least 7 days of data collection (to include both weekdays and a weekend), data are downloaded to a computer where off-line analysis is performed.

Minimal actigraph technical requirements include: a triaxial accelerometer, the ability to record data in 30 seconds or 1-minute epochs, battery power to record data, the ability to store at least 7 days of data, and support for both device and software. Additional recommended features include a waterproof case, an ambient light sensor, an event marker, a nonvolatile memory, a battery that can store data for a minimum of 2 weeks, and a small, comfortable profile.[9] Although actigraphs provide objective data about rest–activity patterns, supplemental information from a sleep log or diary recording the patient's habitual, bed and wake times and any awakenings and their durations, a light sensor, as well as a sensor to light spectrum, and an event marker can improve the usefulness and accuracy of the activity data. Data collected over longer periods can be useful in the diagnosis of non–24-hour or irregular sleep–wake rhythm disorder.[11] Most activity monitors come with automated software packages that score the data as sleep or wake, and the estimates of sleep and wake are typically improved by manual overscoring, referencing the additional data provided by sleep logs and light detection patterns to correctly interpret the actigraphy data. Scoring algorithms differ between manufacturers and can produce different sleep–wake scoring on the same data file. Some are optimized for specific patient populations (adult vs. pediatric).

The evaluation of the sensitivity, specificity, and agreement of actigraphy compared with polysomnography is related to the device itself, the software (algorithm) used to analyze the data, and often settings within the software that can be adjusted by the user. Actigraphy tends to overestimate sleep and underestimate wake time and the accuracy declines as sleep quality declines.[11–14]

Various actigraphy devices and software algorithms have been compared in validation studies to polysomnography with high levels of sensitivity and specificity for rest/activity patterns reported in various patient populations, in terms of rest/activity patterns.[11,15–17] However, it is important to remember that the diagnosis of CRSWDs circadian rhythm disorders does not routinely include polysomnography, which classically in the United States captures a single night of sleep, and thus does not provide information about long-term sleep–wake patterns that are necessary to observe for accurate diagnosis of CRSWDs.[28]

CIRCADIAN RHYTHM DISORDER ASSESSMENT—DLMO

To accurately determine the timing of the circadian system in a patient with a suspected CRSWD, an at-home or clinic assessment of their dim light salivary melatonin onset may be useful.[19–21] Melatonin is a hormone produced by the pineal gland, and production of melatonin is suppressed by light. Melatonin levels are typically undetectable during the daytime hours and begin to rise in the evening, 1 to 2 hours before the individual's usual bedtime. The levels reach a peak in the middle of the usual sleep episode and then decline throughout the latter part of the night, reaching undetectable levels again the next day. Because of suppression by light, melatonin levels must be measured in dim light conditions (ideally less than 20 lux). DMLO measurements are traditionally performed in a laboratory over several days but can also be performed by the patient in their home.[21] For CRSWD patients, a sleep log should be used to determine usual bedtime. The DLMO assessment process should begin 5 to 7 hours before usual bedtime (average time from the past week), with the patient maintained in a dim light environment throughout the study, including for 1 h before the first sample is taken and ensuing hourly saliva samples that are collected every hour from the start until at least 1 hour after usual bedtime. Each sample is frozen after collection, and the next day, the samples are transferred to an assay facility where a commercial ELISA or RIA kit is used to determine the melatonin level in each sample. Linear interpolation between the resulting assay values is used to determine the time at which melatonin values rise above a set threshold (typically 3 pg/mL; 22), the dim light salivary melatonin onset. The timing of the dim light salivary melatonin onset in the patient can then be compared with their usual sleep onset time, and with normative data, to guide diagnosis and treatment.

TIMING AND EFFECT OF LIGHT

The period (cycle length) of the circadian system is close to (although not exactly) 24 hours. In healthy sighted humans, the endogenous period/cycle length averages 24.2 hours, ranging from about 23.5 to 24.5 hours.[23,24] The endogenous circadian clock must be regularly reset to remain synchronized to the 24-hour clock time in the environment, a process called entrainment. Light is the most powerful environmental influence on the human circadian timing system, and it is through regular light–dark exposure that the circadian timing system of humans is synchronized on a daily basis and is reset when traveling across time zones. Many features of the light to which we are exposed determine the entrainment or resetting process, including the spectral composition, intensity, duration, timing, and overall pattern (including timing and duration of darkness).[25] One feature of the circadian response to light is that it is phase dependent. It means that the same light stimulus when applied at different phases (times of day) can produce different responses. Light in the late afternoon or early evening (i.e., 4–7 PM) produces phase delay shifts (shifts to a later hour), whereas light exposure in the late biologic night or early morning biologic day produces phase advance shifts (shifts earlier), as determined by relationship of light exposure to the body core temperature nadir point in the early morning hours. Light exposure in the middle of the biologic day typically produces only minimal changes in phase. These responses can be summarized in a phase response

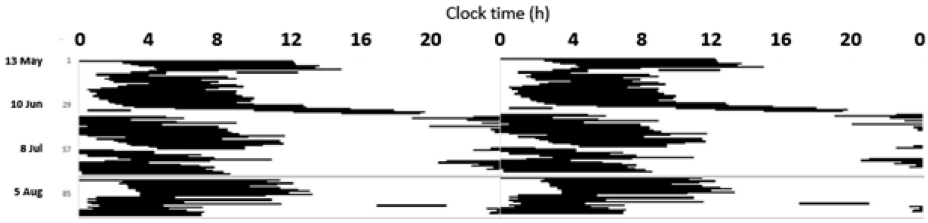

FIG. 1. Actigraphy data of case 1.

curve.[26,27] From our understanding that most humans have a circadian period longer than 24 hours, most people need their overall daily light exposure to produce a slight phase advance (on average 0.2 hours, or 12 minutes) to remain entrained. To achieve entrainment, most people need to get more morning light exposure than evening light exposure. Being able to correctly identify the timing of the circadian phase is critical for effective light therapy for CRSWDs. Mistiming the light by even a few hours can result in either no effect on phase or a phase shift in the wrong direction, which can exacerbate misentrainment and resultant symptoms of insomnia or hypersomnia.

CASES

Case 1

A 27-year-old nonsighted man presented to clinic with a complaint of inability to control a shifting sleep schedule. The patient lost his sight 7 years earlier because of retinitis pigmentosa but was otherwise in good health. After vision loss, his bedtime continually shifted 15 to 30 minutes later each night with a corresponding drift in his awakening time. After 3 to 4 weeks, he would reset to an earlier bedtime and the shifting would begin again. Four months of actigraphy data are shown below in the form of a double raster plot, which compresses the activity data over long periods. Activity, shown by the dark bars, and sleep time, shown by the white space, shift gradually later until they reset after approximately 2 weeks (Fig. 1). This pattern is consistent with non–24-hour sleep–wake phase disorder.

Actigraphy is more accurate than sleep logs, particularly for long periods. Although melatonin is more sensitive than actigraphy, in this case, multiple samples would be required because of the shifting circadian phase. History and actigraphy confirmed diagnosis of non–24-hour sleep–wake disorder.

Case 2

A 44-year-old woman reported lifelong difficulty awakening and performing any cognitive tasks in the morning and preferred performing work-related tasks at night, and it was most common for her to go to her office late in the evening and work overnight until 5 to 6 am.

The top graph shows the daily activity pattern over 7 days (Fig. 2). A cumulative graph of the activity pattern for this patient is shown below (Fig. 3). As this patient's activity pattern was fairly consistent over the course of the recording, this combined graph allows easier visualization of the activity pattern, with minimal activity between 7 AM and 2:30 PM Because DLMO usually precedes typical bedtime by 1 to 2 hours, based on this activity pattern, one might expect that the patient's DLMO is close to 4 to 5 AM. However, the following melatonin profile was obtained:

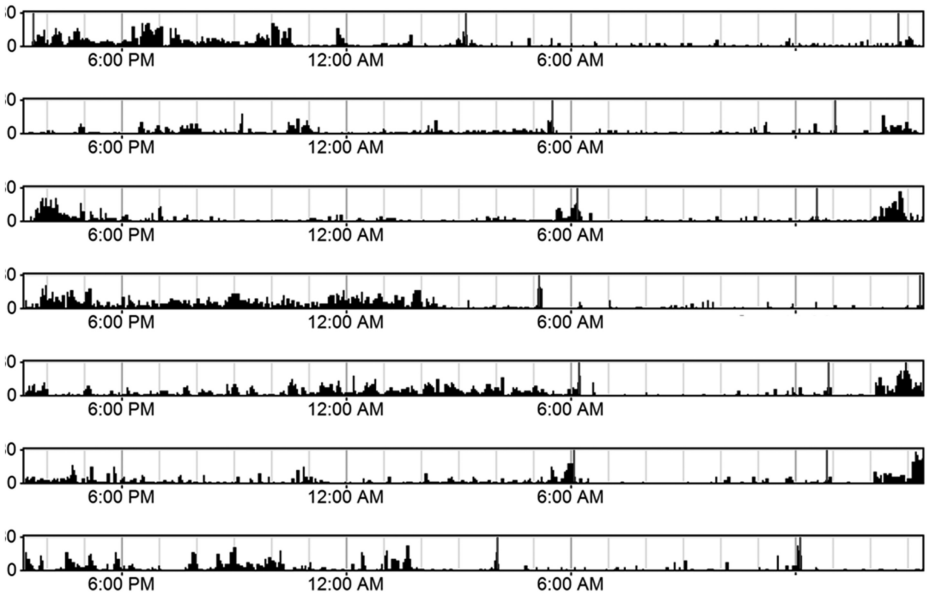

FIG. 2. Melatonin levels (pg\mL) of case 2 by time.

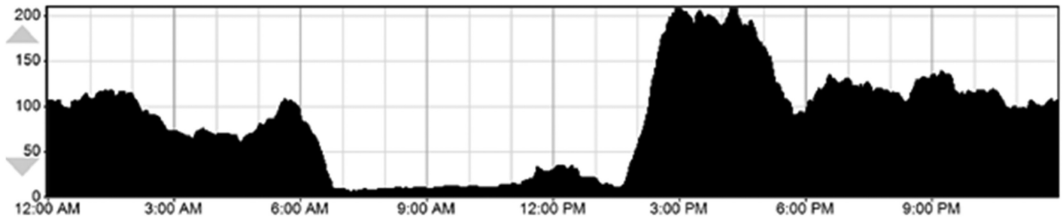

FIG. 3. Daily activity patterns of case 2 (cumulative graph).

As seen, dim light salivary melatonin onset was earlier at 12:30 AM (Fig. 4). For treatment, melatonin 0.5 mg was used to advance this patient's sleep phase, taken at 11:30 PM, and maintaining light levels low after that. Based on the patient's sleep log and actigraphy data, light therapy given at 8 AM, the patient's desired rise time might fall on the part of the phase response curve that would produce phase delay. However, the melatonin measurements provide more precise information, and thus, light therapy at rise time may be beneficial to help advance this patient's sleep phase.

Case 3

An 82-year-old man was reported by his family to have a 5-year history of short-term memory loss, paralleled by erratic sleep habits. Before his memory loss began, he had a regular sleep schedule with a usual 10 PM bedtime and 6 AM awakening time. However, for the last 2 to 3 years, he would become agitated in the evenings, and he would often be unable to initiate sleep until 1 AM and would awaken by 4 or 5 AM, frequently noted to doze off and on through the daytime hours, and he would also take two or three naps, each lasting 1 to 2 hours in duration throughout the afternoon and early evening. His actigraphy is shown below.

Actigraphy shows a highly chaotic sleep–wake schedule, without an average consistent bed or rise time, several short bouts of inactivity and probable sleep, with intervening brief periods of movement and wakefulness (Fig. 5).

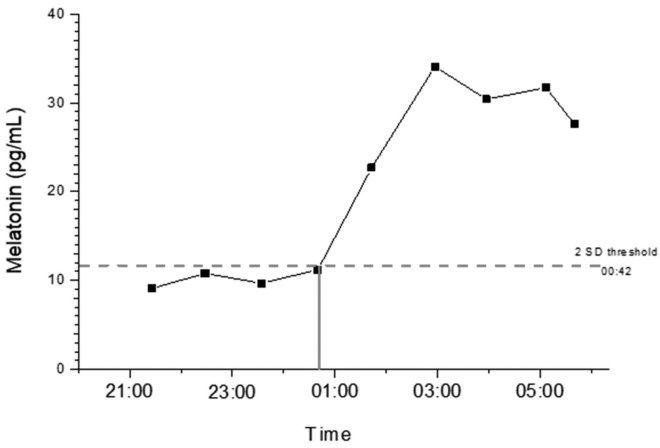

FIG. 4. DLSMO of case 2. DLSMO, dim light salivary melatonin onset.

These actigraphy findings support the clinical history and diagnosis of an irregular sleep–wake rhythm disorder. This disorder is most common in elderly individuals with a neurodegenerative disorder and likely arise from degeneration of the suprachiasmatic nucleus, the brain's master clock that coordinates circadian rhythmicity and a consolidated sleep–wake schedule. Less frequently, this disorder may also be seen in children or adolescents with an underlying neurodevelopmental disorder.

SUMMARY AND CONCLUSIONS

Actigraphy provides an objective, relatively inexpensive, and helpful information about long-term patterns of activity and rest, which can be helpful in evaluating patients with circadian rhythm sleep–wake disorders. Actigraphy provides data on sleep–wake patterns and is not a specific circadian phase marker, so any information provided by actigraphy should be reviewed in the context of each individual patient's clinical scenario, sleep log, and if possible, results of DLMO profile for optimal guidance of therapy.

Appendix

Section 1: Diagnostic Criteria for Delayed Sleep–Wake Phase Disorder

A. There is a significant delay in the phase of the major sleep episode in relation to the desired or required sleep time and wake-up time, as evidenced by a chronic or recurrent complaint by the patient or a caregiver of the inability to fall asleep and difficulty awakening at a desired or required clock time.
B. The symptoms are present for at least 3 months.
C. When patients are allowed to choose their ad libitum schedule, they will exhibit improved sleep quality and duration for age and maintain a delayed phase of the 24-hour sleep–wake pattern.
D. Sleep log and, whenever possible, actigraphy monitoring for at least 7 days (preferably 14 days) demonstrate a delay in the timing of the habitual sleep period. Both work/school days and free days must be included within this monitoring.
E. The sleep disturbance is not better explained by another current sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder.

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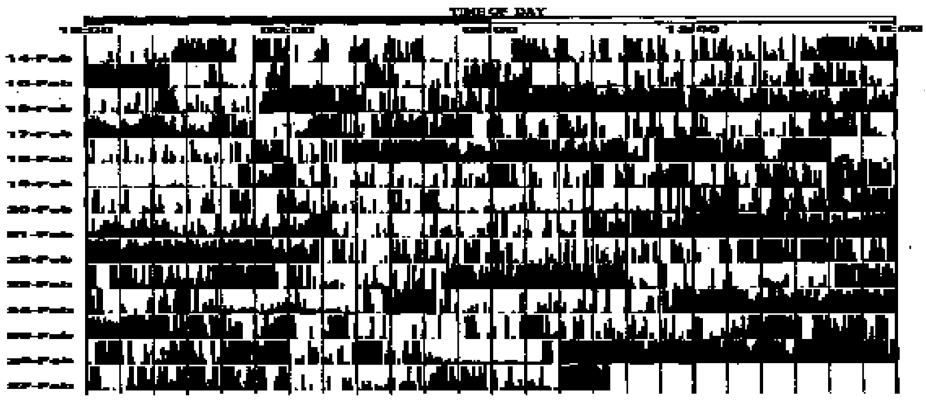

FIG. 5. Actigraphy of case 3.

Section 2: Diagnostic Criteria for Advanced Sleep–Wake Phase Disorder

A. There is an advance (early timing) in the phase of the major sleep episode in relation to the desired or required sleep time and wake-up time, as evidenced by a chronic or recurrent complaint of difficulty staying awake until the required or desired conventional bedtime, together with an inability to remain asleep until the required or desired time for awakening.
B. Symptoms are present for at least 3 months.
C. When patients are allowed to sleep in accordance with their internal biologic clock, sleep quality and duration are improved with a consistent but advanced timing of the major sleep episode.
D. Sleep log and, whenever possible, actigraphy monitoring for at least 7 days (preferably 14 days) demonstrate a stable advance in the timing of the habitual sleep period. Both work/school days and free days must be included within this monitoring.
E. The sleep disturbance is not better explained by another current sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder.

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Section 3: Diagnostic Criteria for Irregular Sleep–Wake Rhythm Disorder

A. The patient or caregiver reports a chronic or recurrent pattern of irregular sleep and wake episodes throughout the 24-hour period, characterized by symptoms of insomnia during the scheduled sleep period (usually at night), excessive sleepiness (napping) during the day, or both.
B. Symptoms are present for at least 3 months.
C. Sleep log and, whenever possible, actigraphy monitoring for at least 7 days (preferably 14 days) demonstrate no major sleep period and multiple irregular sleep bouts with at least three brief sleep periods during a 24-hour period.
D. The sleep disturbance is not better explained by another current sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder.

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Section 4: Diagnostic Criteria for Non–24-Hour Sleep–Wake Rhythm Disorder

A. There is a history of insomnia, excessive daytime sleepiness, or both, which alternate with asymptomatic episodes, because of misalignment between the 24-hour light–dark cycle and the nonentrained endogenous circadian rhythm of sleep–wake propensity.
B. Symptoms persist over the course of at least three months.
C. Daily sleep logs and actigraphy for at least 14 days, preferably longer for blind persons, demonstrate a pattern of sleep and wake times that typically delay each day, with a circadian period that is usually longer than 24 hours.
D. The sleep disturbance is not better explained by another current sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder.

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REFERENCES

1. American Academy of Sleep Medicine. International classification of sleep disorders. 3rd ed. Darien, IL: American Academy of Sleep Medicine, 2014.
2. Schrader H, Bovim G, Sand T. The prevalence of delayed and advanced sleep phase syndromes. J Sleep Res 1993;2:51–55.
3. Horne JA, Östberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol 1976;4:97–110.
4. Allebrandt KV, Roenneberg T. The search for circadian clock components in humans: new perspectives for association studies. Braz J Med Biol Res 2008;41:716–721.
5. Pavlova M. Circadian rhythm sleep-wake disorders. Contin Lifelong Learn Neurol 2017;23(, SleepNeurology):1051–1063.
6. Pandi-Perumal SR, Smits M, Spence W, et al. Dim light melatonin onset (DLMO): a toll for the analysis of the circadian phase in human sleep and chronobiological disorders. Prog Neuropsychopharmacol Biol Psychiatry 2007:31:1–11.

7. Flynn-Evans EE, Tabandeh H, Skene DJ, Lockley SW. Circadian rhythm disorders and melatonin production in 127 blind women with and without light perception. J Biol Rhythms 2014;29:215–224.
8. Smith MT, McCrae CS, Cheung J, et al. Use of actigraphy for the evaluation of sleep disorders. J Clin Sleep Med 2018;14:1231–1237.
9. The Society of behavioral sleep medicine guide to actigraphy monitoring: clinical and research application. Behav Sleep Med 2015;13:S1–S3.
10. Kushida CA, Chang A, Gadkary C, Guilleminault C, Carrillo O, Dement WC. Comparison of actigraphic, polysomnographic, and subjective assessment of sleep parameters in sleep-disordered patients. Sleep Med 2001;2 :389–396.
11. Ancoli-Israel S, Cole R, Alessi C, Chambers M, Moorcroft W, Pollak CP. The role of actigraphy in the study of sleep and circadian rhythms. Sleep 2003;26:342–392.
12. Lichstein KL1, Stone KC, Donaldson J, et al. Actigraphy validation with insomnia. Sleep 2006;29:232–239.).
13. Hauri PJ, Wisbey J. Actigraphy and insomnia: a closer look. Part 2. Sleep 1994;17:408–410.
14. Sadeh A, Acebo C. The role of actigraphy in sleep medicine. Sleep Med Rev 2002;6:113–124.
15. Morgenthaler T, Alessi C, Friedman L, et al; Standards of Practice Committee; American Academy of Sleep Medicine. Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: an update for 2007. Sleep 2007;30:519–529.
16. Marino M, Li Y, Rueschman MN, et al. Measuring sleep: accuracy, sensitivity, and specificity of wrist actigraphy compared to polysomnography. Sleep 2013;36:1747–1755.
17. Pollak CP1, Tryon WW, Nagaraja H, Dzwonczyk R. How accurately does wrist actigraphy identify state of sleep and wakefulness? Sleep 2001;24:957–965.
18. Youngstedt SD, Kripke DF, Elliott JA, Klauber MR. Circadian abnormalities in older adults. J Pineal Res 2001;31:264–272.
19. Kantermann T, Sung H, Burgess HJ. Comparing the morningness-eveningness questionnaire and Munich ChronoType questionnaire to the dim light melatonin onset. J Biol Rhythms 2015;30:449–453.
20. Pullman RE, Roepke SE, Duffy JF. Laboratory validation of an in-home method for assessing circadian phase using dim light melatonin onset (DLMO). Sleep Med 2012;13:703–706.
21. Burgess HJ, Park M, Wyatt JK, Fogg LF. Home dim light melatonin onsets with measures of compliance in delayed sleep phase disorder. J Sleep Res 2016;25:314–317.
22. Benloucif S, Burgess HJ, Klerman EB, et al. Measuring melatonin in humans. J Clin Sleep Med 2008;4:66–69.
23. Czeisler CA, Duffy JF, Shanahan TL, et al. Stability, precision, and near-24-hour period of the human circadian pacemaker. Science 1999;284:2177–2181.
24. Duffy JF, Cain SW, Chang A-M, et al. Sex difference in the near-24-hour intrinsic period of the human circadian timing system. Proc Natl Acad Sci USA 2011;108(Suppl 3):15602–15608.
25. Duffy JF, Czeisler CA. Effect of light on human circadian physiology. [Invited review, Peer-reviewed] Sleep Medicine. Clinics 2009;4:165–177.
26. Khalsa SB, Jewett ME, Cajochen C, Czeisler CA. A phase response curve to single bright light pulses in human subjects. J Physiol 2003;549:945–952.
27. St Hilaire MA, Gooley JJ, Khalsa SB, Kronauer RE, Czeisler CA, Lockley SW. Human phase response curve to a 1 h pulse of bright white light. J Physiol 2012;590:3035–3045.
28. Kushida CA, Littner MR, Morgenthaler T, et al. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. Sleep 2005;28:499–521. Review.

The Clinical Process in Psychiatry: A Clinimetric Approach

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Objective: The aim of this review was to examine the clinical process in psychiatry, with special reference to clinimetrics, a domain concerned with the measurement of clinical phenomena that do not find room in customary taxonomy.

Data Sources: A MEDLINE search from inception to August 2010 was performed for English-language articles using the keywords *clinical judgment*, *clinimetric*, *staging*, *comorbidity*, *sequential treatment*, and *subclinical symptoms* in relation to psychiatric illness. It was supplemented by a manual search of the literature.

Study Selection: Choice of assessment strategies was based on their established or potential incremental increase in clinical information compared to use of diagnostic criteria.

Data Extraction: Contributions were evaluated according to the principles of clinimetrics.

Results: Several innovative assessment strategies were identified: the use of diagnostic transfer stations with repeated assessments instead of diagnostic endpoints, subtyping versus integration of different diagnostic categories, staging methods, and broadening of clinical information through macroanalysis and microanalysis. The most representative examples were selected.

Conclusions: Current assessment strategies in psychiatric research do not reflect the sophisticated thinking that underlies clinical decisions in practice. The clinimetric perspective provides an intellectual home for the reproduction and standardization of these clinical intuitions.

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Psychiatric diagnosis and classification have attracted considerable attention in the past decades.[1] The introduction of diagnostic criteria for the identification of psychiatric syndromes, such as the *DSM*,[2] has considerably decreased the variance of diagnoses due to different assessors and the use of inferential criteria rather than direct observation.

However, clinicians have become increasingly aware of the limitations of the current diagnostic systems[3] and concerned about future *DSM* or *ICD* developments.[4] The customary clinical taxonomy in psychiatry does not include patterns of symptoms, severity of illness, effects of comorbid conditions, timing of phenomena, rate of progression of illness, responses to previous treatments, and other clinical distinctions that demarcate major prognostic and therapeutic differences among patients who otherwise seem to be deceptively similar since they share the same psychiatric diagnosis.

Little consideration has been given to the clinical process in psychiatry, that is, how clinical judgment leading to medical decisions is formulated. The main emphasis has been given to the standardization of the assessment process by use of rating scales leading to diagnostic configuration.[5]

In 1967, Alvan Feinstein dedicated a monograph to an analysis of clinical reasoning that underlies medical evaluations, such as the appraisal of symptoms, signs, and the timing of individual manifestations.[6] In 1982, he introduced the term *clinimetrics*[7] to indicate a domain concerned with the measurement of clinical issues that do not find room in customary clinical taxonomy. Such issues include the types, severity, and sequence of symptoms; rate of progression in illness (staging); severity of comorbidity; problems of functional capacity; reasons for medical decisions (eg, treatment choices); and many other aspects of daily life, such as well-being and distress.[8] Feinstein, in his book on clinimetrics,[8] quotes Molière's bourgeois gentleman who was astonished to discover that he spoke in prose as an example of clinicians who may discover that they constantly communicate with clinimetric indices. Indeed, in clinical practice, psychiatrists weigh factors such as the progression of disease, the overall severity of the disorder, the patient's social support and adaptation, resilience and reaction to stressful life circumstances, and response to previous treatment.[9] However, current formal strategies of assessment fail to capture most of this information.

We will examine some emerging trends and perspectives in the clinical process in psychiatry, with special reference to the diagnostic process, the staging method, and the organization of information.

DATA SOURCES AND STUDY SELECTION

A review of the literature, based on a MEDLINE search from inception to August 2010 using the keywords *clinical judgment*, *clinimetric*, *staging*, *comorbidity*, *sequential treatment*, and *subclinical symptoms* in relation to psychiatric illness was performed. It was supplemented by a manual search of the literature. Choice of assessment strategies was based on clinimetric principles[8] and on the concept of incremental validity,[10] which refers to the unique contribution or incremental increase in predictive power associated with the inclusion of a particular assessment procedure in the

Clinical Points

- Exclusive reliance on diagnostic criteria has impoverished the clinical process and does not reflect the complex thinking that underlies decisions in psychiatric practice.
- The accuracy of clinical judgment can be greatly increased with specific strategies: global formulations, staging methods, and a better organization of clinical information (encompassing macroanalysis and microanalysis).
- The concept of disease is no longer adequate to guide psychiatric care; therefore, clinical decision making should be addressed to attainment of individual goals.

clinical decision process.[11,12] We will then discuss the implications that a renewed interest in these assessment strategies may entail.

DIAGNOSTIC ENDPOINTS VERSUS TRANSFER STATIONS

In most instances of diagnostic reasoning in psychiatry, the process ends with the identification of a disorder,[13] often subsumed under a rubric of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*). A single assessment generates the prognostic and therapeutic judgments of the clinician. A *DSM* diagnosis (eg, major depressive disorder), however, encompasses a wide range of manifestations, comorbidity, seriousness, prognosis, and responses to treatment.

The majority of patients with mood and anxiety disorders do not qualify for 1, but for several Axis I and Axis II disorders.[14] As Cloninger[15] remarks, mental disorders can be characterized as manifestations of complex adaptive systems that are multidimensional in their description and multifactorial in their origins, and they involve nonlinear interactions in their development. As a result, efforts to describe psychopathology in terms of discrete categorical diagnoses result in extensive comorbidity and do not lend themselves to adequate treatment strategies.[15]

Very seldom do comorbid diagnoses undergo hierarchical organization (eg, generalized anxiety disorder and major depression) or is attention paid to the longitudinal development of mental illnesses. There is comorbidity that wanes upon successful treatment of 1 mental disease, eg, recovery from panic disorder with agoraphobia may result in remission from co-occurring hypochondriasis, without any specific treatment for the latter.[10] Other times, treatment of 1 disorder does not result in the disappearance of comorbidity. For instance, successful treatment of depression may not affect preexisting anxiety disturbances.[16]

The diagnostic criteria are particularly helpful in setting a threshold for conditions worthy of clinical attention. Accordingly, the diagnostic criteria for a major depressive disorder identify a syndrome that may be responsive to antidepressant drugs. At least 5 of a set of 9 symptoms should be present (and 1 should be either depressed mood or loss of interest). However, according to the psychometric model, all items are weighed the same, unlike in clinical medicine, where major and minor symptoms are often differentiated (eg, Jones criteria for rheumatic fever).[7] As a result, a patient with severe and pervasive anhedonia, incapacitating fatigue, and difficulties concentrating, which make him unable to work, would not be diagnosed with a major depressive disorder, despite the clinical intuition of potential benefit from pharmacotherapy. This diagnosis could be performed in a patient who barely meets the criteria for 5 symptoms. The hidden conceptual model is psychometric: severity is determined by the number of symptoms, not by their intensity or quality, to the same extent that a score in a depression self-rating scale depends on the number of symptoms that are scored as positive.[10] This is not surprising in view of the fact that the development of psychometrics took place outside of the clinical field, mainly in educational and social areas.[17] Since the phenomena under observation in the development of psychometric principles were not clinical, they could not be automatically adapted to clinical psychology and psychiatry.

Similar considerations apply to the longitudinal development of the disorder (prodromal phase, the fully developed disorder, and residual states).[9] Detre and Jarecki[18] provided a model for relating prodromal and residual symptomatology in psychiatric illness, defined as the rollback phenomenon, ie, as the illness remits, it progressively recapitulates, even though in a reverse order, many of the stages and symptoms that were seen during the time it developed. The rollback phenomenon has been substantiated in mood and anxiety disorders.[19,20] There is limited awareness of the fact that the current patient's symptomatology may have developed over the years and have reflected previous treatments.

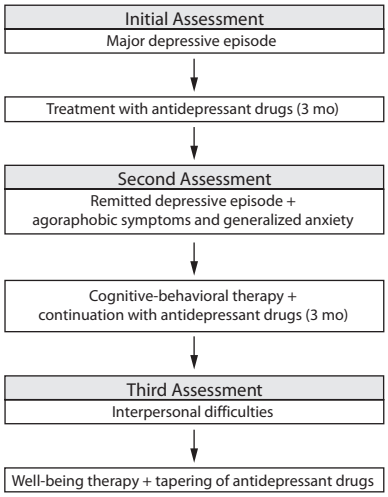
Feinstein[13] remarks that, when making a diagnosis, thoughtful clinicians seldom leap from a clinical manifestation to a diagnostic endpoint. The clinical reasoning goes through a series of "transfer stations," where potential connections between presenting symptoms and pathophysiological process are drawn. These stations are a pause for verification or change to another direction.[13] This strategy particularly applies to psychiatric disorders. An initial state of generalized anxiety may assume phobic connotations at some later point in time. If major depression then ensues, mood symptomatology may overshadow the previous anxiety disturbances, but the diagnosis of depression is only a transfer from prodromal to residual anxiety.

Some assessment strategies have been developed to overcome the flat, cross-sectional view of *DSM*.

Repeated Assessments

The use of diagnostic transfer stations has been suggested by the sequential treatment model,[21] an intensive, 2-stage approach, that includes the use of 1 treatment (eg, pharmacotherapy) after remission has been achieved. One type of treatment is thus employed to address the residual

Figure 1. Effects of Repeated Assessments on the Development of a Diagnostic Work



symptomatology that the other treatment was unable to affect. The sequential model relies on repeated assessments (after each line of treatment has been completed) that may modify an initial diagnosis (eg, preexisting anxiety disturbances may emerge after pharmacotherapy of a major depressive episode). Robins and Guze[22] developed the primary/secondary dichotomy in depression, which was based on chronology and course of follow-up. An episode of depression was defined as secondary when it was superimposed on a preexisting psychiatric or medical disease. The *DSM-IV*,[2] however, does not differentiate primary and secondary manifestations of depressive illness, as is performed in general medicine (eg, hypertension). As outlined in Figure 1, in view of the rollback phenomenon, Robins and Guze's primary/secondary distinction[22] becomes feasible: the major depressive episode appears to be superimposed on longstanding agoraphobic fears and avoidance and generalized anxiety. Symptoms are qualitatively differentiated (eg, the fact they persisted upon treatment against a background of improved symptomatology). They may be elicited by a diary or daily rating scales, which yield information that is not readily apparent in interview.

Subtyping

The need for subtyping major depressive disorder, since this category is too broad to yield meaningful treatment implications, has been recently underscored.[23,24] Lichtenberg and Belmaker,[23] for instance, differentiate between depression with anxiety (maintains functioning, positive response to favorable news or pleasurable activities) and late-life depression (no prior depressive history, reduced energy and interest, impaired cognitive function). Bech[24] has revived Robins and Guze's hierarchical primary/secondary distinction (eg, postnatal depression, poststroke late-life depression).[22] The basic assumption is that clinical manifestations that share the diagnosis of major depressive disorder may display substantial differences in prognostic and therapeutic terms.[23,24]

The underlying assumption is to increase the amount of clinical information that is conveyed by diagnosis. This requires use of instruments that yield a broad spectrum of information, such as hostility, irritable mood, and phobic avoidance, and are not ordinarily available.[24]

Building Unitary Concepts

Tyrer and associates[25] remarked that what is shared by syndromes such as anxiety, panic, phobic disturbances, and irritability may be as important as the differences between them, and conditions that are apparently comorbid could be part of the same clinical syndrome. They argued that the combination of mixed anxiety and depressive disorders together with a certain type of abnormal personality (excessive timidity, poor-self-esteem, avoidance of anxiety-provoking situations, and dependence on others) constitutes a single syndrome, the general neurotic syndrome.[25] The syndrome was shown to be associated with a poor response to treatment, frequent symptoms throughout the neurotic diagnostic spectrum, and tendency to relapse. The concept of neurosis, in its phenomenological[26] and psychodynamic[27] traditions, still has a lot to teach in terms of clinical thinking.[28]

Another example of search for unitary mechanisms of symptom formation is van Praag's Scale for Personality Disturbances.[29] On the basis of a structured interview, the rater is asked to score the following experiential qualities: (1) basic feelings of discontent with one's life situation and psychological make up, (2) unhappiness with one's personal relationships, and (3) emotional instability. The scale aims to overcome the difficulties in incorporating the I and II Axes of *DSM* and was found to allow important differentiations from residual symptomatology.[30]

The concept of allostatic load (the cumulative effects of stressful experiences in daily life) originated from basic science.[31] However, it offers another clinical opportunity of assessing the presence of a source of distress in the form of recent life events and/or chronic stress that exceed the individual's coping skills together with symptomatic manifestations encompassing psychological symptoms.[32] These approaches may be subsumed under the clinimetric rubric of global assessment indices. While the sensitivity of these methods is acknowledged in drug trials, where they often yield the most sensitive discrimination between drug and placebo effects,[33] the clinical value of these global evaluations in assessment and treatment planning is currently underestimated.

STAGING

In 1993, Fava and Kellner[9] introduced the clinimetric concept of staging in psychiatric classification. Unlike in clinical medicine, where this method had achieved wide currency (eg, the New York Heart Association Functional Classification, the Ann Arbor staging classification of Hodgkin's disease), staging was largely neglected in psychiatry. Staging

Table 1. Stages of a Psychiatric Disorder

Stage 1: Prodromal phase
Stage 2: Acute manifestations
Stage 3: Residual phase
Stage 4: Chronic (in attenuated or persistent form)

Table 2. Staging of Levels of Treatment Resistance

Stage 0: No history of failure to respond to therapeutic trial
Stage 1: Failure of at least 1 adequate therapeutic trial
Stage 2: Failure of at least 2 adequate therapeutic trials
Stage 3: Failure of 3 or more adequate therapeutic trials
Stage 4: Failure of 3 or more adequate trials including at least 1 concerned with augmentation/combination

Table 3. Staging of Loss of Therapeutic Effects During Continuation or Maintenance Treatment

Stage 0: No loss of therapeutic effect
Stage 1: Loss of therapeutic effects after adequate response in a therapeutic trial
Stage 2: Loss of therapeutic effects after adequate response in 2 therapeutic trials
Stage 3: Loss of therapeutic effects after adequate responses in 3 or more therapeutic trials

differs from the conventional diagnostic practice in that it not only defines the extent of progression of a disorder at a particular point in time but also reveals a person's current location on the continuum of the course of illness. Thus, once an index defines the existence of a particular disease state, its seriousness, extent, and longitudinal characteristics need to be evaluated.[8]

Fava and Kellner[9] developed staging methods for unipolar depression, bipolar disorder, panic disorder, and schizophrenia. Table 1 outlines the basic steps of development of a psychiatric disorder, ranging from the prodromal to the residual and chronic forms, in a longitudinal view of development of disturbances. Staging models have subsequently been refined in schizophrenia,[34] mood disorders,[35–38] and agoraphobia,[28] and they have been introduced in anorexia.[39] Staging instruments have also been developed.[40,41] In 2 randomized controlled trials,[42,43] psychotherapeutic intervention was applied according to a staging method and was found to yield long-term benefits.[44,45]

Further, the staging method has been applied to treatment response in depression.[46–48] It appears that the more information included in the method, the stronger its predictive value.[49] This information may encompass the number of trials completed,[49] the intensity/optimization of each trial,[49] issues of pseudoresistance (nonresponse to inadequate treatment in terms of duration, doses, or indications),[50] or occurrence of loss of therapeutic effects after clinical response.[51] Table 2 provides an illustration of the various levels of treatment resistance. By a clinical viewpoint, it is quite different to treat a patient with a major depressive episode who displayed positive responses to previous therapeutic trials (stage 0) and a patient who failed to respond to various adequate trials, including one concerned with augmentation/combination (stage 4). Similarly, if we encounter a depressed patient who repeatedly displayed loss of therapeutic response using various antidepressant drugs (Table 3), we should be aware that use of a new antidepressant is likely to yield the same phenomenon, probably because of a mechanism of oppositional tolerance.[51] For instance, many patients who did not respond to initial treatment in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial and went through various types of treatments, including augmentation/combination, were characterized by a refractory state with low remission, high relapse, and high intolerance rates.[35] Accordingly, their likelihood of lasting remission would be very low, as indicated by the staging methods of Tables 2 and 3.

Motivation to treatment and changing behavior has also been submitted to a staging system and may yield valuable insights into psychological resistances of the patient.[52] Di Clemente and Prochaska[52] developed a helpful staging method: "precontemplation" (people do not recognize that a problem exists and have no intention to change), "contemplation" (individuals accept that a problem exists but are ambivalent about it), "preparation/determination" (a perceived discrepancy between current and desired study), "action," and "maintenance" of the new patterns. It is difficult to suggest a psychotherapeutic treatment, despite pertinent indications, to a patient who is in the "precontemplation" stage. However, this is seldom considered, particularly in randomized controlled trials of psychotherapy.

ORGANIZATION OF CLINICAL INFORMATION

The information we previously mentioned adds to other customary domains of the clinical evaluation, such as psychiatric history, background of alcohol and other substance abuse, general medical history, physical examination, laboratory tests, and diagnostic interviews, whether they follow specific instruments or a more personal format.[5] There are other areas, however, that need to be addressed and are currently neglected.

Subclinical Distress and Illness Behavior

A diagnostic interview and a set of criteria have been used extensively in psychosomatic research.[53–55] The Diagnostic Criteria for Psychosomatic Research allow one to translate in clinical terms the spectrum of manifestations of illness behavior, ie, the ways in which individuals experience, perceive, evaluate, and respond to their health status.[53–55] The 2 main forms of abnormal illness behavior (illness affirming and illness denying) have several common expressions in psychiatric practice. However, the psychopathology of insight—as defined by Lewis[56]—is seldom examined. When this happens, the results can be quite interesting. For instance, in a recent investigation on the spectrum of anxiety disorders in the medically ill, agoraphobia without history of panic attacks was found to be closely related to the Diagnostic Criteria for Psychosomatic Research illness denial.[57] Persistent denial of having a medical disorder and

needing treatment frequently occurs in the medical setting.[53] If panic attacks have not taken place (illness denial was not associated with panic disorder and agoraphobia), agoraphobic fears tend to be highly rationalized and do not lead individuals to seek medical attention.[57] The identification of these fears requires careful expert interviewing, well beyond the checklist use of diagnostic instruments, to overcome the denial that underlies agoraphobia and other distress manifestations. The linking between agoraphobia without history of panic attacks and Diagnostic Criteria for Psychosomatic Research illness denial provides an explanation for some discrepancies that have occurred in the literature as to the prevalence of agoraphobia in clinical samples compared to epidemiologic studies.[28] Other important constructs covered by the Diagnostic Criteria for Psychosomatic Research are demoralization,[58] irritable mood,[53] and alexithymia.[27,59]

Psychological Well-Being

An area that is currently neglected in assessment is psychological well-being, despite the availability of validated instruments and its growing importance in establishing resilience.[3,60] Dimensions such as environmental mastery, personal growth, purpose in life, autonomy, self-acceptance, and positive relations with others were found to affect vulnerability to life adversities and complex balance between positive and negative affects in mood and anxiety disorders.[60]

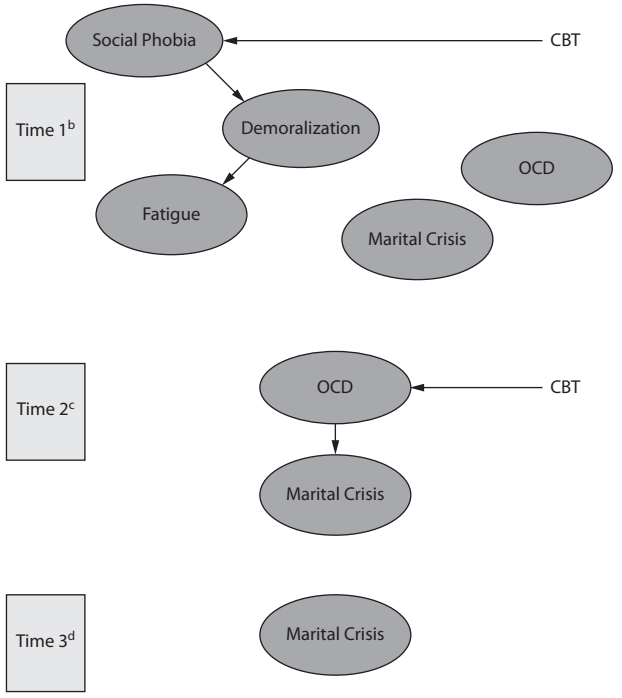
Mezzich and Salloum[3] developed the Person-centered Integrative Diagnosis, which encompasses both the positive and negative aspects of health, in an interactive way, within the person's life context. The Person-centered Integrative Diagnosis includes both the symptomatology of mental disorders and the positive aspects of health (adaptive functioning, protective factors, quality of life, etc) according to a holistic view of the person (including his/her dignity, values, and aspirations).[3] Rehabilitation of mental disorders is targeted as much on the patient's strengths and wishes as it is on alleviating symptoms and psychopathology.[61]

Macroanalysis and Microanalysis

Feinstein, when he introduced the concept of comorbidity, referred to any "additional coexisting ailment" separate from the primary disease, even if this secondary phenomenon does not qualify as a disease per se.[62] Indeed, in clinical medicine, the many methods that are available for measuring comorbidity are not limited to disease entities.[63]

A method has been developed in psychiatry for organizing clinical data as variables in clinical reasoning. Emmelkamp et al[64,65] have introduced the concept of macroanalysis (a relationship between co-occurring syndromes and problems is established on the basis of when treatment should commence). Fava and Sonino[54] have applied macroanalysis to assessing the relationship between medical and psychological variables. Macroanalysis starts from the assumption that, in most cases, there are functional relationships with other more or less clearly defined problem areas[64] and that the targets of treatment may vary during the course of disturbances.[54]

Figure 2. Example of Macroanalysis[a]



[a]A patient presents with work situational social phobia, demoralization, fatigue, obsessive-compulsive disorder (OCD) symptoms, and marital crisis.
[b]At time 1, the therapist could give priority to cognitive-behavioral therapy (CBT) of social phobia, expecting a consequent improvement in demoralization and sense of fatigue.
[c]At time 2, the therapist could decide to intervene on OCD symptoms by using CBT techniques to emphasize the negative effects of the patient's excessive preoccupation for order and precision, leading to a chronic malaise and communicative difficulties with the partner.
[d]At posttherapy assessment (time 3), the therapist could determine the relationship of OCD symptoms to marital crisis.

For instance, a patient may present with work situational social phobia (which leads him or her to avoid important opportunities for improving his or her job), demoralization (which increases his or her sense of fatigue), marital crisis (as a result of obsessional traits of mental order incompatible with that of his or her spouse), and obsessive ruminations (which lead to a chronic state of indecision). In terms of macroanalysis, the clinician, after a thorough interview with the patient, could place into a hierarchy the syndromes and symptoms of comorbidity by considering also the patient's needs. The clinician could thus give priority to the cognitive-behavioral treatment of social phobia, leaving to posttherapy assessment the determination of the relationship of social phobia to demoralization, marital crisis, and obsessional ruminations. Will they wane as anxious epiphenomena or will they persist, despite some degree of improvement? Should, in this latter case, further treatment be necessary? What type of relationship do demoralization and obsessive-compulsive symptoms entertain? If the clinical decision of tackling one syndrome may be taken during the initial assessment, the subsequent steps of macroanalysis require a reassessment after the first line of treatment has terminated (Figure 2).

The hierarchical organization that is chosen may depend on a variety of factors (urgency, availability of treatment tools, etc) that include also the patient's preferences and priorities. Macroanalysis is a tool that allows the therapist to not only increase accuracy in clinical decision making but also inform the patient about the relationship between different problem areas and motivate the patient for changing.[64,65] The concept of shared decision making is getting increasing attention in clinical medicine,[66] but it is still seldom practiced in psychiatry.[67] Macroanalysis also requires reference to the staging method, whereby a disorder is characterized according to seriousness, extension, and longitudinal development.[9] For instance, certain psychotherapeutic strategies can be deferred to a residual stage of depression when state-dependent learning has been improved by use of antidepressant drugs.[68] The planning of treatment thus requires determination of the symptomatic target of the first-line approach (eg, pharmacotherapy) and tentative identification of other areas of concern to be addressed by subsequent treatment (eg, psychotherapy).

Macroanalysis should be supplemented by microanalysis, a detailed analysis of specific symptoms (onset and course of the complaints, circumstances that worsen symptoms and consequences).[64,65] For instance, when anxiety characterizes the clinical picture, it is necessary to know under which circumstances the anxiety become manifest and how the patient responds when he/she becomes anxious, and also to know whether an avoidant behavior occurs and, if so, what are the long-term consequences of the avoidant behavior.

Targum and associates[69] have developed specific criteria (SAFER) to be used in drug trials for improving the assessment accuracy of symptoms: State versus trait (the identified symptoms must reflect the current state of illness and not long-standing traits), Accessibility, Face validity, Ecological validity, and Rule of the 3 *p*'s (symptoms must be present, persistent, and pathological). The SAFER criteria inventory constitutes a valid method of microanalysis. Microanalysis also consists of dimensional measurements, such as observer or self-rating scales for assessing anxiety and fears. Choice of these instruments is dictated by the clinimetric concept of incremental validity.[10–12] Each distinct aspect of psychological measurement should deliver a unique increase in information in order to qualify for inclusion. The concept can also be applied to the selection of instruments in a psychometric battery. In clinical research, several highly redundant scales are often used under the misguided assumption that nothing will be missed. On the contrary, violation of the concept of incremental validity leads to only conflicting results. Microanalysis is consequential and secondary to macroanalysis and leads to overcoming the assumption that there is a common assessment strategy for all clinical encounters.

CONCLUSION

Part of the challenge and, at the same time, fascination of being a clinician lies in applying scientific methods in the care of patients and in understanding disease.[70] Greater knowledge should result in significant benefits for the patients, and, in a sense, continued development on the part of the physician.[71] We are witnessing, however, a progressive detachment of clinicians from research, which is often accompanied by a sense of personal stagnation and tiredness.[71] This detachment is mainly the reflection of an intellectual crisis that has become more and more manifest in recent years.[71–73]

In 1967, Feinstein[6] urged clinicians to develop a "basic science" of their own—to study the clinical phenomena directly, to specify the importance of different types of clinical data, to create appropriate systems of taxonomy for classifying the information, and to develop intellectual models and pragmatic methods that would articulate the clinical process and use the results for quantified analyses.

More recently, Tinetti and Fried[74] have argued that time has come to abandon disease as the focus of medical care. Clinical decision making for all patients should be addressed to attainment of individual goals and identification and treatment of all modifiable and nonbiological factors, rather than solely to the diagnosis and treatment of individual diseases.[74]

Often, in their clinical practice, psychiatrists use sophisticated forms of clinical judgment that are suitable for clinical challenges but are not addressed by current research strategies. Exclusive reliance on diagnostic criteria has impoverished the clinical process and does not reflect the complex thinking that underlies decisions in psychiatric practice. The use of transfer stations with repeated assessments instead of diagnostic endpoints, the building of global formulations of clinical integration, staging methods, and a better organization of clinical information (encompassing subclinical distress, illness behavior, psychological well-being, macroanalysis, and microanalysis) may be an antidote to oversimplified models that derive from biological reductionism, neglect individual responses to treatment, and clash with clinical reality.[71,75]

The clinimetric perspective provides an intellectual home for the reproduction and standardization of the clinical intuitions. It allows the clinician to make full use of the clinical information that is available. It opens a new exciting area of research that is likely to yield improved targets for neurobiological studies and treatment trials.

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REFERENCES

1. Maj M, Gaebel W, Lopez-Ibor JJ, et al, eds. *Psychiatric Diagnosis and Classification*. Chichester, UK: Wiley; 2002.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Washington, DC: American Psychiatric Association; 1994.
3. Mezzich JE, Salloum IM. Towards innovative international classification and diagnostic systems: ICD-11 and person-centered integrative

diagnosis. *Acta Psychiatr Scand*. 2007;116(1):1–5.
4. Frances A. Whither *DSM-V*? *Br J Psychiatry*. 2009;195(5):391–392.
5. American Psychiatric Association. Psychiatric Evaluation of Adults. Second Edition. *Am J Psychiatry*. 2006; 163 (June suppl): 1–36
6. Feinstein AR. *Clinical Judgment*. Baltimore, MD: Williams & Wilkins; 1967.
7. Feinstein AR. T. Duckett Jones Memorial Lecture: The Jones criteria and the challenges of clinimetrics. *Circulation*. 1982;66(1):1–5.
8. Feinstein AR. *Clinimetrics*. New Haven, CT: Yale University Press; 1987.
9. Fava GA, Kellner R. Staging: a neglected dimension in psychiatric classification. *Acta Psychiatr Scand*. 1993;87(4):225–230.
10. Fava GA, Ruini C, Rafanelli C. Psychometric theory is an obstacle to the progress of clinical research. *Psychother Psychosom*. 2004;73(3):145–148.
11. Hunsley J, Meyer GJ. The incremental validity of psychological testing and assessment: conceptual, methodological, and statistical issues. *Psychol Assess*. 2003;15(4):446–455.
12. Garb HN. Incremental validity and the assessment of psychopathology in adults. *Psychol Assess*. 2003;15(4):508–520.
13. Feinstein AR. An analysis of diagnostic reasoning. I. The domains and disorders of clinical macrobiology. *Yale J Biol Med*. 1973;46(3):212–232.
14. Zimmerman M, Chelminski I, McDermut W. Major depressive disorder and Axis I diagnostic comorbidity. *J Clin Psychiatry*. 2002;63(3):187–193.
15. Cloninger CR. Implications of comorbidity for the classification of mental disorders: the need for a psychobiology of coherence. In: Maj M, Gaebel W, Lopez-Ibor JJ, et al, eds. *Psychiatric Diagnosis and Classification*. Chichester, UK: Wiley; 2002:79–106.
16. Sherbourne CD, Wells KB. Course of depression in patients with comorbid anxiety disorders. *J Affect Disord*. 1997;43(3):245–250.
17. Rust J, Golombok S. *Modern Psychometrics: The Science of Psychological Assessment*. London, UK: Routledge; 1989.
18. Detre TP, Jarecki H. *Modern Psychiatric Treatment*. Philadelphia, PA: Lippincott; 1971.
19. Fava GA. Subclinical symptoms in mood disorders: pathophysiological and therapeutic implications. *Psychol Med*. 1999;29(1):47–61.
20. Fava GA, Mangelli L. Subclinical symptoms of panic disorder: new insights into pathophysiology and treatment. *Psychother Psychosom*. 1999;68(6):281–289.
21. Fava GA, Ruini C, Rafanelli C. Sequential treatment of mood and anxiety disorders. *J Clin Psychiatry*. 2005;66(11):1392–1400.
22. Robins E, Guze SB. Classification of affective disorders: the primary-secondary, the endogenous-reactive, and the neurotic-psychotic concepts. In: Williams TA, Katz MM, Shield JA, eds. *Recent Advances in the Psychobiology of the Depressive Illness*. Washington, DC: Government Printing Office; 1972:283–293.
23. Lichtenberg P, Belmaker RH. Subtyping major depressive disorder. *Psychother Psychosom*. 2010;79(3):131–135.
24. Bech P. Struggle for subtypes in primary and secondary depression and their mode-specific treatment or healing. *Psychother Psychosom*. 2010; 79(6):331–338.
25. Tyrer P, Seivewright N, Ferguson B, et al. The general neurotic syndrome: a coaxial diagnosis of anxiety, depression and personality disorder. *Acta Psychiatr Scand*. 1992;85(3):201–206.
26. Slater E, Slater P. A heuristic theory of neurosis. *J Neurol Neurosurg Psychiatry*. 1944;7(1–2):49–55.
27. Taylor GJ. Affects, trauma, and mechanisms of symptom formation: a tribute to John C. Nemiah, MD (1918–2009). *Psychother Psychosom*. 2010;79(6):339–349.
28. Fava GA, Rafanelli C, Tossani E, et al. Agoraphobia is a disease: a tribute to Sir Martin Roth. *Psychother Psychosom*. 2008;77(3):133–138.
29. van Praag HM. Diagnosing depression—looking backward into the future. *Psychiatr Dev*. 1989;7(4):375–394.
30. Rafanelli C, Park SK, Ruini C, et al. Rating well-being and distress. *Stress Med*. 2000;16(1):55–61.
31. McEwen BS. Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiol Rev*. 2007;87(3):873–904.
32. Fava GA, Guidi J, Semprini F, et al. Clinical assessment of allostatic load and clinimetric criteria. *Psychother Psychosom*. 2010;79(5):280–284.
33. Fava M, Evins AE, Dorer DJ, et al. The problem of the placebo response in clinical trials for psychiatric disorders: culprits, possible remedies, and a novel study design approach. *Psychother Psychosom*. 2003;72(3): 115–127.
34. McGorry P, Hickie IB, Yung AR, et al. Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions. *Aust N Z J Psychiatry*. 2006;40(8):612–622.
35. Fava GA, Tomba E, Grandi S. The road to recovery from depression—don't drive today with yesterday's map. *Psychother Psychosom*. 2007;76(5):260–265.
36. Berk M, Hallam KT, McGorry PD. The potential utility of a staging model as a course specifier: a bipolar disorder perspective. *J Affect Disord*. 2007;100(1–3):279–281.
37. Kapczinski F, Dias VV, Kauer-Sant'Anna M, et al. The potential use of biomarkers as an adjunctive tool for staging bipolar disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009;33(8):1366–1371.
38. Reinares M, Colom F, Rosa AR, et al. The impact of staging bipolar disorder on treatment outcome of family psychoeducation. *J Affect Disord*. 2010;123(1–3):81–86.
39. Maguire S, Le Grange D, Surgenor L, et al. Staging anorexia nervosa: conceptualizing illness severity. *Early Interv Psychiatry*. 2008;2(1):3–10.
40. Bilsbury CD, Richman A. A staging approach to measuring patient-centred subjective outcomes. *Acta Psychiatr Scand*. 2002; 106(suppl s414):5–40.
41. Andresen R, Caputi P, Oades L. Stages of recovery instrument: development of a measure of recovery from serious mental illness. *Aust N Z J Psychiatry*. 2006;40(11–12):972–980.
42. Fava GA, Grandi S, Zielezny M, et al. Cognitive behavioral treatment of residual symptoms in primary major depressive disorder. *Am J Psychiatry*. 1994;151(9):1295–1299.
43. Fava GA, Rafanelli C, Grandi S, et al. Prevention of recurrent depression with cognitive behavioral therapy: preliminary findings. *Arch Gen Psychiatry*. 1998;55(9):816–820.
44. Fava GA, Grandi S, Zielezny M, et al. Four-year outcome for cognitive behavioral treatment of residual symptoms in major depression. *Am J Psychiatry*. 1996;153(7):945–947.
45. Fava GA, Ruini C, Rafanelli C, et al. Six-year outcome of cognitive behavior therapy for prevention of recurrent depression. *Am J Psychiatry*. 2004;161(10):1872–1876.
46. Thase ME, Rush AJ. Treatment-resistant depression. In: Bloom FE, Kupfer DT, eds. *Psychopharmacology: the Fourth Generation of Progress*. New York, NY: Raven Press; 1995:1081–1097.
47. Fava M. Diagnosis and definition of treatment-resistant depression. *Biol Psychiatry*. 2003;53(8):649–659.
48. Fekadu A, Wooderson SC, Markopoulou K, et al. The Maudsley Staging Method for treatment-resistant depression: prediction of longer-term outcome and persistence of symptoms. *J Clin Psychiatry*. 2009;70(7): 952–957.
49. Petersen T, Papakostas GI, Posternak MA, et al. Empirical testing of two models for staging antidepressant treatment resistance. *J Clin Psychopharmacol*. 2005;25(4):336–341.
50. Nierenberg AA, Amsterdam JD. Treatment-resistant depression: definition and treatment approaches. *J Clin Psychiatry*. 1990;51(suppl):39–47, discussion 48–50.
51. Fava GA. Can long-term treatment with antidepressant drugs worsen the course of depression? *J Clin Psychiatry*. 2003;64(2):123–133.
52. Di Clemente CC, Prochaska JO. Toward a comprehensive, transtheoretical model of change: stages of change and addictive behaviours. In: Miller WR, Heather N, eds. *Treating Addictive Behaviors*. 2nd ed. New York, NY: Plenum; 1998:3–24.
53. Porcelli P, Sonino N, eds. *Psychological Factors Affecting Medical Conditions. A New Classification for* DSM-V. Basel, Switzerland: Karger; 2007.
54. Fava GA, Sonino N. Psychosomatic assessment. *Psychother Psychosom*. 2009;78(6):333–341.
55. Wise TN. Diagnostic criteria for psychosomatic research are necessary for *DSM V*. *Psychother Psychosom*. 2009;78(6):330–332.
56. Lewis A. The psychopathology of insight. *Br J Med Psychol*. 1934;14: 332–348.
57. Fava GA, Porcelli P, Rafanelli C, et al. The spectrum of anxiety disorders in the medically ill. *J Clin Psychiatry*. 2010;71(7):910–914.
58. Cockram CA, Doros G, de Figueiredo JM. Diagnosis and measurement of subjective incompetence: the clinical hallmark of demoralization. *Psychother Psychosom*. 2009;78(6):342–345.
59. Ogrodniczuk JS, Piper WE, Joyce AS, et al. Alexithymia and treatment preferences among psychiatric outpatients. *Psychother Psychosom*. 2009; 78(6):383–384.
60. Fava GA, Tomba E. Increasing psychological well-being and resilience by psychotherapeutic methods. *J Pers*. 2009;77(6):1903–1934.
61. Ralph RO, Corrigan PW, eds. *Recovery in Mental Illness. Broadening our Understanding of Wellness*. Washington, DC: American Psychological Association; 2005.
62. Feinstein AR. The pre-therapeutic classification of comorbidity in chronic disease. *J Chronic Dis*. 1970;23(7):455–468.
63. de Groot V, Beckerman H, Lankhorst GJ, et al. How to measure

comorbidity. A critical review of available methods. *J Clin Epidemiol*. 2003;56(3):221–229.
64. Emmelkamp PMG, Bouman TK, Scholing A. *Anxiety Disorders*. Chichester, UK: Wiley; 1993:55–67.
65. Emmelkamp PMG. The additional value of clinimetrics needs to be established rather than assumed. *Psychother Psychosom*. 2004;73(3): 142–144.
66. Joosten EAG, DeFuentes-Merillas L, de Weert GH, et al. Systematic review of the effects of shared decision-making on patient satisfaction, treatment adherence and health status. *Psychother Psychosom*. 2008;77(4): 219–226.
67. Joosten EAG, de Jong CAJ, de Weert-van Oene GH, et al. Shared decision-making reduces drug use and psychiatric severity in substance-dependent patients. *Psychother Psychosom*. 2009;78(4):245–253.
68. Reus VI, Weingartner H, Post RM. Clinical implications of state-dependent learning. *Am J Psychiatry*. 1979;136(7):927–931.
69. Targum SD, Pollack MH, Fava M. Redefining affective disorders: relevance for drug development. *CNS Neurosci Ther*. 2008;14(1):2–9.
70. Engel GL. Physician-scientists and scientific physicians: resolving the humanism-science dichotomy. *Am J Med*. 1987;82(1):107–111.
71. Fava GA. The intellectual crisis of psychiatric research. *Psychother Psychosom*. 2006;75(4):202–208.
72. Maj M. Are psychiatrists an endangered species? *World Psychiatry*. 2010; 9(1):1–2.
73. Katschnig H. Are psychiatrists an endangered species? observations on internal and external challenges to the profession. *World Psychiatry*. 2010; 9(1):21–28.
74. Tinetti ME, Fried T. The end of the disease era. *Am J Med*. 2004;116(3): 179–185.
75. Wise TN. Curiosity and crisis. *Psychother Psychosom*. 2006;75(4):199–201.

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Do metacognitions mediate the relationship between irrational beliefs, eating disorder symptoms and cognitive reappraisal?

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EMPIRICAL PAPER

Do metacognitions mediate the relationship between irrational beliefs, eating disorder symptoms and cognitive reappraisal?

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Abstract

Objective: Cognitively oriented therapies, first-line treatment for eating disorders (EDs), still show room for improvement in treatment retention and outcomes. Despite the development of additional cognitive models and therapies, few studies examine the relationship between traditional and third-wave cognitive targets in EDs. The study explores the relationship between irrational beliefs (IBs) and metacognitions and their relationship with ED psychopathology and cognitive reappraisal in ED outpatients. **Method:** Seventy-seven patients (mean age 27.49 ± 12.28 years) were assessed with The Attitudes and Beliefs Scale-ABS-2, Meta-cognitions Questionnaire-MCQ-65, Eating Disorder Inventory 3-EDI-3, Eating Attitudes Test-EAT-40, Emotion Regulation Questionnaire-ERQ. **Results:** Correlational analyses showed that IBs and metacognitions significantly correlated with each other. Metacognitions partially mediated the relationship between IBs and ED-related general psychological maladjustment and completely mediated the relationship between IBs and ED symptom severity. Cognitive reappraisal was predicted only by IBs and metacognitions were not significant mediators. **Conclusions:** While IBs are sufficient in explaining ED-related psychopathology and reduced use of cognitive reappraisal, a potential integration of metacognitions about need to control thoughts in CBT models for EDs may offer incremental validity given their contribution to ED severity. Treatment implications include targeting metacognitions concerning need to control thoughts, as a potential maintenance mechanism of ED symptomatology through cognitive restructuring.

Keywords: Irrational beliefs; metacognitions; eating disorders; cognitive behavioural therapy; CBT

Clinical Significance and Methodological of this Article: A partial overlap between irrational beliefs and metacognitions is supported and integrating multiple concepts of maladaptive cognitions in the clinical assessment and psychotherapeutic treatment planning of EDs might be useful. While metacognitions may not warrant integration in CBT models of EDs in directly predicting cognitive reappraisal and ED-related psychopathology above and beyond the contribution of IBs, on the other hand, metacognitions pertaining to attempts to control and suppress thoughts may offer incremental validity to CBT models of EDs given their important contribution to ED symptom severity.

In terms of methodological significance, despite the expansion of cognitive behavioural therapy variants, this is the only study which explores more than one cognitively-oriented conceptualization of maladaptive cognition in eating disorders. It is the first that tested through mediation models the relationship between irrational beliefs, representing thought content, and metacognitions, which represent thoughts about one's thinking, in relation to cognitive reappraisal and ED symptoms.

Cognitive theory applied to eating disorders (EDs) posits that maladaptive cognitions and evaluations about the self, others, and the world generate emotional distress and perpetuate dysfunctional eating behaviours (Cooper, 2005) such as dietary restraint in anorexia nervosa (AN) and binge-eating in bulimia nervosa (BN). Indeed, EDs like all psychopathologies have been found to be marked by maladaptive thinking (Del Pozo et al., 2018; Möller & Bothma, 2001) conceptualized in second-wave cognitive models as

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irrational beliefs in Rational-Emotive Behaviour Therapy (Ellis, 1958; Vîslă et al., 2016) and cognitive distortions in Beck's (Beck & Haigh, 2014) Cognitive Behavioural Therapy, as well as being characterized by difficulties in cognitive reappraisal, the capacity to alter one's emotional state by cognitively reassessing the situation (Danner et al., 2012). Currently the most evidence-based treatment for adults with an eating disorder is the enhanced transdiagnostic cognitive behavioural therapy (CBT-E) proposed by Fairburn et al. (2003) stemming from specialized psychopathological and maintenance model for EDs.

Although cognitively-oriented therapies are considered first-line treatment in clinical guidelines for EDs (APA, 2006; National Health Service, 2017), room for improvement in treatment retention and outcomes remains, as failure to complete standard CBT-based treatment in ED outpatients is particularly high (Fairburn et al., 2012). CBT-E randomized trials, according to a recent review, do not demonstrate superiority over comparison treatments, especially in the longer-term (Atwood & Friedman, 2020). Clinicians and researchers have called for further development of cognitive models that may enhance interventions for EDs (Cooper et al., 2009; Jones et al., 2007). "Third wave" approaches such as metacognitive therapy (MT), dialectical behaviour therapy (DBT), and acceptance and commitment therapy (ACT), are currently being adapted and tested in EDs to overcome limits of traditional CBT in EDs (Linardon et al., 2017; Vann et al., 2014). Such approaches retain CBT elements but integrate new methods to improve clinical change in psychological functioning by targeting function or awareness of cognitions and emotions rather than directly targeting the content and validity of cognitive processes. Thus, third-wave therapies emphasize metacognition, acceptance, mindfulness, and psychological flexibility, and reduction of experiential avoidance (Hays & Hofmann, 2017; Linardon et al., 2017). To date, however while large pre–post symptom improvements were observed for several third-wave treatments, results on randomized controlled trials have not yet shown superiority compared to the recommended CBT treatments in EDs (Linardon et al., 2017).

Despite the expansion of the number of cognitive models (DiGiuseppe et al., 2017) few studies examine the relationship between traditional CBT and third-wave CBT cognitive targets of therapy and their role on psychological distress and dysfunctional behaviour (DiGiuseppe et al., 2016) specifically in EDs where treatment response is not optimal. While the emergence of novel approaches and psychotherapeutic options might be needed, it would be beneficial to first investigate their possible contribution to already well-validated and tested models and therapies for EDs. In particular, the possibility of integrating in CBT models for EDs the third-wave concept of metacognition which has been previously proposed (Cooper et al., 2009) remains to be investigated. Metacognition refers to the "how" we think, rather than "what" we think (Wells, 2009) and subsequently metacognitive therapy (Wells, 2009) focuses on how we judge and evaulate our thoughts, that is, metacognitions, in addition to focusing on attentional biases, and cognitive processes of worry and repetitive negative thinking (RNT) (Ehring et al., 2011; Ehring & Watkins, 2008; Nolen-Hoeksema et al., 2008). Metacognitions concerning the need to control thoughts and metacognitions about uncontrollability and danger of thoughts, have been both implicated in ED symptomatology and maintenance (Davenport et al., 2015; Olstad et al., 2015; Quattropani et al., 2016; Sun et al., 2017).

Therefore, in the current study, we investigated how the second-wave construct of irrational beliefs (IBs), rigid, absolutistic and inflexible negative thoughts about the self, the world and others (Vîslă et al., 2016), which represent the first and original conceptualization of maladaptive cognitions in the cognitive behavioural framework (Ellis, 1958; Ellis & Dryden, 2007) are related to the third-wave construct of metacognitions, the maladaptive evaluations of one's own thoughts in predicting ED symptomatology and cognitive reappraisal in ED patients. The specific aims of this cross-sectional study are to: 1) explore the relationship between IBs and metacognitions, 2) examine whether IBs in predicting ED severity, ED-related psychopathology, and cognitive reappraisal are mediated by metacognitions, specifically metacognitions about the need to control thoughts and about dangerousness and uncontrollability of thoughts. Understanding such relationships may yield important clinical information on whether they both might contribute to one latent dysfunctional cognitive variable or whether they each contribute uniquely in predicting psychopathological disturbance (DiGiuseppe et al., 2016; Tecuta et al., 2019) specifically in EDs.

Methods

The project was approved by University of Bologna Bioethics Committee and Department of Psychology Ethics Committee. Informed consent was obtained from all participants included in the study.

ED Outpatient Sample

Consecutively recruited patients (n = 79) who met diagnostic criteria for EDs (DSM 5; American

Psychiatric Association, 2013) anorexia nervosa (AN), bulimia nervosa (BN), binge-eating disorder (BED), and other specified feeding or eating disorder (OSFED) were recruited from a specialized ED treatment centre before commencing CBT-based treatment. ED diagnoses were established at intake by the consensus of a psychiatrist and a clinical psychologist independently using the Structured Clinical Interview for DSM 5 (SCID-5: First et al., 2015).

Each diagnostic interview was conducted and recorded by a clinical psychologist expert in assessment (E.T.) and subsequently reviewed by a consulting psychiatrist specialized in EDs who confirmed the diagnosis. Consent to be recorded while interviewed was obtained from all participants. Interrater reliability of ED diagnoses in terms of percent agreement was 83.11%.

With the exception of two patients who refused to participate, all invited patients took part in the study (n = 77). The inclusion criterion was the patients' age between 18 and 65 years. The exclusion criteria were comorbid drug/alcohol abuse, psychotic or neurocognitive disorders, acute suicidality, and pregnancy. The socio-demographic and clinical data of the sample appear in Table I.

Measures

The sample was assessed with the following instruments:

Attitudes and Beliefs Scale 2 (ABS-2: DiGiuseppe et al., 2018, 2020) is composed by 72 likert scale items and attempts to measure the four irrational and four rational belief processes respectively identified by Albert Ellis (1958): demandingness (DEM) versus non-demanding preferences, awfulizing (AWF) versus realisitic negative expectations, low frustration tolerance (LFT) versus high frustration tolerance, and negative global evaluation/self-downing (NGE) versus self-acceptance. The various irrational and rational belief processes are presented in three contextual areas; those that are related to issues (needs or expectations) of comfort, achievement, and affiliation. Demands represent rigid, inflexible, and nonpragmatic beliefs and reflect absolutistic "must statements." Awfulizing statements are instead excessive negative evaluations and expectations of events, while low frustration tolerance beliefs refer to thinking that one cannot tolerate an event or set of circumstances. Negative global self-evaluations/self-downing refer to generalized negative labelling and self-statements. The ABS-2 has demonstrated excellent construct validity pertaining to the four irrational and four rational belief processes (DiGiuseppe et al., 2018, 2020) and good psychometric properties including good internal consistency, divergent and convergent validity in numerous studies (DiGiuseppe et al., 2018; Macavei, 2002, 2005 Sava, 2009; Terjesen et al., 2009).

In the current study only the following four irrational belief process scales were used, all of which are composed of nine items: irrational AWF, irrational DEM, irrational NGE, and irrational LFT. The Italian translation of the ABS-2 utilized in a previous study was used (Tecuta et al., 2019). This translation has already demonstrated excellent internal consistency in the general Italian college-age population (α = 0.926) and cronbach α coefficients for the four irrational belief processes (ranging from 0.738–0.832) (Tecuta et al., 2019). In the current study, Cronbach's alphas for irrational beliefs were similarly acceptable, that is, 0.88 for AWF, 0.85 for DEM,

Table I. ED Outpatient and Control Sample Sociodemographic Data and Comparisons in ABS-2, MCQ, and ERQ-Cognitive Reappraisal Scores.

Variables	Total ED sample (N = 77)	AN group (N = 29)	BN group (N = 15)	BED group (N = 13)	OSFED group (N = 20)
Age (years)	27.49 ± 12.28	23.72 ± 10.71	30.87 ± 13.81	32.08 ± 13.56	27.45 ± 11.49
Marital Status (% single)	80.5	89.7	60	84.6	80
BMI	22.47 ± 8.27	17.53 ± 3.04	22.41 ± 3.62	35.59 ± 9.83	20.67 ± 5.20
Illness Duration (years)	8.87 ± 10.11	7.24 ± 10.23	11.31 ± 12.11	9.33 ± 9.35	9.09 ± 9.18
ABS-2 Irrational Awfulizing	19.26 ± 8.16	19.86 ± 8.90	21.80 ± 8.89	17.00 ± 7.80	17.95 ± 6.46
ABS-2 Irrational Demandingness	16.30 ± 6.68	16.59 ± 7.04	18.80 ± 8.40	13.77 ± 4.97	15.65 ± 5.30
ABS-2 Irrational Negative Global Evaluations	13.65 ± 9.86	14.69 ± 11.11	16.13 ± 9.79	9.54 ± 8.48	12.95 ± 8.50
ABS-2 Irrational Low Frustration Tolerance	19.79 ± 6.18	19.97 ± 6.98	20.67 ± 6.32	17.69 ± 6.33	20.25 ± 4.70
MCQ Positive Beliefs about Worry	35.50 ± 10.11	38.93 ± 11.31	34.87 ± 10.06	31.54 ± 8.80	33.56 ± 7.85
MCQ Negative Beliefs about Worry	42.73 ± 9.28	42.32 ± 10.41	43.67 ± 8.81	40.15 ± 8.08	44.44 ± 8.85
MCQ Cognitive Confidence	18.88 ± 7.02	17.79 ± 6.20	21.40 ± 8.27	17.31 ± 6.52	19.61 ± 7.35
MCQ Need to Control Thoughts	28.51 ± 7.45	28.32 ± 8.97	30.53 ± 8.77	26.38 ± 6.84	28.67 ± 5.12
MCQ Cognitive Self-Consciousness	18.80 ± 3.67	19.18 ± 4.32	18.87 ± 2.70	17.31 ± 3.99	19.22 ± 2.96
ERQ Cognitive Reappraisal	26.42 ± 6.74	26.64 ± 6.23	24.93 ± 7.07	28.77 ± 7.11	25.70 ± 7.00

0.93 for NGE, and 0.85 for LFT and internal consistency also was excellent ($\alpha = 0.971$) in line with validation studies (DiGiuseppe et al., 2018, 2020).

Meta-cognitions Questionnaire (MCQ-65: Cartwright-Hatton & Wells, 1997) is a self-report questionnaire with 65 likert scale items assessing five positive and negative evaluations of one's cognitive processes: positive beliefs about worry (19 items), beliefs about need to control thoughts (16 items), cognitive confidence (10 items), negative beliefs about the uncontrollability and danger of thoughts (13 items), and cognitive self-consciousness (7 items). The Italian translation of the MCQ-65 provided in Wells's (1999; Brazzelli & G. Cocchini Trans.) treatment manual for anxiety disorders was used. In the current study sample, Cronbach's alphas were 0.89 for positive beliefs about worry, 0.86 for beliefs about need to control thoughts, 0.88 for cognitive confidence, 0.87 for negative beliefs about the uncontrollability and danger of thoughts, and 0.66 for cognitive self-consciousness. Such values are in line with the validation of the original English version (Wells, 2009).

Eating Disorder Inventory 3 (EDI-3:Garner, 2008) is a self-rating 91 likert scale item questionnaire assessing clinically relevant psychological traits and constructs in EDs which has been standardized and translated in numerous languages including Italian. In the current study the Italian adaptation of the EDI-3 was used (Giannini et al., 2008). It yields 12 primary scales (three of which are ED-risk scales and nine of which are ED-related psychological scales) and the following six composite scales: eating disorder risk/severity, ineffectiveness, interpersonal problems, affective problems, overcontrol, general psychological maladjustment. Only the latter composite EDI-3 general psychological maladjustment scale was used. It is composed of the following nine psychological scales: low self-esteem (six items), personal alienation (seven items), interpersonal insecurity (seven items), interpersonal alienation (seven items), interoceptive deficits (nine items), emotion dysregulation (eight items), perfectionism (six items), asceticism (six items), and maturity fears (eight items), with a total of 64 items. This composite score represents a total global psychological functioning index and levels of ED-related psychopathology. The Italian EDI-3 adaptation has shown satisfactory internal consistency (Cronbach's alpha ranging from for subscales in 0.70-0.94 in ED patients) and validity. Specifically for the EDI-3 general psychological maladjustment scale, previously reported Cronbach alpha was 0.94 (Giannini et al., 2008) while in the current study sample it was .91.

Eating Attitudes Test-40 (EAT: Garner & Garfinkel, 1979) is a 40 likert scale item screening measure identifying behaviours and cognitive patterns associated with eating disorders where a greater total score indicates greater eating disorder severity. The measure yields a total score and three subscales scores: dieting, body and food preoccupations, and oral control. The measure shows excellent psychometric properties (Garner & Garfinkel, 1979). In this study, we used the Italian version of the EAT-40, which has been validated (Cuzzolaro & Petrilli, 1988) which also exhibits good psychometric properties with reported Cronbach alphas of 0.80 for dieting subscale, 0.70 for food and bulimic preoccupations subscale, and 0.83 for oral control subscale. In the current study only the EAT total score was used for which the reliability coefficient was .90 in the study population.

Emotion Regulation Questionnaire (ERQ: Gross & John, 2003) is a 10 likert item questionnaire that assesses emotion regulation strategies of expressive suppression and cognitive reappraisal. The ERQ is composed of two subscales: Cognitive Reappraisal and Expressive Suppression of six items and four items respectively. Validation studies presented in Gross and John (2003) showed that both subscales have an adequate internal consistency. In this study, the Italian version validated by Balzarotti et al. (2010) was used where Cronbach's alpha were 0.84 for the Reappraisal scale and 0.72 for the Suppression scale. Only the cognitive reappraisal subscale was used in the current study with Cronbach's alpha of .89 in the study population.

Clinical variables. Body mass index (kg/m^2) and illness duration were collected.

Statistical Analyses

Descriptive statistics were run for socio-demographic and clinical characteristics. Correlational analyses were conducted to examine the relationship between ABS-2 irrational beliefs and MCQ-65 meta-cognitions scores.

Using the PROCESS macro created by A. Hayes (2013), several models of mediation were tested to determine whether the relationships between IBs (ABS-2 IB total score) and ED symptomatology and cognitive reppraisal, were mediated by metacognitions. A total of six mediation analyses were conducted, which included bootstrapped confidence intervals (CIs) for assessing the significance of the indirect paths. Such bootstrapped confidence intervals are considered less biased than Sobel's test (Preacher & Hayes, 2004). When lower-level and upper-level confidence intervals (CI) do not overlap zero, the mediation is significant.

The mediational model tests the indirect effect of the independent variable (Irrational beliefs: ABS-2

IB total score) on the consequent dependent variables of EDI-3, EAT-40, ERQ scores through the mediators metacognitions about uncontrollability and danger and metacognitions about need to control thoughts. Path c prime (c^{I}) represents the indirect effect of IV on DV once the mediator is considered. In all the analyses, the level of significance was set at $p < 0.05$ (two-sided). The Statistical Package for Social Sciences Version 23 (SPSS) was used for all calculations.

Results

Correlational Analyses

Bivariate correlational analyses showed that all ABS-2 subscales and MCQ subscales are moderately, positively and significantly correlated with each other. See Table II for all correlational coefficients.

Mediation Analyses

Mediation analyses revealed that both MCQ-negative beliefs about uncontrollability and danger ($F_{(2,69)} = 49.052$, $p < 0.0001$, $R^2 = 0.587$) and MCQ-need to control thoughts ($F_{(2,69)} = 39.827$ $p < 0.0001$, $R^2 = 0.536$) significantly mediate the relationship between IBs (ABS-2-total score) and EDI-3-general psychological maladjustment. However, the ABS-2 IB total score remains a significant predictor in the mediation model, indicating only partial mediation.

Scores in MCQ-negative beliefs about uncontrollability and danger mediate significantly and partially the relationship between IBs (ABS-2 IB total scores) and EAT-40 total scores ($F_{(2,70)} = 13.353$, $p < 0.0001$, $R^2 = 0.276$). Instead, scores in MCQ-need to control thoughts mediate the same relationship ($F_{(2,70)} = 14.716$, $p < 0.0001$, $R^2 = 0.296$) however completely, with ABS-2 IB total score losing significance as a predictor.

To a lesser extent, MCQ-negative beliefs about uncontrollability and danger ($F_{(2,70)} = 7.873$, $p < 0.008$, $R^2 = 0.1836$) mediated the relationship between IBs (ABS-2 IB total score) and ERQ-cognitive reappraisal, while MCQ-need to control thoughts did not ($F_{(2,70)} = 6.087$, $p = 0.0037$, $R^2 = 0.1481$). However, confidence intervals revealed that such mediations are not statistically significant. Please see Table III for all coefficients and confidence intervals and Figure 1 for mediation models with significant partial and complete mediations.

Discussion

The current study is the first, to our knowledge, to investigate the relationship between IBs and metacognitions, as a potential additional contributing factor in predicting ED symptom severity and ED-related psychopathology as well as in predicting the capacity to apply cognitive reappraisal. Overall, IBs and metacognitions seem to be related constructs. While IBs are associated with all outcomes, including ED symptom severity, ED-related psychopathology and cognitive reappraisal, metacognitions were found to contribute, albeit not completely, to the relationship between IBs and ED-related psychopathology, but not to the relationship between IBs and cognitive reappraisal. Instead, the metacognition need to control thoughts contributed significantly to explaining ED severity, where IBs' contribution is lost.

Concerning correlational analyses, IBs and metacognitions were moderately and positively correlated with each other, with the exception of the metacognition of cognitive confidence, in line with the partial overlap that different conceptualizations of maladaptive cognitions within the cognitive framework may conceptually have (DiGiuseppe et al., 2017). For

Table II. Correlational Analyses between ABS-2 Irrational beliefs and MCQ-Metacognitions ($n = 77$).

	MCQ Positive Beliefs about Worry	MCQ Negative Beliefs about Worry	MCQ Cognitive Confidence	MCQ Need to Control Thoughts	MCQ Cognitive Self-Consciousness
ABS-2 Irrational Awfulizing	0.441	0.461	0.165	0.641	0.306
	$p < 0.0001$	$p < 0.0001$	$p=0.160$	$p < 0.0001$	$p=0.008$
ABS-2 Irrational Demandingness	0.423	0.388	0.186	0.579	0.354
	$p < 0.001$	$p=0.001$	$p=0.112$	$p < 0.0001$	$p=0.002$
ABS-2 Irrational Negative global evaluations	0.532	0.497	0.216	0.624	0.362
	$p < 0.0001$	$p < 0.0001$	$p=0.065$	$p < 0.0001$	$p=0.002$
ABS-2 Irrational Low Frustration Tolerance	0.469	0.457	0.114	0.586	0.337
	$p < 0.0001$	$p < 0.0001$	$p=0.334$	$p < 0.0001$	$p=0.003$
ABS-2 Total Irrational Beliefs Score	0.518	0.501	0.193	0.672	0.374
	$p < 0.0001$	$p < 0.0001$	$p=0.100$	$p < 0.0001$	$p=0.001$

Table III. Mediation Analyses Examining the Role of Irrational Beliefs as Predictor and MCQ-Metacognitions as Mediators on ED Symptomatology and Cognitive Reappraisal ($N = 72$).

(a) MCQ-Negative Beliefs about Uncontrollability and Danger as Mediator

	EDI-3 General Psychological Maladjustment		**EAT TOT**		**ERQ Cognitive Reappraisal**	
	β	SE	β	SE	β	SE
Path c (IV-DV)	0.8501**	0.1158	0.3991**	0.0867	−0.0862+	0.0271
Path a (IV-Med)	0.1675**	0.0344	0.1606**	0.0333	0.1672**	0.0340
Path b (Med-DV)	1.7474**	0.3466	0.6379+	0.3018	−0.2060+	0.0920
Path c[1] (Direct IV-DV)	0.5575**	0.1154	0.2966+	0.3018	−0.0518	0.0305
Indirect effect	**Path ab 95% Bootstrapped Confidence Interval**					
	Lower	Upper	Lower	Upper	Lower	Upper
	0.1475	0.4503	0.0000	0.2029	−0.0778	0.0003

(b) MCQ-Beliefs about Need to Control Thoughts as Mediator

Path c (IV-DV)	0.8501**	0.1158	0.3991**	0.0867	−0.0862+	0.0271
Path a (IV-Med)	0.1876**	0.0245	0.1819**	0.0239	0.1873**	0.0242
Path b (Med-DV)	1.9985*	0.5162	1.0613+	0.4141	−0.1816	0.1319
Path c[1] (Direct IV-DV)	0.4752+	0.1434	0.2060	0.1124	−0.0522	0.0365
Indirect effect	**Path ab 95% Bootstrapped Confidence Interval**					
	Lower	Upper	Lower	Upper	Lower	Upper
	0.1559	0.6128	0.0396	0.3574	−0.0983	0.0279

Note: ABS, Attitudes and Beliefs Scale; AN, Anorexia Nervosa; BED, Binge Eating Disorder; BMI, Body Mass Index; BN, Bulimia Nervosa; DV, dependent variable; EAT, Eating Attitudes Test; ED, Eating Disorders; EDI, Eating Disorder Inventory; ERQ, Emotion Regulation Questionnaire; IV, independent variable; MCQ, Meta-cognitions Questionnaire; OSFED, Other Specified Feeding or Eating Disorders; p, statistical significance

Note: 95% CI = bias corrected confidence intervals based on 5000 bootstrapped samples.

$^{+}p = .01$; $^{*}p < .001$; $^{**}p < .0001$.

example, overlap in constructs of cognitions were found in studies on anxiety and depression, where Beck's CBT concepts of maladaptive cognitions overlapped partially with Ellis' irrational beliefs processes (Sava, 2009; Szentagotai & Freeman, 2007; Tecuta et al., 2019; Wong, 2008). In the current study, ED patients who reported greater levels of negative self-beliefs and/or of awfulizing thinking endorse more strongly metacognitions about uncontrollability and danger of thoughts. Both IBs and metacognitions have been found to be associated with higher psychopathology and with negative emotions (Tajrishi et al., 2011; Vîslă et al., 2016).

Considering the mediational relationships explored among the examined constructs, the contribution of metacognitions varied depending on the type of considered metacognition and the type of outcome. Concerning ED symptom severity, the relationship between IBs and ED symptom severity including bulimia symptoms, dietary restraint, bulimic and food preoccupations, was found to be completely mediated by the metacognition of need to control thoughts and partially mediated by uncontrollability and danger of thoughts (See Figure 1). Thus, irrational belief processes contribute to increased ED severity, however the relationship is entirely explained by the patient's tendency of controlling such rigid and negative thought patterns. Integrating in CBT models of EDs the metacognitive tendency to control/suppress thoughts might offer incremental and unique information which is not captured by irrational belief processes, since they do not include elements of control. While the IB of demandingness or "must statements", included in the total IB score used in mediation analyses may be conceptually extendable to rigid expectations of control (e.g. I *must* control my thoughts), the predictive value of this IB has been found to be weaker compared to other IBs in the literature (Tecuta et al., 2019; Vîslă et al., 2016). Similarly to our study, metacognitions concerning the need to control thoughts were found to predict drive for thinness in AN patients (Davenport et al., 2015). A sense of control seems to have an important role in ED etiology (Surgenor et al., 2002) due to a sense of loss of control in other aspects of one's life (Fairburn et al., 1999), as hypothesized by clinical researchers for quite some time (Bruch, 1973; Crisp, 1980; Garfinkel & Garner, 1982). Moreover, higher endorsement of negative beliefs concerning the self were found to

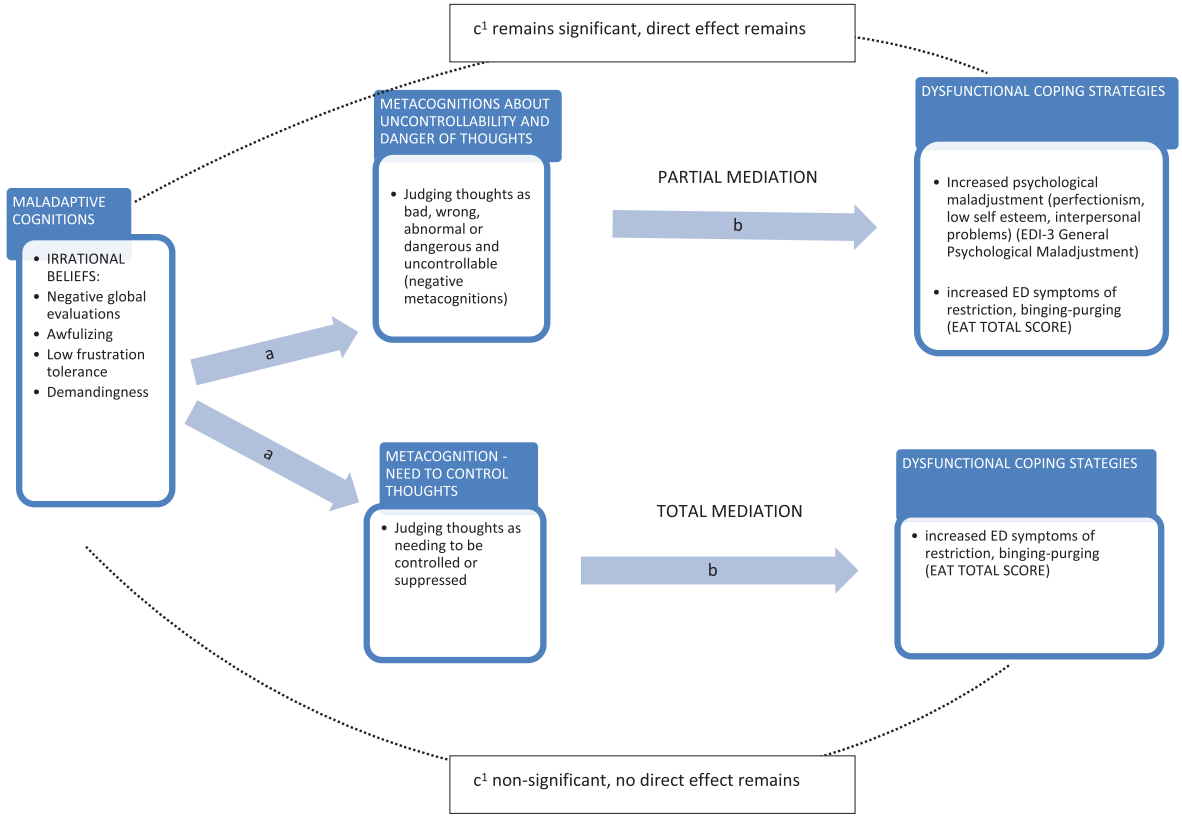

Figure 1. Mediation models.

lead to greater thoughts on loss of control, which predicted binge eating and craving in a sample of BN and BED patients more so than other types of thoughts concerning dietary restraint (Legenbauer et al., 2018). However, the current study findings where IBs lose predictive value on ED symptom severity may be due to not differentiating between the four specific IBs which might have revealed different associations.

With regards to ED-related psychopathology, both metacognitions concerning the need to control thoughts and uncontrollability and danger partially mediated the relationship between IBs and this outcome. IBs retain their predictive role on ED-related psychopathology despite the significant contribution of metacognitions. While a causal relationship between IBs and metacognitions has not yet been investigated, theoretical metacognitive models (Vann et al., 2013) would posit that ED patients in response to negative thought contents may judge such negative thinking negatively as uncontrollable, dangerous or needing to be controlled which in turn might contribute to an increased use of dysfunctional coping strategies encompassed in ED-related psychopathology (See Figure 1). However, considering a REBT theoretical perspective, metacognitions concerning a need to control thoughts and uncontrollability and danger of thoughts, might represent a manifestation of the IB of awfulizing, demandingness or negative global evaluation (e.g. "worrying/having negative thoughts is terrible", "I must control my thoughts").

Concerning cognitive reappraisal, no support was instead found for a possible mediation role of either metacognition considered in the current study. While metacognitions were found to be associated with other cognitive processes in EDs such as worry (Sapuppo et al., 2018) and craving/desire thinking (Spada et al., 2016), metacognitions did not contribute to reduced use of cognitive reappraisal due to irrational belief processes in our ED sample. However, a lack of significant results could be due to the relatively small sample size.

Several important clinical and theoretical implications for ED cognitive models and ED treatment emerge. In particular, in present CBT models and treatment approaches for EDs, irrational belief processes might be sufficient to explain difficulties in cognitive reappraisal as well as in explaining ED-related psychopathology, which may be targeted with cognitive restructuring or cognitive disputation, the primary mechanism of cognitive change in traditional second-wave CBT (Beck & Haigh, 2014; Ellis, 1994; Kazantzis et al., 2018). Such results

might be clinically important in supporting the notion promoted by clinicians of working towards an increasngly optimal transtheoretical approach in CBT rather than persuing a fragmentation of CBT approaches (Ellard et al., 2010).

While metacognitions may not warrant integration in CBT models of EDs in directly predicting cognitive reappraisal and ED-related psychopathology above and beyond the contribution of IBs, on the other hand, metacognitions pertaining to attempts to control and suppress thoughts may offer incremental validity to CBT models of EDs given their important contribution to ED symptom severity. For example, within the CBT-E model (Fairburn et al., 2003), which introduces in the traditional CBT model for EDs four crucial maintenance mechanisms of core low self-esteem, clinical perfectionism, mood intolerance and interpersonal difficulties, metacognitions about the need to control thoughts might be integrated as an additional maintenance mechanism, to be considered as a transdiagnostic feature (Vann et al., 2014). Interventions on metacognitions may include cognitive restructuring, a technique of traditional CBT approaches, of such metacognitions (Wells, 2009). Especially in EDs, the metacognitions that should be targeted concern the need to control thoughts, independently of the content of such thoughts. Additional interventions for RNT through metacognitive therapy (MT) techniques (Wells, 2009) or through rumination-focused CBT techniques (Watkins, 2016) may be warranted to further enhance ED symptom reduction. Thus far, an integration of CBT with MT has been proposed for bulimia nervosa (Cooper et al., 2009), however a transdiagnostic MT model for EDs has not yet been formulated or tested in an randomized controlled trial (Vann et al., 2014).

Limitations of the current study include a small sample size and not considering ED diagnostic differences. The findings may also be due to the ABS-2 instrument's focus on contextual areas of life regarding achievement, approval and comfort rather than focusing on specific ED themes of food, body weight and shape as well as the MCQ-65 measuring general metacognitions rather than specific ED-related metacognitions. Future research should further explore irrational beliefs pertaining to ED themes in relation to metacognitions over time, as well as retest the relationship in predicting cognitive reappraisal with a larger sample.

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References

American Psychiatric Association. (2006). *Practice guideline for the treatment of patients with eating disorders* (3rd ed.). American Psychiatric Association.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of Mental disorders* (5th ed.). American Psychiatric Association.https://doi.org/10.1176/appi.books.9780890425596.

Atwood, M. E., & Friedman, A. (2020). A systematic review of enhanced cognitive behavioral therapy (CBT-E) for eating disorders. *The International Journal of Eating Disorders*, *53*(3), 311–330. https://doi.org/10.1002/eat.23206

Balzarotti, S., John, O. P., & Gross, J. J. (2010). An Italian adaptation of the emotion Regulation Questionnaire. *European Journal of Psychological Assessment*, *26*(1), 61–67. https://doi.org/10.1027/1015-5759/a000009

Beck, A. T., & Haigh, E. A. P. (2014). Advances in cognitive theory and therapy: The generic cognitive model. *Annual Review of Clinical Psychology*, *10*, 1–24. https://doi.org/10.1146/annurev-clinpsy-032813-153734.

Bruch, H. (1973). *Eating disorders: Obesity, anorexia nervosa and the person within*. Basic Books.

Cartwright-Hatton, S., & Wells, A. (1997). Beliefs about worry and intrusions: The meta-cognitions questionnaire and its correlates. *Journal of Anxiety Disorders*, *11*(3), 279–296. https://doi.org/10.1016/S0887-6185(97)00011-X

Cooper, M. (2005). Cognitive theory of anorexia nervosa and bulimia nervosa: Progress, development and future directions. *Clinical Psychology Review*, *25*, 511–531. https://doi.org/10.1016/j.cpr.2005.01.003

Cooper, M. J., Todd, G., & Wells, A. (2009). *Treating bulimia nervosa and binge eating: An integrated metacognitive and cognitive therapy manual*. Routledge.

Crisp, A. H. (1980). *Anorexia nervosa: Let me be*. Academic Press.

Cuzzolaro, M., & Petrilli, A. (1988). Validazione della versione italiana dell'EAT-40 (eating Attitude Test di D. M. Garner e P. E. Garfinkel). *Psichiatria Dell'infanzia e Dell'adolescenza*, *55*, 209–217.

Danner, U. N., Evers, C., Stok, F. M., van Elburg, A. A., & de Ridder, D. T. (2012). A double burden: Emotional eating and lack of cognitive reappraisal in eating disordered women. *European Eating Disorders Review*, *20*(6), 490–495. https://doi.org/10.1002/erv.2184

Davenport, E., Rushford, N., Soon, S., & McDermott, C. (2015). Dysfunctional metacognition and drive for thinness in typical and atypical anorexia nervosa. *Journal of Eating Disorders*, *3*, 24. https://doi.org/10.1186/s40337-015-0060-4

Del Pozo, M. A., Harbeck, S., Zahn, S., Kliem, S., & Kröger, C. (2018). Cognitive distortions in anorexia nervosa and borderline personality disorder. *Psychiatry Research*, *260*, 164–172. https://doi.org/10.1016/j.psychres.2017.11.043

DiGiuseppe, R., David, D., & Venezia, R. (2016). Cognitive theories. In J. C. Norcross, G. R. VandenBos, & D. F. Freedheim (Eds.), *The handbook of clinical psychology volume II of V. Theory and research* (pp. 45–182). American Psychological Association.

DiGiuseppe, R., Gorman, B., & Raptis, J. (2020). The factor Structure of the Attitudes and beliefs scale 2: Implications for rational Emotive behavior therapy. *Journal of Rational Emotive Cognitive-Behavior Therapy*, *38*, 111–142. https://doi.org/10.1007/s10942-020-00349-0

DiGiuseppe, R., Leaf, R., Gorman, B., & Robin, R. (2018). The development of a measure of irrational/rational beliefs. *Journal of Rational-Emotive and Cognitive-Behavior Therapies*, *36*(1), 47–79. https://doi.org/10.1007/s10942-017-0273-3.

DiGiuseppe, R. A., Venezia, R., & Gotterbarn, R. (2017). What is cognitive behavior therapy? In A. Vernon, & K. Doyle (Eds.), *Cognitive behavior therapies: A guidebook for practitioners* (pp. 1–36). American Counseling Association.

Ehring, T., & Watkins, E. R. (2008). Repetitive negative thinking as a transdiagnostic process. *International Journal of Cognitive Therapy*, *1*(3), 192–205. https://doi.org/10.1680/ijct.2008.1.3.192.

Ehring, T., Zetsche, U., Weidacker, K., Wahl, K., Schönfeld, S., & Ehlers, A. (2011). The Perseverative thinking Questionnaire (PTQ): validation of a content-independent measure of repetitive negative thinking. *Journal of Behavior Therapy and Experimental Psychiatry*, *42*(2), 225–232. https://doi.org/10.1016/j.jbtep.2010.12.003.

Ellard, K. K., Fairholme, C. P., Boisseau, C. L., Farchione, T. J., & Barlow, D. H. (2010). Unified Protocol for the transdiagnostic treatment of emotional disorders: Protocol development and initial outcome data. *Cognitive and Behavioral Practice*, *17*(1), 88–101. https://doi.org/10.1016/j.cbpra.2009.06.002

Ellis, A. (1958). Rational Psychotherapy. *Journal of General Psychology*, *59*, 35–49. https://doi.org/10.1080/00221309.1958.9710170

Ellis, A. (1994). *Reason and emotion in psychotherapy* (Rev. ed.). Birch Lane.

Ellis, A., & Dryden, W. (2007). *The Practice of rational Emotive behavior therapy* (2nd ed.). Springer Publishing Company.

Fairburn, C. G., Cooper, Z., Doll, H. A., O'Connor, M. E., Palmer, R. L., & Dalle Grave, R. (2012). Enhanced cognitive behavioural therapy for adults with anorexia nervosa: A UK-Italy study. *Behavior Research & Therapy*, *51*, 2–8. https://doi.org/10.1016/j.brat.2012.09.010.

Fairburn, C. G., Cooper, Z., & Shafran, R. (2003). Cognitive behaviour therapy for eating disorders: A "transdiagnostic" theory and treatment. *Behavior Research and Therapy*, *41*, 509–528. https://doi.org/10.1016/s0005-7967.

Fairburn, C. G., Shafran, R., & Cooper, Z. (1999). A cognitive behavioural theory of anorexia nervosa. *Behavior Research and Therapy*, *37*, 1–13. https://doi.org/10.1016/S0005-7967(98)00102-8

First, M. B., Williams, J. B. W., Karg, R. S., & Spitzer, R. L. (2015). *Structured clinical interview for DSM-5 disorders, Clinician version (SCID-5-CV)*. American Psychiatric Association.

Garfinkel, P. E., & Garner, D. M. (1982). *Anorexia nervosa: A Multidimensional perspective*. Brunner/Mazel Inc.

Garner, D. M. (2008). *EDI-3. Eating disorder Inventory-3. Professional manual*. Psychological Assessment Research, Inc.

Garner, D. M., & Garfinkel, P. E. (1979). The eating Attitude Test: An index of the symptoms of anorexia nervosa. *Psychological Medicine*, *9*(2), 273–279. https://doi.org/10.1017/S0033291700030762

Giannini, M., Pannocchia, L., dalle Grave, R., Muratori, F., & Viglione, V. (2008). *Adattamento italiano dell'EDI-3. Eating disorder Inventory-3 trans*. Giunti Psychometrics.

Gross, J. J., & John, O. P. (2003). Individual differences in two emotion regulation processes: Implications for affect, relationships, and well-being. *Journal of Personality and Social Psychology*, *85*, 348–362. https://doi.org/10.1037/0022-3514.85.2.348

Hayes, A. (2013). *Introduction to mediation, moderation, and conditional process analysis: A regression-based approach*. Guilford Press.

Hays, S. C., & Hofmann, S. G. (2017). The third wave of cognitive behavioral therapy and the rise of process-based care. *World Psychiatry*, *16*(3), 245–246. https://doi.org/10.1002/wps.20442

Jones, C. J., Leung, N., & Harris, G. (2007). Dysfunctional core beliefs in eating disorders: A review. *Journal of Cognitive Psychotherapy*, *21*(2), 156–171. https://doi.org/10.1891/088983907780851531

Kazantzis, N., Luong, H. K., Usatoff, A. S., Impala, T., Ying Yew, R., & Hofmann, S. G. (2018). The processes of cognitive behavioral therapy: A review of meta-analyses. *Cognitive Therapy and Research*, *42*, 349–357. https://doi.org/10.1007/s10608-018-9920-y

Legenbauer, T., Radix, A. K., Augustat, N., & Schütt-Strömel, S. (2018). Power of cognition: How dysfunctional cognitions and Schemas Influence eating behavior in Daily life Among Individuals With eating disorders. *Frontiers in Psychology*, *9*, 2138. https://doi.org/10.3389/fpsyg.2018.02138

Linardon, J., Fairburn, C. G., Fitzsimmons-Craft, E. E., Wilfley, D. E., & Brennan, L. (2017). The empirical status of the third-wave behaviour therapies for the treatment of eating disorders: A systematic review. *Clinical Psychology Review*, *58*, 125–140. https://doi.org/10.1016/j.cpr.2017.10.005

Macavei, B. (2002). A Romanian adaptation of the Attitudes and belief scale 2. *Romanian Journal of Cognitive and Behavioral Psychotherapies*, *2*, 105–122.

Macavei, B. (2005). The role of irrational beliefs in the rational emotive behavior theory of depression. *Journal of Cognitive and Behavioral Psychotherapies*, *5*, 73–83.

Möller, A. T., & Bothma, M. E. (2001). Body dissatisfaction and irrational beliefs. *Psychological Reports*, *88*, 423–430. https://doi.org/10.2466/pr0.2001.88.2.423

National Health Service. (2017). *National Institute for clinical excellence (NICE) clinical guideline for eating disorders*. National Institute for Clinical Excellence.

Nolen-Hoeksema, S., Wisco, B. E., & Lyubomirsky, S. (2008). Rethinking rumination. *Perspectives on Psychological Science*, *3*(5), 400–424. https://doi.org/10.1111/j.1745-6924.2008.00088.x

Olstad, S., Solem, S., Hjemdal, O., & Hagen, R. (2015). Metacognition in eating disorders: Comparison of women with eating disorders, self-reported history of eating disorders or psychiatric problems, and healthy controls. *Eating Behaviors*, *16*, 17–22. https://doi.org/10.1016/j.eatbeh.2014.10.019

Preacher, K. J., & Hayes, A. F. (2004). SPSS and SAS procedures for estimating indirect effects in simple mediation models. *Behavior Research Methods, Instruments, & Computers*, *36*, 717–731. https://doi.org/10.3758/BF03206553

Quattropani, M. C., Lenzo, V., Faraone, C., Pistorino, G., Di Bella, I., & Mucciardi, M. (2016). The role of metacognition in eating behavior: An exploratory study. *Mediterranean Journal of Clinical Psychology*, *4*(3), 1–15.

Sapuppo, W., Ruggiero, G. M., Caselli, G., & Sassaroli, S. (2018). The body of cognitive and metacognitive variables in eating disorders: Need of control, negative beliefs about worry uncontrollability and danger, perfectionism, self-esteem and worry. *The Israel Journal of Psychiatry and Related Sciences*, *55*(1), 55–63.

Sava, F. (2009). Maladaptive Schemas, irrational beliefs, And their relationship With the five-factor Personality model. *Journal of Cognitive and Behavioral Psychotherapies*, *9*(2), 135–147. https://doi.org/10.5829/idosi.mejsr.2013.16.04.11755

Spada, M. M., Caselli, G., Fernie, B. A., Nikčević, A. V., Ruggiero, G. M., Boccaletti, F., Dallari, G., & Sassaroli, S. (2016). Metacognitions about desire thinking predict the severity of binge eating in a sample of Italian women. *Eating and*

Weight Disorders: EWD, *21*(2), 297–304. https://doi.org/10.1007/s40519-015-0205-0

Sun, X., Zhu, C., & So, S. H. W. (2017). Dysfunctional metacognition across psychopathologies: A meta-analytic review. *European Psychiatry*, *45*, 139–153. https://doi.org/10.1016/j.eurpsy.2017.05.029

Surgenor, L. J., Horn, J., Plumridge, E. W., & Hudson, S. M. (2002). Anorexia nervosa and psychological control: A reexamination of selected theoretical accounts. *European Eating Disorder Review*, *10*, 85–101. https://doi.org/10.1002/erv.457.

Szentagotai, A., & Freeman, A. (2007). An analysis of the relationship between irrational beliefs and automatic thoughts in predicting distress. *Journal of Cognitive and Behavioral Psychotherapies*, *7*, 1–9.

Tajrishi, K. Z., Mohammadkhani, S., & Jadidi, F. (2011). Metacognitive beliefs and negative emotions. *Procedia - Social and Behavioral Sciences*, *30*, 530–533. https://doi.org/10.1016/j.sbspro.2011.10.103

Tecuta, L., Tomba, E., Lupetti, A., & DiGiuseppe, R. (2019). Irrational beliefs, cognitive distortions, and Depressive symptomatology in a college-Age sample: A mediational Analysis. *Journal of Cognitive Psychotherapy: An International Quarterly*, *33*(2), 116–127. https://doi.org/10.1891/0889-8391.33.2.116

Terjesen, M. D., Salhany, J., & Sciutto, M. J. (2009). A psychometric review of measures of irrational beliefs: Implications for psychotherapy. *Journal of Rational-Emotive & Cognitive Behavior Therapy*, *27*(2), 83–96. https://doi.org/10.1007/s10942-009-0093-1.

Vann, A., Strodl, E., & Anderson, E. (2013). Thinking about internal states, a qualitative investigation into metacognitions in women with eating disorders. *Journal of Eating Disorders*, *1*, 22. https://doi.org/10.1186/2050-2974-1-22

Vann, A., Strodl, E., & Anderson, E. (2014). The transdiagnostic nature of metacognitions in women with eating disorders. *Eating Disorders*, *22*(4), 306–320. https://doi.org/10.1080/10640266.2014.890447

Vîslă, A., Flückiger, C., Grosse Holtforth, M., & David, D. (2016). Irrational beliefs and psychological distress: A meta-analysis. *Psychotherapy and Psychosomatics*, *85*(1), 8–15. https://doi.org/10.1159/000441231

Watkins, E. R. (2016). *Rumination-focused cognitive-behavioral therapy for depression*. Guildford Press.

Wells, A. (1999). *Appendix in cognitive therapy of anxiety disorders* (M. Brazzelli & G. Cocchini, Trans.). McGraw-Hill.

Wells, A. (2009). *Metacognitive therapy for anxiety and depression*. Guilford Press.

Wong, S. S. (2008). The relations of cognitive triad, dysfunctional attitudes, automatic thoughts, and irrational beliefs with test anxiety. *Current Psychology*, *27*(3), 177–191. https://doi.org/10.1007/s12144-008-9033-y

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ORIGINAL RESEARCH

An innovative approach for the assessment of mood disturbances in patients with eating disorders

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Objective. Assessment of mood in eating disorders (EDs) has important clinical implications, but the current standard psychiatric classification (DSM-5) has limitations. The aim of the current study is to broaden the evaluation of depressive symptomatology by providing a comprehensive and innovative assessment approach in EDs through instruments that capture clinical phenomena of demoralization, subclinical distress, and psychological well-being.

Methods. Seventy-nine patients who met diagnostic criteria for EDs of the *Diagnostic and Statistical Manual of Mental Disorders – Fifth edition* (DSM-5) were evaluated for depressive symptoms through Paykel's Clinical Interview for Depression, the Structured Clinical Interview for DSM-5 for major depressive episode and persistent depressive disorder, and the Diagnostic Criteria for Psychosomatic Research (DCPR) interview for demoralization. Further, self-report inventories encompassing psychological well-being and distress were used.

Results. Guilt, abnormal reactivity to social environment, and depressed mood were the most common depressive symptoms in the sample. DSM-defined depressive disorders were found in 55.7% of patients. The DCPR-demoralization criteria identified an additional 20.3% of the sample that would have been undetected with DSM criteria. Both DSM and DCPR diagnostic categories were associated with compromised psychological well-being and distress. Demoralization, unlike depression, was not associated with the severity of ED symptomatology.

Conclusion. The findings indicate that a standard psychiatric approach, DSM-5-based, captures only a narrow part of the spectrum of mood disturbances affecting patients with EDs. A broadened clinimetric assessment unravels the presence of demoralization and yields clinical distinctions that may entail prognostic and therapeutic differences among patients who would be otherwise simply labeled as depressed.

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Key words: Demoralization, depression, eating disorders, psychological well-being.

Introduction

Depression is a frequent complication of eating disorders (EDs) and eating disturbances are common manifestations of depressive illness. The nature of the relationship, however, has been a source of controversy. A shared etiology postulates a common set of risk factors leading to the development of both EDs and depression.[1] Mood disorder onset might precede, follow, or develop simultaneously to the ED,[2] suggesting the need of specifically evaluating the individual case.

Diagnosis of depression in EDs constitutes a difficult task. Not surprisingly, comorbidity rates of major depressive disorder (MDD) display wide fluctuations from 40% to 80%[2,3] and lack predictive value as to response to antidepressant therapy.[4] Overlapping symptomatology, such as excessive weight loss, over-eating, sleep disturbance, fatigue, irritability, concentrating difficulties, and poor memory,[5,6] may account for inflated depression diagnoses in this clinical population.[7,8]

It has been suggested that exclusive reliance on conventional diagnostic classification systems may not

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provide sufficient clinical information, and assessment may benefit from additional sources of information.[9] One source derives from expanding collection of symptoms to clinical manifestations that frequently occur in the longitudinal development of mood disorder.[10] The Clinical Interview for Depression[11,12] is uniquely suited for capturing such manifestations. Another important element of the clinical process comes from the concept of demoralization,[13,14] a feeling state characterized by the perception of being unable to cope with some pressing problems and/or of lack of adequate support from others.[15] Demoralization, seldom investigated in EDs,[16] may co-occur with major depression or be independent[15] and is associated with adverse health outcomes and poor quality of life. Finally, a neglected area in assessment is psychological well-being, despite the availability of validated instruments and its growing importance in establishing resilience. Dimensions of positive functioning were found to affect the complex balance between positive and negative affects both in mood[17] and eating[18,19] disorders.

The aim of the current study was to broaden the evaluation of depressive symptomatology in EDs with instruments that capture clinical phenomena such as demoralization and subclinical distress and to examine their associations with dimensional measures of psychological well-being. More specifically, the study aimed to provide a comprehensive and innovative assessment of mood in EDs, capturing not only traditional psychiatric disturbances such as depression but also subclinical manifestations and psychological states such as demoralization. We hypothesize that a subset of ED patients exhibits demoralization syndrome in the absence of major depression and vice versa. In addition, we hypothesize that demoralization is associated with significant distress and impaired positive functioning.

Methods

Participants

Consecutively recruited patients ($n = 81$) who met Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) criteria for EDs,[20] anorexia nervosa (AN), bulimia nervosa (BN), binge-eating disorder (BED), and other specified feeding or eating disorder (OSFED) were recruited from specialized ED treatment centers, Centro Gruber and Residenza Gruber (Bologna, Italy), before commencing treatment. ED diagnoses were established at intake by the consensus of a psychiatrist and a clinical psychologist independently using the Structured Clinical Interview for DSM-5 (SCID).[20] With the exception of two patients who refused to participate, all invited patients took part in the study ($n = 79$).

Ethical review committees of the Centro Gruber and Residenza Gruber in Bologna, Italy, approved the study and all patients provided written informed consent after the procedures were explained to them.

Measures and clinical variables

The evaluation was performed during routine assessment visits. Participants underwent detailed clinical interviews by a trained clinical psychologist and completed several self-rating questionnaires for the assessment of distress and psychological well-being. Data were collected between April 2016 and October 2017.

(1) Depressive disorder diagnoses were obtained using the SCID[20] for depressive disorders. For a diagnosis of major depression, patients had to exhibit five out of eight symptoms one of which was depressed mood or loss of interest or pleasure. The criterion of significant weight gain or loss or change in appetite was excluded as ED patients exhibit changes in weight and appetite in accordance with ED disorder diagnosis. For a diagnosis of persistent depressive disorder, in addition to depressed mood for most of the day, for more days than not for 2 years, the patients had to exhibit at least two additional symptoms, with the exception of poor appetite or overeating.

(2) Depressive symptoms were assessed with the change version of the Clinical Interview for Depression 20-item interview,[11,12] a dimensional observer-rated assessment instrument which consists of an expanded version of the Hamilton Rating Scale for Depression.[21] The interview covers 20 symptom areas. In this modified version, two items concerning appetite and weight gain/loss (items 12 and 13) were omitted due to the potentially confounding aspects of ED-related symptomatology. Each item is rated on a 1–7 point scale, with 1 indicating the absence of symptoms and 7 severe incapacitating manifestations. A score of 3 or above in the individual items was considered the cut-off for the presence of the symptom. The scale encompasses a wide range of symptoms (such as irritability and phobic anxiety) compared to other scales and is particularly suitable to assess subclinical symptoms of mood disorders.[10,12,22] One item concerning reactivity to social environment, selected from the full version of the CID, was added to the 18 items.

(3) Demoralization diagnosis was obtained using The revised Structured Interview for the Diagnostic Criteria for Psychosomatic Research (DCPR)-Demoralization Criteria.[14] Diagnoses were formulated independently of DSM diagnostic findings. Items of the interview for DCPR are scored through a yes/no response format. The structured interview has demonstrated high inter-rater reliability, and Cohen's kappa for demoralization was found to be 0.90.[23] The revised DCPR criteria[14] allow differentiation of two expressions of demoralization: helplessness (the individual maintains the capacity to react, but lacks adequate support) and hopelessness (when the individual feels he/she alone is responsible

TABLE 1. Socio-demographic characteristics of ED patient sample ($n = 79$)

Variable	Total ED sample (n = 79)	Outpatients (n = 42)	Inpatients (n = 37)	*p*
Age	28.83 ± 11.25	28.64 ± 12.38	29.06 ± 9.943	0.873+
Education (years)	14.44 ± 3.15	14.40 ± 3.03	14.48 ± 3.355	0.912+
Marital status (% single)	74.7	84.6	74.3	0.087*
Occupation (% employed or student)	75.3	92.3	51.35	0.001*
BMI (kg/m^2)				
AN (*n*)	(42): 15.26 ± 1.76	(17): 15.63 ± 1.69	(25): 15.00 ± 1.79	0.260+
BN (*n*)	(13): 22.60 ± 5.29	(7): 24.05 ± 6.91	(6): 20.90 ± 1.87	0.350+
BED (*n*)	(13): 35.53 ± 9.95	(10): 32.73 ± 9.77	(3): 43.92 ± 4.69	0.092+
OSFED (*n*)	(11): 21.26 ± 8.61	(8): 18.30 ± 3.65	(3): 33.11 ± 14.93	0.392+
Illness duration (years)	9.45 ± 9.17	7.49 ± 8.96	11.69 ± 9.021	0.04+
Antidepressant use within group (%)	27.8	22.2	38.9	0.125*

Note. AN, anorexia nervosa; BED, binge-eating disorders; BN, bulimia nervosa; and OSFED, Other-specified feeding or eating disorder.
*Pearson Chi-squared.
+T-test for independent samples.

for the situation and there is nothing he /she or anyone else can do to overcome the problem).

(4) Self-report depressive symptoms were assessed with the Beck Depression Inventory II (BDI-II)[24] a 21-item questionnaire. A total score ranging 0–63 indicates depression severity with higher total scores indicate more severe depressive symptoms. Composite scales of cognitive and somatic-affective symptoms were calculated.[25]

(5) Positive functioning was evaluated with the Psychological Well-being Scales – PWB,[26,27] an 84-item self-rated questionnaire that covers six inter-related areas of psychological well-being which allow the development of optimal functioning: autonomy, environmental mastery, personal growth, positive relations with others, purpose in life, and self-acceptance. Items are constructed on a six-point 1–6 Likert scale, yielding six subscale scores ranging from 14 to 84. Subscale scores range from 0 to 98 with higher scores indicate greater psychological well-being in specific dimensions.

(6) ED symptomatology was assessed with the Eating Attitudes Test-40,[28,29] a 40-item screening measure identifying behaviors and cognitive patterns of EDs. Items are constructed on a 0–3 four-point Likert scale, yielding three subscale scores for dimensions of dieting, body, and food preoccupation, oral control, and a total score ranging from 0 to 120. Higher scores indicate greater ED psychopathology.

In addition to administering these clinical scales, Body mass index (BMI), illness duration in months, and type of antidepressant therapy were collected from the medical records.

Data analysis

Descriptive analyses were run for frequency of CID-rated specific depression symptoms and frequencies of demoralization and depressive illness (persistent depressive disorder and MDD) in the total sample. Univariate analyses of variance using the general linear model were performed to test for associations between DSM-5 Depressive Disorders and the DCPR-based classification of demoralization and average scores on dimensional psychological measures after controlling for illness duration. DSM-5 and DCPR-based diagnoses were examined separately. For all tests performed, the significance level was set at 0.05, two-tailed. In view of the exploratory nature of the investigation, adjustment for multiple testing was not performed. Age, educational level, and BMI were not significantly correlated with any outcome variable and were therefore excluded from analyses.[30]

Results

ED patients characteristics

The patient response rate was high with 97.53% ($n = 79$) of ED outpatients out of 81 agreeing to participate (see Table 1 for descriptive socio-demographic and clinical data). Data on specific depression symptoms through CID interview were available for 72 patients. The 79 ED patients were all female with mean age 28.83 ± 11.25 years, range 15–58 years, and mean educational years 14.44 ± 3.15. About half, 53.2% ($n = 42$), were outpatients and the remaining 46.8% were inpatients ($n = 37$). Outpatients and inpatients did not differ significantly in main socio-demographic characteristics, that is age, education, or in BMI. They differed significantly in illness duration ($p = 0.04$) with inpatients reporting longer length of illness (11.69 ± 9.02 years) compared to outpatients (7.49 ± 8.96 years). Almost a third ($n = 22$, 27.8%) of patients were currently on antidepressants, the most common being selective serotonin-reuptake

TABLE 2. Frequency of depression symptoms (CID items) in ED patients ($n = 72$)

CID ITEM	Symptom frequency (*n*)	Symptom frequency (%)
Guilt	57	79.2
Environmental reactivity	56	77.8
Depressed mood	55	76.4
Energy and fatigue	51	70.8
Generalized anxiety	46	63.9
Work and interests	42	58.3
Somatic anxiety	41	56.9
Pessimism	38	52.8
Delayed insomnia	33	45.8
Phobic anxiety	29	40.3
Suicidal tendencies	25	34.7
Phobic avoidance	23	31.9
Irritability	23	31.9
Early insomnia	22	30.6
Depressed appearance	22	30.6
Panic attacks	14	19.4
Psychomotor retardation	14	19.4
Agitation	7	9.7
Hostility	4	5.6

Note. CID, Clinical Interview for Depression.

inhibitors ($n = 18$). Inpatient and outpatient groups did not differ significantly in severity (BDI and CID total scores) of depression. Diagnostic subgroups (AN, BN, BED, and OSFED) also did not differ in severity of depression. See Table 1.

Frequency of depressive symptoms in ED patients

The most common CID depressive symptoms in the ED sample ($n = 72$) were feelings of guilt, environmental reactivity, depressed mood, and low energy or fatigue, which were present in about two-thirds of the sample. Please see Table 2 for frequencies of these and of other depressive symptoms.

Relationship of DSM depression diagnoses and DCPR demoralization

Diagnoses are displayed in Figure 1. Nineteen patients (24.0%) were without any mood-related comorbidity (i.e., unaffected). A fifth of patients reported only demoralization (20.3%), 12 with helpless demoralization, and 4 cases of hopeless demoralization. In terms of DSM-defined diagnoses, comorbid persistent depressive disorder was reported by 16.5% of the patients, while MDD was the most prevalent (39.2%). Demoralization overlapped partially with both persistent depressive disorder and MDD. None of the unaffected ED patients and about half ($n = 16$) of the comorbid MDD group were on antidepressant medications. Three demoralized and four ED patients with persistent depressive disorder were also on antidepressants.

Associations between DSM 5 Depressive Disorders and dimensional psychological variables

According to univariate analyses of variance comparisons, comorbid depressive disorder (MDD or persistent depressive disorder) was associated with significantly greater distress in terms of depressive symptoms in BDI-II as well as in EAT-eating-related pathology, including oral control, food and bulimic worry, and dietary restraint. In terms of psychological well-being, presence of a depressive illness was associated with significantly worse functioning in PWB dimensions of environmental mastery, positive relations with others, purpose in life, and self-acceptance. Table 3 displays the comparisons between ED patients with and without comorbid DSM depressive illness.

Associations between DCPR demoralization and dimensional psychological variables

Univariate analyses of variance yielded some significant associations between diagnoses formulated according to the DCPR-based demoralization and dimensional psychological variables. Demoralization diagnosis in ED patients was also associated with significantly greater distress in terms of BDI-II scores but not in terms of EAT-eating-related pathology, in which no significant differences between demoralized and non-demoralized ED patients emerged. Nonetheless, in PWB dimensions of psychological well-being, occurrence of demoralization was associated with significantly worse functioning in environmental mastery, positive relations with others, purpose in life, and self-acceptance. Table 3 illustrates the comparisons between demoralized and non-demoralized ED patients.

Discussion

Despite some limitations of the current study, namely the small sample size and cross-sectional design, the joint use of a comprehensive clinical interview for depression[11,12] with the DSM diagnostic criteria[20] and demoralization and psychological well-being assessment has yielded important clinical insights into mood disturbances in EDs.

First, diagnostic criteria place particular emphasis on a specific set of symptoms within a certain symptomatology. Such priority, however, does not necessarily apply to a setting of comorbidity, where other symptoms may be prominent and characteristic. The innovativeness of the applied assessment approach resides in the use of the clinimetric approach. Clinimetrics refers to clinically

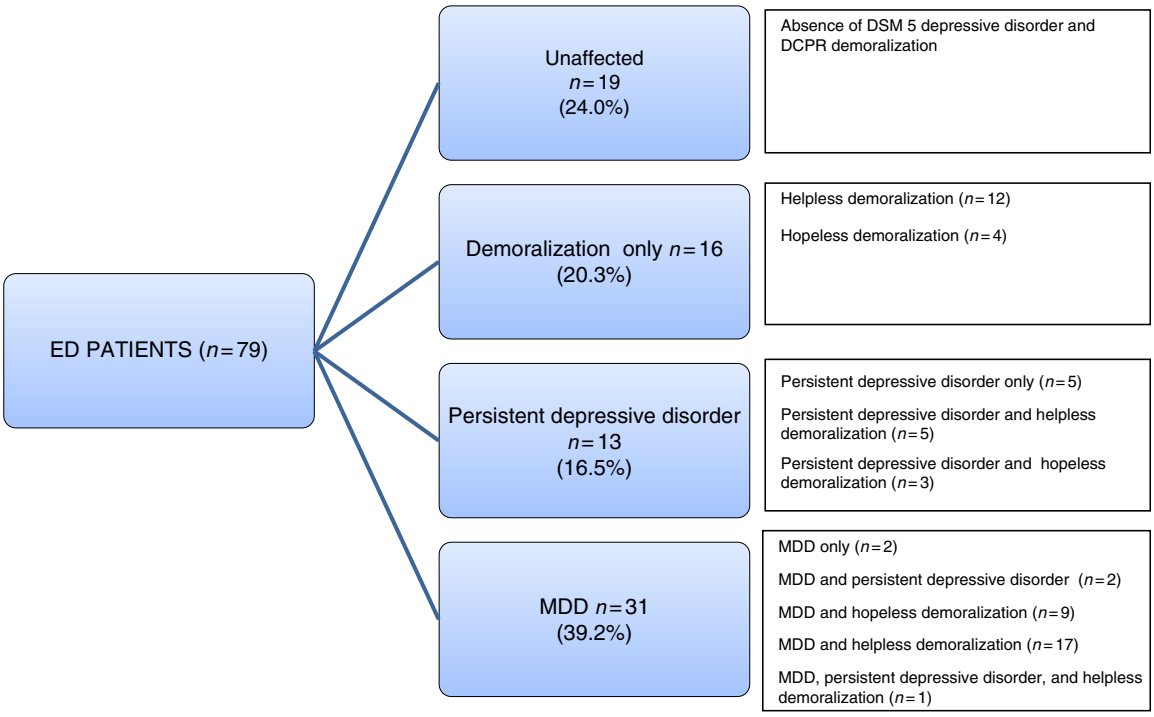

FIGURE 1. Prevalence of demoralization subtypes, persistent depressive disorder, and major depression in ED patients.
Notes: DCPR, Diagnostic Criteria for Psychosomatic Research; ED, eating disorder; MDD, major depressive disorder.

relevant information frequently ignored by traditional psychiatric approaches such as patterns of symptoms, severity of illness, effects of comorbid conditions, timing of phenomena, rate of progression of illness, functional capacity, and other aspects such as positive functioning. The use of a macro-analytic evaluation using clinician-rated scales such as the CID and DCPR, followed by the use of a micro-analysis of specific symptoms through self-rating scales, allows to capture subclinical symptoms, which would have been otherwise undetected.[9] Using the CID, the most common depression symptoms in EDs were depressed mood, feelings of guilt, and abnormal reactivity to social environment. Guilt has been found to be exceedingly common in ED patients, not globally, but in particular, in relation to eating and eating behaviors[31,32] and in relation to body shame.[33] Moreover, it has been found to persist throughout the recovery process from the disorder.[31] Reactivity to social environment refers to the changes in mood and symptomatology, as a result of environmental circumstances, either improvement or worsening. It has been found to characterize cyclothymia[34] and to be prevalent in the prodromal phase of BN compared to unaffected controls.[35] Recent studies on emotional reactivity in EDs[36] suggest that such reactivity in AN and BN might be related to social situations in which patients are pressured to consume high-calorie food, evoking states of anxiety, and depression.[37]

Anxiety, whether generalized, somatic or phobic, was also found to be very common. Studies have shown that anxiety symptomatology is often comorbid and may precede EDs.[38] More specifically, EDs have been found to be associated with body anxiety, eating and food preoccupations, pre-meal anxiety,[39] and avoidance behaviors relating to food, body, and interpersonal situations.[40,41] Indeed, recent research explores the efficacy of exposure therapy and response prevention in the treatment of AN.[42]

Figure 1 illustrates the complexity of mood assessment in EDs. Using DCPR criteria, 20% of patients met the criteria for demoralization. Such patients would not be identified using DSM criteria only. The percentage of demoralization cases is in line with varying prevalence rates in the medical and psychiatric setting.[15] In EDs, a previous study which had not taken into account a possible overlap with major depression and dysthymic disorder had reported higher rates.[16] Interestingly, cases of demoralization in the absence of depressive disorder were mostly of the helpless subtype.

Associations of DCPR demoralization with dimensional psychological measures provide further support to its validity and utility. Consistent with previous studies,[15,43] demoralization was found to be associated with lower psychological well-being and greater distress. Moreover, the same number of significant associations was found between demoralization and depressive illness and psychological variables, with the exception of ED-related symptoms, which were not associated with demoralization. Findings lend support to the hypothesis

TABLE 3. Associations of DSM-5 depressive disorders and DCPR-based demoralization with dimensional psychological measures ($n = 79$)

VARIABLE	Depressive disorder (+) $n = 44$	Depressive disorder (–) $n = 35$				Demoralization (+) $n = 51$	Demoralization (–) $n = 28$			
	Estimated marginal mean (S.E.)	Estimated marginal mean (S.E.)	F (1.72)	p	Partial eta squared	Estimated marginal mean (S.E.)	Estimated marginal mean (S.E.)	F (1.72)	p	Partial eta squared
BDI-II Cognitive subscale	17.667 (1.092)	9.764 (1.124)	25.122	<0.0001	0.273	11.641 (.808)	5.234 (1.044)	22.062	<0.0001	0.253
BDI-II Somatic-affective subscale	12.297 (.856)	6.086 (.856)	26.145	<0.0001	0.287	17.272 (1.018)	8.345 (1.309)	26.883	<0.0001	0.286
EAT oral control	12.493 (1.326)	7.071 (1.520)	7.211	0.009	0.092	10.533 (1.333)	9.439 (1.848)	0.217	0.643	0.003
EAT food -bulimic worry	12.232 (.938)	6.383 (1.075)	16.777	<0.0001	0.191	10.648 (.984)	7.957 (1.364)	2.409	0.125	0.033
EAT dietary restraint	27.497 (2.281)	13.347 (2.614)	16.597	<0.0001	0.189	23.717 (2.388)	17.061 (3.312)	2.499	0.118	0.034
PWB autonomy	47.035 (2.356)	54.367 (2.499)	4.557	0.037	0.066	46.595(2.095)	58.097 (3.005)	9.230	0.003	0.124
PWB environmental mastery	55.965 (1.772)	64.767 (1.772)	12.318	0.001	0.161	42.342 (1.612)	56.549 (2.312)	23.779	<0.0001	0.268
PWB personal growth	57.388 (1.888)	64.063 (2.002)	5.880	0.018	0.083	58.228 (1.750)	65.033 (2.510)	4.631	0.035	0.067
PWB positive relations	50.666 (2.184)	63.564 (2.317)	16.398	<0.0001	0.201	51.021(1.924)	67.915 (2.758)	23.625	<0.0001	0.267
PWB purpose in life	47.537 (1.779)	55.614 (1.887)	9.694	0.003	0.130	47.425 (1.562)	58.994 (2.240)	16.799	<0.0001	0.205
PWB self-acceptance	46.150 (2.356)	35.227 (2.221)	11.375	0.001	0.149	34.705 (1.890)	51.447 (2.711)	24.025	<0.0001	0.270

Note. (+) Disorder or syndrome present; (–) Disorder or syndrome absent; BDI-II, Beck Depression Inventory II; EAT, Eating Attitudes Test; PWB, Psychological Well-Being scales.

that DCPR demoralization might be suitable for classifying psychological distress in EDs that is not confounded by the ED symptoms themselves. Indeed, demoralization does not seem to depend on illness type or severity, affecting a wide range of psychiatric and medical illnesses alike.[15]

Subjective incompetence (a feeling of being trapped or blocked because of a sense of inability to plan or start actions toward goals) is a major component of demoralization.[44,45] Such feelings of inadequacy and low self-efficacy have been previously documented in EDs.[46,47] Individuals, who perceive themselves as incompetent are uncertain and indecisive as to their directions, display high reactivity to environmental stimuli and low psychological well-being. Not surprisingly, patients with EDs were found to present with very high rates of dropout.[48]

In both standard assessment and treatment approaches, most studies focus on pathological symptomatology and its reduction, as well as modifications of physical and behavioral aspects, ignoring gains in positive aspects such as quality of life and psychological well-being.[18,19,49] The pursuit of euthymia, defined as how the individual adjusts the psychological dimensions of well-being to changing needs, may thus become one of the targets of treatment. Such positive functioning characteristics have been found to be persistently compromised in various psychiatric illnesses including EDs[18] and their impairments are correlated with increased vulnerability to future adversity and may thus be a viable psychotherapeutic target.[50-53]

The high comorbidity rates found in the current study between EDs and depression are in line with those in the literature, ranging from 40% to 80%, as well as high comorbidity rates with dysthymic disorder which surpass those found in the general population.[2-4] In the current study, depressive disorders were associated with worse overall functioning in terms of both psychological distress and well-being, a result that is in line with the literature. Depressed ED patients exhibit greater dietary restriction, body dissatisfaction, and worse quality of life,[54] social[55]and global functioning compared to unaffected ED patients.[56-58] Moreover, it is well-documented that ED severity is significantly associated with severity of the depression.[59]

As expected, an overlap between the demoralization and depressive illness was found, as in other medical psychiatric populations.[15]

Clinical guidelines for the screening of depression in EDs recommend the Beck Depression Inventory-II and the Hamilton Depression Rating Scale.[60,61] However, such standardized screening measures mainly based on DSM criteria might not be sufficient in such a complex clinical population with frequent medical complications.

Conclusion

The presence of demoralization syndrome in EDs is undoubtedly relevant to treatment and recovery from

EDs. Hopelessness and helplessness[62] and poor self-efficacy[63,64] have been identified by ED patients themselves as barriers to change and recovery in qualitative studies. In chronic AN patients, the recovery process may be hindered by feelings of hopelessness and "feeling stuck."[65] Indeed, demoralization has been found to affect response to psychotherapy.[66,67]

Moreover, the clinical utility of depression diagnoses in ED populations is called into question by treatment trials. Depression comorbidity in EDs has an unclear role in treatment response with inconsistent results across ED categories.[68,69] For instance, inconclusive or mixed findings have been reported for FDA-approved fluoxetine in BN[70-72] with lack of improvement in AN.[73] Antidepressants in ED patients were devoid of impact on likelihood and persistence of recovery from MDD in a longitudinal study.[4]

Fava, Rafanelli, and Tomba[9] have advocated that exclusive reliance on diagnostic criteria has impoverished the clinical process in psychiatry. Customary clinical taxonomy in psychiatry does not include clinical distinctions that demarcate major prognostic and therapeutic differences among patients who otherwise seem to be deceptively similar since they share the same psychiatric diagnosis.[9] This investigation has illustrated how a broader perspective in evaluation of mood disturbances in EDs may lead to an individualized assessment of the complex balance between euthymia, dysthymia, and eating behavior which may entail important treatment implications. Further studies, using a comprehensive clinimetric approach,[74] with larger samples and a longitudinal design, are needed.

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REFERENCES:

1. Puccio F, Fuller-Tyszkiewicz M, Ong D, *et al.* A systematic review and meta-analysis on the longitudinal relationship between eating pathology and depression. *Int J Eat Disord*. 2016; **49**(5): 439–454.
2. Godart N, Radon L, Curt F,, *et al.* Mood disorders in eating disorder patients: Prevalence and chronology of onset. *J Affect Disord*. 2015; **185**: 115–122.
3. Godart NT, Perdereau F, Rein Z, *et al.* Comorbidity studies of eating disorders and mood disorders: Critical review of the literature. *J Affect Disord*. 2007; **97**(1-3): 37–49.
4. Mischoulon D, Eddy KT, Keshaviah A, *et al.* Depression and eating disorders: Treatment and course. *J Affect Disord*. 2011; **130**(3): 470–477.
5. Meehan KG, Loeb KL, Roberto CA, *et al.* Mood change during weight restoration in patients with anorexia nervosa. *Int J Eat Disord*. 2006; **39**: 587–589.
6. Mattar L, Huas C, Duclos J, *et al.* Relationship between malnutrition and depression or anxiety in Anorexia Nervosa: A critical review of the literature. *J Affect Disord*. 2010; **132**(3): 311–318.
7. Garfinkel PE, Garner DM. *Anorexia Nervosa: A Multidimensional Perspective*. New York, NY: Brunner/Mazel Inc; 1982.
8. Casper R. Depression in eating disorders. *Depress Anxiety* 1998; **8**: 96–104.
9. Fava GA, Rafanelli C, Tomba E. The clinical process in psychiatry: A clinimetric approach. *J Clin Psychiatry* 2012; **73**(2): 177–184.
10. Fava GA. Subclinical symptoms in mood disorders. *Psychol Med*. 1999; **29**(1): 47–61.
11. Paykel ES. The clinical interview for depression: Development, reliability and validity. *J Affect Disord*. 1985; **9**(1): 85–96.
12. Guidi J, Fava GA, Bech P, *et al.* The clinical interview for depression: A comprehensive review of studies and clinimetric properties. *Psychother Psychosom*. 2011; **80**(1): 10–27.
13. Fava GA, Freyberger HJ, Bech P, *et al.* Diagnostic criteria for use in psychosomatic research. *Psychother Psychosom*. 1995; **63**(1): 1–8.
14. Fava GA, Cosci F, Sonino N. Current psychosomatic practice. *Psychother Psychosom*. 2017; **86**(1): 13–30.
15. Tecuta L, Tomba E, Grandi S, *et al.* Demoralization and its clinical characterization. *Psychol Med*. 2015; **45**(4): 673–691.
16. Abbate-Daga G, Delsedime N, Nicotra B, *et al.* Psychosomatic syndromes and anorexia nervosa. *BMC Psychiatry*. 2013; **13**: 14.
17. Fava GA, Cosci F, Guidi J, *et al.* Well-being therapy in depression: new insights into the role of psychological well-being in the clinical process. *Depress Anxiety*. 2017; **34**(9): 801–808.
18. Tomba E, Offidani E, Tecuta L, *et al.* Psychological well-being in outpatients with eating disorders: A controlled study. *Int J Eat Disord*. 2014; **47**(3): 252–258.
19. Tomba E, Tecuta L, Schumann R, *et al.* Does psychological well-being change following treatment? An exploratory study on outpatients with eating disorders. *Compr Psychiatry*. 2017; **74**: 61–69.
20. First MB, Williams JBW, Karg RS, *et al. Structured Clinical Interview for DSM-5 Disorders, Clinician Version (SCID-5-CV)*. Arlington, VA: American Psychiatric Association; 2015.
21. Hamilton M. Development of a rating scale for primary depressive illness. *Brit J Soc Clin Psychol*. 1967; **6**(4): 278–296.
22. Bech P. Fifty years with the Hamilton Scales for Anxiety and Depression. *Psychother Psychosom*. 2009; **78**(4): 202–211.
23. Galeazzi GM, Ferrari S, Mackinnon A, *et al.* Inter-rater reliability, prevalence and relation to ICD-10 diagnoses of the Diagnostic Criteria for Psychosomatic Research in consultation-liaison psychiatry patients. *Psychosom*. 2004; **45**(5): 386–393.
24. Beck AT, Steer RA, Brown GK. *Manual for the Beck Depression Inventory-II*. San Antonio, TX: Psychological Corporation; 1996.
25. Wang YP, Gorenstein C. Psychometric properties of the Beck Depression Inventory-II: A comprehensive review. *Rev Bras Psiquiatr*. 2013; **35**(4): 416-431.
26. Ryff CD. Happiness is everything, or is it? Explorations on the meaning of psychological well-being. *J Pers Soc Psychol*. 1989; **57**(6): 1069-1081.
27. Ryff CD. Psychological well-being revisited: advances in the science and practice of eudaimonia. *Psychother Psychosom*. 2014; **83**(1): 10-28.
28. Garner DM, Garfinkel PE. The eating attitude test: An index of the symptoms of anorexia nervosa. *Psychol Med*. 1979; **9**(2): 273–279.
29. Garfinkel PE, Newman A. The eating attitudes test: Twenty-five years later. *Eat Weight Disord*. 2001; **6**(1): 1–24.
30. Miller GA, Chapman JP. Misunderstanding analysis of covariance. *J Abnorm Psychol*. 2001; **110**(1): 40–48.
31. Frank ES. Shame and guilt in eating disorders. *Am J Orthopsychiatry*. 1991; **61**(2): 303–306.

32. Petry N, Vasconcelos FAG, Costa LDCF. Feelings and perceptions of women recovering from anorexia nervosa regarding their eating behavior. *Cad Saude Publica*. 2017; **33**(9): e00048716.
33. Burney J, Irwin HJ. Shame and guilt in women with eating-disorder symptomatology. *J Clin Psychol*. 2000; **56**(1): 51–61.
34. Tomba E, Rafanelli C, Grandi S, *et al*. Clinical configuration of cyclothymic disturbances. *J Affect Disord*. 2012; **139**(3): 244–249.
35. Raffi AR, Rondini M, Grandi S, *et al*. Life events and prodromal symptoms in bulimia nervosa. *Psychol Med*. 2000; **30**(3): 727–731.
36. Tapajóz P, de Sampaio F, Soneira S, *et al*. Emotional reactivity to social stimuli in patients with eating disorders. *Psychiatry Res*. 2015; **229**(3): 887–894.
37. Gutiérrez-Maldonado J, Ferrer-García M, Caqueo-Urízar A, *et al*. Assessment of emotional reactivity produced by exposure to virtual environments in patients with eating disorders. *Cyberpsychol Beh*. 2006; **9**(5): 507–513.
38. Swinbourne JM, Touyz SW. The co-morbidity of eating disorders and anxiety disorders: A review. *Eur Eat Disord Rev*. 2007; **15**(4): 253–274. .
39. Steinglass J, Albano AM, Simpson HB, *et al*. Fear of food as a treatment target: Exposure and response prevention for anorexia nervosa in an open series. *Int J Eat Disord*. 2012; **45**(4): 615–621.
40. Arkell J, Robinson P. A pilot case series using qualitative and quantitative methods: Biological, psychological and social outcome in severe and enduring eating disorder (anorexia nervosa). *Int J Eat Disord*. 2008; **41**(7): 650-656.
41. Bamford BH, Attoe C, Mountford VA, *et al*. Body checking and avoidance in low weight and weight restored individuals with anorexia nervosa and non-clinical females. *Eat Behav*. 2014; **15**(1): 5-8.
42. Steinglass JE, Albano AM, Simpson HB, *et al*. Confronting fear using exposure and response prevention for anorexia nervosa: A randomized controlled pilot study. *Int J Eat Disord*. 2014; **47**(2): 174–180.
43. Grandi S, Sirri L, Tossani E, *et al*. Psychological characterization of demoralization in the setting of heart transplantation. *J Clin Psychiatry*. 2011; **72**(5): 648–654.
44. de Figueiredo JM. Depression and demoralization: Phenomenologic differences and research perspectives. *Compr Psychiatry*. 1993; **34**(5): 308–311.
45. de Figueiredo JM. Distress, demoralization and psychopathology: Diagnostic boundaries. *Eur J Psychiatry*. 2013; **27**(1): 61–73.
46. Garner DM. *EDI2—Eating Disorders Inventory 2. Professional manual*. Odessa, FL: Psychological Assessment Resources; 1991.
47. Surgenor LJ, Maguire S, Russell J, *et al*. Self-liking and self-competence: Relationship to symptoms of anorexia nervosa. *Eur Eat Disord Rev*. 2007; **15**(2): 139–145.
48. Fassino S, Pierò A, Tomba E, *et al*. Factors associated with dropout from treatment for eating disorders: A comprehensive literature review. *BMC Psychiatry*. 2009; **9**: 67.
49. Ackard DM, Richter S, Egan A, *et al*. The meaning of (quality of) life in patients with eating disorders: A comparison of generic and disease-specific measures across diagnosis and outcome. *Int J Eat Disord*. 2014; **47**(3): 259–267.
50. Jahoda M. *Current concepts of positive mental health*. New York, NY: Basic Books; 1958.
51. Fava GA, Bech P. The concept of euthymia. *Psychother Psychosom*. 2016; **85**(1): 1–5.
52. Tomba E, Tecuta L. Well-being therapy in a patient with anorexia nervosa. *Psychother Psychosom*. 2016; **85**: 369–370.
53. Fava GA. *Well-being therapy. Treatment Manual and Clinical Applications*. Basel: Karger; 2016.
54. Padierna A, Quintana J, Arostegui I, *et al*. The health-related quality of life in eating disorders. *Qual Life Res*. 2000; **9**(6): 667–674.
55. Hatsukami DK, Mitchell JE, Eckert ED, *et al*. Characteristics of patients with bulimia only, bulimia with affective disorder, and bulimia with substance abuse problems. *Addict Behav*. 1986; **11**(4): 399–406.
56. Bulik CM, Sullivan PF, Carter FA, *et al*. Lifetime anxiety disorders in women with bulimia nervosa. *Compr Psychiatry*. 1996; **37**(5): 368–374.
57. Hughes EK, Goldschmidt AB, Labuschagne Z, *et al*. Eating disorders with and without comorbid depression and anxiety: Similarities and differences in a clinical sample of children and adolescents. *Eur Eat Disord Rev*. 2013; **21**(5): 386–394.
58. Brand-Gothelf A, Leor S, Apter A, *et al*. The impact of comorbid depressive and anxiety disorders on severity of anorexia nervosa in adolescent girls. *J Nerv Ment Dis*. 2014; **202**(10): 759–762.
59. Herpertz-Dahlmann B, Remschimdt H. Depression in anorexia nervosa at follow-up. *Int J Eat Disord*. 1993; **14**(2): 163–169.
60. Anderson DA, Lundgren JD, Shapiro JR, *et al*. Assessment of eating disorders: Review and recommendations for clinical use. *Behav Modif*. 2004; **28**(6): 63–82.
61. Bowers WA, Haedt-Matt AA. Psychological assessment of eating disorders. In: Preedy VR, Watson RR, Colin RM, eds. *Handbook of Behavior, Food and Nutrition*. New York, NY: Springer; 2011: 3425-3435.
62. Waller G. The myths of motivation. Time for a fresh look at some received wisdom in the eating disorders? *Int J Eat Disord*. 2012; **45**(1): 1-16.
63. Wade TD, Wilksch SM, Paxton SJ, *et al*. How perfectionism and ineffectiveness influence growth of eating disorder risk in young adolescent girls. *Beh Res Ther*. 2015; **66**: 56-63.
64. Dawson L, Rhodes P, Touyz S. "Doing the Impossible": The process of recovery from chronic anorexia nervosa. *Qual Health Res*. 2014; **24**(4): 494–505.
65. Nordbø RHS, Espeset EMS, Gulliksen KS, *et al*. Reluctance to recover in anorexia nervosa. *Eur Eat Disord Rev*. 2012; **20**(1): 60–67.
66. Frank JD. *Persuasion and healing*. Baltimore: Johns Hopkins University Press; 1961.
67. Tomba E, Tecuta L, Guidi J, *et al*. Demoralization and response to psychotherapy: A pilot study comparing the sequential combination of cognitive-behavioral therapy and well-being therapy with clinical management in cyclothymic disorder. *Psychother Psychosom*. 2016; **85**(1): 56–57.
68. Agras WS, Walsh BT, Fairburn CG, *et al*. A multicenter comparison of cognitive-behavioral therapy and interpersonal psychotherapy for bulimia nervosa. *Arch Gen Psychiatry*. 2000; **57**(5): 459–466.
69. Collin P, Power K, Karatzias T, *et al*. The effectiveness of and predictors of response to inpatient treatment of anorexia nervosa. *Eur Eat Disord Rev*. 2010; **18**(6): 464–474.
70. Fluoxetine Bulimia Nervosa Collaborative Study Group. Fluoxetine in the treatment of bulimia nervosa. *Arch Gen Psychiatry*. 1992; **49**(2): 139–147.
71. Walsh BT, Wilson GT, Loeb KL, *et al*. Medication and psychotherapy in the treatment of bulimia nervosa. *Am J Psychiatry*. 1997; **154**(4): 523–531.
72. Romano SJ, Halmi KA, Sarkar NP, *et al*. A placebo-controlled study of fluoxetine in continued treatment of bulimia nervosa after successful acute fluoxetine treatment. *Am J Psychiatry*. 2002; **159**(1): 96–102.
73. Walsh BT, Kaplan AS, Attia E, *et al*. Fluoxetine after weight restoration in anorexia nervosa: A randomized controlled trial. *JAMA*. 2006; **295**(22): 2605–2612.
74. Fava GA, Carrozzino D, Lindberg L, *et al*. The clinimetric approach to psychological assessment. *Psychother Psychosom*. 2018; **87**(6): 321–326.

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Sequential Combination of Cognitive-Behavioral Treatment and Well-Being Therapy in Depressed Patients with Acute Coronary Syndromes: A Randomized Controlled Trial (TREATED-ACS Study)

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Keywords
Acute coronary syndrome · Cognitive-behavioral therapy · Depression · Sequential treatment · Well-being therapy

Abstract
Introduction: Randomized controlled trials (RCT) of psychotherapeutic interventions have addressed depression and demoralization associated with acute coronary syndromes (ACS). The present trial introduces psychological well-being, an increasingly recognized factor in cardiovascular health, as a therapeutic target. ***Objective:*** This study was designed to determine whether the sequential combination of cognitive-behavioral therapy (CBT) and well-being therapy (WBT) may yield more favorable outcomes than an active control group (clinical management; CM) and to identify subgroups of patients at greater risk for cardiac negative outcomes. ***Methods:*** This multicenter RCT compared CBT/WBT sequential combination versus CM, with up to 30 months of follow-up. One hundred consecutive depressed and/or demoralized patients (out of 740 initially screened by cardiologists after a first episode of ACS) were randomized to CBT/WBT associated with lifestyle suggestions ($n = 50$) and CM ($n = 50$). The main outcome measures included: severity of depressive symptoms according to the Clinical Interview for Depression, changes in subclinical psychological distress, well-being, and biomarkers, and medical complications and events. ***Results:*** CBT/WBT sequential combination was associated with a significant improvement in depressive symptoms compared to CM. In both groups, the benefits persisted at follow-up, even though the differences faded. Treatment was also related to a significant amelioration of biomarkers (platelet count, HDL, and D-dimer), whereas the 2 groups showed similar frequencies of adverse cardiac events. ***Con-***

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clusions: Addressing psychological well-being in the psychotherapeutic approach to ACS patients with depressive symptoms was found to entail important clinical benefits. It is argued that lifestyle changes geared toward cardiovascular health may be facilitated by a personalized approach that targets well-being.

Introduction

There is extensive evidence that the presence of depressive symptoms in acute coronary syndromes (ACS) is associated with poor therapeutic adherence, a higher frequency of relapses, and increased mortality [1]. Mood disturbances may consist of major or minor depressive episodes, chronic depression, and demoralization [1–3], which is characterized by a sense of subjective incompetence [4].

The relationship of depression to ACS has generated the hypothesis that treatment of mood disturbances may yield improved medical and psychological outcomes. A number of randomized controlled trials (RCT) have indicated the effectiveness of antidepressant drugs compared to placebo in relieving depression, yet a favorable effect on cardiovascular events was not detected [1] or could not be generalized [5]. Similar findings have been reported for the application of cognitive-behavioral therapy (CBT) to ACS [6], pioneered by the ENRICHD trial [7].

Psychotherapeutic approaches, however, have been mainly shifted to the side of psychological dysfunction and have neglected psychological well-being. There is increasing evidence of the role of positive psychological assets on lifestyle and cardiovascular health [8].

In this trial, the sequential use of distress and well-being psychotherapeutic strategies was selected. The first phase of treatment (CBT) was concerned with distress associated with hospitalization and medical events. In the second phase, well-being therapy (WBT), a specific psychotherapeutic approach for modulating psychological well-being [9], was introduced and suggestions for lifestyle modifications geared to cardiovascular health were provided [10]. The sequential combination of CBT and WBT has been found to yield enduring clinical benefits in the setting of psychiatric disorders [9, 10], with particular reference to recurrent depression [11].

The aim of the trial was to evaluate the efficacy of the sequential combination of CBT and WBT, compared to clinical management (CM), in terms of depressive symptoms (primary outcome), psychological distress, and well-being, as well as cardiovascular events, biomarkers, and mortality (secondary outcomes), both after treatment and up to a 30-month follow-up. The identification of subgroups of patients at greater risk for cardiac negative outcomes was included.

Materials and Methods

Sample

Participants were patients hospitalized for a first episode of acute myocardial infarction or unstable angina at the Cardiology Divisions of Maggiore Hospital (Bologna, Italy) and Molinette Hospital (Torino, Italy). Myocardial infarction was documented based on cardiac symptoms (presence of acute chest, epigastric, neck, jaw, or arm pain or discomfort or pressure without an apparent noncardiac source) and signs (acute congestive heart failure or cardiogenic shock in the absence of non-CHD causes) associated with ECG findings (characteristic evolutionary ST-T changes or new Q waves) and/or cardiac biomarkers (blood measures of myocardial necrosis, specifically CK, CK-MB, CK-MBm, or troponin, and cTn). Instable angina was documented based on cardiac symptoms (chest pain lasting less than 20 min) with likely ECG findings (ST-segment depression and an abnormal T-wave) in absence of myocardial necrosis biomarkers.

Medically eligible patients underwent a psychological evaluation by 2 clinical psychologists with expertise in the field of psychosomatic aspects of cardiovascular diseases about 30 days after ACS. The inclusion criteria were: a current diagnosis of major/minor depression or dysthymia according to DSM-IV-TR [12] and/or demoralization according to Diagnostic Criteria for Psychosomatic Research (DCPR) criteria [13]. The exclusion criteria included a positive history of bipolar disorder (DSM-IV-TR), major depression with psychotic features, a positive history of substance abuse/dependence during the previous 12 months, suicide risk, and current use of antidepressants and/or psychotherapy.

A psychological evaluation was performed in 288 patients with a first episode of ACS, and the first 100 depressed and/or demoralized consecutive patients were enrolled (Fig. 1).

Assessment

Medical Variables

Data on ACS, traditional cardiac risk factors (smoking habit, hypertension, dyslipidemia, a family history of cardiovascular disease, diabetes mellitus, and left ventricular ejection fraction <40), medications, and comorbidities were collected from medical records. The cardiologists involved in this study evaluated the patients at intake and once every 6 months to monitor changes in the clinical course of cardiac disease. Data from electrocardiograms, echocardiograms, X-rays, blood pressure and blood samples (cholesterol levels, creatinine, glycosylated hemoglobin, C-reactive protein, and coagulation/fibrinolysis biomarkers) were provided at intake. The Global Registry of Acute Coronary Events (GRACE) risk index [14] was calculated during hospital admission for ACS to determine the risk of morbidity and mortality both in hospital and 6 months after discharge. From the beginning of the psychological treatment and up to a 30-month follow-up after the end of the intervention, information about cardiac negative outcomes,

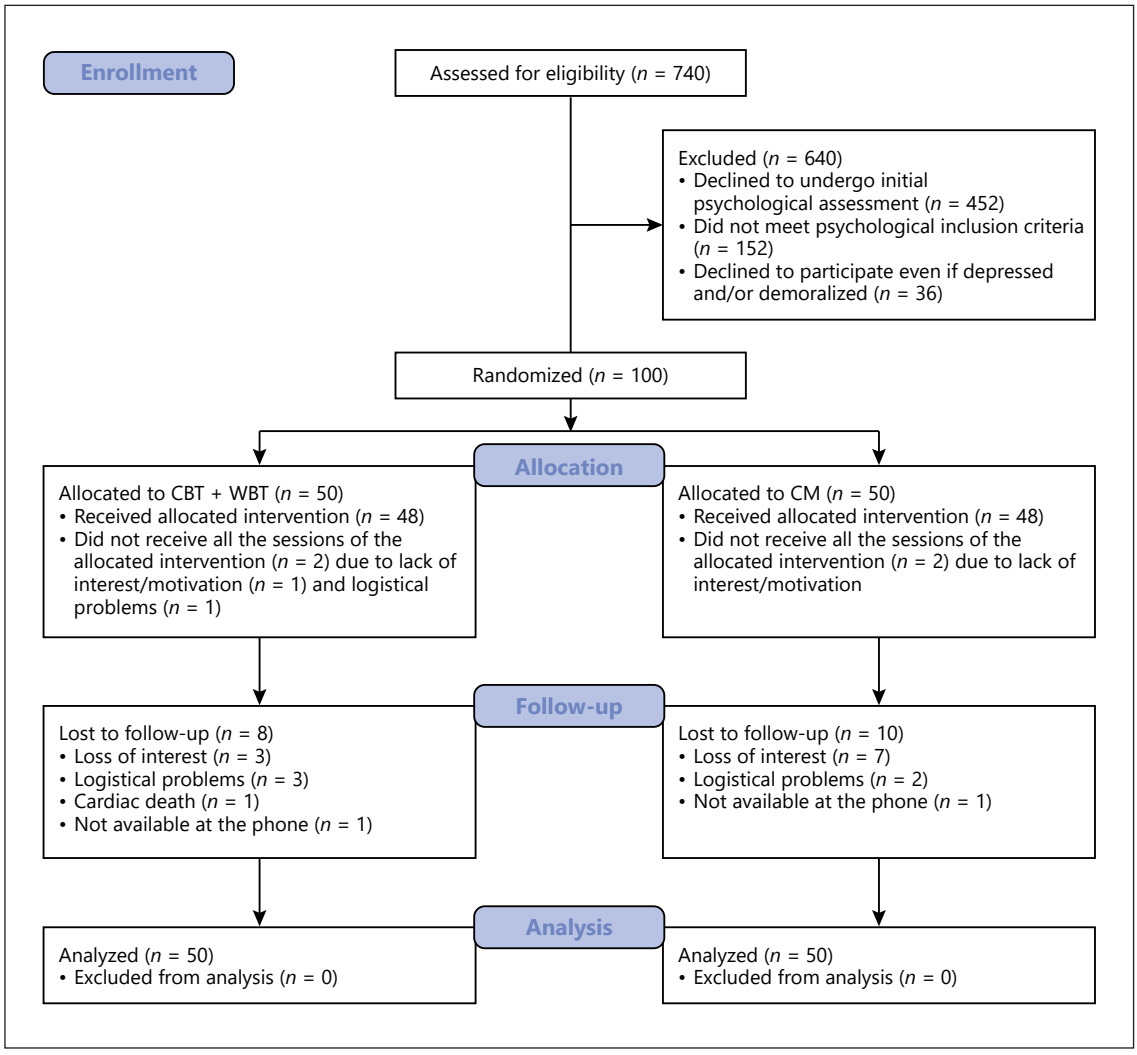

Fig. 1. CONSORT flow diagram of this study.

such as rehospitalizations due to cardiac complications, acute myocardial infarction, unstable angina, angioplasty, cardiac surgery, and cardiac mortality after the first ACS, was collected.

Psychological Variables

Psychological assessment included both observer-rated and self-reported measures before the beginning of the interventions (baseline, pretreatment), at the end (posttreatment), and 3, 6, 12, and 30 months after the end of treatment. The Structured Clinical Interview for DSM-IV-TR, Axis I Disorders [15], was used to investigate the presence of major/minor depression and dysthymia. The Semi-Structured Interview based on the DCPR (SSI-DCPR) [16] was administered to assess the presence of demoralization [17]. This interview has shown excellent interrater reliability, with κ values ranging from 0.69 to 0.97 [18]. The 20-item change version of the Clinical Interview for Depression (CID) [19, 20], a modified version of the Hamilton Rating Scale for Depression [21, 22], was used to perform a comprehensive assessment of affective symptoms. It contains 20 items rated on a 7-point Likert scale, with specification of each anchor point based on the severity, frequency, and/or quality of the symptoms. The higher the score, the worse the psychological condition. The CID has been shown to be a sensitive assessment tool in clinical trials [20]. The Symptom Questionnaire (SQ) [23, 24] is a 92-item self-report questionnaire that yields 4 main scales, i.e., depression, anxiety, hostility-irritability, and somatization. The higher the score, the higher the psychological distress. The Psychological Well-Being scales (PWB) [25–26], an 84-item questionnaire, was used to evaluate 6 psychological well-being dimensions (autonomy, environmental mastery, personal growth, positive relations, purpose in life, and self-acceptance). Higher scores correspond to greater psychological well-being.

Study Design

This study is a 2-center RCT with a longitudinal and prospective design. The enrolled patients were randomly assigned to either CBT/WBT or CM and assessed at the beginning and the end of the CBT/WBT or CM sessions, and at subsequent follow-ups up to 30 months after the conclusion of the interventions. Treatment allo-

cation was accomplished through random computerized assignment that allocated 50% of the patients to each treatment group, with assignments concealed until the time of group assignment. Patients were assessed by 2 clinical psychologists, who were blind to treatment assignment, at pretreatment and posttreatment, and 3, 6, 12, and 30 months after the end of treatment. Both the sequential combination of CBT/WBT and the CM were performed by psychotherapists who had received specific training. Both interventions consisted of 12 weekly, 45-min sessions. The sequential administration of CBT (8 sessions) and WBT (4 sessions) was based on a written protocol [9–10]. The WBT techniques were used to improve or balance one or more of the 6 dimensions of psychological well-being (environmental mastery, purpose in life, personal growth, autonomy, self-acceptance, and positive relations with others), and they were supplemented with suggestions for lifestyle modifications geared toward cardiovascular health, including treatment adherence.

CM entails the same amount of time and attention from a professional figure than the experimental group, but specific interventions (such as exposure strategies, diary work, and cognitive restructuring) were proscribed [27]. Such a form of active control – unlike in previous trials that have used treatment as usual [6] – allows discrimination of specific and nonspecific ingredients of the psychotherapeutic approach. It consists of empathic listening, review of the patient's clinical status and providing opportunities for disclosure of distress and worries, and encouragement of treatment adherence.

Statistical Analyses

Data were analyzed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA). The quality of data collection was monitored regularly to assure accuracy and completeness. For all tests performed, significance level was set at 0.05 (two-tailed). The sample size was estimated using Piface software, which identified a minimum of 16 participants per arm to detect the expected superiority of CBT/WBT on CM [11], with a power of 80% and a significance level of 5%. Thus, with 50 patients per group we expected a "large" effect size (Cohen's $d = 0.8$) [28].

A multivariate ANOVA was used to examine differences in dimensional psychological variables (i.e., CID-20 total score and PWB and SQ scale scores) between patients assigned to CBT/WBT and CM at preintervention.

A mixed-model ANOVA (repeated measures) was performed to test differences between groups (CBT/WBT or CM) on the CID-20 total score, PWB scales, and SQ scales scores at different follow-up evaluations. All analyses were performed by using intention-to-treat analysis, where missing values were managed by means of a multiple-imputations procedure. Greenhouse-Geisser correction was applied when appropriate. All analyses were adjusted for cardiac illness severity (i.e., GRACE index for the 6-month probability of cardiac mortality) [14].

Each biomarker was dichotomized around the baseline median of the sample in order to identify subgroups of patients at a higher cardiovascular risk. The McNemar test (applied to contingency tables) was used to identify significant changes over time in the frequencies of DSM, DCPR diagnoses, and subgroups of patients at a higher cardiovascular risk.

Survival analyses (Cox Regression and Kaplan-Meier) to identify cardiac events and mortality that occurred between pretreatment and the 30-month follow-up were performed.

Results

Baseline Profile of the Sample

The first 100 consecutive depressed and/or demoralized patients 1 month after ACS were enrolled, yielding 50 patients in each treatment group. The mean age of the sample was 58.8 years (SD = 10.5, range 40–84). The participants were mainly men (69%), married (69%), employed (58%), and graduated from high school (44%). No significant differences based on group allocation were found (Table 1).

As for the cardiac profile of the sample, ST-elevation myocardial infarction (STEMI) was the most frequent form of ACS (66%) and almost all of the patients (94%) underwent percutaneous transluminal coronary angioplasty – 77% with the application of a single stent and 17% with 2 or more stents. The most frequent cardiovascular risk factors registered at hospital admission were dyslipidemia (58%) and hypertension (52%). No differences concerning ACS-related aspects or GRACE risk scores were found when comparing CBT/WBT versus CM (Table 1).

Among the medications prescribed at discharge, the most frequent were statins (96%), β-blockers (96%), and platelet aggregation inhibitors (96%). Patients allocated to CM were prescribed significantly more frequently β-blockers, calcium antagonists, and α-adrenergic receptor inhibitors compared to the CBT/WBT group (Table 1). The sample presented with a number of medical comorbidities; the most frequent were gastrointestinal (43%) and endocrine diseases (14%). As for comorbid medical diagnoses and levels of biomarkers assessed at baseline, the 2 groups did not show any significant difference (Table 1). From the psychological point of view, the most frequent diagnosis was demoralization (91%), followed by minor depression (56%). The 2 groups did not show any statistical difference, except for PWB "personal growth" scores ($F = 4.45$; df = 1, 98; $p = 0.038$) and frequency of depression/demoralization comorbidity ($\chi^2 = 4.86$; df = 1; $p = 0.028$), which were significantly higher among the CBT/WBT patients (Table 1).

Pre-/Postintervention Modifications

Psychological Variables

Forty-eight patients completed the CBT/WBT treatment, and 48 patients attended CM sessions. Two patients in each group dropped out early, mainly due to a lack of interest or motivation. Forty and 38 patients, respectively, completed follow-up evaluations (Fig. 1).

Table 1. Baseline sociodemographic, medical, and psychological profile of the sample

Variable	CBT/WBT group (n = 50)	CM group (n = 50)
Mean age (SD), years	57.64 (9.99)	60.02 (10.94)
Sex, *n* (%)		
Males	31 (62)	38 (76)
Females	19 (38)	12 (24)
Marital status, *n* (%)		
Single	4 (8)	7 (14)
Married	33 (66)	36 (72)
Separated	5 (10)	4 (8)
Divorced	2 (4)	1 (2)
Widow/widower	6 (12)	2 (4)
Occupation, *n* (%)		
Employed	34 (68)	24 (48)
Unemployed	1 (2)	4 (8)
Retired	13 (26)	19 (38)
Homemaker	2 (4)	3 (6)
Education, *n* (%)		
Primary school	5 (10)	5 (10)
Middle school	16 (32)	18 (36)
High school	19 (38)	25 (50)
University	8 (16)	1 (2)
Postgraduate education	2 (4)	1 (2)
Type of ACS, *n* (%)		
STEMI acute myocardial infarction	33 (66)	33 (66)
NSTEMI acute myocardial infarction	14 (28)	13 (26)
Unstable angina	3 (6)	4 (8)
Medical procedure for ACS, *n* (%)		
Single PTCA	38 (76)	39 (78)
PTCA with 2 or more stents	9 (18)	8 (16)
None	3 (6)	3 (6)
Drug-eluting stent	24 (51.1)	18 (38.3)
Cardiovascular risk factors, *n* (%)		
Dyslipidemia	31 (62)	27 (54)
Hypertension	27 (54)	25 (50)
Smoker (current)	22 (44)	20 (40)
Familiarity	17 (34)	11 (22)
Diabetes	10 (20)	9 (18)
LVEF <40	4 (8)	3 (6)
Mean GRACE risk index at admission (mortality) (SD)		
In-hospital risk, %	3.51 (8.58)	4.56 (7.90)
6-month risk, %	6.60 (11.60)	8.69 (10.57)
Mean GRACE risk index at admission (mortality + AMI) (SD)		
In-hospital risk, %	15.50 (9.85)	16.56 (10.49)
6-month risk, %	25.30 (12.73)	27.50 (15.00)
Medications, *n* (%)		
Cholesterol reducers	49 (98)	47 (94)
β-blockers*	46 (92)	50 (100)
Platelet aggregation inhibitors	48 (96)	48 (96)
Cardioaspirin	47 (94)	48 (96)
Vasodilators	36 (72)	35 (70)
Angiotensin-converting enzyme inhibitors	31 (62)	35 (70)
Polyunsaturated fatty acids – omega-3	11 (22)	10 (20)
Antihyperglycemics	6 (12)	8 (16)
Diuretics	6 (12)	5 (10)
Angiotensin receptor blockers	5 (10)	4 (8)
Calcium antagonists*	1 (2)	6 (12)

Table 1 (continued)

Variable	CBT/WBT group (n = 50)	CM group (n = 50)
α-adrenergic receptor inhibitors*	0 (0)	4 (8)
Antihyperuricemics	0 (0)	2 (4)
Antiarrhythmic	1 (2)	0 (0)
Heart rate reducers	0 (0)	1 (2)
7 or more medications*	11 (22)	23 (46)
Medical comorbidities, n (%)		
Digestive system diseases	18 (36)	25 (50)
Endocrine diseases	9 (18)	5 (10)
Circulatory/cardiac comorbidities	2 (4)	4 (8)
Prostatic and male reproductive system diseases	3 (6)	2 (4)
Urinary system diseases	2 (4)	2 (4)
Orthopedic diseases	1 (2)	3 (6)
Asthma	3 (6)	1 (2)
Chronic obstructive pulmonary disease	2 (4)	1 (2)
Stroke/aneurysm	2 (4)	1 (2)
Heteroplasia/neoplasia	2 (4)	1 (2)
Hyperuricemia	0 (0)	3 (6)
Glaucoma	1 (2)	0 (0)
Multiple sclerosis	1 (2)	0 (0)
Cluster headache	1 (2)	0 (0)
Cushing disease	1 (2)	0 (0)
Sarcoidosis	1 (2)	0 (0)
Thalassemia	0 (0)	1 (2)
Rheumatoid arthritis	0 (0)	1 (2)
2 or more medical comorbidities	12 (24)	13 (26)
Mean biomarkers (SD)		
Hemoglobin, g/dL	13.91 (1.21)	13.93 (1.33)
Platelets, $n \times 10^3$/mm^3	235.42 (57.64)	232.96 (50.20)
Creatinine, mg/dL	0.94 (1.78)	0.95 (0.20)
Triglycerides, mg/dL	115.96 (52.91)	121.69 (58.68)
HDL cholesterol, mg/dL	51.98 (16.59)	46.51 (12.01)
LDL cholesterol, mg/dL	87.40 (25.48)	93.96 (29.25)
Total cholesterol, mg/dL	156.44 (31.07)	160.90 (37.45)
Glycated hemoglobin, mmol/mol	41.20 (8.36)	42.97 (10.21)
Fibrinogen, mg/dL	347.84 (66.04)	356.49 (68.28)
D-dimer, mg/L FEU	0.68 (1.39)	0.45 (0.39)
HRV[a], ms	51.10 (27.66)	41.50 (12.29)
C-reactive protein		
BO, mg/dL	0.19 (0.21)	0.39 (0.69)
TO, mg/L	0.28 (0.39)	0.64 (1.16)
Mean SQ (SD)		
Anxiety	8.60 (4.73)	7.24 (4.67)
Depression	7.92 (4.77)	6.90 (4.87)
Somatization	9.82 (5.65)	7.82 (5.12)
Hostility	4.70 (4.00)	5.34 (4.36)
Mean PWB (SD)		
Autonomy	62.20 (9.18)	61.80 (9.25)
Environmental mastery	55.28 (11.52)	55.32 (10.65)
Personal growth*	60.48 (9.88)	56.18 (10.50)
Positive relations with others	61.26 (13.26)	60.20 (10.68)
Purpose in life	56.80 (11.51)	56.22 (11.59)
Self-acceptance	54.48 (11.63)	55.80 (13.68)
Mean CID-20 (SD)		
CID-20 total score	38.18 (8.48)	36.20 (8.57)
Depression (DSM), n (%)	35 (70)	27 (54)

Table 1 (continued)

Variable	CBT/WBT group (n = 50)	CM group (n = 50)
Major depression	2 (4)	3 (6)
Minor depression	32 (64)	24 (48)
Dysthymia	1 (2)	0 (0)
History of depression (DSM), n (%)	34 (68)	26 (52)
Demoralization (DCPR), n (%)	47 (94)	44 (88)
History of demoralization (DCPR), n (%)	36 (72)	32 (64)
Comorbidities, n (%)		
Depression + demoralization*	32 (64)	21 (42)
Chronicity of depression/demoralization, n (%)		
Current + previous episode of depression	26 (52)	19 (38)
Current + previous episode of demoralization	35 (70)	31 (62)

ACS, acute coronary syndrome; AMI, acute myocardial infarction; CBT, Cognitive-Behavioral Therapy; CID-20, 20-item Clinical Interview for Depression; CM, clinical management; DCPR, diagnostic criteria for psychosomatic research; GRACE, Global Registry of Acute Coronary Events; HRV, heart rate variability; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; PWB, Psychological Well-Being scales; SQ, Symptom Questionnaire; STEMI, ST-segment elevation myocardial infarction; WBT, Well-Being Therapy; BO, Bologna; TO, Torino. * $p \leq 0.05$.
[a] Assessed only in Torino.

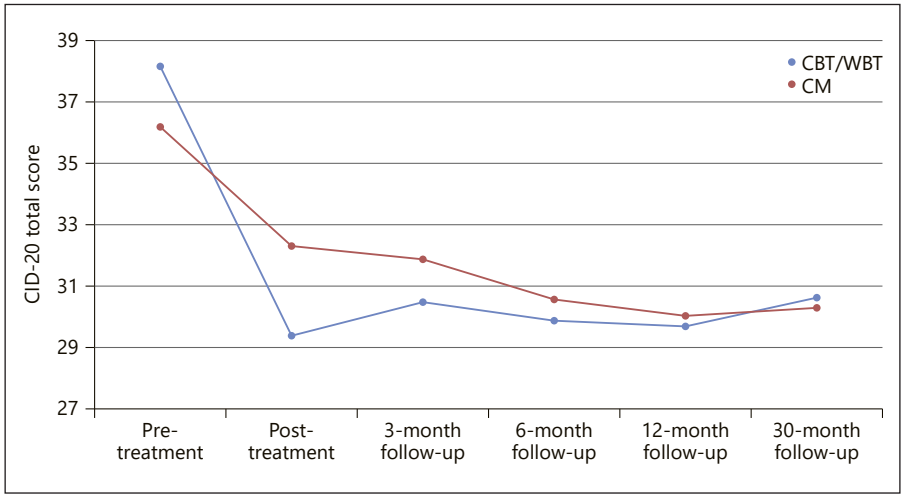

Fig. 2. CID-20 total scores at different time points (intention-to-treat analysis).

As for the CID-20 total score, a significant interaction between group allocation and time was found (F = 2.75; df = 3.85; $p < 0.05$; Fig. 2). Significant decreases in symptom scores from pre- to posttreatment were found in both the CBT/WBT ($p < 0.001$) and CM ($p < 0.01$) groups. However, the effect sizes for score modifications were strong in the CBT/WBT treatment group (Cohen's d = 1.161 and 1.393, respectively) and weak/medium among CM patients (Cohen's d = 0.492 and 0.589, respectively) (Table 2). Patients allocated to CBT/WBT reported significant lower scores posttreatment (p = 0.040) compared to those assigned to CM. Starting from the 3-month follow-up, the CID-20 score differences between the 2 groups were no longer significant. The benefits, however, tended to persist in both groups.

No significant interactions were found between time and group allocation in relation to SQ and PWB mean scores, except for hostility as assessed by the SQ (F = 3.12;

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Table 2. Effects of treatment groups on psychological characteristics

Variable	Pretreatment	Posttreatment	3-month follow-up	6-month follow-up	12-month follow-up	30-month follow-up	Time × group			Cohen's *d**	Within-group score change*, [a]
							F	df	*p* value		
Intention-to-treat analysis											
CBT/WBT group (*n* = 50), mean (SD)											
PWB autonomy	62.20 (9.18)	64.58 (9.42)	64.54 (9.24)	64.40 (9.12)	65.50 (8.53)	64.93 (9.67)	0.173	3.846	0.948	–0.26	–2.38 (–5.51 to 0.76)
PWB environmental mastery	55.28 (11.52)	57.33 (12.93)	59.48 (11.32)	58.02 (11.83)	58.36 (12.15)	58.69 (10.97)	0.309	4.353	0.886	–0.17	–2.09 (–5.61 to 1.43)
PWB personal growth	60.48 (9.88)	61.46 (9.92)	61.95 (9.91)	60.79 (9.58)	60.55 (9.54)	59.94 (9.34)	0.982	4.253	0.420	–0.10	–0.93 (–3.91 to 2.06)
PWB positive relations	61.26 (13.26)	61.82 (13.50)	61.88 (12.86)	60.60 (13.08)	61.27 (12.08)	60.48 (11.60)	0.709	4.183	0.592	–0.04	–0.57 (–3.33 to 2.19)
PWB purpose in life	56.80 (11.51)	57.31 (11.21)	58.35 (10.09)	57.88 (10.85)	57.42 (9.81)	57.63 (9.70)	1.104	3.803	0.353	–0.04	–0.49 (–4.14 to 3.17)
PWB self-acceptance	54.48 (11.63)	55.70 (14.36)	57.59 (13.51)	55.83 (14.19)	56.66 (11.92)	56.15 (13.90)	1.593	4.325	0.170	–0.09	1.30 (–4.48 to 1.89)
SQ anxiety	8.60 (4.73)	7.04 (5.23)	6.60 (4.87)	6.67 (4.19)	6.62 (4.51)	6.00 (4.35)	1.008	4.180	0.405	0.31	1.54 (–0.10 to 3.19)
SQ depression	7.92 (4.77)	7.21 (5.42)	6.38 (5.03)	7.06 (5.22)	6.91 (5.08)	5.99 (4.64)	0.605	4.180	0.667	0.14	0.70 (–0.98 to 2.37)
SQ somatization	9.82 (5.65)	8.80 (5.73)	8.67 (5.42)	8.96 (5.02)	9.49 (5.19)	8.17 (5.00)	0.787	3.981	0.534	0.18	1.04 (–0.75 to 2.84)
SQ hostility	4.70 (4.00)	5.19 (4.96)	5.18 (4.46)	4.41 (3.71)	5.32 (4.71)	3.81 (3.37)	3.121	4.288	0.013	–0.11	–0.51 (–1.91 to 0.89)
CID-20 total score	38.18 (8.48)	29.39 (6.55)	30.48 (5.81)	29.89 (5.88)	29.70 (6.51)	30.64 (7.02)	2.748	3.853	0.030	1.16	8.73 (5.39 to 12.07)
CM group (*n* = 50), mean (SD)											
PWB autonomy	61.80 (9.25)	62.82 (8.77)	63.20 (8.51)	63.21 (9.00)	64.57 (9.34)	63.71 (9.26)				–0.11	–1.02 (–4.16 to 2.11)
PWB environmental mastery	55.32 (10.65)	56.69 (8.81)	57.81 (10.15)	57.51 (8.78)	58.03 (11.19)	58.81 (8.10)				–0.14	–1.33 (–4.85 to 2.19)
PWB personal growth	56.18 (10.50)	56.54 (8.70)	56.67 (9.65)	57.10 (8.90)	57.64 (10.24)	57.00 (8.85)				–0.04	–0.41 (–3.40 to 2.57)
PWB positive relations	60.20 (10.68)	59.90 (10.93)	59.93 (12.13)	58.78 (10.82)	58.95 (11.54)	60.56 (10.78)				0.03	0.31 (–2.45 to 3.07)
PWB purpose in life	56.22 (11.59)	54.97 (9.41)	55.47 (10.32)	55.96 (10.12)	55.63 (10.82)	57.76 (8.16)				0.12	1.23 (–2.42 to 4.89)
PWB self-acceptance	55.80 (13.68)	56.03 (11.52)	57.86 (12.84)	58.32 (12.39)	59.69 (13.38)	59.94 (10.52)				–0.02	–0.15 (–3.34 to 3.04)
SQ anxiety	7.24 (4.67)	6.39 (4.41)	6.13 (4.21)	7.10 (5.14)	6.33 (5.09)	5.69 (4.07)				0.19	0.87 (–0.78 to 2.51)
SQ depression	6.90 (4.87)	5.94 (4.22)	5.83 (4.75)	6.80 (5.45)	6.22 (5.09)	5.83 (4.18)				0.21	0.98 (–0.69 to 2.66)
SQ somatization	7.82 (5.12)	8.24 (4.90)	7.87 (4.58)	8.15 (5.64)	7.90 (5.38)	7.61 (4.72)				–0.08	–0.44 (–2.23 to 1.36)
SQ hostility	5.34 (4.36)	4.12 (3.78)	4.71 (3.92)	6.01 (4.73)	5.17 (4.14)	4.56 (4.11)				0.30	1.24 (–0.16 to 2.64)
CID-20 total score	36.20 (8.57)	32.30 (7.26)	31.89 (7.11)	30.59 (7.28)	30.03 (7.05)	30.30 (6.82)				0.49	3.97 (0.63 to 7.31)

All analyses were adjusted for the GRACE index (6-month probability of cardiac mortality). CID-20, 20-item Clinical Interview for Depression; CBT, Cognitive-Behavioral Therapy; CM, clinical management; PWB, Psychological Well-Being scales; SQ, Symptom Questionnaire; WBT, Well-Being Therapy. * Pre-/posttreatment scores change. [a] Values are expressed as mean differences (95% CI).

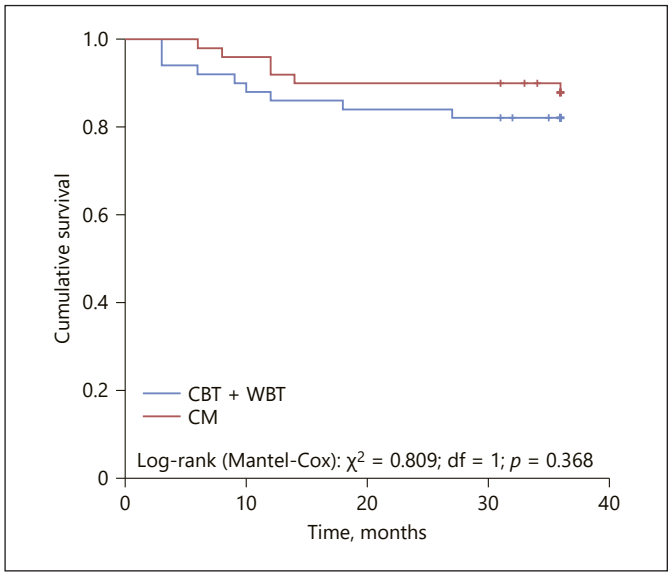

Fig. 3. Survival curves of the CBT/WBT and CM groups.

Color version available online

df = 4.29; $p < 0.05$), with CM group showing significantly higher scores at the 6-month follow-up than CBT/WBT ($p = 0.039$; Table 2).

Biomarkers

At the 3-month post-intervention follow-up, we observed a significant reduction of the frequencies of patients with biomarker levels considered to be at risk (below or above the median) only among patients allocated to the CBT/WBT group. In particular, we found a significant decrease in cases with a high platelet count (from 52 to 36%; $p < 0.05$; median = $226 \times 10^3/mm^3$), lower HDL cholesterol (from 52 to 34%; $p < 0.05$; median = 47 mg/dL), and a higher D-dimer level (from 56 to 40%; $p < 0.05$; median = 0.31 mg/L FEU) in patients assigned to CBT/WBT compared to those receiving CM. No significant decrease in patients with risky levels of biomarkers was observed in the CM group.

Survival Analyses

Within 36 months from baseline, 15% of the total sample had an adverse cardiac outcome. As for cardiac morbidity and mortality, we did not find any significant difference between the CBT/WBT and CM groups in terms of survival. Indeed, among the patients allocated to CBT/WBT 16% ($n = 8$) had nonfatal cardiac events and 1 patient (2%) had a cardiac death (occurring after 18 months from baseline), whereas among the CM patients 10% ($n = 5$) had nonfatal events and 1 patient (2%) had a cardiac death (after 36 months from baseline). Nonetheless, the CBT/WBT patients displayed most of the negative cardiac outcomes within the first 9 months, with almost half of them (4 out of 9) relapsing during treatment sessions. On the contrary, CM participants were more likely to relapse after a longer period (starting after 8 months from baseline) (Fig. 3).

Stratifying the sample by group allocation, among CBT/WBT patients the probabilities of cardiac death, both in hospital (Wald = 4.235; df = 1; HR = 1.040; 95% CI 1.002–1.079; $p = 0.040$) and at 6 months postdischarge (Wald = 4.594; df = 1; HR = 1.031; 95% CI 1.003–1.060; $p = 0.032$) as calculated with GRACE indices, were found to predict a worse cardiac prognosis. On the contrary, in the CM group adverse cardiac outcomes were predicted by baseline scores of depression, as assessed by CID (Wald = 5.540; df = 1; HR = 1.204; 95% CI 1.031–1.404; $p = 0.019$).

Discussion

To our knowledge, this is the first RCT demonstrating a significant improvement in depressive symptoms and biomarkers in patients with ACS following sequential CBT/WBT when compared with CM. This study provides new important clinical insights regarding the treatment of depression in the setting of ACS. The sequential combination of CBT/WBT was effective in significantly decreasing depressive symptoms compared to CM. In both groups the benefits persisted at follow-up, even though the differences between them faded (Fig. 2). It is noteworthy the different trend observed in the 2 groups concerning hostility, since it represents a key variable in the literature on the psychological issues embedded in depressive states [29] and it has been found to have a negative effect on the cardiac prognosis [30].

Medical outcomes did not differ between the 2 groups, yet among the CBT/WBT patients a negative cardiac prognosis was associated with a greater severity of the cardiac illness (as indicated by the GRACE indexes and the timing of relapses), whereas in the CM group it was associated with the severity of baseline depressive symptomatology. Moreover, patients who were assigned to the treatment group displayed significant decreases in placement according to normative values of platelet counts, HDL cholesterol, and D-dimer. There is evidence that these biomarkers may indicate a prognostic significance of the occurrence of cardiovascular events [31–33].

The findings are important in view of the methodology that was used. The patients were not assessed during hospitalization but rather after 1 month, when stress linked to hospitalization and the impact of acute illness are likely to subside and the evaluation of depressive symptoms is likely to be more reliable [34]. The impact of the CBT/WBT sequential combination was not compared to treatment as usual, as occurred in other studies [6], but rather to CM, where patients received the nonspecific elements of psychotherapy [27, 35]. Indeed, also CM yielded significant improvement in affective symptoms. This indicates that nonspecific support after ACS may be important, but specific psychotherapeutic strategies are associated with greater benefits and it underlines the need to schedule booster sessions (i.e., WBT or brief CBT) in order to reinforce progress or address potential obstacles to the continuance of the positive changes made during the therapy.

WBT is a short-term psychotherapeutic strategy that emphasizes self-observation of psychological well-being via the use of a structured diary, cognitive restructuring of interfering thoughts and/or behaviors, and homework assignments [9, 10]. The working hypothesis was that lifestyle changes could only be achieved with a personalized approach that targets psychological well-being [9]. Based on examples taken from post-ACS everyday life, the patients allocated to CBT/WBT were instructed on how to overcome specific obstacles concerning lifestyle (i.e., specific strategies for medication adherence, scheduling of gradual physical exercises, and dietary modification according to specific prescriptions following hospital guidelines). In the phase that immediately follows ACS, interventions that bring the person out of negative functioning and distress may be important, and this was the target of the first phase of psychotherapy (CBT). However, facilitating progression toward restoration of the positive ("there is life after ACS") and appreciation of healthy lifestyle is another target that requires specific interventions (WBT). The results of this investigation confirm previous studies on the role of psychotherapeutic strategies in the setting of ACS [6] and provide a valid alternative/integration to pharmacological strategies, which carry the disadvantages of side effects of antidepressant drugs [36–37], with particular reference to cardiovascular safety [38]. The sequential psychotherapeutic strategy that was used may also be applied after pharmacological treatment of depression, if appropriate, and may have potential in extending therapeutic benefits beyond the time of medication administration, as it has been found to be the case in psychiatric settings [39].

This therapeutic approach may be potentially extended to cardiovascular rehabilitation in view of the suitability of WBT for the rehabilitation process [40] and the adverse prognostic role of an unhealthy lifestyle and depressive symptoms in these settings [41–43]. A number of clinical situations (delayed recovery after treatment, discrepancy between cardiovascular status/functioning, presence of a psychological comorbidity, problems with lifestyle and risky behavior, and presence of stressful circumstances) may be addressed by the sequential strategy we have outlined.

The findings of this investigation targeting psychological well-being in ACS should be seen as preliminary and await proper replication studies. It should also be noted that more than a quarter of the ACS patients diagnosed with depression and/or demoralization (36 out of 136; 26.5%) refused to join the RCT. This percentage, however, is lower than the refusal rates found in the literature on secondary prevention programs, which range from 31.4 [44] to 72.2% [45] among depressed patients. Moreover, about half of the 740 patients initially screened by the cardiologists refused to undergo psychological assessment and almost half of those who agreed refused to join the trial or revoked the initial consent. The results are thus likely to reflect a self-selected population. Nonetheless, they indicate a road to the practice of lifestyle medicine [46] that is worth perusing.

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Statement of Ethics

This study was approved by the institutional review board of the ethics committees of both centers (identifier: Studio CE 09058). Written informed consent was secured from all of the patients for both the initial psychological evaluation and trial participation, after the procedures had been fully explained to them. The participants did not receive any compensation. The authors assert that all of the procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Conflict of Interest Statement

The authors have no conflict of interests to declare.

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Author Contributions

C.R., G.A.-D., and G.A.F. conceptualized and designed this study. C.R., S.G., G.A.-D., and G.A.F. collected, analyzed, and interpreted the data. C.R., S.G., and G.A.F. wrote the first draft of this paper. S.G. performed the statistical analyses. All of the authors critically revised this work for important intellectual content and provided administrative, technical, or material support. C.R., G.A.-D. and G.A.F. supervised the whole process.

References

1 Carney RM, Freedland KE. Depression and coronary heart disease. Nat Rev Cardiol. 2017 Mar;14(3):145–55.
2 Rafanelli C, Roncuzzi R, Milaneschi Y, Tomba E, Colistro MC, Pancaldi LG, et al. Stressful life events, depression and demoralization as risk factors for acute coronary heart disease. Psychother Psychosom. 2005 Apr;74(3):179–84.
3 Kuhlmann SL, Arolt V, Haverkamp W, Martus P, Ströhle A, Waltenberger J, et al. Prevalence, 12-month prognosis, and clinical management need of depression in coronary heart disease patients. Psychother Psychosom. 2019 Sep;88(5):300–11.
4 de Figueiredo JM, Frank JD. Subjective incompetence, the clinical hallmark of demoralization. Compr Psychiatry. 1982 Jul-Aug; 23(4):353–63.
5 Kim JM, Stewart R, Lee YS, Lee HJ, Kim MC, Kim JW, et al. Effect of escitalopram vs placebo treatment for depression on long-term cardiac outcomes in patients with acute coronary syndrome: a randomized clinical trial. JAMA. 2018 Jul;320(4):350–8.
6 Reavell J, Hopkinson M, Clarkesmith D, Lane DA. Effectiveness of cognitive behavioral therapy for depression and anxiety in patients with cardiovascular disease: A systematic review and meta-analysis. Psychosom Med. 2018 Oct;80(8):742–53.
7 Berkman LF, Blumenthal J, Burg M, Carney RM, Catellier D, Cowan MJ, et al.; Enhancing Recovery in Coronary Heart Disease Patients Investigators (ENRICHD). Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. JAMA. 2003 Jun;289(23):3106–16.
8 Kubzansky LD, Huffman JC, Boehm JK, Hernandez R, Kim ES, Koga HK, et al. Positive psychological well-being and cardiovascular disease: JACC health promotion series. J Am Coll Cardiol. 2018 Sep;72(12):1382–96.
9 Fava GA. Well-being therapy: Treatment manual and clinical applications. Basel, Switzerland: Karger Medical & Scientific Publishers; 2016. https://doi.org/10.1159/isbn.978-3-318-05822-2.
10 Guidi J, Rafanelli C, Fava GA. The clinical role of well-being therapy. Nord J Psychiatry. 2018 Aug;72(6):447–53.
11 Fava GA, Rafanelli C, Grandi S, Conti S, Belluardo P. Prevention of recurrent depression with cognitive behavioral therapy: preliminary findings. Arch Gen Psychiatry. 1998 Sep; 55(9):816–20.
12 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed., revised. Washington (DC): American Psychiatric Association; 2000.
13 Fava GA, Freyberger HJ, Bech P, Christodoulou G, Sensky T, Theorell T, et al. Diagnostic criteria for use in psychosomatic research. Psychother Psychosom. 1995;63(1):1–8.
14 Tang EW, Wong CK, Herbison P. Global Registry of Acute Coronary Events (GRACE) hospital discharge risk score accurately predicts long-term mortality post acute coronary syndrome. Am Heart J. 2007 Jan;153(1):29–35.
15 First MB, Spitzer RL, Gibbon M, Williams J. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, research version. New York (NY): Biometrics Research, New York State Psychiatric Institute; 2002.
16 Porcelli P, Sonino N. Psychological factors affecting medical conditions: a new classification for DSM-V. Adv Psychosom Med. Basel: Karger; 2007.
17 Tecuta L, Tomba E, Grandi S, Fava GA. Demoralization: a systematic review on its clinical characterization. Psychol Med. 2015 Mar; 45(4):673–91.
18 Galeazzi GM, Ferrari S, Mackinnon A, Rigatelli M. Interrater reliability, prevalence, and relation to ICD-10 diagnoses of the Diagnostic Criteria for Psychosomatic Research in consultation-liaison psychiatry patients. Psychosomatics. 2004 Sep-Oct;45(5):386–93.
19 Paykel ES. The clinical interview for depression. Development, reliability and validity. J Affect Disord. 1985 Jul;9(1):85–96.
20 Guidi J, Fava GA, Bech P, Paykel E. The Clinical Interview for Depression: a comprehensive review of studies and clinimetric properties. Psychother Psychosom. 2011 Dec;80(1): 10–27.
21 Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol. 1967 Dec;6(4):278–96.
22 Carrozzino D, Patierno C, Fava GA, Guidi J. The Hamilton Rating Scales for Depression: a critical review of clinimetric properties of different versions. Psychother Psychosom. 2020 May;89(3):133–50.
23 Kellner R. A symptom questionnaire. J Clin Psychiatry. 1987 Jul;48(7):268–74.
24 Benasi G, Fava GA, Rafanelli C. Kellner's Symptom Questionnaire, a highly sensitive patient-reported outcome measure: systematic review of clinimetric properties. Psychother Psychosom. 2020 Mar;89(2):74–89.
25 Ryff CD. Happiness is everything, or is it? Explorations on the meaning of psychological well-being. J Pers Soc Psychol. 1989;57(6): 1069–81.
26 Ryff CD. Psychological well-being revisited: advances in the science and practice of eudaimonia. Psychother Psychosom. 2014 Dec; 83(1):10–28.
27 Guidi J, Brakemeier EL, Bockting CL, Cosci F, Cuijpers P, Jarrett RB, et al. Methodological recommendations for trials of psychological interventions. Psychother Psychosom. 2018 Sep;87(5):276–84.
28 Cohen J. Statistical power analysis for the behavioral sciences. New York (NY): Routledge Academic; 1988.
29 Brummett BH, Babyak MA, Barefoot JC, Bosworth HB, Clapp-Channing NE, Siegler IC, et al. Social support and hostility as predictors of depressive symptoms in cardiac patients one month after hospitalization: a prospective study. Psychosom Med. 1998 Nov-Dec;60(6): 707–13.
30 Rafanelli C, Gostoli S, Tully PJ, Roncuzzi R. Hostility and the clinical course of outpatients with congestive heart failure. Psychol Health. 2016 Oct;31(2):228–38.
31 von Känel R. Acute mental stress and hemostasis: when physiology becomes vascular harm. Thromb Res. 2015 Feb;135(1):S52–5.
32 Vinholt PJ, Hvas AM, Frederiksen H, Bathum L, Jørgensen MK, Nybo M. Platelet count is associated with cardiovascular disease, cancer and mortality: a population-based cohort study. Thromb Res. 2016 Dec;148:136–42.

33 Ishida M, Itoh T, Nakajima S, Ishikawa Y, Shimoda Y, Kimura T, et al. A low early high-density lipoprotein cholesterol level is an independent predictor of in-hospital death in patients with acute coronary syndrome. Intern Med. 2019 Feb;58(3):337–43.
34 Fava GA, Sonino N. Depression associated with medical illness. CNS Drugs. 1996 Oct; 5(3):175–89.
35 Fava GA, Guidi J, Rafanelli C, Rickels K. The clinical inadequacy of the placebo model and the development of an alternative conceptual framework. Psychother Psychosom. 2017 Nov;86(6):332–40.
36 Carvalho AF, Sharma MS, Brunoni AR, Vieta E, Fava GA. The safety, tolerability and risks associated with the use of newer generation antidepressant drugs: a critical review of the literature. Psychother Psychosom. 2016; 85(5):270–88.
37 Fava GA, Rafanelli C. Iatrogenic factors in psychopathology. Psychother Psychosom. 2019 Jun;88(3):129–40.
38 Grace SL, Medina-Inojosa JR, Thomas RJ, Krause H, Vickers-Douglas KS, Palmer BA, et al. Antidepressant use by class: association with major adverse cardiac events in patients with coronary artery disease. Psychother Psychosom. 2018 Mar;87(2):85–94.
39 Guidi J, Tomba E, Fava GA. The sequential integration of pharmacotherapy and psychotherapy in the treatment of major depressive disorder: a meta-analysis of the sequential model and a critical review of the literature. Am J Psychiatry. 2016 Feb;173(2):128–37.
40 Nierenberg B, Mayersohn G, Serpa S, Holovatyk A, Smith E, Cooper S. Application of well-being therapy to people with disability and chronic illness. Rehabil Psychol. 2016 Feb;61(1):32–43.
41 Rafanelli C, Roncuzzi R, Finos L, Tossani E, Tomba E, Mangelli L, et al. Psychological assessment in cardiac rehabilitation. Psychother Psychosom. 2003 Nov-Dec;72(6):343–9.
42 Gostoli S, Roncuzzi R, Urbinati S, Morisky DE, Rafanelli C. Unhealthy behaviour modification, psychological distress, and 1-year survival in cardiac rehabilitation. Br J Health Psychol. 2016 Nov;21(4):894–916.
43 Gostoli S, Roncuzzi R, Urbinati S, Rafanelli C. Clinical and subclinical distress, quality of life and psychological well-being after cardiac rehabilitation. Appl Psychol Health Well-Being. 2017 Nov;9(3):349–69.
44 Turk-Adawi KI, Oldridge NB, Tarima SS, Stason WB, Shepard DS. Cardiac rehabilitation enrollment among referred patients: patient and organizational factors. J Cardiopulm Rehabil Prev. 2014 Mar-Apr;34(2):114–22.
45 Zullo MD, Gathright EC, Dolansky MA, Josephson RA, Cheruvu VK, Hughes JW. The influence of depression on utilization of cardiac rehabilitation post-myocardial infarction: a study of 158,991 Medicare beneficiaries. J Cardiopulm Rehabil Prev. 2017 Jan;37(1):22–9.
46 Rippe JM. Are we ready to practice lifestyle medicine? Am J Med. 2019 Jan;132(1):6–8.

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REVIEW ARTICLE

Insomnia disorder: State of the science and challenges for the future

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Summary

Insomnia disorder comprises symptoms during night and day that strongly affect quality of life and wellbeing. Prolonged sleep latency, difficulties to maintain sleep and early morning wakening characterize sleep complaints, whereas fatigue, reduced attention, impaired cognitive functioning, irritability, anxiety and low mood are key daytime impairments. Insomnia disorder is well acknowledged in all relevant diagnostic systems: Diagnostic and Statistical Manual of the American Psychiatric Association, 5th revision, International Classification of Sleep Disorders, 3rd version, and International Classification of Diseases, 11th revision. Insomnia disorder as a chronic condition is frequent (up to 10% of the adult population, with a preponderance of females), and signifies an important and independent risk factor for physical and, especially, mental health. Insomnia disorder diagnosis primarily rests on self-report. Objective measures like actigraphy or polysomnography are not (yet) part of the routine diagnostic canon, but play an important role in research. Disease concepts of insomnia range from cognitive-behavioural models to (epi-) genetics and psychoneurobiological approaches. The latter is derived from knowledge about basic sleep–wake regulation and encompass theories like rapid eye movement sleep instability/restless rapid eye movement sleep. Cognitive-behavioural models of insomnia led to the conceptualization of cognitive-behavioural therapy for insomnia, which is now considered as first-line treatment for insomnia worldwide. Future research strategies will include the combination of experimental paradigms with neuroimaging and may benefit from more attention to dysfunctional overnight alleviation of distress in insomnia. With respect to therapy, cognitive-behavioural therapy for insomnia merits widespread implementation, and digital cognitive-behavioural therapy may assist delivery along treatment guidelines. However, given the still considerable proportion of patients responding insufficiently to cognitive-behavioural therapy for insomnia, fundamental studies are highly necessary to better understand the brain and behavioural mechanisms underlying insomnia. Mediators and moderators of treatment

response/non-response and the associated development of tailored and novel interventions also require investigation. Recent studies suggest that treatment of insomnia may prove to add significantly as a preventive strategy to combat the global burden of mental disorders.

KEYWORDS
anxiety, CBT-I, depression, insomnia, insomnia models, prevention, treatment guidelines

1 | DEFINITION AND DIAGNOSIS OF INSOMNIA DISORDER (ID)—DSM-5, ICSD-3, ICD-11

In the last 50 years all medical diagnostic classification systems have included ID. DSM (Diagnostic and Statistical Manual of the American Psychiatric Association) in its previous versions DSM-III-R/DSM-IV (American Psychiatric Association, 1987, 1998) suggested a distinction between primary and secondary insomnias, whereas DSM-5 (American Psychiatric Association, 2013) heralded a paradigmatic change by establishing ID as an overarching diagnostic category, eliminating artificial distinctions. The ICSD (International Classification of Sleep Disorders) in its third version (American Academy of Sleep Medicine, 2014) confirmed this new nosology (see Table 1; diagnostic criteria for chronic ID according to ICSD-3).

The ICD-10 (International Classification of Diseases, 10th edition; World Health Organization, 1993) distinguished between organic and non-organic sleep disorders; however, ICD-11 will follow the avenue paved by DSM-5 and ICSD-3 (World Health Organization, 2019). When analysing the "new" criteria for ID all systems list both night-time and daytime symptoms and, notably, the symptom of non-restorative sleep was dropped from the criteria due to lack of specificity.

Abandoning the distinction between primary/secondary insomnia constituted a major advance in acknowledging that insomnia frequently is not just a symptom of any other somatic or mental disorder, but constitutes an independent disorder, deserving specific consideration in clinical practice. It is important to note that insomnia probably more frequently occurs as a co-morbid condition together with somatic and mental disorders, than it does occur in its isolated form. DSM-5, ICSD-3 and ICD-11 pay respect to this by explicitly allowing co-morbidity. Furthermore, it turned out that cognitive-behavioural treatment for insomnia (CBT-I) not only has decisive effects on sleep/insomnia complaints, but also positively influences somatic/mental co-morbidities and quality of life. At present, evidence is accumulating that insomnia treatment with CBT-I may even have surplus benefits with respect to general treatment and prevention especially of mental disorders (Benz et al., 2020; Cheng et al., 2019; Hertenstein et al., 2022; Irwin et al., 2022; Leerssen et al., 2021).

Nevertheless, ID as a "one size fits all" category is seen critical by many working in the field. There is still a lively and ongoing discussion about different insomnia phenotypes, for example focussing on the main nocturnal complaint, that is, insomnia with or without "objective" short sleep (Vgontzas et al., 2013), or sleep-onset insomnia versus sleep-maintenance insomnia (Pillai et al., 2015). Indeed, the profile of dominant sleep complaints matters for the risk of developing first-onset major depressive disorder (Blanken et al., 2020). However, subtyping based on sleep characteristics may not be that robust, even across 2 nights (Johann et al., 2017), let alone across months or years (Edinger et al., 2011). Apparently, insomnia complaints change over time. More robust insomnia subtypes surfaced by multivariate profiling of personality features rather than sleep features (Blanken, Benjamins et al., 2019).

As it would be beyond the scope of this article to comprehensively describe the diagnostic and differential diagnostic procedure for insomnia, the interested reader is referred to Riemann et al. (2022) and other textbooks (Sateia & Buysse, 2010). Some important issues

TABLE 1 Diagnostic criteria for chronic ID according to ICSD-3 (AASM, 2014)

A. The patient reports, or the patient's parent or caregiver observes, one or more of the following:
   1. Difficulty initiating sleep.
   2. Difficulty maintaining sleep.
   3. Waking up earlier than desired.
   4. Resistance to going to bed on appropriate schedule.
   5. Difficulty sleeping without parent or caregiver intervention.
B. The patient reports, or the patient's parent or caregiver observes, one or more of the following related to the night-time sleep difficulty:
   1. Fatigue/malaise.
   2. Attention, concentration or memory impairment.
   3. Impaired social, family, occupational or academic performance.
   4. Mood disturbance/irritability.
   5. Daytime sleepiness.
   6. Behavioural problems (e.g. hyperactivity, impulsivity, aggression).
   7. Reduced motivation/energy/initiative.
   8. Proneness for errors/accidents.
   9. Concerns about or dissatisfaction with sleep.
C. The reported sleep/wake complaints cannot be explained purely by inadequate opportunity (i.e. enough time is allotted for sleep) or inadequate circumstances (i.e. the environment is safe, dark, quiet and comfortable) for sleep.
D. The sleep disturbance and associated daytime symptoms occur at least three times per week.
E. The sleep disturbance and associated daytime symptoms have been present for at least 3 months.
F. The sleep/wake difficulty is not better explained by another sleep disorder.

Abbreviation: ICSD-3, International Classification of Sleep Disorders, 3rd version.

concerning diagnostic procedures, however, should be highlighted here. The use of sleep diaries constitutes an integral part of insomnia assessment for both research and/or clinical purposes (e.g. consensus sleep diary by Carney et al., 2012). Sleep diaries are easy to apply and to evaluate. Sleep diaries focus on the experience of sleep and can be reviewed by the clinician as they are presented, but the inherent information can also be used to create highly informative graphical displays of sleep and bedtimes (Figure 1).

Beyond sleep diaries, other insomnia-specific questionnaires like the Insomnia Severity Index (Bastien et al., 2001) or the Sleep Condition Indicator (Espie et al., 2014) should be used.

For both clinical and fundamental research, it is favourable to take note of the recommendations for a standard research assessment of insomnia (Buysse et al., 2006). Several paradigms were developed to elucidate specific aspects of insomnia, for example, the attentional bias paradigm (Espie et al., 2006; Harris et al., 2015). This paradigm suggests that patients with chronic insomnia have developed a bias in their perception and processing of stimuli related to insomnia. Other highly promising paradigms investigate failing overnight amelioration of distress, which seems key to persistence of hyperarousal (Wassing et al., 2016; Wassing, Benjamins et al., 2019; Wassing, Lakbila-Kamal, et al., 2019; Wassing, Schalkwijk, et al., 2019). At present, not yet being ready for standard clinical practice, it is conceivable that these paradigms might be used in the future to measure responsiveness to CBT-I, also in combination with neuroimaging methods.

As the diagnosis of insomnia is solely based on subjective complaints and their measurement, it remains a matter of long-standing debate what the role of technical methods like actigraphy or polysomnography (PSG) might be. It is a highly controversial issue as to whether PSG should be part of the diagnostic process. Doubtlessly PSG helps to unravel suspected occult pathology of sleep, that is, periodic limb movements during sleep (periodic limb movement disorder) or sleep apnea (obstructive sleep apnea syndrome). US guidelines clearly deny the usefulness of PSG to diagnose insomnia (Kushida et al., 2005), whereas guidelines of the German and the European Sleep Research Society (Riemann, Baum, et al., 2017; Riemann, Baglioni, et al., 2017) suggest that PSG be used for patients with therapy-refractory insomnia who have not responded to a previous adequate "dose" of pharmaco- or psychotherapy.

The frequently described discrepancy between subjective (i.e. data from sleep diaries) and objective data (PSG) called paradoxical insomnia or sleep state misperception is seen as a major clinical and scientific challenge. PSG contrasted with subjective data does not reveal as pronounced disturbances of sleep as indicated by subjective data (Feige et al., 2008). A PSG meta-analysis revealed mean total sleep time differences between insomnia and good sleepers of about 25 min, whereas subjective estimates demonstrated an almost 2-hr difference (Baglioni, Regen, et al., 2014; Baglioni, Spiegelhalder, et al., 2014). Traditional PSG reveals only a glimpse of the brain activity during sleep. Advanced analyses have commenced to reveal electroencephalogram (EEG) correlates of subjective wakefulness during sleep, like simultaneous wake-like and sleep-like brain activity in people with insomnia (Christensen et al., 2019; Stephan et al., 2021). Furthermore, classification of individual insomnia patients based on their PSG and EEG power-spectral variables can distinguish between those with objective short sleep and those with sleep state misperception (Kao et al., 2021). Accordingly, the "misperception" may in fact be "mismeasurement": an inappropriate use or interpretation of traditional PSG features by clinicians, rather than inappropriate interpretation of subjective experiences by people with insomnia. It is important to bear in mind that these same challenges apply to mental disorders in general. There is no objective "test" for depression, anxiety or psychosis. The validation of any such tests needs to apply self-report coupled with clinical judgement as the "gold-standard."

Vgontzas and colleagues have postulated that the long-term health consequences of insomnia may be related specifically to objective short sleep duration of less than 6 hr (Vgontzas et al., 2013). However, patients with short sleep insomnia during one night do not fulfil that criteria on another night, and an increased risk of hypertension in short sleeping insomnia could not be replicated (Johann et al., 2017). Also, the hypothesis that the presence of objectively documented short sleep may be of relevance for the choice of therapy (Riemann et al., 2011), that is, pharmacotherapy for insomnia patients with objective short sleep duration versus psychotherapy for insomnia patients with objective normal sleep duration, has yet to be resolved and deserves further consideration (Vgontzas et al., 2013). More details will be provided in the aetiology/pathophysiology section. Figure 2 gives some examples of PSG determined sleep profiles of a good sleeper and two patients with ID.

2 | EPIDEMIOLOGY OF INSOMNIA AND INSOMNIA AS A RISK FACTOR FOR OTHER DISORDERS

Insomnia more frequently afflicts females than males (60% versus 40%), and its prevalence increases with age (for an overview, see Ohayon, 2002). The European Academy for CBT-I has summarized prevalence data for ID across some European countries (Baglioni et al., 2020), varying strongly from country to country. Data for Germany indicate a prevalence of 5.7%, whereas French surveys indicate figures up to 20%. On average, approximately 10% of the adult European population suffer from chronic insomnia. The heterogenous data clearly stress the need for the prospective collection of pan-European samples with state-of-the-art methods to obtain the full picture for planning of insomnia healthcare services.

The costs of insomnia for the individual and society are staggering: it was demonstrated that insomnia conveys increased risks for cardiovascular diseases (Li et al., 2014), obesity and diabetes (Anothaisintawee et al., 2016; Chan et al., 2018), depression (Baglioni et al., 2011; Hertenstein et al., 2019), anxiety (Hertenstein et al., 2019) and suicide (Pigeon et al., 2012). Wickwire (2019) reported that untreated insomnia leads to increased all-cause healthcare utilization based on a randomly selected and nationally representative sample from the USA. Data from Norway indicate that insomnia strongly predicts sick leave and disability pension (Overland

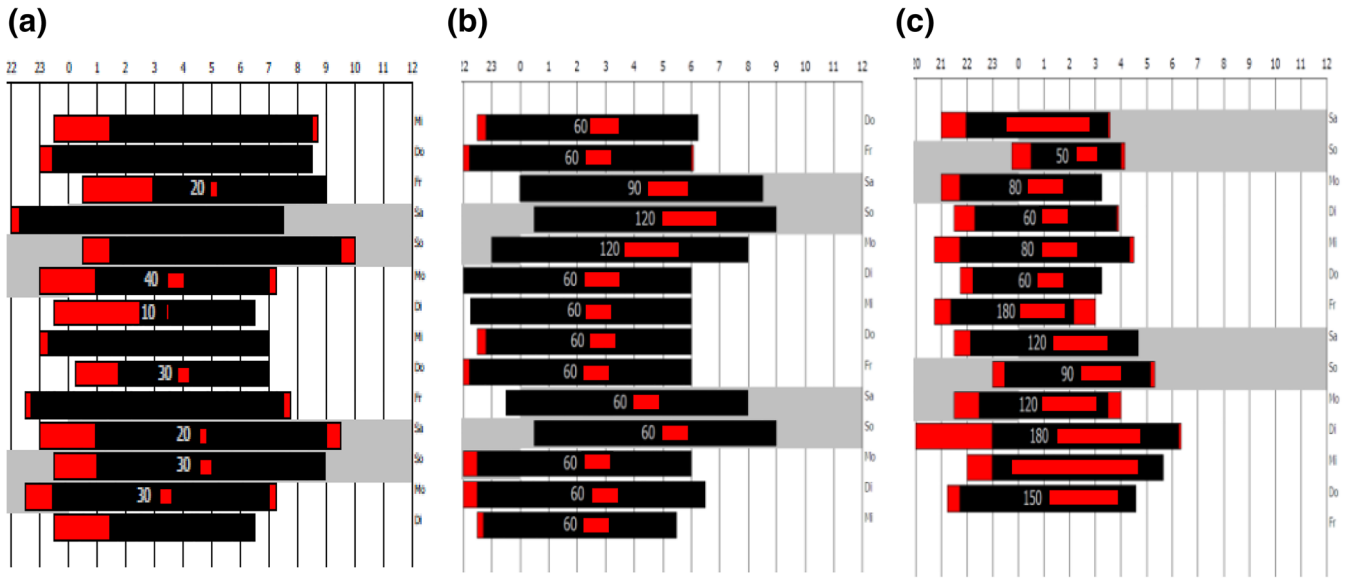

FIGURE 1 Sleep diary data from different patients with insomnia. (a) An insomnia patient who shows an increased sleep-onset latency. (b) A patient with insomnia experiencing difficulty in maintaining sleep. (c) A patient with mixed insomnia showing difficulty in both sleep onset and sleep maintenance

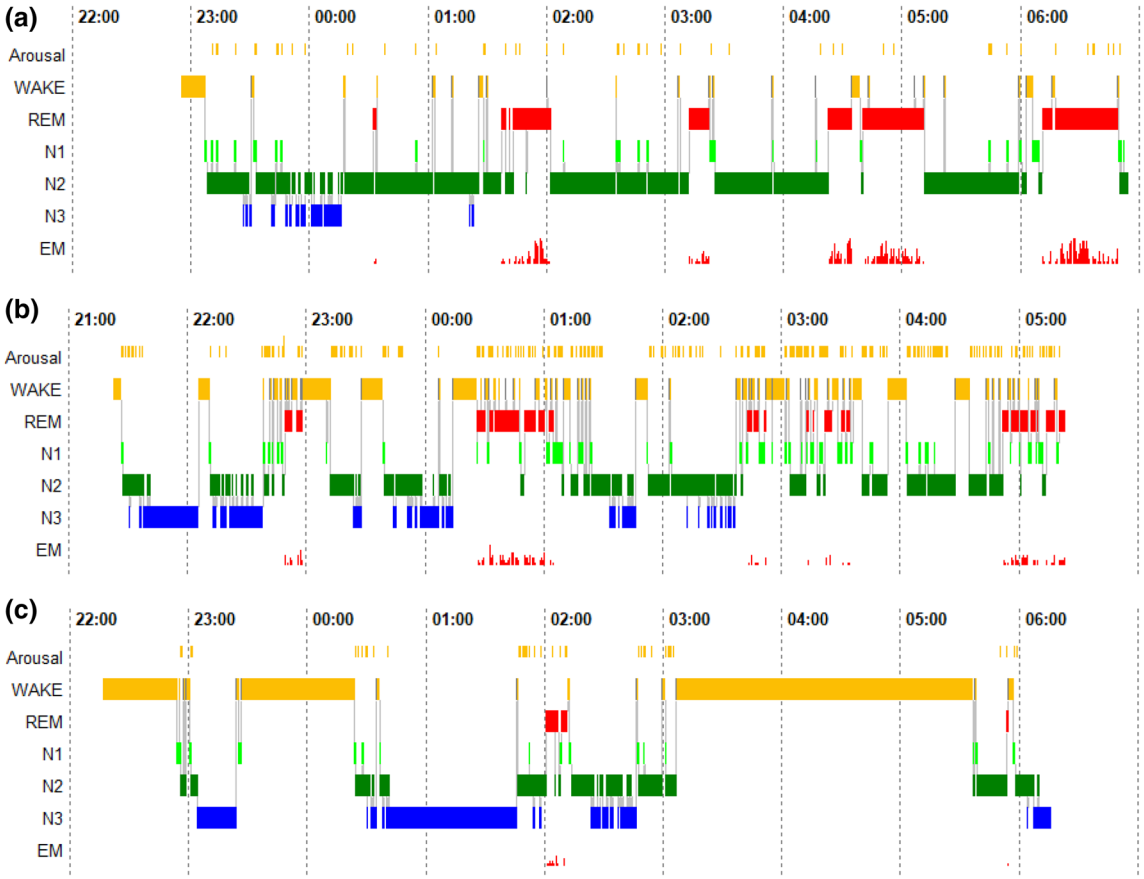

FIGURE 2 Polysomnographic (PSG) profiles of a good sleeper (upper panel; a) and patients with insomnia (lower panels; b,c). The *y*-axis displays arousal (micro-arousals), wake and sleep stages (rapid eye movement [REM], stage N1, N2 and N3) as well as eye movements. The *x*-axis is the time axis. (b) A patient with insomnia who has only a slightly reduced total sleep time, but a high number of arousals during sleep and a fragmented REM sleep. (c) A patient with insomnia who has an objectively shortened sleep duration

et al., 2008; Sivertsen et al., 2009). Data from France indicated a sum of 2 billion USD in 1995 (Leger et al., 1999). Data from the USA resulted in a sum of 150 billion US dollars for direct and indirect costs of insomnia (Reynolds & Ebben, 2017). A Canadian study (Daley et al., 2009) reported total annual costs for ID alone to be about 6.5 billion Canadian dollars. Recent data indicate that treatment using digital CBT-I reduces healthcare expenditure, and Markov health economic modelling indicates that digital CBT-I may be highly cost-effective when offered at scale (Darden et al., 2021). Further details of the costs and risks of insomnia are given in the European Academy for Cognitive Behavioural Therapy for Insomnia Report (Baglioni et al., 2020). An important clinical and research question relates to the hypothesis that adequate insomnia treatment might not only effectively target insomnia symptoms but might reduce subclinical and clinical psychopathology, and also be of general preventive value for mental disorders and physical diseases.

3 | AETIOLOGICAL AND PATHOPHYSIOLOGICAL CONSIDERATIONS

Recent reviews synthesized current neurobiological, cognitive, behavioural and emotional models for insomnia and its relationship to psychopathology (Figure 3; Espie, 2022; Riemann et al., 2020; Van Someren, 2021).

Current theoretical approaches span from cognitive-behavioural to neurobiological models, and models taking into account both levels simultaneously.

The basic structure of the model depicted in Figure 3 is taken from the so-called 3P model of insomnia (Spielman et al., 1987). The 3Ps signify: predisposing, precipitating and perpetuating factors.

"Predisposing" factors come from the areas of (epi-)genetics and early life stress that contribute to individual differences at the level of brain function and personality. Genetic and epigenetic factors have been shown to be involved in the aetiology of insomnia by family and twin studies (for an overview, see Palagini et al., 2014). Genome-wide association studies point to an involvement of a very large number of genes, each with a very small contribution, and shared genetic factors for insomnia and restless legs, cardiometabolic, and especially psychiatric traits (Jansen et al., 2019; Lane et al., 2019). Interestingly, the brain tissues and cell types expressing sets of insomnia risk genes are not primarily part of the known circuitry regulating sleep but are rather part of circuitries involved in emotion regulation (Van Someren, 2021).

Still, for completeness, a discussion on the development and maintenance of insomnia should include the neurobiological mechanisms of sleep, notably homeostatic and biological time-keeping mechanisms (Borbély, 1982). The flip-flop switch model of sleep regulation (Saper et al., 2005) suggests a bistable switch mechanism between sleep and wake promoting centres of neuronal cell groups. Wakefulness is governed by a network of cell populations in the hypothalamus (including orexinergic neurons), basal forebrain and brain stem, activating thalamus and cortical structures. These structures include and extend beyond the cell groups in the reticular formation of the brainstem (originally described as ascending reticular activating system). The main sleep-inducing centres are located in the ventrolateral-preoptic nucleus (VLPO), which becomes active during sleep and inhibits all major wake-promoting centres in the hypothalamus and brain stem, with the neurotransmitters galanin and gamma-aminobutyric acid. The VLPO receives afferent input from each of the major monoaminergic systems, and is inhibited by noradrenaline and serotonin. A mutual inhibitory circuit between both systems, the wake and the sleep system, leads to a flip-flop switch with "sharp" transitions between sleeping and waking. Thus, insomnia on this level can be conceptualized as imbalance between sleep-inducing and wake (i.e. arousal)-inducing mechanisms. A hyperactivity of the arousal system or a hypoactivity of the sleep system or both simultaneously could thus "drive" the insomnia. Circadian and homeostatic mechanisms are also involved in this switch process, and it has been speculated that a dysfunctional "key switch" (see above) could play a role in the pathogenesis of insomnia. According to the two-process model of sleep regulation (Borbély, 1982), sleep–wake behaviour is governed by circadian time-keeping mechanisms and a homeostatically controlled process S, representing the sleep drive. Being out of synchrony with the internal body clock (e.g. due to shift work) or having a decreased sleep drive would logically result in sleep complaints. Indeed, the main effective component of CBT-I, sleep restriction, is hypothesized to act on the sleep drive (Maurer et al., 2018), and long-term effectiveness of CBT-I improves with the addition of circadian interventions (Dekker et al., 2020; Leerssen et al., 2021). Notwithstanding these effects, decades of research in insomnia have failed to reveal circadian and homeostatic mechanisms as primary factors involved the origin and pathophysiology of the majority of people suffering from ID (Van Someren, 2021). One might conclude that enhancement of homeostatic sleep pressure and support of circadian rhythm amplitude alleviates insomnia, but that we may have to look beyond hourglass and clock to find underlying causes predisposing to insomnia.

A third factor involved in sleep and predisposing to insomnia is emotion (Saper et al., 2005). This factor is frequently overlooked, in spite of the ubiquitous experience that sleep initiation is difficult under threatening conditions—no matter what our hourglass and clock suggest. Indeed, from an evolutionary perspective this would be extremely disadvantageous. An increasing number of observations suggests a key role of this third factor in the origin and pathophysiology of the predisposition to insomnia (for review, see Van Someren, 2021). For example, the trait to exhibit a pronounced disturbed sleep response to stressful events has been shown to be a major risk factor for insomnia (Drake et al., 2014). Also other personality traits related to emotion regulation have been linked to insomnia, including neuroticism, perfectionism, sensitivity to anxiety symptoms, and the tendency to internalize problems (Dekker et al., 2017; van de Laar et al., 2010). The major early developmental factors predisposing to insomnia involve emotion as well: risk genes seem to have a preference for brain circuitries involved in emotion regulation, and early childhood adversity likewise affects these circuitries (Van Someren, 2021).

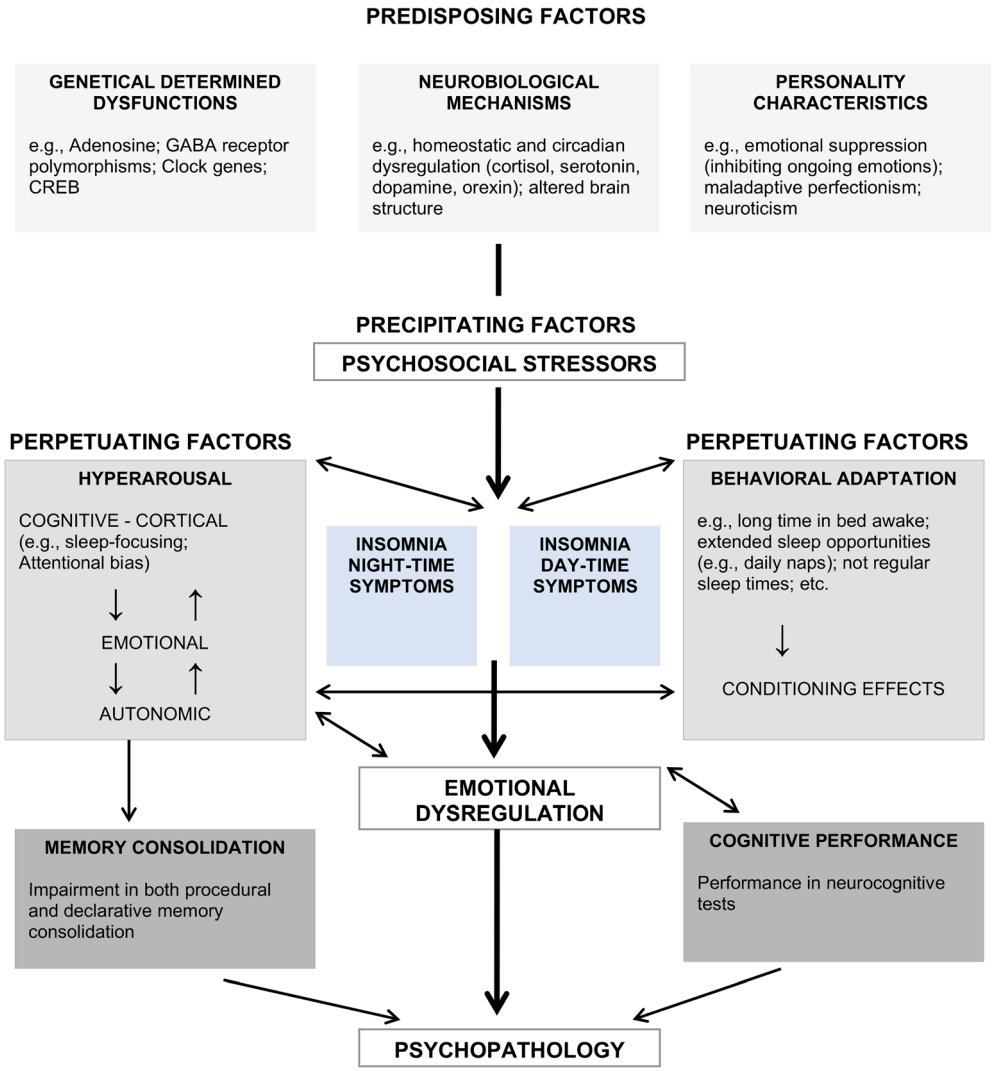

FIGURE 3 Comprehensive insomnia model (see text)

"Precipitating" factors can be readily identified in many cases. These are usually significant life events that facilitate the onset of acute episodes of insomnia. Most frequently, reported triggers of acute episodes of insomnia are stressful life events related to a threat of security to family, health and work–school living that are coupled with negative emotional valence. Fortunately, not everyone exposed to stress in adulthood develops insomnia, most likely only those that have a predisposing profile.

"Perpetuating" factors can be discussed with respect to hyperarousal, which can be conceptualized as overactivity of the arousal-promoting systems, out of balance with the activity in sleep-inducing systems. Hyperarousal includes physiological, cognitive and emotional components, and has been considered a stable characteristic of people with insomnia both during the night and during the day (Morin et al., 2015; Riemann et al., 2010, 2015). It has been demonstrated that patients with insomnia show increased levels of autonomic activity (though the issue is discussed critically with respect to heart rate variability; Dodds et al., 2017) and an overactivity of the HPA-axis, as documented by increased levels of cortisol output during day- and night-time (see meta-analysis by Dressle et al., 2022). Central nervous system (CNS) indicators of hyperarousal in people with insomnia are increased amounts of micro-arousals and increases in fast EEG frequencies (in the sigma and beta bands) during sleep (Christensen et al., 2019; Feige et al., 2013; Perlis et al., 1997, 2001; Spiegelhalder et al., 2012), and also wake EEG shows signatures of increased excitation (Colombo, Ramautar, et al., 2016; Colombo, Wei, et al., 2016) and somatic awareness and responsivity (Wei et al., 2016; Wei, Blanken, & Van Someren, 2018; Wei, Ramautar, et al., 2018). Although still too small for voxel-wise consistent findings (Tahmasian et al. 2018), the rapidly increasing number of neuroimaging studies on insomnia (Riemann et al., 2015) suggests an overactivity of cortico-limbic networks relative to sleep-promoting neuronal networks. Most interestingly, in recent years a special role of rapid eye movement (REM) sleep disturbance (REM sleep instability/restless REM sleep) has been postulated to be of utmost relevance for the experience of insomnia, and specifically their altered perception of sleep and inability to discard hyperarousal (Riemann et al., 2012; Van Someren, 2021). This lead was primarily based on the finding of increased micro-arousals during REM sleep in insomnia (Feige et al., 2008)—further studies revealed that upon awakening out of REM sleep, patients with insomnia

more frequently stated having been awake compared with non-REM (NREM) sleep and good sleepers (Feige et al., 2018). Following up on these findings, Feige et al. (2021) used an event-related potentials paradigm to demonstrate that ID patients differed from good sleepers by showing reduced P2 amplitudes only in phasic REM sleep. These studies highlight a special role of REM sleep for insomnia.

The mechanisms underlying this special role of REM sleep in the predisposition, perpetuation and psychiatric consequences were addressed in a series of seminal studies (Wassing et al., 2016; Wassing, Benjamins, et al., 2019; Wassing, Lakbila-Kamal, et al., 2019; Wassing, Schalkwijk, et al., 2019). In brief, Wassing et al. showed that the restless REM sleep that is characteristic of people with insomnia interferes with overnight adaptation in limbic circuits of the brain. The consequential difficulties with dissolving of distress could be key to the development and perpetuation of hyperarousal as well to the risk of developing psychiatric disorders, as supported by other studies (Halonen et al., 2021; Pesonen et al., 2019). Restless sleep lacks the prolonged silencing of the locus coeruleus and consequential drop in cerebral noradrenaline that characterizes normal restful REM sleep (Kjearby et al., 2020). Because REM sleep is a period of pronounced limbic reactivation of emotional memory traces, it has been hypothesized that the increased level of noradrenaline during restless REM sleep interferes with the synaptic plasticity processes underlying adaptation of the neuronal engrams that represent distress, and could even result in sensitization, indicating maladaptive sleep (Van Someren, 2021). Others have proposed that the low level of noradrenaline during REM sleep is key to restore the noradrenergic tone, to enable a low tonic and high phasic locus coeruleus activity during wakefulness (Goldstein & Walker, 2014).

Restless REM sleep thus has a specific contribution to "emotional" perpetuating factors, and may explain why patients with insomnia are so prone to develop anxiety and depressive disorders in the long run. Indeed, sleep has been conceptualized as a basic psychophysiological process that is fundamental for stress, behaviour and emotion regulation (Hagger, 2010; Palmer & Alfano, 2017). Consistently, most mental disorders are associated with sleep impairment (Baglioni et al., 2016), and insomnia-related problems in children have been linked with difficulties in socio-emotional development (Sadeh et al., 2014; Vermeulen et al., 2021). In adults, insomnia has been found to be a predictor of years-long lingering of emotional distress (Wassing et al., 2016; Wassing, Lakbila-Kamal, et al., 2019), of depression, and of anxiety disorders (Baglioni et al., 2011; Hertenstein et al., 2019; Leerssen et al., 2021). Experimental studies have shown that patients with insomnia report more negative emotions than good sleepers (McCrae et al., 2008; Scott & Judge, 2006). Psychophysiological studies have also evidenced an emotional bias in people with insomnia to sleep-related stimuli with negative valence compared with good sleepers (Baglioni et al., 2010; Baglioni, Spiegelhalder, et al., 2014).

Perpetuating factors also include inadequate "behaviours", like prolonged bedtimes, irregular sleep–wake schedules, napping during the day and other maladaptive behaviours, such as using alcohol to combat insomnia. Usually, these strategies are attempted to compensate for lost sleep; however, in the end insomnia is maintained and exacerbated by decreasing sleep drive.

In addition, "cognitive perpetuating factors" have been identified, such as beliefs, worry and attentional bias (Espie, 2002; Harvey, 2002; Morin et al., 2007). These cognitions include unrealistic beliefs about sleep requirements and excessive worry for not meeting these standards. In recent years, the literature has emphasized the role of selective attention processes in people with insomnia. Specifically, it has been argued that the attentional system of patients with insomnia may be abnormally sensitive to sleep-related information (Harris et al., 2015). It has been hypothesized that such attention bias may exacerbate sleep-related rumination and lead to sleep effort (Espie et al., 2006; Harvey, 2002).

Summarizing, acute precipitating life events can "set the wheels in motion"—acute insomnia is triggered. The question of why most individuals who develop acute insomnia do not go on to develop the chronic condition has not yet been clarified (Ellis et al., 2012)—but likely involves genetic and early life stress-induced neurobiological vulnerability to keep "the train rolling." A complex network of associated symptoms including cognitive-, emotional- and cerebral hyperarousal, unstable REM sleep and maladaptive behaviours will keep the furnace burning. Sleep-preventing learned associations (conditioning effects) are strongly involved in this process as well, giving credit to Bootzin's assumption that in insomnia the original connection between the bed (stimulus) and the behaviour of sleep (response) has been lost or "unlearned" (Bootzin et al., 1991).

The CBT-I (see below) mainly targets the perpetuating factors, for example, relaxation techniques and mindfulness aim to address psychophysiological hyperarousal; sleep hygiene, stimulus control and sleep restriction try to correct maladaptive behaviours and enhance sleep drive; whereas cognitive strategies aim to alter "racing thoughts", dysfunctional beliefs and attitudes, and to reduce nocturnal worrying and ruminations.

4 | TREATMENT (S)—FOCUS ON PSYCHOLOGICAL APPROACHES: PRESENT GUIDELINES, WHAT IS CBT-I, STEPPED CARE AND DIGITAL CBT-I?

All insomnia-related guidelines published in the last 5 years agree that CBT-I should be the first-line treatment for insomnia, based on the accumulated scientific evidence from the literature. These guidelines include the American College of Physicians (Brasure et al., 2016; Kathol & Arnedt, 2016; Qaseem et al., 2016; Wilt et al., 2016), the American Academy of Sleep Medicine (AASM; Edinger et al., 2021a, b), the German and the European Sleep Society (Riemann, Baum, et al., 2017; Riemann, Baglioni, et al., 2017), and the British Association for Psychopharmacology consensus statement (Wilson et al., 2019). Overall, these guidelines make a strong case for CBT-I as first-line treatment for insomnia, and hypnotics are recommended for short-term use and only if CBT-I is either not available or ineffective. As hypnotics in this context, melatonin agonists, benzodiazepines,

benzodiazepine receptor antagonists, some sedating antidepressants and orexin receptor antagonists are recommended mainly for short-term use (less than 4 weeks) only. An overview of the present state of hypnotic treatment can be found in reviews (Herring et al., 2019; Riemann & Nissen, 2012; Roehrs & Roth, 2012).

The CBT-I comprises a family of interventions and is not "one" homogenous therapeutic strategy *per se* (Table 2).

The CBT-I is in essence a multicomponent approach, comprising cognitive and behavioural parts, within each of which domain there is a wide range of treatment options. The principal behavioural therapies are sleep restriction and stimulus control. Cognitive techniques include reappraisal, cognitive control and paradoxical intention. There is also a range of relaxation therapies, and sleep hygiene education, although not effective as a standalone treatment, is commonly part of the CBT-I toolkit. A brief description of these techniques is given in the table. For further details, the interested reader is referred to a new CBT-I textbook that will be published in 2022 (Baglioni et al., 2022). A new clinician handbook on insomnia will also be available shortly (Espie, 2022).

Logically therefore CBT-I is not "a treatment" but is "a system of cognitive and behavioural therapeutics", akin to pharmacotherapy (which is not a drug treatment but a "pharmaceutical approach" to clinical care; Espie, 2022). The history of evidence-based psychotherapy (in most disorders) reveals a period of time during which there was a tendency towards "lumping" of therapeutic elements, rather than the creation of precision techniques that "may" be used in combination. This is certainly true of the non-pharmacological management of insomnia, and the term CBT-I has for the past 20 years or more been used rather generically in the literature because the majority of studies have deployed a CBT-I package.

In earlier times there was a focus upon more specific interventions. For example, comparing the effectiveness of abbreviated progressive relaxation, stimulus control therapy and paradoxical intention (Espie et al., 1989), or even investigating components of a single therapy (Woolfolk & McNulty, 1983: compared progressive relaxation, progressive relaxation without tension release, imagery with tension release, and imagery without tension release). Interestingly, of late, there has been renewed interest in single-component therapies. We now find ourselves unpicking or deconstructing CBT to evaluate its active component treatments, and even its active treatment ingredients. The best example is sleep restriction therapy (SRT), widely regarded to be the most effective element of CBT (Edinger et al., 2021a; Maurer, Schneider et al., 2021). A series of laboratory-based experiments has recently explored the homeostatic, arousal and circadian mechanisms of sleep restriction (Maurer et al., 2020, 2022; Maurer, Ftouni et al., 2021).

In support of this is the fact that CBT protocols are effective even when they vary. The AASM practice parameters task force recently grappled with the question, what are the "minimal characteristics" of effective CBT (Edinger et al., 2021a). They concluded that "all studies included SRT, stimulus control and some form of cognitive therapy"; however, the cognitive component varied widely. Whether or not relaxation strategies or sleep hygiene were included in the CBT-I regimen varied across studies as well. It was beyond the scope of this (group) to recommend a specific CBT protocol, and "these variations did not appear to systematically impact the effectiveness of the treatment" (p. 261). This evidences the versatility and robustness of what is sometimes now referred to as CBTx (cognitive and behavioural therapeutics), that is, a "therapeutic formulary", where not everyone needs the same content, or the same order of content (Espie, 2022). Analysis of how SRT is configured suggests there is gross variability between studies and protocols (Kyle et al., 2015); it would be prudent to establish what is the most effective combination of SRT parameters, including tailoring to presenting insomnia phenotype. Indeed, the widespread development of "precision medicine" (Ginsburg & Willard, 2009; Jain, 2002) has spawned interest in how "personalized behavioural sleep medicine" for insomnia may evolve in the future (Kyle et al., 2014).

Despite the impressive evidence base for CBT-I, its recognition internationally as the treatment of first choice for the management of insomnia and the fact that the CBTx formulary of treatments is quite wide ranging, in practice the majority of insomnia patients seeking medical help continue to receive medication. The issue here is not so much overprescribing of drugs as it is under-provision of CBT-I. Two innovations have been developed to address this problem. The first, at the level of the treatment itself there has been growing interest in, and a rapidly accelerating evidence base for digital CBT-I, that is CBT-I delivered by fully automated web and mobile means. The second, at the level of the service, has been the development of the "stepped care" model of insomnia service delivery.

The effectiveness of digital CBT-I has been robustly and rigorously demonstrated against psychological placebo (Espie et al., 2012), attention control (Christensen et al., 2016; Kaldo et al., 2015), sleep hygiene (Espie et al., 2019; Ritterband et al., 2017; Vedaa et al., 2020), waitlist (Zachariae et al., 2018) and usual care (Freeman et al., 2017) in a range of clinical and co-morbid populations. Several meta-analyses report large between-group effects on insomnia severity, and medium effects on sleep diary outcomes (Seyffert et al., 2016; Soh et al., 2020; Zachariae et al., 2016), and benefits to sleep are durable, being maintained up to a year and beyond (Blom et al., 2017; Luik et al., 2020; Vedaa et al., 2019). Whereas meta-analyses report effect sizes in the range of face-to-face CBT-I thereby suggesting non-inferiority, head-to-head comparisons have shown mixed findings (Blom et al., 2015; De Bruin et al., 2016; Kallestad et al., 2021; Lancee et al., 2016). It seems likely, however, that the evolution of highly engaging clinically evidenced software will address engagement and treatment implementation challenges that are apparent for all forms of CBT-I delivery. It may also be the case that differences exist between different digital CBT-I formats (Hasan et al., 2022). These outstanding questions warrant further investigation.

Beyond improved sleep, digital CBT-I, like "traditional" CBT-I, yields benefits to additional clinical and functional outcomes of relevance to insomnia. Several studies have documented reductions in symptoms of anxiety and depression, including in individuals with clinically significant depressive symptoms (Blom et al., 2015, 2017; Cheng et al., 2019; Henry et al., 2021; Pillai et al., 2015; van der Zweerde

TABLE 2 CBT-I ingredients (from Baglioni et al., 2020)

CBT-I strategy	Description
Sleep restriction	*Behavioural strategy*: A method that aims at strengthening homeostatic sleep pressure and stabilizing circadian control of sleep and wakefulness, by decreasing the opportunity to sleep over successive nights. Patients are instructed to restrict their time in bed to match their average (self-report in sleep diaries) total sleep duration. The time in bed is then gradually increased until reaching patients' optimal sleep need. An alternative method, called *sleep compression*, consists in gradual constriction of time in bed until reaching the optimal sleep need.
Stimulus control	*Behavioural strategy*: Several instructions aiming at strengthening the bed as a cue for sleep, weakening it as a cue for activities that might interfere with sleep, and helping the insomniac acquire a consistent sleep rhythm, based on operant conditioning model: (1) lie down to go to sleep only when you are sleepy; (2) do not use your bed for anything except your sleep and sexual activity; (3) if you find yourself unable to fall asleep, get up and go to another room. Stay up as long as you wish, and come back to bed when you feel sleepy; (4) If you still cannot fall asleep, repeat step (3). Do this as often as is necessary throughout the night; (5) Set your alarm and get up at the same time every morning irrespective of how much sleep you got during the night; (6) no napping during daytime.
Sleep hygiene education	Behavioural and educational strategy: General health instructions about internal and external factors that might influence sleep (e.g. sport, light, temperature, etc.).
Relaxation	Behavioural and cognitive strategy: A set of methods aiming at reducing somatic or cognitive hyperarousal (e.g. progressive muscle relaxation, autogenic training, imagery training, meditation).
Cognitive reappraisal	Cognitive strategy: Strategies directed to reduce dysfunctional beliefs, attitudes, concerns and false beliefs about the cause of insomnia and about the inability to sleep.
Cognitive control/ Worry time	Cognitive strategy: The patient is instructed to sit comfortably in an armchair, and write down a list of worries and list of what to do the next day. The rationale of this strategy is to prevent emotionally loaded intrusive thoughts during the sleep-onset period, as all worries have been "already" processed before going to bed.
Paradoxical intention	Cognitive strategy: Strategy aimed at reducing the anticipatory anxiety at the time of falling asleep. Patients are instructed to remain still in bed with the eyes closed and to try to keep awake as long as they can. This takes away the responsibility to try to fall asleep, which in turn often leads to falling asleep quicker.

Abbreviation: CBT-I, cognitive-behavioural treatment for insomnia.

et al., 2019). From a scientific perspective, digital CBT-I confers advantages such that it permits examination of potential mediators of treatment effects using a standardized therapeutic approach. Large randomized-controlled trials and secondary analyses show that insomnia symptom reduction mediates improvements in mental health symptoms (Freeman et al., 2017; Henry et al., 2021), and improvements in quality of life, health and wellbeing, and cognitive function (Espie et al., 2019; Kyle, Hurry, et al., 2020). This evidence therefore supports treating insomnia complaints whenever it presents. Emerging data also suggest that demographic variables including age, race, gender or socio-economic status do not moderate the effectiveness of digital CBT-I (Cheng et al., 2019).

Real-world evidence further underscores the value of digital CBT-I. Recent uncontrolled data evaluating digital CBT-I in existing healthcare settings in the UK show reductions in insomnia and augmentation of the effects of in-person therapy for anxiety and depression (Cliffe et al., 2020; Luik et al., 2017; Stott et al., 2021). Importantly, from a health economic perspective, analyses suggest that digital CBT-I is cost-effective, and may lead to cost savings if made available at scale (Darden et al., 2021; Sampson et al., 2021). This growing body of evidence behind digital CBT-I has led to increased recognition of it as a viable and effective treatment option. Indeed, in the USA, Somryst has been cleared by the FDA as a prescription digital therapeutic (Morin, 2020). Likewise, Sleepio (www.sleepio.com) is widely available in the USA, integrated into healthcare pathways and on the digital formulary, and is available in major parts of the UK National Health Service.

By overcoming the barriers preventing access to therapist-delivered CBT-I, digital CBT-I has the potential to provide access to clinically effective, evidenced-based and guideline-recommended insomnia treatment. These fundamental properties of effectiveness and scalability make digital CBT-I attractive as a first-line insomnia intervention, providing an accessible alternative to pharmacotherapy (Figure 4).

The stepped-care model is a population health service approach to providing people with insomnia with access to evidence-based care (Espie, 2009; Espie et al., 2013). Stepped care is often conceptualized as a pyramid consisting of different levels, with at the bottom the least specialized help applicable for those with less severe and more generic complaints and highly specialized help for those with more severe, complex and rare problems as the top. The level of intervention is naturally not arbitrary; treatment is tailored to and based on the needs of the patient and the nature of their complaints. The number of steps in any stepped care model would be determined by the levels of intervention that are proven and available, and by what within the healthcare system would be affordable. Stepped care models have been recommended for use in insomnia (Baglioni et al., 2020, 2022), and are sometimes adopted in healthcare systems (Vincent & Walsh, 2013).

With regard to insomnia, therefore, digital CBT might be particularly suitable to be one of the entry-level methods for the treatment

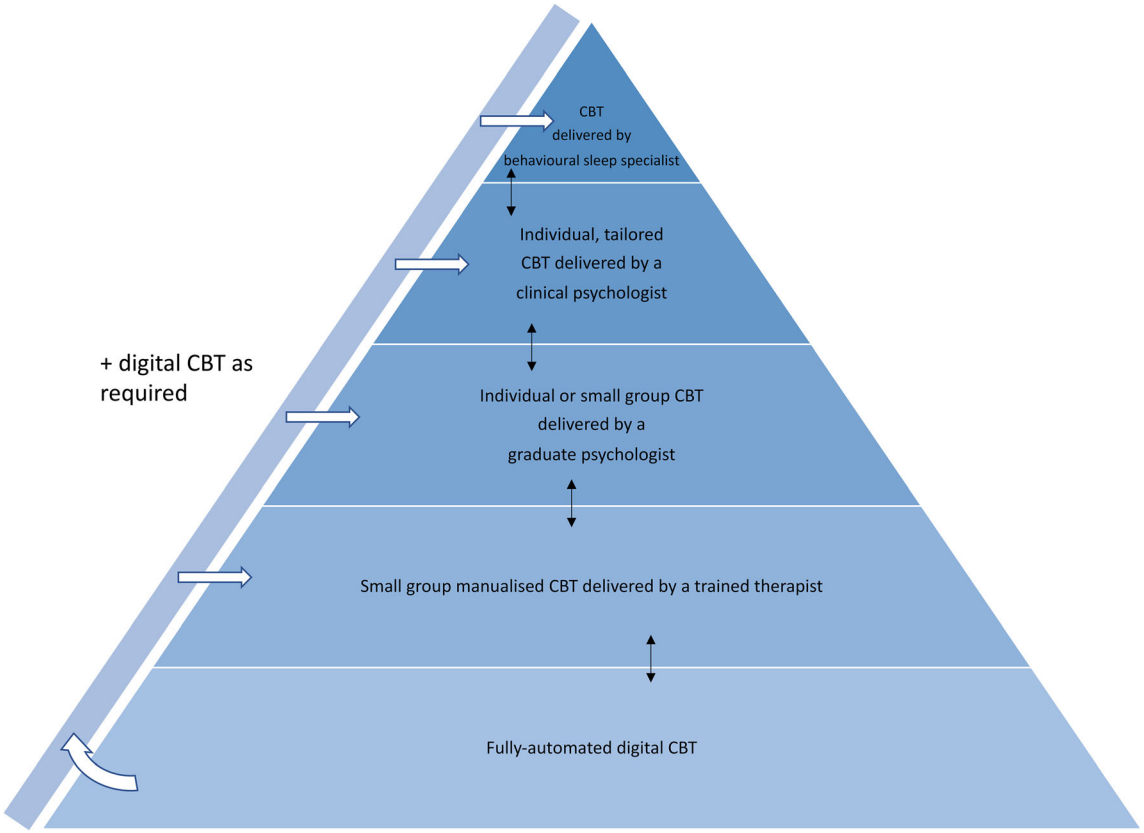

FIGURE 4 A proposed stepped care model for delivery of cognitive-behavioural therapy (CBT) as clinical guideline care. Digital CBT offers accessible treatment for all, but also may be integrated into the care pyramid supporting in-person therapy. The stepped care model conserves expert resources for more complex and treatment-resistant cases

of insomnia, as it has considerable "scalability", particularly when fully automated. Another approach at this level might be using self-help books of good standing, perhaps as part of a "books on prescription" scheme. Next in the hierarchy might be insomnia services that require some in-person support, but thought would be given to how such care could be provided with efficiency. Examples here might include telehealth rather than in a clinic, and the use of small group therapy rather than individual treatment. Other factors to be considered would be the nature of the treatment itself and the expertise of the therapist. For example, it could be possible to train healthcare workers in the provision of manualized CBT-I without them having to have a deep understanding of sleep medicine or mental health (training primary care nurses, for example). This approach is very protocol-driven and can be readily standardized (Kyle, Madigan, et al., 2020). As you then continue up the hierarchy there is greater need for insomnia-specific expertise and for the use of tailored therapy. At the peak of the pyramid the likelihood is that not only specialist expertise but also specialized facilities such as those available at a sleep centre may be required to address the needs of the most complex patients.

Stepped care systems require decision algorithms for two processes. First, to ensure that people are correctly allocated to the appropriate level of care in the first instance; and secondly, to ensure that people are able to step up to more advanced care depending on their treatment response.

5 | FUTURE PERSPECTIVES WITH RESPECT TO DIAGNOSIS, MEASUREMENT, AETIOLOGY AND PATHOPHYSIOLOGY; NEW TREATMENTS

Given the drastic changes we have been witnessing concerning insomnia and its diagnosis, pathophysiology/aetiology and treatment in the last 30 years, one might be tempted to answer the question "Can we rest yet?" (Harvey & Tang, 2003) with "Yes!." However, this would be premature and inadequate with respect to the many open questions still facing us in the insomnia field. Therefore, at this point, we would like to highlight some issues/avenues for future research and clinical practice we consider of utmost importance.

Given the fact that at present we have reached the unique situation that all major diagnostic systems (DSM-5, ICSD-3, ICD-11) have agreed upon ID (American Academy of Sleep Medicine, 2014; American Psychiatric Association, 2013; World Health Organization, 2019), the situation seems ideal that all types of studies into ID use more or less the same diagnostic criteria, which would be ideal to make data coming from all over the world easily comparable. This would also entail homogenization of our diagnostic and research instruments (questionnaires, PSG, etc.). However, as mentioned before, there definitely are different insomnia phenotypes that should not be neglected. A data-driven approach to delineate and characterize these

phenotypes seems warranted (Blanken, Benjamins, et al., 2019; Kao et al., 2021), possibly further refined by adding physiological data by means of PSG to questionnaire datasets.

In this regard, pooling data from different sleep labs could be beneficial in order to address the issues of small sample sizes and poor replicability in the insomnia field. This would require the use of standard methodology and paradigms across different labs. The UK Biobank (www.ukbiobank.ac.uk; see Allen et al., 2014 for a detailed description), a large biomedical database including a sample of about 500,000 adults, has already proven to be useful for insomnia research (Jansen et al., 2019; Kyle et al., 2017; Lane et al., 2019). Although the UK Biobank is not specifically optimized for insomnia research, cross-validation showed the available phenotype to very accurately match diagnosed insomnia patients (Hammerschlag et al., 2017).

Given the costs and artificiality of the traditional sleep laboratory, home-based easy to apply measures need to be developed, allowing repetitive CNS-based measurements in the natural environments of our patients, reaching beyond actigraphy (Debener et al., 2015; Mikkelsen et al., 2019). This would allow to study the dynamics of features reflecting the sleep drive and REM sleep characteristics longitudinally and in relation to different treatments and their outcomes in much more detail.

Given the prominence of the hyperarousal concept in almost all insomnia models, one should also start to think about developing a hyperarousal test, which at best could be applied during daytime or routine office/hospital hours. One could think about a stress/challenge paradigm, measuring autonomous nervous system activity (e.g. heart rate, galvanic skin response, etc.), cortisol as main marker of the stress response and EEG during baseline, rest and different stress conditions. One of the best accepted stress paradigms now is the Trier social stress test—its usefulness has already been tested (Chen et al., 2017). Alternatively, probably just the instruction "please try to sleep now" probably might offset a marked stress response in insomniacs. Such a psychophysiological paradigm administered during the day can also easily be coupled with neuroimaging methods, that is, functional magnetic resonance imaging. Needless to say, these data should be coupled with descriptive questionnaire data. Assuming that it will be possible to develop an easy to apply and valid hyperarousal test, this instrument could be used for phenotyping, relating the data to (epi-)genetic data, general diagnostics, differential-therapeutics and therapy outcomes. Given the emerging evidence of maladaptive sleep (Van Someren, 2021), essential insights could require repeated assessment of hyperarousal from evening to morning across recorded nights. Analyses can then address which sleep features determine the overnight fate of distress—which could range from full adaptation even to maladaptive sensitization (Wassing, Benjamins, et al., 2019; Wassing, Lakbila-Kamal, et al., 2019). Nevertheless, deeper insights into the mechanisms of hyperarousal in insomnia, its causes and consequences for cognitive processes and brain health in general are needed. This will help to further increase the value of the hyperarousal concept for insomnia research and could also help to identify a valid hyperarousal test.

Interestingly, also with therapeutics at present we have reached a unique situation concerning treatment—all presently published relevant guidelines agree that CBT-I should be the first-line treatment for insomnia. A statement like this would have caused a lot of many raised eyebrows even just 10 years ago! This development is probably because on one hand, the CBT-I literature is blooming and has generated a solid and ever-increasing evidence base, but on the other hand maybe also due to a stagnation in the sector of hypnotic development and the withdrawal of many major players in psychopharmacology from CNS-oriented Research & Development. It has to be judged in the next few years whether the worldwide introduction of orexin receptor antagonists will markedly alter the hypnotic market. From a future perspective, we would like to suggest that research into the roles of histamine and noradrenaline and sleep regulation could lead to new discoveries (Thakkar, 2011; Van Someren, 2021). Maybe also approaches encompassing non-invasive brain stimulation might complement insomnia treatment strategies (Herrero Babiloni et al., 2021).

A better understanding of the psychoneurobiological mechanisms of insomnia is urgently needed to monitor and evaluate treatment effects of CBT-I beyond subjective measures, and further develop complementary treatment strategies. First, preliminary findings suggest that 1 night of experimental sleep restriction (delaying bedtime by 2 hr) may help to stabilize restless REM sleep (Kao et al., 2021). However, it remains to be seen whether this stabilization is observed in therapeutic SRT, and whether it translates into improvements in regulation of emotional distress, hyperarousal and the risk of developing mental disorders. Second, notwithstanding the established efficacy of CBT-I, it is important to acknowledge that two out of five patients do not show full remission, even after boosting CBT-I effects with subsequent pharmacological treatment (Morin et al., 2020). We still have very limited insight into who will respond and who will not. Novel graph theory-based analyses like network outcome analysis and network intervention analysis may reveal how non-responders differ in their initial symptom profiles and trajectories of change of symptoms during the intervention (Blanken, Benjamins, et al., 2019; Blanken et al., 2020; Blanken, van der Zweerde, et al., 2019). Pinpointing such differences could provide leads to novel strategies.

Also the gradual wearing off of initial benefits of CBT-I deserves attention (van der Zweerde et al., 2019). Two recent studies indicate that beneficial effects of CBT-I may be preserved longer if CBT-I is combined with interventions aimed at supporting circadian rhythms (Dekker et al., 2020; Leerssen et al., 2021).

What we consider probably the most important challenge for the future is the integration of CBT-I into the standard treatment of patients with mental disorders, especially anxiety and depression. It is known that almost all mental disorders are afflicted with disturbances of sleep continuity (Baglioni et al., 2016), and we also know that paying proper therapeutic respect to including insomnia-related components into the overall therapeutic concept will improve outcomes in general and speed up the therapeutic process (Gee et al., 2019; Hertenstein et al., 2022; Manber et al., 2008). Models how to do this have been suggested by several authors (Kraepelien et al., 2022; Schneider et al., 2020)—thus, the times seem right to postulate insomnia as a transdiagnostic mechanism for mental disorders (Harvey et al., 2011, 2021; Van Someren, 2021) and also insomnia treatment

based on CBT-I as a basic mode in psychiatric/psychotherapeutic treatment.

One step further will address the primary prevention of mental disorders. There is a strong probability that adequate insomnia treatment will reduce the incidence and recurrence of depressive episodes and anxiety disorders (Benz et al., 2020; Cheng et al., 2019; Irwin et al., 2022; Leerssen et al., 2021). In a first step, one might address risk groups especially prone to mental illness and offer sleep treatment versus a control condition and compare longitudinal outcomes, as recently demonstrated by Leerssen et al. (2021). In a next step it might be tested whether educating and training of the general population to utilize the principles that underlie CBT-I could prevent insomnia. Such efforts may be especially relevant to prevent mental disorders that tend to surface during important transition periods, like in students moving from high school to university.

CONFLICT OF INTEREST

Dieter Riemann is a member of the Executive Board of FAVT (Freiburg Institute for Behavioural Therapy/non for profit), a salaried activity. He is Editor-in-Chief of the *Journal of Sleep Research*, which is owned by the European Sleep Research Society (non-profit body) and receives payments for this task. Dieter Riemann receives royalties from publishing and honoraria for lecturing (no pharmaceutical industry), and is funded by several grants from the German Federal state. Colin A. Espie reports research support from NIHR-HTA (UK), receiving payments from book publishing and lecture fees. He also reports being a cofounder and Chief Scientist of Big Health Ltd (the developer of Sleepio). He is a shareholder of and receiving salary from Big Health. Alasdair L. Henry is employed by, receives a salary from and is a shareholder of Big Health. All other authors report no conflicts of interest.

AUTHOR CONTRIBUTIONS

Dieter Riemann provided an outline of the article and did the final editing. All the other authors contributed equally.

DATA AVAILABILITY STATEMENT

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REFERENCES

Allen, N. E., Sudlow, C., Peakman, T., & Collins, R. (2014). UK Biobank data: Come and get it. *Science Translational Medicine*, *6*(224), 224ed4. https://doi.org/10.1126/scitranslmed.3008601

American Academy of Sleep Medicine. (2014). *International classification of sleep disorders* (3rd. ed.). American Academy of Sleep Medicine.

American Psychiatric Association. (1987). *Diagnostic and statistical manual of mental disorders* (3rd ed.). American Psychiatric Association.

American Psychiatric Association. (1998). *Diagnostic and statistical manual of mental disorders (DSM-IV)* (4th ed.). American Psychiatric Association.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). American Psychiatric Association.

Anothaisintawee, T., Reutrakul, S., Van Cauter, E., & Thakkinstian, A. (2016). Sleep disturbances compared to traditional risk factors for diabetes development: Systematic review and meta-analysis. *Sleep Medicine Reviews*, *30*, 11–24. https://doi.org/10.1016/j.smrv.2015.10.002

Baglioni, C., Altena, E., Bjorvatn, B., Blom, K., Bothelius, K., Devoto, A., … Riemann, D. (2020). The European Academy for Cognitive Behavioural Therapy for Insomnia: An initiative of the European insomnia network to promote implementation and dissemination of treatment. *Journal of Sleep Research*, *29*(2), e12967. https://doi.org/10.1111/jsr.12967

Baglioni, C., Battagliese, G., Feige, B., Spiegelhalder, K., Nissen, C., Voderholzer, U., … Riemann, D. (2011). Insomnia as a predictor of depression: A meta-analytic evaluation of longitudinal epidemiological studies. *Journal of Affective Disorders*, *135*(1–3), 10–19. https://doi.org/10.1016/j.jad.2011.01.011

Baglioni, C., Espie, C. A., & Riemann, D. (2022). *Cognitive-behavioural therapy for insomnia (CBT-I) across the lifespan. Guidelines and clinical protocols for health professionals*. Wiley & Sons (in press).

Baglioni, C., Lombardo, C., Bux, E., Hansen, S., Salveta, C., Biello, S., … Espie, C. A. (2010). Psychophysiological reactivity to sleep-related emotional stimuli in primary insomnia. *Behaviour Research and Therapy*, *48*(6), 467–475. https://doi.org/10.1016/j.brat.2010.01.008

Baglioni, C., Nanovska, S., Regen, W., Spiegelhalder, K., Feige, B., Nissen, C., … Riemann, D. (2016). Sleep and mental disorders: A meta-analysis of polysomnographic research. *Psychological Bulletin*, *142*(9), 969–990. https://doi.org/10.1037/bul0000053

Baglioni, C., Regen, W., Teghen, A., Spiegelhalder, K., Feige, B., Nissen, C., & Riemann, D. (2014). Sleep changes in the disorder of insomnia: A meta-analysis of polysomnographic studies. *Sleep Medicine Reviews*, *18*(3), 195–213. https://doi.org/10.1016/j.smrv.2013.04.001

Baglioni, C., Spiegelhalder, K., Regen, W., Feige, B., Nissen, C., Lombardo, C., … Riemann, D. (2014). Insomnia disorder is associated with increased amygdala reactivity to insomnia-related stimuli. *Sleep*, *37*(12), 1907–1917. https://doi.org/10.5665/sleep.4240

Bastien, C. H., Vallières, A., & Morin, C. M. (2001). Validation of the insomnia severity index as an outcome measure for insomnia research. *Sleep Medicine*, *2*(4), 297–307. https://doi.org/10.1016/s1389-9457(00)00065-4

Benz, F., Knoop, T., Ballesio, A., Bacaro, V., Johann, A. F., Rücker, G., … Baglioni, C. (2020). The efficacy of cognitive and behavior therapies for insomnia on daytime symptoms: A systematic review and network meta-analysis. *Clinical Psychology Review*, *80*, 101873. https://doi.org/10.1016/j.cpr.2020.101873

Blanken, T. F., Benjamins, J. S., Borsboom, D., Vermunt, J. K., Paquola, C., Ramautar, J., … Van Someren, E. J. W. (2019). Insomnia disorder subtypes derived from life history and traits of affect and personality. *Lancet Psychiatry*, *6*(2), 151–163. https://doi.org/10.1016/S2215-0366(18)30464-4

Blanken, T. F., Borsboom, D., Penninx, B. W., & Van Someren, E. J. (2020). Network outcome analysis identifies difficulty initiating sleep as a primary target for prevention of depression: A 6-year prospective study. *Sleep*, *43*(5), zsz288. https://doi.org/10.1093/sleep/zsz288

Blanken, T. F., van der Zweerde, T., Van Straten, A., Van Someren, E. J. W., Borsboom, D., & Lancee, J. (2019). Introducing network intervention analysis to investigate sequential, symptom-specific treatment effects: A demonstration in co-occurring insomnia and depression. *Psychotherapy and Psychosomatics*, *88*(1), 52–54. https://doi.org/10.1159/000495045

Blom, K., Jernelöv, S., Rück, C., Lindefors, N., & Kaldo, V. (2017). Three-year follow-up comparing cognitive behavioral therapy for depression to cognitive behavioral therapy for insomnia, for patients with both diagnoses. *Sleep*, *40*(8). https://doi.org/10.1093/sleep/zsx108

Blom, K., Tarkian Tillgren, H., Wiklund, T., Danlycke, E., Forssén, M., Söderström, A., … Kaldo, V. (2015). Internet-vs. group-delivered cognitive behavior therapy for insomnia: A randomized controlled non-inferiority trial. *Behaviour Research and Therapy*, *70*, 47–55. https://doi.org/10.1016/j.brat.2015.05.002

Bootzin, R. R., Epstein, D., & Wood, J. M. (1991). Stimulus control instructions. In P. J. Hauri (Ed.), *Case studies in insomnia* (pp. 19–28). Springer US. https://doi.org/10.1007/978-1-4757-9586-8_2

Borbély, A. A. (1982). A two process model of sleep regulation. *Human Neurobiology*, *1*(3), 195–204.

Brasure, M., Fuchs, E., MacDonald, R., Nelson, V. A., Koffel, E., Olson, C. M., … Kane, R. L. (2016). Psychological and behavioral interventions for managing insomnia disorder: An evidence report for a clinical practice guideline by the American College of Physicians. *Annals of Internal Medicine*, *165*(2), 113–124. https://doi.org/10.7326/M15-1782

Buysse, D. J., Ancoli-Israel, S., Edinger, J. D., Lichstein, K. L., & Morin, C. M. (2006). Recommendations for a standard research assessment of insomnia. *Sleep*, *29*(9), 1155–1173. https://doi.org/10.1093/sleep/29.9.1155

Carney, C. E., Buysse, D. J., Ancoli-Israel, S., Edinger, J. D., Krystal, A. D., Lichstein, K. L., & Morin, C. M. (2012). The consensus sleep diary: Standardizing prospective sleep self-monitoring. *Sleep*, *35*(2), 287–302. https://doi.org/10.5665/sleep.1642

Chan, W. S., Levsen, M. P., & McCrae, C. S. (2018). A meta-analysis of associations between obesity and insomnia diagnosis and symptoms. *Sleep Medicine Reviews*, *40*, 170–182. https://doi.org/10.1016/j.smrv.2017.12.004

Chen, I. Y., Jarrin, D. C., Ivers, H., & Morin, C. M. (2017). Investigating psychological and physiological responses to the trier social stress test in young adults with insomnia. *Sleep Medicine*, *40*, 11–22. https://doi.org/10.1016/j.sleep.2017.09.011

Cheng, P., Kalmbach, D. A., Tallent, G., Joseph, C. L., Espie, C. A., & Drake, C. L. (2019). Depression prevention via digital cognitive behavioral therapy for insomnia: A randomized controlled trial. *Sleep*, *42*(10), zsz150. https://doi.org/10.1093/sleep/zsz150

Christensen, H., Batterham, P. J., Gosling, J. A., Ritterband, L. M., Griffiths, K. M., Thorndike, F. P., … Mackinnon, A. J. (2016). Effectiveness of an online insomnia program (SHUTi) for prevention of depressive episodes (the GoodNight Study): A randomised controlled trial. *Lancet Psychiatry*, *3*(4), 333–341. https://doi.org/10.1016/S2215-0366(15)00536-2

Christensen, J. A. E., Wassing, R., Wei, Y., Ramautar, J. R., Lakbila-Kamal, O., Jennum, P. J., & Van Someren, E. J. W. (2019). Data-driven analysis of EEG reveals concomitant superficial sleep during deep sleep in insomnia disorder. *Frontiers in Neuroscience*, *13*, 598. https://doi.org/10.3389/fnins.2019.00598

Cliffe, B., Croker, A., Denne, M., Smith, J., & Stallard, P. (2020). Digital cognitive behavioral therapy for insomnia for adolescents with mental health problems: Feasibility open trial. *JMIR Mental Health*, *7*(3), e14842. https://doi.org/10.2196/14842

Colombo, M. A., Ramautar, J. R., Wei, Y., Gomez-Herrero, G., Stoffers, D., Wassing, R., … Van Someren, E. J. W. (2016). Wake high-density electroencephalographic spatiospectral signatures of insomnia. *Sleep*, *39*(5), 1015–1027. https://doi.org/10.5665/sleep.5744

Colombo, M. A., Wei, Y., Ramautar, J. R., Linkenkaer-Hansen, K., Tagliazucchi, E., & Van Someren, E. J. W. (2016). More severe insomnia complaints in people with stronger long-range temporal correlations in wake resting-state EEG. *Frontiers in Physiology*, *7*, 576. https://doi.org/10.3389/fphys.2016.00576

Daley, M., Morin, C. M., LeBlanc, M., Grégoire, J.-P., & Savard, J. (2009). The economic burden of insomnia: Direct and indirect costs for individuals with insomnia syndrome, insomnia symptoms, and good sleepers. *Sleep*, *32*(1), 55–64.

Darden, M., Espie, C. A., Carl, J. R., Henry, A. L., Kanady, J. C., Krystal, A. D., & Miller, C. B. (2021). Cost-effectiveness of digital cognitive behavioral therapy (Sleepio) for insomnia: A Markov simulation model in the United States. *Sleep*, *44*(4), zsaa223. https://doi.org/10.1093/sleep/zsaa223

De Bruin, E. J., van Steensel, F. J. A., & Meijer, A. M. (2016). Cost-effectiveness of group and internet cognitive behavioral therapy for insomnia in adolescents: Results from a randomized controlled trial. *Sleep*, *39*(8), 1571–1581. https://doi.org/10.5665/sleep.6024

Debener, S., Emkes, R., De Vos, M., & Bleichner, M. (2015). Unobtrusive ambulatory EEG using a smartphone and flexible printed electrodes around the ear. *Scientific Reports*, *5*, 16743. https://doi.org/10.1038/srep16743

Dekker, K., Benjamins, J. S., Maksimovic, T., Filardi, M., Hofman, W. F., van Straten, A., & Van Someren, E. J. W. (2020). Combined internet-based cognitive-behavioral and chronobiological intervention for insomnia: A randomized controlled trial. *Psychotherapy and Psychosomatics*, *89*(2), 117–118. https://doi.org/10.1159/000503570

Dekker, K., Blanken, T. F., & Van Someren, E. J. W. (2017). Insomnia and personality-a network approach. *Brain Sciences*, *7*(3), E28. https://doi.org/10.3390/brainsci7030028

Dodds, K. L., Miller, C. B., Kyle, S. D., Marshall, N. S., & Gordon, C. J. (2017). Heart rate variability in insomnia patients: A critical review of the literature. *Sleep Medicine Reviews*, *33*, 88–100. https://doi.org/10.1016/j.smrv.2016.06.004

Drake, C. L., Pillai, V., & Roth, T. (2014). Stress and sleep reactivity: A prospective investigation of the stress-diathesis model of insomnia. *Sleep*, *37*(8), 1295–1304. https://doi.org/10.5665/sleep.3916

Dressle, R. J., Feige, B., Spiegelhalder, K., Schmucker, C., Benz, F., Mey, N. C., & Riemann, D. (2022). HPA axis activity in patients with chronic insomnia: A systematic review and meta-analysis of case-control studies. *Sleep Medicine Reviews*, *62*, 101588. https://doi.org/10.1016/j.smrv.2022.101588

Edinger, J. D., Arnedt, J. T., Bertisch, S. M., Carney, C. E., Harrington, J. J., Lichstein, K. L., … Martin, J. L. (2021a). Behavioral and psychological treatments for chronic insomnia disorder in adults: An American Academy of sleep medicine clinical practice guideline. *Journal of Clinical Sleep Medicine*, *17*(2), 255–262. https://doi.org/10.5664/jcsm.8986

Edinger, J. D., Arnedt, J. T., Bertisch, S. M., Carney, C. E., Harrington, J. J., Lichstein, K. L., … Martin, J. L. (2021b). Behavioral and psychological treatments for chronic insomnia disorder in adults: An American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. *Journal of Clinical Sleep Medicine*, *17*(2), 263–298. https://doi.org/10.5664/jcsm.8988

Edinger, J. D., Wyatt, J. K., Stepanski, E. J., Olsen, M. K., Stechuchak, K. M., Carney, C. E., … Krystal, A. D. (2011). Testing the reliability and validity of DSM-IV-TR and ICSD-2 insomnia diagnoses: Results of a multitrait-multimethod analysis. *Archives of General Psychiatry*, *68*(10), 992–1002. https://doi.org/10.1001/archgenpsychiatry.2011.64

Ellis, J. G., Gehrman, P., Espie, C. A., Riemann, D., & Perlis, M. L. (2012). Acute insomnia: Current conceptualizations and future directions. *Sleep Medicine Reviews*, *16*(1), 5–14. https://doi.org/10.1016/j.smrv.2011.02.002

Espie, C. A. (2002). Insomnia: Conceptual issues in the development, persistence, and treatment of sleep disorder in adults. *Annual Review of Psychology*, *53*, 215–243. https://doi.org/10.1146/annurev.psych.53.100901.135243

Espie, C. A. (2009). "Stepped care": A health technology solution for delivering cognitive behavioral therapy as a first line insomnia treatment. *Sleep*, *32*(12), 1549–1558. https://doi.org/10.1093/sleep/32.12.1549

Espie, C. A. (2022). *A clinician's guide to cognitive and behavioural therapeutics (CBTx) for insomnia*. Cambridge University Press (in press).

Espie, C. A., Brooks, D. N., & Lindsay, W. R. (1989). An evaluation of tailored psychological treatment of insomnia. *Journal of Behavior Therapy and Experimental Psychiatry*, *20*(2), 143–153. https://doi.org/10.1016/0005-7916(89)90047-5

Espie, C. A., Broomfield, N. M., MacMahon, K. M. A., Macphee, L. M., & Taylor, L. M. (2006). The attention-intention-effort pathway in the development of psychophysiologic insomnia: A theoretical review. *Sleep Medicine Reviews*, *10*(4), 215–245. https://doi.org/10.1016/j.smrv.2006.03.002

Espie, C. A., Emsley, R., Kyle, S. D., Gordon, C., Drake, C. L., Siriwardena, A. N., … Luik, A. I. (2019). Effect of digital cognitive behavioral therapy for insomnia on health, psychological well-being, and sleep-related quality of life: A randomized clinical trial. *JAMA Psychiatry*, *76*(1), 21–30. https://doi.org/10.1001/jamapsychiatry.2018.2745

Espie, C. A., Hames, P., & McKinstry, B. (2013). Use of the internet and mobile media for delivery of cognitive behavioral insomnia therapy. *Sleep Medicine Clinics*, *8*(3), 407–419. https://doi.org/10.1016/j.jsmc.2013.06.001

Espie, C. A., Kyle, S. D., Hames, P., Gardani, M., Fleming, L., & Cape, J. (2014). The sleep condition indicator: A clinical screening tool to evaluate insomnia disorder. *BMJ Open*, *4*(3), e004183. https://doi.org/10.1136/bmjopen-2013-004183

Espie, C. A., Kyle, S. D., Williams, C., Ong, J. C., Douglas, N. J., Hames, P., & JSL, B. (2012). Randomized, placebo-controlled trial of online cognitive behavioral therapy for chronic insomnia disorder delivered via an automated media-rich web application. *Sleep*, *35*(6), 769–781. https://doi.org/10.5665/sleep.1872

Feige, B., Al-Shajlawi, A., Nissen, C., Voderholzer, U., Hornyak, M., Spiegelhalder, K., … Riemann, D. (2008). Does REM sleep contribute to subjective wake time in primary insomnia? A comparison of polysomnographic and subjective sleep in 100 patients. *Journal of Sleep Research*, *17*(2), 180–190. https://doi.org/10.1111/j.1365-2869.2008.00651.x

Feige, B., Baglioni, C., Boehm, P., Heinrich, A., Trumm, S., Benz, F., … Riemann, D. (2021). Event-related potentials in insomnia reflect altered perception of sleep. *Sleep*, *44*(10), zsab137. https://doi.org/10.1093/sleep/zsab137

Feige, B., Baglioni, C., Spiegelhalder, K., Hirscher, V., Nissen, C., & Riemann, D. (2013). The microstructure of sleep in primary insomnia: An overview and extension. *International Journal of Psychophysiology*, *89*(2), 171–180. https://doi.org/10.1016/j.ijpsycho.2013.04.002

Feige, B., Nanovska, S., Baglioni, C., Bier, B., Cabrera, L., Diemers, S., … Riemann, D. (2018). Insomnia-perchance a dream? Results from a NREM/REM sleep awakening study in good sleepers and patients with insomnia. *Sleep*, *41*(5). https://doi.org/10.1093/sleep/zsy032

Freeman, D., Sheaves, B., Goodwin, G. M., Yu, L.-M., Nickless, A., Harrison, P. J., … Espie, C. A. (2017). The effects of improving sleep on mental health (OASIS): A randomised controlled trial with mediation analysis. *Lancet Psychiatry*, *4*(10), 749–758. https://doi.org/10.1016/S2215-0366(17)30328-0

Gee, B., Orchard, F., Clarke, E., Joy, A., Clarke, T., & Reynolds, S. (2019). The effect of non-pharmacological sleep interventions on depression symptoms: A meta-analysis of randomised controlled trials. *Sleep Medicine Reviews*, *43*, 118–128. https://doi.org/10.1016/j.smrv.2018.09.004

Ginsburg, G. S., & Willard, H. F. (2009). Genomic and personalized medicine: Foundations and applications. *Translational Research*, *154*(6), 277–287. https://doi.org/10.1016/j.trsl.2009.09.005

Goldstein, A. N., & Walker, M. P. (2014). The role of sleep in emotional brain function. *Annual Review of Clinical Psychology*, *10*, 679–708. https://doi.org/10.1146/annurev-clinpsy-032813-153716

Hagger, M. S. (2010). Sleep, self-regulation, self-control and health. *Stress and Health*, *26*(3), 181–185. https://doi.org/10.1002/smi.1345

Halonen, R., Kuula, L., Makkonen, T., Kauramäki, J., & Pesonen, A.-K. (2021). Self-conscious affect is modulated by rapid eye movement sleep but not by targeted memory reactivation-a pilot study. *Frontiers in Psychology*, *12*, 730924. https://doi.org/10.3389/fpsyg.2021.730924

Hammerschlag, A. R., Stringer, S., de Leeuw, C. A., Sniekers, S., Taskesen, E., Watanabe, K., Blanken, T. F., Dekker, K., te Lindert, B. H. W., Wassing, R., Jonsdottir, I., Thorleifsson, G., Stefansson, H., Gislason, T., Berger, K., Schormair, B., Wellmann, J., Winkelmann, J., Stefansson, K., … Posthuma, D. (2017). Genome-wide association analysis of insomnia complaints identifies risk genes and genetic overlap with psychiatric and metabolic traits. *Nature Genetics*, *49*, 1584–1592.

Harris, K., Spiegelhalder, K., Espie, C. A., MacMahon, K. M. A., Woods, H. C., & Kyle, S. D. (2015). Sleep-related attentional bias in insomnia: A state-of-the-science review. *Clinical Psychology Review*, *42*, 16–27. https://doi.org/10.1016/j.cpr.2015.08.001

Harvey, A. G. (2002). A cognitive model of insomnia. *Behaviour Research and Therapy*, *40*(8), 869–893. https://doi.org/10.1016/S0005-7967(01)00061-4

Harvey, A. G., Dong, L., Hein, K., Yu, S. H., Martinez, A. J., Gumport, N. B., … Buysse, D. J. (2021). A randomized controlled trial of the Transdiagnostic Intervention for Sleep and Circadian Dysfunction (TranS-C) to improve serious mental illness outcomes in a community setting. *Journal of Consulting and Clinical Psychology*, *89*(6), 537–550. https://doi.org/10.1037/ccp0000650

Harvey, A. G., Murray, G., Chandler, R. A., & Soehner, A. (2011). Sleep disturbance as transdiagnostic: Consideration of neurobiological mechanisms. *Clinical Psychology Review*, *31*(2), 225–235. https://doi.org/10.1016/j.cpr.2010.04.003

Harvey, A. G., & Tang, N. K. (2003). Cognitive behaviour therapy for primary insomnia: Can we rest yet? *Sleep Medicine Reviews*, *7*, 237–262.

Hasan, F., Tu, Y.-K., Yang, C.-M., James Gordon, C., Wu, D., Lee, H.-C., … Chiu, H.-Y. (2022). Comparative efficacy of digital cognitive behavioral therapy for insomnia: A systematic review and network meta-analysis. *Sleep Medicine Reviews*, *61*, 101567. https://doi.org/10.1016/j.smrv.2021.101567

Henry, A. L., Miller, C. B., Emsley, R., Sheaves, B., Freeman, D., Luik, A. I., … Espie, C. A. (2021). Insomnia as a mediating therapeutic target for depressive symptoms: A sub-analysis of participant data from two large randomized controlled trials of a digital sleep intervention. *Journal of Sleep Research*, *30*(1), e13140. https://doi.org/10.1111/jsr.13140

Herrero Babiloni, A., Bellemare, A., Beetz, G., Vinet, S.-A., Martel, M. O., Lavigne, G. J., & De Beaumont, L. (2021). The effects of non-invasive brain stimulation on sleep disturbances among different neurological and neuropsychiatric conditions: A systematic review. *Sleep Medicine Reviews*, *55*, 101381. https://doi.org/10.1016/j.smrv.2020.101381

Herring, W. J., Roth, T., Krystal, A. D., & Michelson, D. (2019). Orexin receptor antagonists for the treatment of insomnia and potential treatment of other neuropsychiatric indications. *Journal of Sleep Research*, *28*(2), e12782. https://doi.org/10.1111/jsr.12782

Hertenstein, E., Feige, B., Gmeiner, T., Kienzler, C., Spiegelhalder, K., Johann, A., … Baglioni, C. (2019). Insomnia as a predictor of mental disorders: A systematic review and meta-analysis. *Sleep Medicine Reviews*, *43*, 96–105. https://doi.org/10.1016/j.smrv.2018.10.006

Hertenstein, E., Trinca, E., Wunderlin, M., Schneider, C., Züst, M., Fehér, K., … Nissen, C. (2022). Cognitive behavioral therapy for insomnia in patients with mental disorders and comorbid insomnia: A systematic review and meta-analysis. *Sleep Medicine Reviews*, *62*, 101597. https://doi.org/10.1016/j.smrv.2022.101597

Irwin, M. R., Carrillo, C., Sadeghi, N., Bjurstrom, M. F., Breen, E. C., & Olmstead, R. (2022). Prevention of incident and recurrent major

depression in older adults with insomnia: A randomized clinical trial. *JAMA Psychiatry*, *79*(1), 33–41. https://doi.org/10.1001/jamapsychiatry.2021.3422

Jain, K. K. (2002). Personalized medicine. *Current Opinion in Molecular Therapeutics*, *4*(6), 548–558.

Jansen, P. R., Watanabe, K., Stringer, S., Skene, N., Bryois, J., Hammerschlag, A. R., … Posthuma, D. (2019). Genome-wide analysis of insomnia in 1,331,010 individuals identifies new risk loci and functional pathways. *Nature Genetics*, *51*(3), 394–403. https://doi.org/10.1038/s41588-018-0333-3

Johann, A. F., Hertenstein, E., Kyle, S. D., Baglioni, C., Feige, B., Nissen, C., … Spiegelhalder, K. (2017). Insomnia with objective short sleep duration is associated with longer duration of insomnia in the Freiburg insomnia cohort compared to insomnia with normal sleep duration, but not with hypertension. *PLoS One*, *12*(7), e0180339. https://doi.org/10.1371/journal.pone.0180339

Kaldo, V., Jernelöv, S., Blom, K., Ljótsson, B., Brodin, M., Jörgensen, M., … Lindefors, N. (2015). Guided internet cognitive behavioral therapy for insomnia compared to a control treatment—A randomized trial. *Behaviour Research and Therapy*, *71*, 90–100. https://doi.org/10.1016/j.brat.2015.06.001

Kallestad, H., Scott, J., Vedaa, Ø., Lydersen, S., Vethe, D., Morken, G., … Langsrud, K. (2021). Mode of delivery of cognitive behavioral therapy for insomnia: A randomized controlled non-inferiority trial of digital and face-to-face therapy. *Sleep*, *44*(12), zsab185. https://doi.org/10.1093/sleep/zsab185

Kao, C.-H., D'Rozario, A. L., Lovato, N., Wassing, R., Bartlett, D., Memarian, N., … Gordon, C. J. (2021). Insomnia subtypes characterised by objective sleep duration and NREM spectral power and the effect of acute sleep restriction: An exploratory analysis. *Scientific Reports*, *11*(1), 24331. https://doi.org/10.1038/s41598-021-03564-6

Kathol, R. G., & Arnedt, J. T. (2016). Cognitive behavioral therapy for chronic insomnia: Confronting the challenges to implementation. *Annals of Internal Medicine*, *165*(2), 149–150. https://doi.org/10.7326/M16-0359

Kjaerby, C., Andersen, M., Hauglund, N., Ding, F., Wang, W., Xu, Q., … Nedergaard, M. (2020). Dynamic fluctuations of the locus coeruleus-norepinephrine system underlie sleep state transitions. *bioRxiv*.

Kraepelien, M., Forsell, E., & Blom, K. (2022). Large-scale implementation of insomnia treatment in routine psychiatric care: Patient characteristics and insomnia-depression comorbidity. *Journal of Sleep Research*, *31*(1), e13448. https://doi.org/10.1111/jsr.13448

Kushida, C. A., Littner, M. R., Morgenthaler, T., Alessi, C. A., Bailey, D., Coleman, J., … Wise, M. (2005). Practice parameters for the indications for polysomnography and related procedures: An update for 2005. *Sleep*, *28*(4), 499–521. https://doi.org/10.1093/sleep/28.4.499

Kyle, S. D., Aquino, M. R. J., Miller, C. B., Henry, A. L., Crawford, M. R., Espie, C. A., & Spielman, A. J. (2015). Towards standardisation and improved understanding of sleep restriction therapy for insomnia disorder: A systematic examination of CBT-I trial content. *Sleep Medicine Reviews*, *23*, 83–88. https://doi.org/10.1016/j.smrv.2015.02.003

Kyle, S. D., Espie, C. A., Gehrman, P., Ong, J., & Hames, B. (2014). Tailoring CBT for insomnia to specific needs: A personalised behavioural medicine approach. In C. Bassetti, Z. Dogas, & P. Peigneux (Eds.), *European sleep medicine textbook*. ESRS & Wiley.

Kyle, S. D., Hurry, M. E. D., Emsley, R., Marsden, A., Omlin, X., Juss, A., … Sexton, C. E. (2020). The effects of digital cognitive behavioral therapy for insomnia on cognitive function: A randomized controlled trial. *Sleep*, *43*(9), zsaa034. https://doi.org/10.1093/sleep/zsaa034

Kyle, S. D., Madigan, C., Begum, N., Abel, L., Armstrong, S., Aveyard, P., … Espie, C. A. (2020). Primary care treatment of insomnia: Study protocol for a pragmatic, multicentre, randomised controlled trial comparing nurse-delivered sleep restriction therapy to sleep hygiene (the HABIT trial). *BMJ Open*, *10*(3), e036248. https://doi.org/10.1136/bmjopen-2019-036248

Kyle, S. D., Sexton, C. E., Feige, B., Luik, A. I., Lane, J., Saxena, R., … Spiegelhalder, K. (2017). Sleep and cognitive performance: Cross-sectional associations in the UK Biobank. *Sleep Medicine*, *38*, 85–91. https://doi.org/10.1016/j.sleep.2017.07.001

van de Laar, M., Verbeek, I., Pevernagie, D., Aldenkamp, A., & Overeem, S. (2010). The role of personality traits in insomnia. *Sleep Medicine Reviews*, *14*(1), 61–68. https://doi.org/10.1016/j.smrv.2009.07.007

Lancee, J., van Straten, A., Morina, N., Kaldo, V., & Kamphuis, J. H. (2016). Guided online or face-to-face cognitive behavioral treatment for insomnia: A randomized wait-list controlled trial. *Sleep*, *39*(1), 183–191. https://doi.org/10.5665/sleep.5344

Lane, J. M., Jones, S. E., Dashti, H. S., Wood, A. R., Aragam, K. G., van Hees, V. T., … Saxena, R. (2019). Biological and clinical insights from genetics of insomnia symptoms. *Nature Genetics*, *51*(3), 387–393. https://doi.org/10.1038/s41588-019-0361-7

Leerssen, J., Lakbila-Kamal, O., Dekkers, L. M. S., Ikelaar, S. L. C., Albers, A. C. W., Blanken, T. F., … Van Someren, E. J. W. (2021). Treating insomnia with high risk of depression using therapist-guided digital cognitive, behavioral, and circadian rhythm support interventions to prevent worsening of depressive symptoms: A randomized controlled trial. *Psychotherapy and Psychosomatics*, 1–12. https://doi.org/10.1159/000520282

Leger, D., Levy, E., & Paillard, M. (1999). The direct costs of insomnia in France. *Sleep*, *22*, S394–S401.

Li, M., Zhang, X.-W., Hou, W.-S., & Tang, Z.-Y. (2014). Insomnia and risk of cardiovascular disease: A meta-analysis of cohort studies. *International Journal of Cardiology*, *176*(3), 1044–1047. https://doi.org/10.1016/j.ijcard.2014.07.284

Luik, A. I., Bostock, S., Chisnall, L., Kyle, S. D., Lidbetter, N., Baldwin, N., & Espie, C. A. (2017). Treating depression and anxiety with digital cognitive behavioural therapy for insomnia: A real world NHS evaluation using standardized outcome measures. *Behavioural and Cognitive Psychotherapy*, *45*(1), 91–96. https://doi.org/10.1017/S1352465816000369

Luik, A. I., Marsden, A., Emsley, R., Henry, A. L., Stott, R., Miller, C. B., & Espie, C. A. (2020). Long-term benefits of digital cognitive behavioural therapy for insomnia: Follow-up report from a randomized clinical trial. *Journal of Sleep Research*, *29*(4), e13018. https://doi.org/10.1111/jsr.13018

Manber, R., Edinger, J. D., Gress, J. L., Pedro-Salcedo, M. G. S., Kuo, T. F., & Kalista, T. (2008). Cognitive behavioral therapy for insomnia enhances depression outcome in patients with comorbid major depressive disorder and insomnia. *Sleep*, *31*(4), 489–495. https://doi.org/10.1093/sleep/31.4.489

Maurer, L. F., Espie, C. A., & Kyle, S. D. (2018). How does sleep restriction therapy for insomnia work? A systematic review of mechanistic evidence and the introduction of the triple-R model. *Sleep Medicine Reviews*, *42*, 127–138. https://doi.org/10.1016/j.smrv.2018.07.005

Maurer, L. F., Espie, C. A., Omlin, X., Emsley, R., & Kyle, S. D. (2022). The effect of sleep restriction therapy for insomnia on sleep pressure and arousal: A randomized controlled mechanistic trial. *Sleep*, *45*(1), zsab223. https://doi.org/10.1093/sleep/zsab223

Maurer, L. F., Espie, C. A., Omlin, X., Reid, M. J., Sharman, R., Gavriloff, D., … Kyle, S. D. (2020). Isolating the role of time in bed restriction in the treatment of insomnia: A randomized, controlled, dismantling trial comparing sleep restriction therapy with time in bed regularization. *Sleep*, *43*(11), zsaa096. https://doi.org/10.1093/sleep/zsaa096

Maurer, L. F., Ftouni, S., Espie, C. A., Bisdounis, L., & Kyle, S. D. (2021). The acute effects of sleep restriction therapy for insomnia on circadian timing and vigilance. *Journal of Sleep Research*, *30*(4), e13260. https://doi.org/10.1111/jsr.13260

Maurer, L. F., Schneider, J., Miller, C. B., Espie, C. A., & Kyle, S. D. (2021). The clinical effects of sleep restriction therapy for insomnia: A meta-analysis of randomised controlled trials. *Sleep Medicine Reviews*, *58*, 101493. https://doi.org/10.1016/j.smrv.2021.101493

McCrae, C. S., McNamara, J. P. H., Rowe, M. A., Dzierzewski, J. M., Dirk, J., Marsiske, M., & Craggs, J. G. (2008). Sleep and affect in older adults: Using multilevel modeling to examine daily associations. *Journal of Sleep Research*, *17*(1), 42–53. https://doi.org/10.1111/j.1365-2869.2008.00621.x

Mikkelsen, K. B., Tabar, Y. R., Kappel, S. L., Christensen, C. B., Toft, H. O., Hemmsen, M. C., … Kidmose, P. (2019). Accurate whole-night sleep monitoring with dry-contact ear-EEG. *Scientific Reports*, *9*(1), 16824. https://doi.org/10.1038/s41598-019-53115-3

Morin, C. M. (2020). Profile of somryst prescription digital therapeutic for chronic insomnia: Overview of safety and efficacy. *Expert Review Medical Devices*, *17*, 1239–1248. https://doi.org/10.1080/17434440.2020.1852929

Morin, C. M., Drake, C. L., Harvey, A. G., Krystal, A. D., Manber, R., Riemann, D., & Spiegelhalder, K. (2015). Insomnia disorder. *Nature Reviews. Disease Primers*, *1*, 15026. https://doi.org/10.1038/nrdp.2015.26

Morin, C. M., Edinger, J. D., Beaulieu-Bonneau, S., Ivers, H., Krystal, A. D., Guay, B., … Busby, M. (2020). Effectiveness of sequential psychological and medication therapies for insomnia disorder: A randomized clinical trial. *JAMA Psychiatry*, *77*(11), 1107–1115. https://doi.org/10.1001/jamapsychiatry.2020.1767

Morin, C. M., Vallières, A., & Ivers, H. (2007). Dysfunctional beliefs and attitudes about sleep (DBAS): Validation of a brief version (DBAS-16). *Sleep*, *30*(11), 1547–1554. https://doi.org/10.1093/sleep/30.11.1547

Ohayon, M. M. (2002). Epidemiology of insomnia: What we know and what we still need to learn. *Sleep Medicine Reviews*, *6*(2), 97–111. https://doi.org/10.1053/smrv.2002.0186

Overland, S., Glozier, N., Sivertsen, B., Stewart, R., Neckelmann, D., Krokstad, S., & Mykletun, A. (2008). A comparison of insomnia and depression as predictors of disability pension: The HUNT Study. *Sleep*, *31*(6), 875–880. https://doi.org/10.1093/sleep/31.6.875

Palagini, L., Biber, K., & Riemann, D. (2014). The genetics of insomnia-evidence for epigenetic mechanisms? *Sleep Medicine Reviews*, *18*(3), 225–235. https://doi.org/10.1016/j.smrv.2013.05.002

Palmer, C. A., & Alfano, C. A. (2017). Sleep and emotion regulation: An organizing, integrative review. *Sleep Medicine Reviews*, *31*, 6–16. https://doi.org/10.1016/j.smrv.2015.12.006

Perlis, M. L., Giles, D. E., Mendelson, W. B., Bootzin, R. R., & Wyatt, J. K. (1997). Psychophysiological insomnia: The behavioural model and a neurocognitive perspective. *Journal of Sleep Research*, *6*(3), 179–188. https://doi.org/10.1046/j.1365-2869.1997.00045.x

Perlis, M. L., Smith, M. T., Andrews, P. J., Orff, H., & Giles, D. E. (2001). Beta/gamma EEG activity in patients with primary and secondary insomnia and good sleeper controls. *Sleep*, *24*(1), 110–117. https://doi.org/10.1093/sleep/24.1.110

Pesonen, A.-K., Gradisar, M., Kuula, L., Short, M., Merikanto, I., Tark, R., … Lahti, J. (2019). REM sleep fragmentation associated with depressive symptoms and genetic risk for depression in a community-based sample of adolescents. *Journal of Affective Disorders*, *245*, 757–763. https://doi.org/10.1016/j.jad.2018.11.077

Pigeon, W. R., Pinquart, M., & Conner, K. (2012). Meta-analysis of sleep disturbance and suicidal thoughts and behaviors. *The Journal of Clinical Psychiatry*, *73*(9), e1160–e1167. https://doi.org/10.4088/JCP.11r07586

Pillai, V., Roth, T., & Drake, C. L. (2015). The nature of stable insomnia phenotypes. *Sleep*, *38*(1), 127–138. https://doi.org/10.5665/sleep.4338

Qaseem, A., Kansagara, D., Forciea, M. A., Cooke, M., & Denberg, T. D. (2016). Management of chronic insomnia disorder in adults: A clinical practice guideline from the American College of Physicians. *Annals of Internal Medicine*, *165*(2), 125–133. https://doi.org/10.7326/M15-2175

Reynolds, S. A., & Ebben, M. R. (2017). The cost of insomnia and the benefit of increased access to evidence-based treatment: Cognitive behavioral therapy for insomnia. *Sleep Medicine Clinics*, *12*(1), 39–46. https://doi.org/10.1016/j.jsmc.2016.10.011

Riemann, D., Baglioni, C., Bassetti, C., Bjorvatn, B., Dolenc Groselj, L., Ellis, J. G., … Spiegelhalder, K. (2017). European guideline for the diagnosis and treatment of insomnia. *Journal of Sleep Research*, *26*(6), 675–700. https://doi.org/10.1111/jsr.12594

Riemann, D., Baum, E., Cohrs, S., Crönlein, T., Hajak, G., Hertenstein, E., … Spiegelhalder, K. (2017). S3-Leitlinie Nicht erholsamer Schlaf/Schlafstörungen. *Somnologie*, *21*(1), 2–44. https://doi.org/10.1007/s11818-016-0097-x

Riemann, D., Krone, L. B., Wulff, K., & Nissen, C. (2020). Sleep, insomnia, and depression. *Neuropsychopharmacology*, *45*(1), 74–89. https://doi.org/10.1038/s41386-019-0411-y

Riemann, D., & Nissen, C. (2012). Sleep and psychotropic drugs. In *Oxford handbook of sleep and sleep disorders* (pp. 190–222). Oxford University Press.

Riemann, D., Nissen, C., Palagini, L., Otte, A., Perlis, M. L., & Spiegelhalder, K. (2015). The neurobiology, investigation, and treatment of chronic insomnia. *Lancet Neurology*, *14*(5), 547–558. https://doi.org/10.1016/S1474-4422(15)00021-6

Riemann, D., Spiegelhalder, K., Espie, C. A., Gavriloff, D., Frase, L., & Baglioni, C. (2022). Introduction to insomnia disorder. In C. Baglioni, C. A. Espie, & D. Riemann (Eds.), *Cognitive-behavioural therapy for insomnia (CBT-I) across the lifespan. Guidelines and clinical protocols for health professionals*. Wiley & Sons (in press).

Riemann, D., Spiegelhalder, K., Espie, C., Pollmächer, T., Léger, D., Bassetti, C., & Van Someren, E. (2011). Chronic insomnia: Clinical and research challenges-an agenda. *Pharmacopsychiatry*, *44*(1), 1–14. https://doi.org/10.1055/s-0030-1267978

Riemann, D., Spiegelhalder, K., Feige, B., Voderholzer, U., Berger, M., Perlis, M., & Nissen, C. (2010). The hyperarousal model of insomnia: A review of the concept and its evidence. *Sleep Medicine Reviews*, *14*(1), 19–31. https://doi.org/10.1016/j.smrv.2009.04.002

Riemann, D., Spiegelhalder, K., Nissen, C., Hirscher, V., Baglioni, C., & Feige, B. (2012). REM sleep instability—A new pathway for insomnia? *Pharmacopsychiatry*, *45*, 167–176. https://doi.org/10.1055/s-0031-1299721

Ritterband, L. M., Thorndike, F. P., Ingersoll, K. S., Lord, H. R., Gonder-Frederick, L., Frederick, C., … Morin, C. M. (2017). Effect of a web-based cognitive behavior therapy for insomnia intervention with 1-year follow-up: A randomized clinical trial. *JAMA Psychiatry*, *74*(1), 68–75. https://doi.org/10.1001/jamapsychiatry.2016.3249

Roehrs, T., & Roth, T. (2012). Insomnia pharmacotherapy. *Neurotherapeutics*, *9*(4), 728–738. https://doi.org/10.1007/s13311-012-0148-3

Sadeh, A., Tikotzky, L., & Kahn, M. (2014). Sleep in infancy and childhood: Implications for emotional and behavioral difficulties in adolescence and beyond. *Current Opinion in Psychiatry*, *27*(6), 453–459. https://doi.org/10.1097/YCO.0000000000000109

Sampson, C., Bell, E., Cole, A., Miller, C. B., Marriott, T., Williams, M., & Rose, J. (2022). Digital cognitive behavioural therapy for insomnia and primary care costs in England: An interrupted time series analysis. *BJGP Open*. https://doi.org/10.3399/BJGPO.2021.0146

Saper, C. B., Cano, G., & Scammell, T. E. (2005). Homeostatic, circadian, and emotional regulation of sleep. *The Journal of Comparative Neurology*, *493*(1), 92–98. https://doi.org/10.1002/cne.20770

Saper, C. B., Scammell, T. E., & Lu, J. (2005). Hypothalamic regulation of sleep and circadian rhythms. *Nature*, *437*(7063), 1257–1263. https://doi.org/10.1038/nature04284

Sateia, M. J., & Buysse, D. J. (2010). *Insomnia: Diagnosis and treatment*. Informa Healthcare.

Schneider, C. L., Hertenstein, E., Fehér, K., Maier, J. G., Cantisani, A., Moggi, F., … Nissen, C. (2020). Become your own SLEEPexpert: Design, implementation, and preliminary evaluation of a pragmatic behavioral treatment program for insomnia in inpatient psychiatric

care. *SLEEP Advances*, *1*(1), zpaa005. https://doi.org/10.1093/sleepadvances/zpaa005

Scott, B. A., & Judge, T. A. (2006). Insomnia, emotions, and job satisfaction: A multilevel study. *Journal of Management*, *32*(5), 622–645. https://doi.org/10.1177/0149206306289762

Seyffert, M., Lagisetty, P., Landgraf, J., Chopra, V., Pfeiffer, P. N., Conte, M. L., & Rogers, M. A. M. (2016). Internet-delivered cognitive behavioral therapy to treat insomnia: A systematic review and meta-analysis. *PLoS One*, *11*(2), e0149139. https://doi.org/10.1371/journal.pone.0149139

Sivertsen, B., Krokstad, S., Øverland, S., & Mykletun, A. (2009). The epidemiology of insomnia: Associations with physical and mental health. The HUNT-2 study. *Journal of Psychosomatic Research*, *67*(2), 109–116. https://doi.org/10.1016/j.jpsychores.2009.05.001

Soh, H. L., Ho, R. C., Ho, C. S., & Tam, W. W. (2020). Efficacy of digital cognitive behavioural therapy for insomnia: A meta-analysis of randomised controlled trials. *Sleep Medicine*, *75*, 315–325. https://doi.org/10.1016/j.sleep.2020.08.020

Spiegelhalder, K., Regen, W., Feige, B., Holz, J., Piosczyk, H., Baglioni, C., … Nissen, C. (2012). Increased EEG sigma and beta power during NREM sleep in primary insomnia. *Biological Psychology*, *91*(3), 329–333. https://doi.org/10.1016/j.biopsycho.2012.08.009

Spielman, A. J., Caruso, L. S., & Glovinsky, P. B. (1987). A behavioral perspective on insomnia treatment. *The Psychiatric Clinics of North America*, *10*(4), 541–553.

Stephan, A. M., Lecci, S., Cataldi, J., & Siclari, F. (2021). Conscious experiences and high-density EEG patterns predicting subjective sleep depth. *Current Biology*, *31*(24), 5487–5500.e3. https://doi.org/10.1016/j.cub.2021.10.012

Stott, R., Pimm, J., Emsley, R., Miller, C. B., & Espie, C. A. (2021). Does adjunctive digital CBT for insomnia improve clinical outcomes in an improving access to psychological therapies service? *Behaviour Research and Therapy*, *144*, 103922. https://doi.org/10.1016/j.brat.2021.103922

Tahmasian, M., Noori, K., Samea, F., Zarei, M., Spiegelhalder, K., Eickhoff, S. B., Van Someren, E., Khazaie, H., & Eickhoff, C. R. (2018). A lack of consistent brain alterations in insomnia disorder: An activation likelihood estimation meta-analysis. *Sleep Medicine Reviews*, *42*, 111–118.

Thakkar, M. M. (2011). Histamine in the regulation of wakefulness. *Sleep Medicine Reviews*, *15*(1), 65–74. https://doi.org/10.1016/j.smrv.2010.06.004

Van Someren, E. J. W. (2021). Brain mechanisms of insomnia: New perspectives on causes and consequences. *Physiological Reviews*, *101*(3), 995–1046. https://doi.org/10.1152/physrev.00046.2019

Vedaa, Ø., Hagatun, S., Kallestad, H., Pallesen, S., Smith, O. R. F., Thorndike, F. P., … Sivertsen, B. (2019). Long-term effects of an unguided online cognitive behavioral therapy for chronic insomnia. *Journal of Clinical Sleep Medicine*, *15*(1), 101–110. https://doi.org/10.5664/jcsm.7580

Vedaa, Ø., Kallestad, H., Scott, J., Smith, O. R. F., Pallesen, S., Morken, G., … Sivertsen, B. (2020). Effects of digital cognitive behavioural therapy for insomnia on insomnia severity: A large-scale randomised controlled trial. *Lancet Digital Health*, *2*(8), e397–e406. https://doi.org/10.1016/S2589-7500(20)30135-7

Vermeulen, M. C. M., van der Heijden, K. B., Kocevska, D., Treur, J. L., Huppertz, C., van Beijsterveldt, C. E. M., Boomsma, D. I., Swaab, H., Van Someren, E. J. W., & Bartels, M. (2021). Associations of sleep with psychological problems and well-being in adolescence: Causality or common genetic predispositions? *Journal of Child Psychology and Psychiatry*, *62*, 28–39.

Vgontzas, A. N., Fernandez-Mendoza, J., Liao, D., & Bixler, E. O. (2013). Insomnia with objective short sleep duration: The most biologically severe phenotype of the disorder. *Sleep Medicine Reviews*, *17*(4), 241–254. https://doi.org/10.1016/j.smrv.2012.09.005

Vincent, N., & Walsh, K. (2013). Stepped care for insomnia: An evaluation of implementation in routine practice. *Journal of Clinical Sleep Medicine*, *09*(03), 227–234. https://doi.org/10.5664/jcsm.2484

Wassing, R., Benjamins, J. S., Dekker, K., Moens, S., Spiegelhalder, K., Feige, B., … Van Someren, E. J. W. (2016). Slow dissolving of emotional distress contributes to hyperarousal. *Proceedings of the National Academy of Sciences of the United States of America*, *113*(9), 2538–2543. https://doi.org/10.1073/pnas.1522520113

Wassing, R., Benjamins, J. S., Talamini, L. M., Schalkwijk, F., & Van Someren, E. J. W. (2019). Overnight worsening of emotional distress indicates maladaptive sleep in insomnia. *Sleep*, *42*(4), zsy268. https://doi.org/10.1093/sleep/zsy268

Wassing, R., Lakbila-Kamal, O., Ramautar, J. R., Stoffers, D., Schalkwijk, F., & Van Someren, E. J. W. (2019). Restless REM sleep impedes overnight amygdala adaptation. *Current Biology: CB*, *29*(14), 2351–2358.e4. https://doi.org/10.1016/j.cub.2019.06.034

Wassing, R., Schalkwijk, F., Lakbila-Kamal, O., Ramautar, J. R., Stoffers, D., Mutsaerts, H. J. M. M., … Van Someren, E. J. W. (2019). Haunted by the past: Old emotions remain salient in insomnia disorder. *Brain*, *142*(6), 1783–1796. https://doi.org/10.1093/brain/awz089

Wei, Y., Blanken, T. F., & Van Someren, E. J. W. (2018). Insomnia really hurts: Effect of a bad night's sleep on pain increases with insomnia severity. *Frontiers in Psychiatry*, *9*, 377. https://doi.org/10.3389/fpsyt.2018.00377

Wei, Y., Ramautar, J. R., Colombo, M. A., Stoffers, D., Gómez-Herrero, G., van der Meijden, W. P., … Van Someren, E. J. W. (2016). I keep a close watch on this heart of mine: Increased interoception in insomnia. *Sleep*, *39*(12), 2113–2124. https://doi.org/10.5665/sleep.6308

Wei, Y., Ramautar, J. R., Colombo, M. A., Te Lindert, B. H. W., & Van Someren, E. J. W. (2018). EEG microstates indicate heightened somatic awareness in insomnia: Toward objective assessment of subjective mental content. *Frontiers in Psychiatry*, *9*, 395. https://doi.org/10.3389/fpsyt.2018.00395

Wickwire, E. M. (2019). The value of digital insomnia therapeutics: What we know and what we need to know. *Journal of Clinical Sleep Medicine*, *15*(1), 11–13. https://doi.org/10.5664/jcsm.7558

Wilson, S., Anderson, K., Baldwin, D., Dijk, D.-J., Espie, A., Espie, C., … Sharpley, A. (2019). British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders: An update. *Journal of Psychopharmacology*, *33*(8), 923–947. https://doi.org/10.1177/0269881119855343

Wilt, T. J., MacDonald, R., Brasure, M., Olson, C. M., Carlyle, M., Fuchs, E., … Kane, R. L. (2016). Pharmacologic treatment of insomnia disorder: An evidence report for a clinical practice guideline by the American College of Physicians. *Annals of Internal Medicine*, *165*(2), 103–112. https://doi.org/10.7326/M15-1781

Woolfolk, R. L., & McNulty, T. F. (1983). Relaxation treatment for insomnia: A component analysis. *Journal of Consulting and Clinical Psychology*, *51*(4), 495–503. https://doi.org/10.1037//0022-006x.51.4.495

World Health Organization. (1993). *International statistical classification of diseases and related health problems* (10th ed.). World Health Organization.

World Health Organization. (2019). *International statistical classification of diseases and related health problems* (11th ed.). World Health Organization Retrieved from https://icd.who.int/

Zachariae, R., Amidi, A., Damholdt, M. F., Clausen, C. D. R., Dahlgaard, J., Lord, H., … Ritterband, L. M. (2018). Internet-delivered cognitive-behavioral therapy for insomnia in breast cancer survivors: A randomized controlled trial. *Journal of the National Cancer Institute*, *110*(8), 880–887. https://doi.org/10.1093/jnci/djx293

Zachariae, R., Lyby, M. S., Ritterband, L. M., & O'Toole, M. S. (2016). Efficacy of internet-delivered cognitive-behavioral therapy for insomnia—A systematic review and meta-analysis of randomized controlled trials. *Sleep Medicine Reviews*, *30*, 1–10. https://doi.org/10.1016/j.smrv.2015.10.004

van der Zweerde, T., Bisdounis, L., Kyle, S. D., Lancee, J., & van Straten, A. (2019). Cognitive behavioral therapy for insomnia: A meta-analysis of long-term effects in controlled studies. *Sleep Medicine Reviews*, *48*, 101208. https://doi.org/10.1016/j.smrv.2019.08.002

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Review

A systematic review of socio-ecological factors contributing to risk and protection of the mental health of refugee children and adolescents

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ABSTRACT

In the past decade, millions of children and adolescents have been forced to flee from protracted or newly erupted violent conflicts. Forcibly displaced children are particularly vulnerable for developing mental health problems. However, a timely and systematic review of the current evidence is lacking. We conducted a systematic review of factors contributing to the mental health of refugee children across different socio-ecological levels (individual, family, community, sociocultural). We systematically searched the databases Medline, PsycINFO, Web of Science, and Cochrane for English studies published in peer-reviewed journals between August 2010 and May 2020. Of the 2413 identified studies, 63 were included in the analyses. Only 24 studies were considered to be of high quality. Pre-migration individual (risk: exposure to war-related trauma, female gender) and post-migration family factors (risk: parental mental health problems and impaired parenting, protective: family cohesion) currently have the best evidence base. Post-migration community (protective: school connectedness, support by peers) and sociocultural factors (risk: discrimination and acculturative stress, protective: integrative acculturation) have gained some support in high-income settings. Prevention and intervention approaches should integrate factors across different socio-ecological levels. More longitudinal studies and research in low- and middle-income countries are needed to advance our knowledge on causal mechanisms behind factors contributing to refugee youth's mental health.

1. Introduction

According to the latest report of the United Nation High Commissioner for Refugees (UNHCR), the global number of people forcibly displaced by persecution, conflict and organized violence has increased from 43.3 million in 2009 up to 70.8 million in 2018 (UNHCR, 2019). This population consists of 25.9 million refugees, who fled across national borders, 41.3 million internally displaced people (IDP) and 3.5 million asylum seekers (UNHCR, 2019). Within the past decade, a number of new conflicts have erupted, e.g. civil wars in Syria and South Sudan as well as the Rohingya crisis, while protracted crises such as in Afghanistan, Somalia, and the Democratic Republic of Congo continue to displace millions of people. About 85% of all refugees flee to neighboring countries, which are often low- and middle-income countries (LMIC) (UNHCR, 2019). In fact, the four countries hosting the largest numbers of refugees in 2018 were Turkey, Pakistan, Uganda and Sudan (UNHCR, 2019). This means that only a small number of refugees embark on the often long journey to high-income countries (HIC), e.g. Europe, North America, and Australia. In the European Union, the highest numbers of refugees, mostly from Syria, Afghanistan and Iraq, arrived in 2015 and 2016 with about 1.3 million asylum applications in each year (Eurostat, 2020).

Children and adolescents below 18 years of age make up about half of the worldwide refugee population (UNHCR, 2019). They have to face the atrocities of conflict-related violence and the numerous hardships of flight and resettlements during crucial phases of their physical, emotional, social and cognitive development. This makes youth particularly vulnerable to mental health problems following war, uprooting and flight (Reed, Fazel, Jones, Panter-Brick, & Stein, 2012). Accordingly, prevalence rates of up to 53% for posttraumatic stress disorder (PTSD), up to 33% for depression and up to 32% for anxiety disorders have been reported for young refugees resettled in European countries

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(Kien et al., 2019). A systematic review focusing on refugee youth living in refugee camps reports similar peak rates for depression and anxiety, and rates for PTSD of up to 87%, yet there was large variation in prevalence rates of mental health problems across studies (Vossoughi, Jackson, Gusler, & Stone, 2018). Although the prevalence of mental health problems is high in refugee children and adolescents, it is important to note that a substantial number of refugee children does not develop mental health problems and is able to adjust to the new living situation. This finding has stimulated research on the notion of resilience in war-affected children, which refers to good developmental outcomes despite exposure to significant adversity (Luthar, Cicchetti, & Becker, 2001). The identification of factors that contribute to risk and resilience in displaced children provides the foundation for any effort to support these children's healthy development (Fazel, Reed, Panter-Brick, & Stein, 2012).

From a socio-ecological perspective (Bronfenbrenner, 1979), child development is viewed as a dynamic process arising from complex interactions between different levels of the social ecology (e. g. individual, family, school, community, society). Such a framework has been applied to conceptualize not only the stressful experiences that refugee children face, but also the protective resources they may draw on (Betancourt & Khan, 2008; Elbedour, ten Bensel, & Bastien, 1993; Reed et al., 2012).Factors contributing to risk and protection can further be classified according to their temporal occurrence within the refugee experience, i.e. pre-, peri-, and post-migration (Lustig et al., 2004). In their home countries, youth are often exposed to severe interpersonal violence. During their flight, they may experience detention, deprivation of food or separation from their guardians. In the host country, refugee children continue to face many challenges, in part depending on where they resettle. While the conditions in HIC may ensure safety from external harm and provide basic necessities, youth may struggle to cope in an often completely different society and culture. They have to learn a new language, may face discrimination by peers or encounter bureaucratic obstacles related to school and their asylum process. In LMIC, refugee children often resettle in large refugee camps with high levels of violence, bad sanitary conditions, lack of food and material resources and overcrowded housing. Independent of the specific setting, all these daily post-migration stressors represent a significant risk for refugees` mental health and wellbeing over and above pre-migration traumatic experiences (Li, Liddell, & Nickerson, 2016; Miller & Rasmussen, 2010).

The most comprehensive systematic reviews of factors contributing to refugee children's mental health to date have been conducted by Fazel et al. (2012) for children in HIC and by Reed et al. (2012) for children in LMIC. Both reviews included studies that had been published before July 2010. Since then research has advanced and various studies focusing on refugee children's mental health and factors that influence psychological outcomes have been published. However, a comprehensive systematic review that synthesizes and evaluates the essential results and implications of these studies is lacking. Several systematic and narrative reviews have been recently published, but these mostly focused on specific subpopulations, e.g. Syrian or unaccompanied refugee children (Mitra & Hodes, 2019; Mohwinkel, Nowak, Kasper, & Razum, 2018; Yaylaci, 2018), particular mental health outcomes, e.g. PTSD and depression (El Baba & Colucci, 2018; Reavell & Fazil, 2017; Tam, Houlihan, & Melendez-Torres, 2017), or specific factors, e.g. placement type (O'Higgins, Ott, & Shea, 2018) or acculturative stressors (d'Abreu, Castro-Olivo, & Ura, 2019). Other reviews adopted a broader focus (Eruyar, Huemer, & Vostanis, 2018; Hodes & Vostanis, 2018), yet did not apply systematic methods including rigorous selection criteria or evaluate the quality of included studies. In this systematic review, we systematically investigate the factors contributing to risk and protection of the mental health of refugee children and adolescents from a socio-ecological perspective.

2. Methods

2.1. Study selection

The electronic databases Medline, PsycINFO, Web of Science, and Cochrane were systematically searched for studies in English that were published in peer-reviewed journals between August 2010 and May 2020. The following search terms were used: ("asylum seeker" or "refugee" or "displaced person" or "migrant") and ("child" or "adolescent" or "young" or "minor" or "teenage" or "youth") and ("psychiatr*" or "psycholog*" or "psychosocial" or "mental" or "wellbeing" or "adaptation" or "adjustment" or "emotion" or "behaviour" or "behavior" or "trauma" or "traumatic" or "PTSD" or "posttraumatic stress" or "internalizing" or "externalizing" or "anxiety" or "depression") and ("resilience" or "protective factor" or "modifying factor" or "recovery" or "outcome" or "risk factor" or "vulnerability factor"). Moreover, reference lists of previous related reviews and key studies were manually reviewed to identify additional studies. Studies were selected based on the following inclusion and exclusion criteria, all of which had to be fulfilled:

Criterion A: The study investigated the mental health of refugee or internally displaced children in HIC or LMIC. Studies about other topics than refugee mental health, e.g. politics, general health care, physical health, or child maltreatment, were excluded.

Criterion B: The mean age of study participants was 18 years or younger. Studies with older refugees were excluded.

Criterion C: The study had a cross-sectional or longitudinal design and presented quantitative data with a minimum sample size of 50 participants. Qualitative studies were not eligible for inclusion. Similarly, other kinds of empirical studies, e.g. intervention or validation studies, and scientific works, e.g. reviews or commentaries, were excluded.

Criterion D: The study assessed factors contributing to refugee children's mental health. Studies reporting only prevalence rates of mental health problems without investigating potential factors of influence were excluded.

Criterion E: The majority of participants were directly exposed to war and flight. Studies with children whose parents were refugees and who were born in the host country, and studies with non-refugee samples such as immigrants or non-displaced children in conflict zones were excluded.

Criterion F: The study applied a statistical analysis that theoretically allowed for the control of potentially confounding factors, e.g. age, gender and time since displacement, on refugee children's mental health, e. g. (M)ANCOVA, regression analysis or structural equation modeling. However, studies were not required to actually control for potentially confounding variables. Studies using only bivariate correlational analyses or simple group comparisons to draw inferences about contributing factors were excluded.

After the removal of duplicates, the titles and abstracts of the remaining articles were screened for eligibility according to these criteria in a hierarchical manner from criteria A to E. Most studies were excluded for several reasons, but were attributed to the category of the highest unmet criterion. Fig. 1 graphically displays the study selection process.

The large variability and lack of consistency across studies in terms of research designs, study samples, relationships and outcomes assessed, all of which have been shown to be influential confounds in research on refugee children's mental health (Fazel et al., 2012; Kien et al., 2019; Vossoughi et al., 2018), precluded a meta-analysis of the data. However, as we aimed to provide a comprehensive overview of the recent developments in research on refugee children's mental health, we adopted a broad focus and did not pose limits on certain factors, samples or outcomes. Therefore, we opted for a detailed narrative synthesis of the included studies.

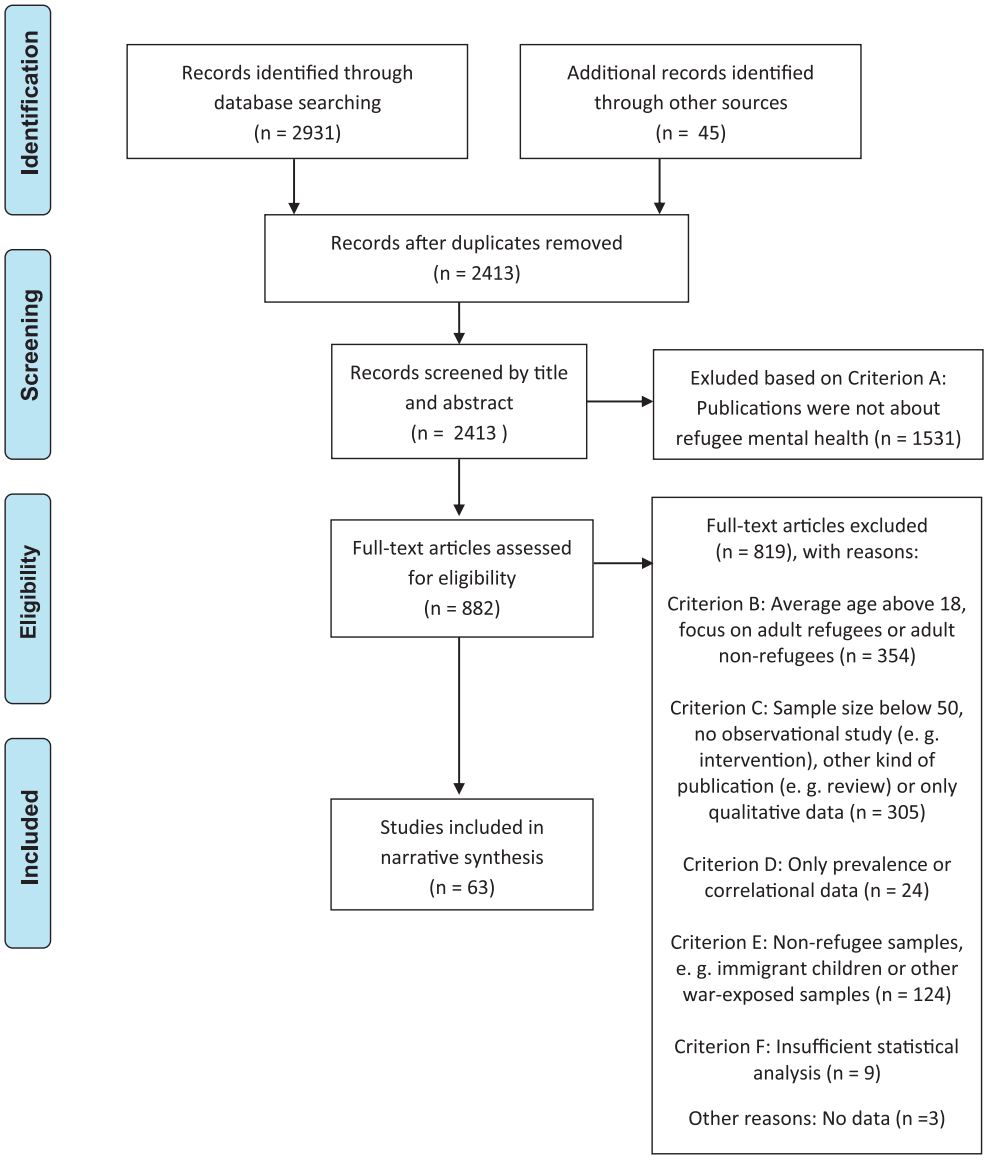

Fig. 1. Flow diagram of the study selection process. Template from Moher, Liberati, Tetzlaff, and Altman (2009).

2.2. Quality appraisal

We used the Systematic Assessment of Quality in Observational Research (SAQOR) system to evaluate the quality of the studies to be included in the systematic review. SAQOR was developed to assess the quality of observational studies in the field of psychiatry within six domains: sample, control/comparison group, quality of exposure/outcome measures, follow-up, distorting influences and reporting domains (Ross et al., 2011). Each domain is further broken down into sub-criteria, for instance the 'sample' domain includes the criteria representativeness of the population, clearly stated source of sample, explicitly stated sampling method, sample size/power calculation and inclusion/exclusion criteria. The presence of each criterion is rated as 'yes' (satisfied), 'no' (not satisfied), 'unclear' or 'not applicable'. The entire domain is evaluated as 'adequate` if a minimum of 3 out of 5 criteria are fulfilled or otherwise as 'inadequate'. A final quality level (high, moderate, low) is determined based on the assessments of the six domains.

To increase the flexibility and sensitivity of the rating system with regard to the specific type of study, we adapted SAQOR according to its use by Betancourt et al. (2013) in their systematic review on the psychosocial adjustment and mental health in former child soldiers: the 'control/comparison group' domain was only considered for those studies that actually included such a group and the 'follow-up' domain was only required for longitudinal studies. Given certain methodological and practical challenges inherent to research with conflict-affected populations in often unstable settings we considered the criterion 'representativeness' within the sample domain met if a randomized sample was chosen from a base population across multiple sources (i.e. refugee camps, schools). Following Betancourt et al. (2013), the quality of longitudinal studies was rated 'high' if at least four out of five (without comparison group) or five out of six domains (with comparison group) were rated as adequate; for observational studies, at least three out of four (without comparison group) and four out of five (with comparison group) adequate domains were required for a rating of 'high' quality. 'Moderate' quality was assigned to longitudinal and observational studies with two (without comparison group) or three adequate domains (with comparisnon group). Longitudinal studies rated inadequate in four or more domains and observational studies rated inadequate in three or more domains were considered 'low' quality. Two of the authors independently conducted the quality ratings.

3. Results

3.1. Characteristics of the included studies

Out of the 63 selected studies, 41 were conducted in HIC and 22 were conducted in LMIC according to the World Bank classification (World Bank, 2019). The refugee children came from 53 different countries: Africa (21 countries), Asia (17), Middle and South America (10) and Eastern Europe (5). The most frequent countries of origin were Syria, Iraq, Afghanistan, Iran, Burma, Somalia, South Sudan, and Eritrea. In total, 15 studies included unaccompanied refugee minors (URM). The majority of studies had a cross-sectional one-group design, 7 cross-sectional studies included a comparison group and 12 studies had a longitudinal one-group design. Table 1 shows a detailed description of the included studies.

3.2. Results of quality appraisal

Of the 63 studies, 13 were rated as 'low' quality, 26 as 'moderate' quality, and 24 as 'high' quality. The two independent raters agreed in the overall rating of 42 studies and resolved disagreements in the other 21 studies through discussions. Studies deemed 'low' quality were retained in the systematic review in order to provide a comprehensive and unbiased view of the evidence base. The results of the quality appraisal are displayed in detail in Supplementary Tables A1-A3.

3.3. Study findings

The findings are structured according to the different levels of the socio-ecological framework (individual, family, community, society and culture), similar to previous systematic reviews (Fazel et al., 2012; Reed et al., 2012) The findings of the individual studies are displayed in SupplementaryTable B.

3.4. Individual level

3.4.1. Exposure to trauma

About half of the studies ($n = 31$) investigated the association between pre-migration exposure to war-related traumatic events and children's mental health. Cumulative exposure to traumatic events was related to higher levels of mental health problems, including PTSD, depression, anxiety, and externalizing problems in most studies (e. g. Bronstein, Montgomery, & Dobrowolski, 2012; Jensen, Skar, Andersson, & Birkeland, 2019; Lincoln, Lazarevic, White, & Ellis, 2016; Müller, Büter, Rosner, & Unterhitzenberger, 2019; Vervliet et al., 2014). A few studies looked at singular traumatic events and found that particularly those involving severe interpersonal violence (Nasıroğlu, Çeri, Erkorkmaz, & Semerci, 2018; Sapmaz et al., 2017) and family members as victims (Çeri & Nasıroğlu, 2018; Gormez et al., 2018) were associated with worse mental health outcomes. Studies that did not report a consistent association between traumatic exposure and psychopathology often indexed trauma exposure by single items or trauma types (Beiser & Hou, 2016; Flink et al., 2013; Nasıroğlu & Çeri, 2016; Oppedal & Idsoe, 2012). Longitudinal studies with URM indicated that pre-migration trauma continued to impact their mental health years after arrival in the host country (Jensen et al., 2019; Keles, Friborg, Idsøe, Sirin, & Oppedal, 2016b; Vervliet, Lammertyn, Broekaert, & Derluyn, 2014). The role of post-migration trauma has only been assessed in two studies: Trauma exposure after arrival was not associated with mental health problems in one study (Jensen et al., 2019), whereas an increase in stressful life events after arrival predicted an increase in PTSD symptoms in another study (Jensen, Skårdalsmo, & Fjermestad, 2014). However, as the authors of the latter study note, events classified as occurring after arrival may have included pre-migration events that were not recalled or reported before.

3.4.2. Physical, psychological or developmental disorders

There has been scant investigation of the impact of pre-existing health and developmental conditions on refugee children's mental health. In a study with Syrian refugee children, the effect of war exposure on PTSD was strongest for highly sensitive children with low levels of childhood adversities, whereas sensitivity did not moderate the effect of war on PTSD for children with high childhood adversities (Karam et al., 2019). Variants of the monoamine oxidase A (MAOA) gene in Syrian boys were associated with decreases in psychosocial distress over time (Clukay et al., 2019). This link was most pronounced in children with either low trauma exposure or high resilience. Children's poorer physical health as rated by parents was related to more emotional and behavioral problems (Lau et al., 2018), while children with a positive history of a psychiatric disorder were more likely to receive a psychiatric diagnosis than children with a negative history (Sapmaz et al., 2017). Longitudinal studies suggest that refugee minors' depressive symptoms represent a risk factor for the development of later PTSD symptoms (Müller et al., 2019; Smid, Lensvelt-Mulders, Knipscheer, Gersons, & Kleber, 2011).

3.4.3. Time since displacement

Evidence on the association between length of stay in the host country and mental health is inconsistent. Seven studies, six of which were conducted in HIC, found that longer duration of time spent in the host country was related to lower levels of mental health problems and higher well-being (Correa-Velez, Gifford, & Barnett, 2010; Goosen, Stronks, & Kunst, 2014; Khamis, 2019; Lincoln et al., 2016; Müller, Gossmann, et al., 2019; Oppedal & Idsoe, 2012, 2015). A recent longitudinal study reported an amelioration of PTSD, depression and anxiety symptoms from baseline to follow-up assessment 1 year later (Müller, Gossmann, et al., 2019). Other longitudinal studies with URM provide evidence for a chronic trajectory of mental health problems (Jakobsen, DeMott, Wentzel-Larsen, & Heir, 2017; Jensen et al., 2019, 2014; Keles et al., 2016b; Vervliet, Lammertyn, et al., 2014). Two studies conducted in refugee camps suggest that an increased length of stay in camp settings was associated with exacerbated mental health problems (Braun-Lewensohn & Al-Sayed, 2018; Nasıroğlu et al., 2018).

3.4.4. Age and gender

The findings regarding age are inconsistent. The evidence is largely based on studies with older children and adolescents above 11 years of age and there is very limited information on young and middle childhood. In studies including adolescents until the age of 18, youth aged 16 and older had higher levels of internalizing problems (Braun-Lewensohn & Al-Sayed, 2018; Meyer, Yu, et al., 2017; Smid et al., 2011). Older URM were also more likely to develop late-onset PTSD (Smid et al., 2011), probably due to their higher exposure to traumatic experiences, an association also found in a number of other studies (Eruyar, Maltby, & Vostanis, 2018; Müller, Büter, et al., 2019; Oppedal & Idsoe, 2015). In a sample of refugee youth ranging from 13 to 27 years of age (mean 18.9), older age was related directly to fewer conduct problems, but indirectly to more depressive symptoms through less host culture competence and more outgroup hassles (Oppedal & Idsoe, 2012). Children who arrived in the Netherlands at an older age, i.e., between 4 and 11 or between 12 and 17 rather than in the first three years of life, had an increased risk of mental distress as recorded by asylum health services (Goosen et al., 2014). A study with repatriated adolescents between 11 and 18 years found that, for children who had a residence permit in the host country, peer problems decreased with age, whereas the opposite was true for children without a residence permit in the host country (Zevulun, Post, Zijlstra, Kalverboer, & Knorth, 2018). Notwithstanding, other studies with predominantly adolescent samples found that older age was a protective factor for internalizing problems (Ahmad, Smetana, & Klimstra, 2015; Lau et al., 2018; Park, Lee, & Jeon, 2017) and a substantial number of studies did not find associations between youth's age and mental health outcomes (Betancourt et al., 2012; Buchanan, Abu-Rayya,

Table 1
Description of included studies.

Authors (year)	Study site	Study population	Age in years (mean)	Domain assessed Socio-ecological/Temporal	Measurements
Ahmad et al. (2015)	Jordan	491 Palestinian refugee youth in a refugee camp	14–17 (15)	Individual, family/pre- and peri-migration	Adapted measures of maternal control, knowledge, solicitation, parent-child relationship and norm-breaking, family climate and secretiveness with mothers, SCARED
Beiser and Hou (2016)	Canada	152 refugee and 326 immigrant mother-child-dyads	11–13	Individual, family, community, society/ pre-, peri- and post-migration	Self-developed and adapted scales for emotional problems, aggressive behavior and other study variables
Beni Yonis et al. (2019)	Jordan	1773 Syrian refugee adolescents	12–18 (14.5)	Individual, family, society/pre- and peri-migration	Culturally adapted version of CPSS
Betancourt, Salhi, et al. (2012)	Ethiopia	Caregiver-child dyads in a refugee camp (T1: 168 adolescents, 162 caregivers T2: 153 adolescents, 152 caregivers)	11–18	Family, community/ peri-migration	Adapted version of YSR and CBCL, HSCL-25, multidimensional scale of perceived social support, self-developed items
Betancourt, Yudron, et al. (2012)	Russia	183 internally displaced Chechen youth	10–17 (13.6)	Individual, family, community, society/ pre- and peri-migration	YSR, adapted school connectedness scale, self-devised questions
Braun-Lewensohn and Al-Sayed (2018)	Unspecified refugee camp in Europe	110 Syrian refugee adolescents	12–18 (15.5)	Individual, family, community, society/ pre- and peri-migration	YSR, SOC, self-developed scales for other study variables
Bronstein et al. (2012) Bronstein et al. (2013)	UK	222 male Afghan URM	13–18 (16.3)	Individual, society/ pre- and post-migration	SLE, RATS, categorial indicators for asylum and care status SLE, HSCL-37A
Bryant et al. (2018)	Australia	394 refugee caregivers of 639 children	5–18 (12)	Family, society/pre- and post-migration	HTQ, PTSD-8, SDQ parent report, Postmigration Stressor Index (self-developed), warmth scale of Child Rearing Questionnaire, hostility scale of Early Chilhood Longitudinal Study of Children
Buchanan et al. (2018)	Australia	106 refugee youth and 223 non-refugee immigrant youth	Refugees: 13–21 (16.8) Immigrants: 13–18 (15.4)	Indidvidual, society/ pre- and post-migration	RSES, adapted scales for school adjustment, perceived discrimination and language proficiency
Çeri & Nasıroğlu (2018)	Turkey	77 Syrian refugee minors	7–17 (12.1)	Individual, family/pre- and post-migration	SDQ parent-report, self-devised questions for other study variables
Clukay et al. (2019)	Jordan	Syrian refugee youth in urban centers (T1: 399. T2: 263, T3: 157)	12–18 (14.3)	Individual/pre-migration	TEC, PSS, Human Distress and Human Insecurity, AYMH, SDQ, CRIES-8, CYRM, genetic analysis
Correa-Velez et al. (2010) Correa-Velez et al. (2015)	Australia	97 Refugee youth from 11 different countries (Wave 1) Wave 1: 120 Wave 5: 51	11–19 (15.1) Wave 5: 18–27 (22.8)	Individual, family, community, society/ pre- and post-migration	Subjective well-being measure (WHOQOL-BREF), adapted scales for other study measures, purposive-built items for subjective health and happiness, RSES
Elklit et al. (2012)	Denmark	119 Bosnian refugee youth	15–27 (18.5)	Individual, community/pre-, peri- and post-migration	HTQ, CSQ, CSS
Eruyar et al. (2018) Eruyar et al. (2020)	Turkey	263 Syrian child-parent dyads 322 Syrian refugee children	8–18 (11.6)	Individual, family/pre- and post-migration	SDQ parent- and self-report, GHQ-12, PSI, SLE, CRIES-8 CRIES-8, SDQ, Security Scale, Egna Minnen Betraffande Uppfostran for Children
Flink et al. (2013)	Colombia	Primary caretakers of 279 internally displaced and non-displaced children	2–6 (4.2)	Individual, family, community/pre- and post-migration	CBCL, GHQ-12, K-SADS-PL PTSD traumatic event checklist, general functioning scale of family assessment device (FAD), categorical indicator of social support
Giordano et al. (2019)	Italy	271 Syrian and Palestinian children in transit to Northern Europe	6–14 (10)	Individual (trauma exposure)/pre-migration	CWTQ, PTSRC, SDQ parent report, CYRM-28
Goosen et al. (2014)	Nether-lands	8047 accompanied asylum-seeking children	4–17	Individual, family, society/pre-, peri- and post-migration	Electronic database indicators, International Classification of Primary Care codes
Gormez et al. (2018)	Turkey	218 Syrian refugee children	9–15 (12)	Individual, society/ pre- and post-migration	Self-developed tool for traumatic events, UCLA-PTSD-RI, SCAS, SDQ
Jakobsen et al. (2017)	Norway	Male URM from Afghanistan, Somalia, Algeria and Iran (T1: 138, T2: 101, T3: 84, T4: 69)	14–20 (15.22)	Individual, family, society/pre- and post-migration	HSCL-25, SLE, HTQ
Javanbakht et al. (2018)	USA	53 Syrian refugee families (mostly with 2 parents) with 131 children	6–17 (11)	Family/post-migration	UCLA-PTSD-RI, SCARED, PCL-C, HSCL-25
Jensen et al. (2014) Jensen et al. (2019)	Norway	URM (T1: 93, T2: 75) (T1: 95, T2: 78, T3: 47)	T1: 13.8 T2: 16.5 T3: 20.0	Individual, family, community, society/ pre- and post-migration	HSCL-37A, CPSS, SLE, Self-developed check list for postmigration trauma, DSSYR, FSSQ
Karam et al. (2019)	Lebanon	549 Syrian refugee children and adolescents	7–17 (11.9)	Individual/pre-migration	UCLA-PTSD-RI, self-developed war exposure checklist, ISPCAN Child Abuse Screening Tool,

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Table 1 (*continued*)

Authors (year)	Study site	Study population	Age in years (mean)	Domain assessed Socio-ecological/Temporal	Measurements
					self-developed list of childhood adversities, Highly Sensitive Child Questionnaire
Keles, Friborg, Idsøe, Sirin, and Oppedal (2016a, 2016b)	Norway	895 URM with a permanent residence permit (T1: 918, T2: 580, T3: 229)	18.6 18.8–19.17	Individual, community, society/ pre- and post-migration	CES-D, YCC Hassles Battery, self-developed scales for host and heritage culture competence, self-developed pre-migration trauma checklist
Khamis (2019)	Lebanon, Jordan	1000 Syrian refugee children	7–18 (11.30)	Individual, family, community, society/ pre- and post-migration	Trauma Exposure Scale, structured clinical interview for PTSD DSM-IV Criteria, DERS-SF, KidCope, Family Environment Scale, School Environment Scale
Khawaja et al. (2017)	Australia	221 refugee and immigrant youth (55.8% refugees)	11–18 (14.9)	Individual, community, society/ post-migration	SCWBS, Acculturation and Resilience Scale, Psychological Sense of School Membership, Support Functions Scale
Kim et al. (2015)	South Korea	144 North Korean refugee youth	13–21 (18.2)	Individual, society/ pre- and post-migration	HSCL-25, UCLA PTSD-RI DSM-IV, ASC, self-developed Ego Resiliency Scale
Lau et al. (2018)	Australia	426 caregivers of 694 refugee children and adolescents	5–17	Individual, family, community/pre-, peri- and post-migration	SDQ-parent and child versions, self-developed items for study variables in individual, family, school and community domains
Lee et al. (2020)	South Korea	157 North Korean refugee youth	13–26 (18.7)	Individual, family/pre- and post-migration	ACE questionnaire, ERQ, CES-D, Conners-Wells Adolescent Self-Report Scale-Short Form
Lincoln et al. (2016)	USA	135 Somali adolescent refugees	11–20 (15.4)	Individual, society/ pre- and post-migration	Behavioral Acculturation Scale from LIB, Family Hassles Subscale of Acculturative Hassles Inventory, WTSS, UCLA-PTSD-RI, DSRS
Mace, Mulheron, Jones, and Cherian (2014)	Australia	332 refugee children reviewed by a health service	4–17 (9.58)	Family, society/pre- and peri-migration	Revised health-screening questionnaire for new patients at the Refugee Health Service
MacLean et al. (2019)	USA	425 immigrant children held at US detention centers and their mothers (UCLA self-report data for 150 children)	4–17 UCLA data: 13.4	Family/peri-migration	SDQ parent report, UCLA-PTSD-RI
McGregor et al. (2015)	Australia	50 resettled refugee youth from 16 different countries	12–21 (16.6)	Individual, family/pre- and peri-migration	CPSS, CCSC, YES-R
Meyer, Steinhaus, Bangirana, Onyango-Mangen, and Stark (2017) Meyer, Yu, Rieders, and Stark (2020)	Uganda	463/470 South Sudanese caregiver-adolescent dyads in two camps	13–17 (14.6)	Individual, family, society/pre- and peri-migration	IPSCAN Child Abuse Screening, SCARED, MFQ-C, HSCL-25, purposive-built questions for socioeconomic status and child labour
Meyer, Yu, Hermosilla, and Stark (2017)	Rwanda, Uganda	129 Congolese and 471 South Sudanese refugee adolescents in three camps	13–17	Individual, family/pre- and peri-migration	SCARED, MFQ-C, SDQ
Müller, Büter, et al. (2019) Müller, Gossmann, et al. (2019)	Germany	30 Accompanied and 68 unaccompanied refugee minors 1-year-follow-up (T2: 72)	16.3 17.3	Individual, family, society/pre-. peri- and postmigration	CATS, HSCL-37A, ERSS
Nasıroğlu & Çeri (2016) Nasıroğlu et al. (2018)	Turkey	55 Yazidi refugee children and their parents (46 families) 136 Yazidi refugee children	6–17 (11)	Individual, family/pre- and peri-migration	K-SADSPL-T
Oppedal and Idsoe (2012) Oppedal and Idsoe (2015)	Norway	566 URM 895 URM	13–27 (18.9) 18.6	Individual, family, community, society/ pre- and post-migration	Adapted scales for conduct problems, CES-D, purposive-built items for impact of war-related trauma, acculturation hassles, perceived discrimination and social support, Host and Heritage Culture Competence Scale for Adolescents
Oppedal et al. (2018)	Turkey	285 Syrian children in a refugee camp	12.5	Individual, family, community/pre- and post-migration	CDI, SLE, Social Provisions Scale
Park et al. (2017)	South Korea	136 North Korean adolescent refugees	12–24 (18.5)	Individual, family, community/pre- and postmigration	CDI, AUDIT, CRIES, Aggression Questionnaire, BRS, purposive-built questions for social support
Park et al. (2019)	South Korea	North Korean adolescent refugees (T1: 174, T2 (1-year-follow-up): 108	13–26 (17.8)	Individual, family, community/pre- and post-migration	CES-D, ERQ, RSES, BRS, purposive-built questions for social support
Samara et al. (2019)	UK	149 refugee children and 120 non-refugee British-born children	6–16	Family, community/ post-migration	Satisfaction with Life Scale, CPSS, Coopersmith Self-Esteem Inventory, Cambridge Hormones and Moods Friendship Questionnaire, Popularity Questionnaire, self-developed scale for bullying and victimization, SDQ parent (below 11) and child versions, Psychosomatic and Health Questionnaire
Sapmaz et al. (2017)	Turkey	89 refugee children	5–18 (10)	Individual, family/pre- and post-migration	K-SADSPL-T, SDQ parent (over 11) and child versions
Sierau et al. (2018)	Germany		14–19 (17.3)		MSSI, PCL-5, PHQ-9, GAD-7, SSS-8, SDQ

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Table 1 (*continued*)

Authors (year)	Study site	Study population	Age in years (mean)	Domain assessed Socio-ecological/Temporal	Measurements
		105 male URM living in group homes		Individual, family, community/pre- and post-migration	
Sim et al. (2018)	Lebanon	291 Syrian refugee children's mothers	2–12 (7.4)	Family/post-migration	TEC, HESPER, PCL—C, DASS, PARQ, Discipline Module of UNICEF's Multiple Indicator Cluster Survey, SDQ
Sleijpen, van der Aa, Mooren, Laban, and Kleber (2019)	Nether-lands	117 refugee adolescents and 138 Dutch peers	12–17 (14.3)	Individual/pre- and postmigration	CRIES, SDQ, Satisfaction with Life, Resilience Scale
Smetana and Ahmad (2018)	Jordan	277 Iraqi, 275 Syrian and 331 Palestinian refugee youth	15.01	Individual, Family/pre- and post-migration	Adapted measures of adolescents` war exposure and norm-breaking, mothers` and fathers` support, knowledge, behavioral and psychological control, harsh punishment, BSI-18
Smid et al. (2011)	Nether-lands	URM (T1: 920, T2: 582)	11–17.5	Individual, society/ pre- and post-migration	HSCL-25, SLE, RATS
Tozer et al., 2018)	Australia	93 refugee students at a special English language school	12–18 (15.5)	Individual, community, society/ pre- and post-migration	HSCL-25, SCWBS, PSSM, AARS, R-MATS
Vervliet, Lammertyn, et al. (2014)	Norway, Belgium	307 URM (risk factor analysis only for the 291 males)	14–18 (16.1)	Individual, family/pre-migration	HSCL-37A, SLE; RATS, HTQ
Vervliet, Meyer Demott, et al. (2014)	Belgium	URM (T1: 103, T2: 79, T3: 77)	16.0 at T3	Individual, family, community, society/ pre- and post-migration	HSCL-37A, SLE, RATS, DSSYR
Wiegersma et al. (2011)	Nether-lands	297 asylum-seeking children in reception centers	4–16 (9.9)	Individual, family, society/pre-. peri- and post-migration	SDQ parent, child and teacher versions, medical files
Zevulun et al. (2018)	Kosovo, Albania	106 repatriated asylum-seeking children	11–18 (14.4)	Individual, family, community, society/ post-migration	BIC-Q, SDQ child report
Zwi et al. (2018)	Australia	Asylum-seeking children in detention (48) and in community (38)	4–15 (8.4)	Society /peri-migration	SDQ parent-version

Note: Studies that are based on largely the same sample are listed in one row, URM, unaccompanied refugee minors. Instruments: AARS, Adult Acculturation and Resiliency Scale; ACE, Adverse Childhood Experiences; ASC, Acculturation Stress Scale; AUDIT, Alcohol Use Disorders Identification Test; AYMH, Arab Youth Mental Health Scale; BIC-Q, Best Interests of the Child-Questionnaire; BSI-18, Brief Symptom Inventory; CATS, Child and Adolescent Trauma Screen; CBCL, Child Behavior Checklist; CCSC, Children's Coping Strategies Checklist–Revision 1; CRIES, Children's Revised Impact of Events Scale; CPSS, Child Posttraumatic Stress Disorder Symptom Scale; CYRM, Child and Youth Resilience Measure; CDI, Children's Depression Inventory; CES-D, Center for Epidemiologic Studies Depression Scale for adolescents; CSQ, Coping Style Questionnaire; CSS, Crisis Support Scale; CSSI-8, Children's Somatization Inventory Short form; CWTQ, Childhood War Trauma Questionnaire; DASS, Depression Anxiety and Stress Scale; DSRS, Depression Self-Rating Scale; DSSYR, Daily Stressors Scale for Young Refugees; DERS-SF, Emotion Regulation Scale Short Form; ERSS, Everyday Resources and Stressors Scale; FSSQ, Duke-UNC Functional Social Support Questionnaire; GAD-7, Generalized Anxiety Disorder Scale; GHQ-12, General Health Questionnaire 12-item; HESPER, Humanitarian Emergency Settings Perceived Needs Scale; HSCL-25/37A, Hopkins Symptom Checklist; HTQ, Harvard Trauma Questionnaire; K-SADS-PL(−T), Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime Version (−Turkish); LIB, Language, Identity and Behavioral Acculturation Scale; MFQ-C, Mood and Feelings Questionnaire Child Self Report; MSSI, Multi- Sector Social Support Inventory; PARQ, Parental Acceptance Rejection Questionnaire; PCL-5/C, PTSD Checklist (Civilian); PHQ-9, Patient Health Questionnaire; PSI, Parenting Stress Index; PSS, Perceived Stress Scale; PSSM, Psychological Sense of School Membership; PTSD-8, Post-Traumatic Stress Disorder–8 items; PTSRC, Post-Traumatic Stress Reaction Checklist – Child Version; RATS, Reactions of Adolescents to Traumatic Stress; R-MATS, Resilience Questionnaire for Middle-Adolescents in Township Schools; RSES, Rosenberg Self-Esteem Scale; SCARED, Screen for Child Anxiety Related Emotional Disorders; SCAS, Spence Children's Anxiety Scale; SCWBS, Stirling Children's Well-being Scale; SDQ, Strength and Difficulties Questionnaire; SLE, Stressful Life Events Questionnaire; SOC, Sense of Coherence Scale; SSS-8, Somatic Symptoms Scale; TEC, Traumatic Events Checklist of HTQ; UCLA-PTSD-RI, University of California at Los Angeles Posttraumatic Stress Disorder Reaction Index; WTSS, War Trauma Screening Scale; WHOQOL-BREF, World Health Organization Quality of Life-Bref, YCC, Youth, Culture and Competence Study Hassles Battery; YES-R, Youth Experience Scale for Refugees; YSR, Youth Self-Report.

Kashima, Paxton, & Sam, 2018; Giordano, Cipolla, Ragnoli, & Bruno, 2019; Jensen et al., 2019; Tozer, Khawaja, & Schweitzer, 2018; Vervliet, Meyer Demott, et al., 2014).

The evidence for gender differences yields a more consistent picture. Eleven studies found that girls were at a higher risk of internalizing problems than boys (e. g. Ahmad et al., 2015; Betancourt, Salhi, et al., 2012; Çeri & Nasıroğlu, 2018; Keles et al., 2016b; Meyer, Steinhaus, Bangirana, Onyango-Mangen, & Stark, 2017; Oppedal & Idsoe, 2015). Girls were also more likely to have higher levels of PTSD symptoms in a number of studies (Beni Yonis et al., 2019; Braun-Lewensohn & Al-Sayed, 2018; Elklit, Ostergard Kjaer, Lasgaard, & Palic, 2012; Jensen et al., 2019). Six studies found no differences between girls and boys regarding PTSD (Giordano et al., 2019; Karam et al., 2019; Khamis, 2019) and other mental health problems (Lau et al., 2018; Samara, El Asam, Khadaroo, & Hammuda, 2019; Tozer et al., 2018). One study found male gender to be associated with a higher PTSD risk (Gormez et al., 2018). Three studies corroborate evidence that boys are at an increased risk for externalizing problems (Çeri & Nasıroğlu, 2018; Eruyar, Maltby, & Vostanis, 2020; Oppedal & Idsoe, 2012). There is also some evidence for an interaction of age and gender. In pre-pubertal children, boys had a higher risk for mental health problems than girls, whereas in adolescents, girls were at a higher risk (Goosen et al., 2014; Wiegersma, Stellinga-Boelen, & Reijneveld, 2011). In a study with Syrian children in a Turkish camp, gender differences in depression were observed only in children 13 or older, which was attributable to significantly lower levels of depression in older compared to younger

boys (Oppedal, Özer, & Şirin, 2018).

3.4.5. Education and academic performance

A longer period of schooling was associated with fewer PTSD symptoms (Müller, Büter, et al., 2019) and fewer self- and parent-rated emotional and behavioral problems (Wiegersma et al., 2011). A higher educational level of South Sudanese adolescents in a Ugandan camp was associated with fewer anxiety symptoms (Meyer, Yu, et al., 2017). Minors reporting 3 or fewer years of education were significantly more likely to develop late-onset PTSD in a longitudinal study (Smid et al., 2011). Two Australian studies found that better self-perceived (Correa-Velez et al., 2010) and parent-reported school performance (Lau et al., 2018) were linked to higher psychological wellbeing and fewer emotional and behavioral problems respectively. In an Australian study (Tozer et al., 2018), fewer years of schooling prior to arrival was associated with higher levels of depression in bivariate, but not multivariate, analysis and in a longitudinal study education level did not predict PTSD symptoms and other mental health problems (Jensen et al., 2014).

3.4.6. Personal resources

Mental health and well-being are likely to be influenced by the way refugee children cope in the aftermath of war and flight. A study with Syrian children who resettled in Jordan and Lebanon found that coping through acquiring social support and trying to think differently about events was associated with fewer PTSD symptoms (Khamis, 2019), while a higher use of the emotion regulation strategy of cognitive reappraisal differentiated North Korean youth with consistently low levels of depressive symptom from those whose depressive symptoms deteriorated over a one year period (Park, Kim, Lee, & Jun, 2019). However, greater use of problem-focused coping strategies was related to PTSD in Bosnian adolescents who were waiting for their asylum decisions (Elklit et al., 2012), which suggests that engaging too much with problems and circumstances that cannot be actively changed may increase youth's psychological symptoms. On the other hand, avoiding the engagement with problems and distressing emotions through behavioral and cognitive efforts has also been found to be associated with the presence of PTSD (Elklit et al., 2012; Khamis, 2019) and higher levels of depressive symptoms (Lee, Lee, Jun, & Park, 2020; Park et al., 2019). However, the association between avoidant coping and PTSD disappeared when controlling for the avoidance symptoms related to PTSD in one study (McGregor, Melvin, & Newman, 2015). Children's appraisals of their life circumstances and their future appear to be important as well. A higher sense of coherence, a personal resource reflecting individuals` ability to cope with and make meaning of adverse events, was associated with lower levels of PTSD symptoms, internalizing and externalizing problems (Braun-Lewensohn & Al-Sayed, 2018). In the same study, higher hopeful expectations for the future were related to children's fewer externalizing problems, whereas future-oriented wishes were not linked to mental health outcomes. Youth experiencing more control over their life also reported higher levels of psychological and physical well-being (Correa-Velez et al., 2010). Other more practical personal resources, such as physical activity (Lau et al., 2018) as well as instrumental and social competence (Beiser & Hou, 2016) were not associated with adolescents` emotional and behavioral problems.

A number of studies investigated the role of protective personal resources using different conceptualizations of resilience. Lower resilience conceptualized as an individual's perceived ability to bounce back from stress was related to higher levels of depression in North-Korean youth in two cross-sectional (Kim, Cho, & Kim, 2015; Park et al., 2017) and one longitudinal study (Park et al., 2019) and influenced whether a longer stay as an asylum seeker was associated with more or fewer emotional problems (Sleijpen, van der Aa, Mooren, Laban, & Kleber, 2019). Higher levels of resilience viewed as a set of interpersonal and intrapersonal strengths were related to higher levels of well-being (Khawaja, Ibrahim, & Schweitzer, 2017; Tozer et al., 2018), while resilience assessed as protective factors on different socio-ecological levels predicted reductions in Syrian children's psychosocial stress over time (Clukay et al., 2019).

3.5. Family level

3.5.1. Family composition

Youth who were separated from immediate family members had higher levels of PTSD symptoms than youth who stayed in Australia with all their immediate family members (McGregor et al., 2015). Both previous and current separation from the nuclear family was associated with a diagnosis of PTSD (Mace, Mulheron, Jones, & Cherian, 2014). Children in an US detention center who had been separated from their mothers had higher levels of mother-rated emotional and behavioral problems compared to children who had not been separated from their mothers (MacLean et al., 2019). Having left one parent behind in the country of origin was associated with more self- and teacher-reported emotional and behavioral problems in a Dutch study (Wiegersma et al., 2011). The only study comparing unaccompanied and accompanied youth found that being unaccompanied was associated with a higher exposure to traumatic events and with more externalizing problems (Müller, Büter, et al., 2019). Although the integrity of the whole family unit appears to be crucial, other findings indicate that the presence of at least one biological parent is already protective (Correa-Velez et al., 2010; Lau et al., 2018; Meyer, Steinhaus, et al., 2017).

Evidence regarding the role of parental loss is inconsistent. In two studies in LMIC, adolescents who had lost one or both parents were more likely to have PTSD (Beni Yonis et al., 2019) and higher levels of internalizing problems (Meyer, Yu, et al., 2017). In a study with URM shortly after their arrival in Belgium and Norway, the death of one or both parents was not associated with mental health outcomes (Vervliet, Meyer Demott, et al., 2014). Household size did not seem to be associated with mental health problems in two studies (Beni Yonis et al., 2019; Meyer, Yu, et al., 2017), but a smaller family size was associated with more parent- and teacher-rated emotional and behavioral problems of adolescents resettled in the Netherlands (Wiegersma et al., 2011).

3.5.2. Family functioning and parental mental health

A more positive, i.e. warm and stable, family climate was associated with lower levels of anxiety for Palestinian adolescents living in refugee camps in Jordan (Ahmad et al., 2015). Higher connectedness, i.e. perceived understanding, care and respect, by the family predicted lower levels of internalizing problems in displaced Chechen youth, particularly in boys (Betancourt, Salhi, et al., 2012). A family environment that encouraged the direct expression of emotions was related to a decreased risk for PTSD in Syrian children (Khamis, 2019).

Supporting evidence for the role of refugee parents` wellbeing for their children's mental health has been found by 10 studies in both HIC and LMIC (e. g. Beiser & Hou, 2016; Bryant et al., 2018; Meyer, Steinhaus, et al., 2017; Sim, Bowes, & Gardner, 2018). For instance, higher caregiver distress was prospectively associated with higher levels of internalizing and externalizing problems in Eritrean adolescents living in a camp in Ethiopia (Betancourt, Yudron, Wheaton, & Smith-Fawzi, 2012). In a study with Syrian parent-child dyads living in Turkey, parental psychopathology was not related to children's PTSD symptoms, but to higher levels of parent- and child-reported emotional and parent-reported behavioral problems (Eruyar, Maltby, & Vostanis, 2018). Poorer caregiver mental health and lower family functioning were associated with more internalizing and externalizing problems in young displaced Colombian children, but not in non-displaced children (Flink et al., 2013). While these studies focused on parent-child dyads and mostly mothers, a study with Syrian families who resettled in the USA found only mothers`, but not fathers` psychopathology to be associated with children's anxiety symptoms (Javanbakht, Rosenberg, Haddad, & Arfken, 2018).

Two studies investigating a potential mechanism underlying these associations suggested that parents` own exposure to war trauma and

post-migration stressors were associated with higher levels of parental mental health problems, which in turn were related to more negative parenting behaviors (e. g. harsh parenting), which in turn negatively impacted their children's mental health (Bryant et al., 2018; Sim et al., 2018). In further support of this, children and adolescents` self-reported experiences of maltreatment by parents were associated with higher levels of mental health problems including PTSD (Karam et al., 2019), depression (Lee et al., 2020; Meyer, Steinhaus, et al., 2017; Meyer, Yu, et al., 2017), anxiety (Meyer, Steinhaus, et al., 2017; Meyer, Yu, et al., 2017) and attention deficit hyperactivity disorders symptoms (Lee et al., 2020). An insecure attachment to mothers and fathers as perceived by Syrian children was related to higher levels of PTSD symptoms, general mental health and conduct problems (Eruyar et al., 2020), whereas a positive mother-child relationship was related to lower levels of anxiety for Palestinian adolescents living in camps (Ahmad et al., 2015). Parenting styles perceived as negative, i.e. low in emotional warmth and support, harsh, rejecting and controlling, were associated with higher levels of internalizing and externalizing problems (Eruyar et al., 2020; Lau et al., 2018; Smetana & Ahmad, 2018). In contrast, positive, i.e. supportive and emotionally warm parenting was linked to lower levels of emotional and behavioral problems (Lau et al., 2018; Smetana & Ahmad, 2018; Zevulun et al., 2018).

3.5.3. Household assets and parental education

While no study has systematically assessed preflight socioeconomic status (SES), findings suggested that post-migration SES could be particularly relevant in very poor settings: in an Ethiopian camp, the possession of valuable household assets, i.e. a radio and cattle, was associated with lower levels of adolescents` internalizing problems (Betancourt, Yudron, et al., 2012). In a study in a Ugandan camp, higher SES conceptualized as lower household hunger, caregiver employment status and number of valuable household assets was related to lower levels of adolescents` depression (Meyer, Steinhaus, et al., 2017). In resource-poor settings, such as refugee camps, low SES may also be an indirect risk factor for children's wellbeing as it increases their risk to be engaged in child labor, which was associated with higher levels of depression (Meyer, Yu, Rieders, & Stark, 2020). Fathers` current unemployment was associated with an increased risk of a psychiatric disorder in refugee children living in a Turkish city (Sapmaz et al., 2017). Having a less educated father was linked to higher levels of children's emotional problems in one study (Çeri & Nasıroğlu, 2018), whereas no independent association between parents' level of education and child mental health outcomes was found in other studies (Beiser & Hou, 2016; Beni Yonis et al., 2019; Sapmaz et al., 2017).

3.6. Community level

3.6.1. Social support

Social support can be provided by various persons within children's social ecology, e.g. by family members, friends, teachers or other adults within the community, and thus operates both on the micro- and exosystem. Although a number of studies investigated associations between social support and refugee children's adjustment, they varied considerably in their conceptualization and assessment of social support. Studies that assessed social support in general and did not differentiate between sources of support produced mixed findings, with some studies reporting no independent associations with mental health problems (Elklit et al., 2012; Flink et al., 2013; Jensen et al., 2019) and others presenting links between general social support and higher wellbeing (Correa-Velez, Gifford, & McMichael, 2015; Khawaja et al., 2017) as well as lower levels of depression (Oppedal et al., 2018). One study differentiated between the type of support and found that lower psychological, but not practical support by family, friends and other people predicted North Korean youth's depression (Park et al., 2017). Some studies separately investigated the role of social support provided by family members, peers and community members. Lower support by mentors and peers, but not by the family, increased the risk of PTSD and depression (mentors) as well as anxiety (mentors and peers) after stressful life events (Sierau, Schneider, Nesterko, & Glaesmer, 2018). In another study, social support within the family was not significantly associated with unaccompanied and accompanied minors' mental health, whereas social support in the host country was related to lower levels of anxiety symptoms (Müller, Büter, et al., 2019). In a study with URM in Norway (Oppedal & Idsoe, 2015), both support from family and friends were associated with lower depression levels directly (family) and indirectly through promoted acculturation (family and friends). Connectedness with the family appeared to be more important in protecting displaced Chechen adolescents from internalizing problems than connectedness with peers and adult community members (Betancourt, Salhi, et al., 2012). Caregiver-rated ethnic and religious community support was not associated with children's emotional and behavioral problems in an Australian study (Lau et al., 2018).

3.6.2. Neighborhood quality

Caregiver-perceived neighborhood friendliness and safety were not associated with children's emotional and behavioral problems in an Australian study (Lau et al., 2018). Similarly, poor neighborhood quality as perceived by refugee youth in Canada was not related to their internalizing and externalizing problems (Beiser & Hou, 2016). In refugee camps, the existence of and access to NGO's services may benefit the livelihoods of communities and families and thus children's adjustment. Caregiver-perceived access to health services was associated with lower levels of youth's internalizing and externalizing program in an Ethiopian camp and for youth who were satisfied with an education program offered by an NGO, the association between caregiver distress and adolescents' mental health problems was weaker compared to those who were not satisfied (Betancourt, Yudron, et al., 2012). However, receiving aid from organizations was not associated with mental health problems in Syrian adolescents living in a European refugee camp (Braun-Lewensohn & Al-Sayed, 2018). Housing quality was not associated with children's psychopathology in two studies (Beni Yonis et al., 2019; Betancourt, Salhi, et al., 2012).

3.6.3. School and peer relationships

Schools can play a vital role for the adjustment and wellbeing of resettled refugee children and youth, as they not only provide opportunities of learning and academic progress, but also constitute the context in which a major part of socialization and acculturation processes take place. Feeling accepted and supported by teachers and fellow students at school was associated with lower levels of aggressive behavior (Beiser & Hou, 2016), emotional dysregulation (Khamis, 2019) and psychological distress (Tozer et al., 2018) and with higher levels of wellbeing (Khawaja et al., 2017; Tozer et al., 2018). On the other hand, perceived discrimination by teachers and peers was related to more emotional and behavioral problems in one study (Beiser & Hou, 2016) and being bullied by peers at school was associated with lower levels of self-esteem (Samara et al., 2019) and happiness (Correa-Velez et al., 2010). The importance of having supportive and understanding friends for children's mental health was underlined by findings from two studies (Correa-Velez et al., 2010; Samara et al., 2019).

3.7. Society and culture

3.7.1. Post-migration difficulties

Higher cumulative exposure to daily hassles was associated with URMs' higher levels of PTSD symptoms, internalizing and externalizing problems as well as somatization 5 years after their arrival in Norway (Jensen et al., 2019). In a longitudinal follow-up of URM in Belgium, the number of daily stressors, particularly experiences of discrimination, increased over time and predicted PTSD symptoms, depression and anxiety 18 months after arrival, over and above the effects of pre-migration war exposure (Vervliet, Lammertyn, et al., 2014). Apart

from these direct effects, two studies found cross-sectional evidence for an indirect effect of post-migration difficulties on refugee children's mental health by increasing parental psychopathology and subsequently negative parenting behaviors (Bryant et al., 2018; Sim et al., 2018). With the exception of one study (Sim et al., 2018), accumulated daily hardships and their relations to youth's mental health have not been investigated in LMIC where refugees often live in camp settings with precarious living conditions such as widespread violence, poverty and bad sanitary conditions (Reed et al., 2012).

3.7.2. Acculturation

A number of studies from HIC investigated the role of sociocultural adaptation and its relation to refugee children's mental health using the concept of acculturation. While its definition and assessment have stirred controversy (Oppedal & Idsoe, 2012), the studies generally supported the idea that acculturation refers to the dynamic process of psychological and behavioral change that arises from a prolonged confrontation with a new culture's norms, customs and values (Berry, 2005). Higher levels of integration into the host society, i.e. adopting aspects of the new culture while maintaining values and practices of the original culture, were associated with lower levels of depression and anxiety (Tozer et al., 2018) as well as with higher levels of well-being (Khawaja et al., 2017; Tozer et al., 2018) in refugee youth resettled in Australia. Increased competence, i.e. knowledge and skills about interpersonal behaviors and underlying values, regarding both host and heritage culture, was related to lower levels of depression in URM in Norway (Oppedal & Idsoe, 2012, 2015). Support from family and co-ethnic friends was associated with ethnic competence, while support from Norwegian friends was related to host culture competence (Oppedal & Idsoe, 2015). A higher social status of the family within the broader Australian community (Correa-Velez et al., 2010), but also a stronger ethnic identity (Correa-Velez et al., 2015), were linked to refugee youth's well-being and happiness respectively. While a balance between adaptation to the host and heritage culture appears to be associated with better mental health, marginalized (disengaging both from host and heritage culture) and separated (maintaining high levels of heritage culture/identity while avoiding contact with the host culture/society) acculturation styles were associated with higher levels of depression in Somali adolescents resettled in the USA (Lincoln et al., 2016).

Learning the host country's dominant language is a crucial part of sociocultural adaptation. Poorer German language proficiency was related to higher levels of PTSD and depression symptoms (Müller, Büter, et al., 2019) and better perceived English skills were associated with higher self-esteem and school adjustment (Buchanan et al., 2018). However, two studies did not find an association between children's proficiency in the host language and their adjustment (Correa-Velez et al., 2015; Gormez et al., 2018).

Part of the acculturation process may be exposure to a number of stressful experiences for refugee children and youth, such as conflicts with family and in-group members, discrimination and ethnic identity crisis (Keles, Friborg, Idsøe, Sirin, & Oppedal, 2016a). More severe family-related acculturative hassles, such as being criticized for codes (e.g. clothes, behaviors) adopted from the host culture and having to translate for parents were associated with higher levels of PTSD symptoms and depression, particularly in youth with a marginalized acculturation style (Lincoln et al., 2016). Higher perceived discrimination was related to higher levels of depression (Oppedal & Idsoe, 2015) and lower levels of self-esteem and school adjustment (Buchanan et al., 2018) as well as lower happiness (Correa-Velez et al., 2015). Higher cumulative acculturation stress was associated with higher levels of depression in cross-sectional studies (Keles et al., 2016a; Kim et al., 2015) and with an increase in depression symptoms over time in a longitudinal study with unaccompanied minors in Norway (Keles et al., 2016b). A decrease in acculturative stressors was related to a decrease in depressive symptoms over time in the latter study. No study has investigated acculturation-related factors in LMIC.

3.7.3. Resettlement location

Refugee camps are one of the most common displacement settings for refugees worldwide, particularly in LMIC. However, only 9 studies were actually conducted in camp contexts and no study assessed whether children currently residing in a camp were at greater risk for mental health problems than children living in other forms of accommodation. Living in a camp (Beiser & Hou, 2016; Lau et al., 2018) and duration of stay in a camp (Elklit et al., 2012) before coming to a HIC were not related to youth's emotional and behavioral problems and PTSD. Living in proximity to ongoing war and/or in poorly developed regions may perpetuate children's feelings of insecurity and helplessness. The prevalence of PTSD was higher among Syrian adolescents living in a Jordanian city close to the Syrian border with limited access to jobs, health and education compared to those living in a more distant and industrialized city (Beni Yonis et al., 2019). In a similar vein, rates of PTSD were higher among Syrian youth living in Lebanon compared to Jordan, which is probably attributable to relatively higher levels of post-migration stressors (e.g. discrimination, bad sanitary conditions, and restrictive living arrangements) in Lebanon (Khamis, 2019). However, in a study with internally displaced Chechen youth perceived insecurity in the region of resettlement was not related to internalizing problems (Betancourt, Salhi, et al., 2012). Not being satisfied with life in Turkey was associated with more conduct problems in one study with Syrian children (Çeri & Nasıroğlu, 2018), but no independent association with children's mental health was found in another study (Gormez et al., 2018). For asylum-seeking children who had returned to Kosovo and Albania, living in a rural or urban area was not related to emotional and peer problems (Zevulun et al., 2018).

3.7.4. Ethnic origin

African-born youth reported higher levels of well-being than youth from other regions in a Australian study (Correa-Velez et al., 2010). In another study, parents of children with African origin reported more emotional and behavioral problems for their children than children from the Middle East and Eastern Europe in a Dutch study (Wiegersma et al., 2011). In a database study of accompanied asylum seeking children in the Netherlands (Goosen et al., 2014), children from Iran had the highest and children from Iraq the lowest risk of mental distress recorded by medical services. Belonging to a visible minority (e.g. Afghan, Sri Lankan) was associated with more emotional problems reported by refugee youth resettled in Canada (Beiser & Hou, 2016). Repatriated children who belonged to the Ethnic Roma minority faced a lower quality of child-rearing environment, which was linked to more internalizing problems (Zevulun et al., 2018).

3.7.5. Placement type and immigration process

The comparability of findings regarding the asylum process is limited due to country-specific regulations. However, the type and quality of living arrangements as well as the outcome of the asylum decision appear to be particularly important with regard to refugee youth's mental health and wellbeing. Studies with URM suggest that staying in settings characterized by lower supervision and support, e.g. living independently or in large-scale reception centers, is associated with higher levels of PTSD, depression and anxiety when compared to settings with more support and supervision, e.g. foster care or living groups (Bronstein et al., 2012; Jakobsen et al., 2017; Smid et al., 2011). A Norwegian longitudinal study found that URM who were assessed as 18 years or older and were subsequently placed in low-support adult reception centers had higher levels of psychological distress at follow-up assessments compared to youth who remained in high-support reception centers for youth (Jakobsen et al., 2017). However, the type of living arrangements was not associated with Afghan URMs' emotional and behavioral problems when controlling for age, pre-migration trauma and length of stay in the UK (Bronstein,

Montgomery, & Ott, 2013). Post-migration detention is a form of placement that seems to be especially harmful to children's wellbeing. Both past and current mandatory detention was associated with an increased likelihood of PTSD, depression and anxiety (Mace et al., 2014) and children who were detained on a small island on their way to Australia had significantly higher levels of parent-rated emotional and behavioral problems than children living in a community setting in Australia (Zwi, Mares, Nathanson, Tay, & Silove, 2018). Evidence about the influence of changes in the living situation within the host country is inconsistent. A high annual relocation rate was associated with an increased risk for mental distress particularly in children who had experienced violence and whose mother had PTSD or depression (Goosen et al., 2014). However, the number of relocations was not related to emotional and behavioral problems as reported by children themselves, parents, and teachers in another study (Wiegersma et al., 2011).

The time spent waiting for the asylum decision is marked by great uncertainty about the future and constant fear of deportation. Increased length of stay as an asylum seeker in the Netherlands was associated with adolescents` lower levels of life satisfaction and individual resilience (Sleijpen et al., 2019). In another study, time until determination of asylum status was not related to URMs` externalizing problems (Bronstein et al., 2013). Two longitudinal studies found that minors whose asylum applications had been rejected between assessments (compared to those who were granted asylum) had significantly higher levels of PTSD symptoms and externalizing problems (Müller, Gossmann, et al., 2019) as well as depression and anxiety symptoms (Jakobsen et al., 2017; Müller, Gossmann, et al., 2019). Asylum status was not associated with children and adolescents` mental health problems in two cross-sectional studies, which was explained by the unequal distribution by the respective variable (Bronstein et al., 2012) and the potentially higher relevance of other context variables such as maternal mental health and family size (Wiegersma et al., 2011). Having a permanent visa was related to higher levels of wellbeing in a Australian study (Tozer et al., 2018), while a stable residence permit in the host country was related to a higher-quality child rearing environment and in turn lower levels of internalizing problems in repatriated children (Zevulun et al., 2018).

4. Discussion

Within the past decade, an unprecedented number of people, of which many are minors, have been forced to flee their homes due to ongoing and emerging violent conflicts and wars in the world. Researchers have responded to the need to better understand which factors contribute to the mental health and well-being of vulnerable refugee youth by conducting various new studies. Table 2 summarizes the contributing factors identified by this systematic review across different socio-ecological levels (individual, family, community, society/culture) and stages of the refugee experience (pre-. peri- and post-migration).

Several limitations of the recent research studies have to be taken into account when interpreting the findings: first, there is a lack of evidence on pre- and peri-migration factors, particularly on the family, community and societal level, as well as the role of experiences during flight and migration. Second, there are few studies from LMIC and particularly refugee camps. While this may be due to the ethical and practical challenges related to conducting research in these settings (Reed et al., 2012), it means that findings do not encompass the lived realities of most refugees worldwide. Third, the current evidence is largely based on cross-sectional studies without comparison groups, which preclude firm conclusions on the direction of associations between presumed factors of influence and outcomes. Fourth, the studies are very heterogeneous in the applied research designs, measures and target refugee populations, thereby making it difficult to draw unifying conclusions. For instance, some studies used instruments that were specifically created or adapted for the study context, whereas others applied established measures that were not validated for the samples` cultural background.

Notwithstanding these limitations, our synthesis of the individual findings provides useful information by strengthening the evidence base for some established factors and shedding light on hitherto underexplored factors. Our findings corroborate previous evidence establishing children's exposure to pre-migration trauma as significant individual-level factor contributing to the risk of developing mental health problems (Fazel et al., 2012; Reed et al., 2012). This is in line with the building block effect of trauma (Neuner et al., 2004), which specifies a dose-response relation between the number of traumatic event types and

Table 2
Factors contributing to risk and protection of refugee children's mental health according to socio-ecological context and stage in the refugee phase.

	Individual	Family	Community	Society/culture
Pre-migration	Exposure to war-related traumatic events (risk)[22] (25) Being female (risk for internalizing symptoms and PTSD)[14] (21) Being male (risk for externalizing symptoms)[3] (3) **Longer period of schooling (protective)[6]**	**Loss of a parent (risk)[2]**		
Peri-migration	**Length of current stay in a refugee camp (risk)[2]**	Separation from immediate family members (risk)[4] (3) **Socioeconomic status in a refugee camp (protective)[2]**		**Detention (risk)[2]**
Post-migration	**Depression and anxiety symptoms (risk)[2]** **Better perceived school performance (protective)[2]** **Avoidant coping strategies (risk)[4]** **Individual resilience (protective)[6]**	**Living with at least one biological parent (protective)[2]** Parental mental health problems (risk)[10] (2) **Negative parenting behaviors (risk)[5]** **Parental abuse (risk)[4]** Family cohesion (protective)[4] (3) **Warm parent-child relationship (protective)[3]**	Support by peers (protective)[2] (4) **Close relationships with friends (protective)[2]** School connectedness (protective)[4] (3) **Cumulative exposure to daily stressors (risk)[5]**	Perceived discrimination (risk)[4] (3) **Integrative acculturation style (protective)[6]** **Exposure to acculturation stressors (risk)[4]** **Resettlement in a poor region (risk)[2]** **Low-support living arrangements (risk for unaccompanied minors)[3]** **Asylum granted in host country (protective)[4]**

Note: Only factors that were found in at least two studies are shown. Factors not included in the previous reviews by Fazel et al. (2012) and Reed et al. (2012) are highlighted in bold. The numbers indicate the number of studies that found the respective factor in the current review (without brackets) and in the reviews by Fazel et al. (2012) and Reed et al. (2012) (with brackets).

the severity of PTSD and other trauma-related psychopathology. While girls have been identified at heightened risk for internalizing symptoms before (Fazel et al., 2012; Reed et al., 2012), the more recent studies also provide evidence for female gender as contributing to the risk for PTSD. A newly found factor contributing to resilience is a longer period of pre-migration schooling, underscoring the pivotal role of education for the well-being and development of conflict-affected children (Nicolai & Triplehorn, 2003). Our review suggests several individual-level factors contributing to risk (internalizing symptoms, avoidant coping) and protection (better perceived school performance, individual resilience) in the post-migration phase. However, these are based on a small number of studies solely from HIC.

The new evidence on family-level factors strengthens the view that the family constitutes a powerful source of both risk and resilience to the mental health and wellbeing of conflict-affected children (Betancourt & Khan, 2008). In particular, a link between parents` own mental health problems and refugee children's mental health has been found across a variety of cultural and socioeconomic settings. The mechanisms underlying this intergenerational transmission of psychopathology remain to be elucidated in refugee families. This review provides preliminary evidence for the mediating role of maladaptive parenting behaviors, which goes along with research on other conflict-affected populations documenting the complex interplay between war trauma, family violence and children's mental health problems (Catani, 2018). However, some studies show the protective nature of a cohesive and supportive family environment for refugee youth's mental health after resettlement in the host country, which has also been found in previous reviews (Fazel et al., 2012). In line with previous reviews (El Baba & Colucci, 2018; Fazel et al., 2012), being separated from family members before and during flight constitutes a factor contributing torefugee youth's risk. However, there is a lack of studies comparing accompanied and unaccompanied youth and investigating the role of family separations in LMIC.

Evidence on post-migration community-level and on sociocultural factors comes almost exclusively from HIC, precluding the generalizability of these findings beyond these settings. In line with previous reviews (d'Abreu et al., 2019; Fazel et al., 2012), higher exposure to acculturative stressors in the host country, in particular perceived discrimination, was associated with worse mental health outcomes for refugee youth. In keeping with research with non-refugee immigrant youth (Abu-Rayya & Sam, 2017), an integrative acculturation style, i.e. being engaged both in the host and heritage culture, appears to be associated with refugee youth's higher wellbeing. Even though discrimination and other acculturation stressors may be particularly salient in HIC whose culture is often quite different from the home countries of most refugees, studies from LMIC with seemingly similar cultures of refugees and host societies would be valuable. Discrimination may be also prevalent in contexts where refugee and host communities compete for scarce resources. Relatedly, the nature of daily stressors differs for refugee youth in these contexts and consist rather in a severe lack of material resources and ongoing threats to safety (Reed et al., 2012). In terms of factors contributing to protection, the review expands the evidence base for an important role of school connectedness and self-reported support by peers for refugee youth (Fazel et al., 2012). In line with specialized systematic reviews (Mitra & Hodes, 2019; O'Higgins et al., 2018), being placed in living arrangements characterized by lower support, e.g. semi-independent care or reception centers, puts URM at an increased risk for mental health problems compared to more supportive arrangements, e.g. foster care. Unsurprisingly, acceptance of asylum claims in the host country appears to be protective, marking the end of a period of uncertainty and offering a long-term perspective.

Placing the current evidence in the wider context of clinical psychological research with children and adolescents, it can be noted that the contributing factors on the family and community level such as parental mental health problems, maladaptive parenting and peer support are for the most part well in line with established evidence from non-refugee populations (Lambert, Holzer, & Hasbun, 2014; McLeod, Weisz, & Wood, 2007). On the one hand, this supports a universal perspective on refugee children's development and well-being and emphasizes the importance of proximal socio-ecological contexts, particularly the family. On the other hand, our systematic review is the first to establish the importance of these factors for the mental health of refugee children. In fact, they may be particularly salient in this population given the consistently higher prevalence rates of mental health problems found in adult refugees compared to the general population (Silove, Ventevogel, & Rees, 2017). Besides more or less universal factors, our review also identified a number of factors that can be considered unique for the context of refugee children and adolescents, at least those resettling in HIC, such as acculturation, discrimination, placement type (for URM) and the asylum decision. Overall, our systematic overview emphasizes the joint consideration of a range of universal and specific contributing factors across the pre-, peri- and post-migration phases and different ecological contexts in order to understand mental health risk and resilience of refugee youth.

4.1. Recommendations for future research

Future studies should aim to expand the evidence base for the factors identified by this and previous systematic reviews. This way the status of factors with inconsistent evidence should be clarified (e.g. age, time since displacement) and potentially relevant factors that have been understudied so far should be examined (e.g. refugee youth's attribution of events, intra-familial communication, genetic and biological factors, neighborhood characteristics, ideological and religious beliefs). Most importantly, studies should strive to use longitudinal designs to elucidate causal pathways between socio-ecological factors and refugee youth's mental health and adjustment at different stages of their experience and development. While it may be extremely difficult to track children across their flight journey, studies could include children shortly after their arrival at a camp or reception center and prospectively assess post-migration factors and mental health at multiple regular follow-ups. In doing so, it will be important to record the relevant predictor and outcome variables at each time point and model complex research designs such as cross-lagged panel and latent growth models to examine causal mechanisms of change. Among the reviewed studies, positive examples for longitudinal and rather complex designs are the high-quality study by Smid et al. (2011), which combined multinomial regression and path analysis to examine the interplay of individual-level (trauma exposure, age, and internalizing symptoms) and socio-cultural (supervision) variables in shaping PTSD symptomatology over time, as well as the study by Keles et al. (2016b), which used a person-based approach to identify pre-migration (trauma exposure and gender) and post-migration (acculturative stressors) risk factors for long-term trajectories of depression symptoms among URM. The inclusion of comparison groups, for example accompanied and unaccompanied minors, repatriated and non-repatriated youth, children in refugee camps and in community settings, is also important. Ultimately, the validity and generalizability of research findings depend both on the psychometric quality and the cultural applicability of the used assessment instruments. Researchers should aim to strike a balance between using established measures that enhance comparability between studies and taking into account culture-bound mental health concepts to improve the cultural applicability of measures. Finally, more research in LMIC and particularly in refugee camps is needed to adequately represent the experience realm of the vast majority of refugee youth worldwide.

4.2. Practical implications

Factors on multiple socio-ecological levels contribute to risk and resilience among refugee youth. Consequently, practical efforts aiming to support this vulnerable group's mental health should be integrated across these levels and target several factors. Existing interventions and

challenges related to the delivery and implementation of mental health services for refugee youth in HIC and LMIC have been reviewed and discussed recently (Eruyar et al., 2018; Fazel & Betancourt, 2018; Hodes & Vostanis, 2018). At this point we briefly present what we consider direct practical implications of the contributing factors with the best current evidence base.

The pervasive impact of pre-migration war trauma calls for trauma-focused treatments such as narrative exposure therapy for children (Ruf et al., 2010) and trauma-focused cognitive behavioral therapy (Unterhitzenberger, Wintersohl, Lang, König, & Rosner, 2019). Early screening for mental health problems and established factors contributing to mental health risk shortly after resettlement and regular follow-ups for vulnerable children could help to quickly introduce children to existing service programs and prevent the development of late-onset disorders. On a policy level, governments and international organizations should make any effort to protect children from exposure to violent conflicts and wars in the countries of origin if international agreements such as the United Nation's Convention on the Rights of the Child shall have any meaning. On a family level, the findings further suggest parents` mental health and parenting as key targets for interventions, which need to be tailored both to the cultural background of families and to the demands of the specific setting. Moreover, fast reunification of youth with their parents and other family members needs to be prioritized by authorities and organizations. Within children's exosystem, schools are not only important in terms of formal learning, but they are also hubs for social relationships with peers and friends. Educational authorities should consider activities and programs in the school setting that encourage social support and cohesion among peers. The post-migration challenges refugee youth and their families face in HIC may often be directly modifiable by policy makers. This includes, for example, the provision of high-support living arrangements for unaccompanied youth as well as the swift, yet careful and transparent, resolution of asylum claims. The potentially beneficial impact of an integrative acculturation style may be promoted through targeted activities on a family, school and community level, which aid refugee youth to adopt elements of the host culture and at the same time maintain bonds to their heritage culture's traditions and values.

4.3. Limitations of review

First, owing to the marked heterogeneity of included studies in terms of the study designs, populations and measures used, we were not able to conduct a meta-analysis of the evidence. Second, we only included quantitative studies in our review. However, we emphasize that qualitative research is important to gain further insights into refugee youth's perspectives and to capture aspects that may be missed by quantitative approaches. Third, although our strict application of inclusion and exclusion criteria probably increased the validity of the findings, we also had to exclude studies with interesting findings.

5. Conclusions

Exposure to violent conflict, flight and the challenges of resettlement can adversely affect refugee youth's mental health and well-being. However, risk and resilience is determined by a complex interplay of various factors in youth's socio-ecological environment at different stages of their life experience. Although research has provided valuable insights, there is still much to learn about the conditions that shape refugee children's adjustment. More longitudinal studies that take into account moderating and mediating factors on different contextual levels are needed. In the meantime, evidence on established factors contributing to risk (exposure to war-related violence, female gender, caregivers` mental health problems and parenting, acculturative stress and discrimination) and protection (family cohesion, school connectedness, peer support, integrative acculturation style) has to be transferred to practice by developing and evaluating interventions and by informing policy. This serves both to prevent detrimental long-term consequences to the well-being of refugee youth and to contribute to peaceful and prosperous societies characterized by diversity, solidarity and mutual respect.

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Contributors

FS and TH designed the study. FS and TH conducted the literature search and study selection. FS and EK rated study quality. FS wrote the first draft of the manuscript and all authors contributed to and have approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Abu-Rayya, H. M., & Sam, D. L. (2017). Is integration the best way to acculturate? A Reexamination of the bicultural-adaptation relationship in the "ICSEY dataset" using the Bilineal method. *Journal of Cross-Cultural Psychology, 48*(3), 287–293. https://doi.org/10.1177/0022022116685846.

Ahmad, I., Smetana, J. G., & Klimstra, T. (2015). Maternal monitoring, adolescent disclosure, and adolescent adjustment among Palestinian refugee youth in Jordan. *Journal of Research on Adolescence*. https://doi.org/10.1111/jora.12133.

Beiser, M., & Hou, F. (2016). Mental health effects of Premigration trauma and Postmigration discrimination on refugee youth in Canada. *The Journal of Nervous and Mental Disease, 204*(6), 464–470. https://doi.org/10.1097/NMD.0000000000000516.

Beni Yonis, O., Khader, Y., Jarboua, A., Al-Bsoul, M. M., Al-Akour, N., Alfaqih, M. A., … Amarneh, B. (2019). Post-traumatic stress disorder among Syrian adolescent refugees in Jordan. *Journal of Public Health (Oxford, England)*, (March)https://doi.org/10.1093/pubmed/fdz026.

Berry, J. W. (2005). Acculturation: Living successfully in two cultures. *International Journal of Intercultural Relations, 29*(6 SPEC. ISS), 697–712. https://doi.org/10.1016/j.ijintrel.2005.07.013.

Betancourt, T. S., Borisova, I., Williams, T. P., Meyers-Ohki, S. E., Rubin-Smith, J. E., Annan, J., & Kohrt, B. A. (2013). Research review: Psychosocial adjustment and mental health in former child soldiers - a systematic review of the literature and recommendations for future research. *Journal of Child Psychology and Psychiatry, and Allied Disciplines, 54*, 17–36. https://doi.org/10.1111/j.1469-7610.2012.02620.x. January.

Betancourt, T. S., & Khan, K. T. (2008). The mental health of children affected by armed conflict: Protective processes and pathways to resilience. *International Review of Psychiatry, 20*(3), 317–328. https://doi.org/10.1080/09540260802090363.

Betancourt, T. S., Salhi, C., Buka, S., Leaning, J., Dunn, G., & Country, F. (2012). Connectedness, social support and internalising emotional and behavioural problems in adolescents displaced by the Chechen conflict NIH public access. *Disasters, 36*(4), 635–655. https://doi.org/10.1111/j.1467-7717.2012.01280.x.

Betancourt, T. S., Yudron, M., Wheaton, W., & Smith-Fawzi, M. C. (2012). Caregiver and adolescent mental health in ethiopian kunama refugees participating in an emergency education program. *Journal of Adolescent Health, 51*(4), 357–365. https://doi.org/10.1016/j.jadohealth.2012.01.001.

Braun-Lewensohn, O., & Al-Sayed, K. (2018). Syrian adolescent refugees: How do they cope during their stay in refugee camps? *Frontiers in Psychology, 9*. https://doi.org/10.3389/fpsyg.2018.01258.

Bronfenbrenner, U. (1979). *The ecology of human development : Experiments by nature and design*. Cambridge: Harvard University Press.

Bronstein, I., Montgomery, P., & Dobrowolski, S. (2012). PTSD in asylum-seeking male adolescents from Afghanistan. *Journal of Traumatic Stress, 25*(5), 551–557. https://doi.org/10.1002/jts.21740.

Bronstein, I., Montgomery, P., & Ott, E. (2013). Emotional and behavioural problems amongst afghan unaccompanied asylum-seeking children: Results from a large-scale cross-sectional study. *European Child & Adolescent Psychiatry, 22*(5), 285–294. https://doi.org/10.1007/s00787-012-0344-z.

Bryant, R. A., Edwards, B., Creamer, M., O'Donnell, M., Forbes, D., Felmingham, K. L., … Hadzi-Pavlovic, D. (2018). The effect of post-traumatic stress disorder on refugees' parenting and their children's mental health: A cohort study. *The Lancet Public Health, 3*(5), e249–e258. https://doi.org/10.1016/S2468-2667(18)30051-3.

Buchanan, Z. E., Abu-Rayya, H. M., Kashima, E., Paxton, S. J., & Sam, D. L. (2018). Perceived discrimination, language proficiencies, and adaptation: Comparisons between refugee and non-refugee immigrant youth in Australia. *International Journal of Intercultural Relations*. https://doi.org/10.1016/j.ijintrel.2017.10.006.

Catani, C. (2018). Mental health of children living in war zones: a risk and protection perspective. *World Psychiatry, 17*(1), 104–105. https://doi.org/10.1002/wps.20496.

Çeri, V., & Nasıroğlu, S. (2018). The number of war-related traumatic events is associated with increased behavioural but not emotional problems among Syrian refugee children years after resettlement. *Archives of Clinical Psychiatry, 45*(4), 100–105. https://doi.org/10.1590/0101-60830000000167.

Clukay, C. J., Dajani, R., Hadfield, K., Quinlan, J., Panter-Brick, C., & Mulligan, C. J. (2019). Association of MAOA genetic variants and resilience with psychosocial stress: A longitudinal study of Syrian refugees. *PLoS One, 14*(7), Article e0219385. https://doi.org/10.1371/journal.pone.0219385.

Correa-Velez, I., Gifford, S. M., & Barnett, A. G. (2010). Longing to belong: Social inclusion and wellbeing among youth with refugee backgrounds in the first three years in Melbourne, Australia. *Social Science & Medicine, 71*(8), 1399–1408. https://doi.org/10.1016/j.socscimed.2010.07.018.

Correa-Velez, I., Gifford, S. M., & McMichael, C. (2015). The persistence of predictors of wellbeing among refugee youth eight years after resettlement in Melbourne, Australia. *Social Science & Medicine, 142*, 163–168. https://doi.org/10.1016/j.socscimed.2015.08.017.

d'Abreu, A., Castro-Olivo, S., & Ura, S. K. (2019). Understanding the role of acculturative stress on refugee youth mental health: A systematic review and ecological approach to assessment and intervention. *School Psychology International, 40*(2), 107–127. https://doi.org/10.1177/0143034318822688.

El Baba, R., & Colucci, E. (2018). Post-traumatic stress disorders, depression, and anxiety in unaccompanied refugee minors exposed to war-related trauma: A systematic review. *International Journal of Culture and Mental Health, 11*(2), 194–207. https://doi.org/10.1080/17542863.2017.1355929.

Elbedour, S., ten Bensel, R., & Bastien, D. T. (1993). Ecological integrated model of children of war: Individual and social psychology. *Child Abuse and Neglect, 17*(6), 805–819. https://doi.org/10.1016/S0145-2134(08)80011-7.

Elklit, A., Ostergard Kjaer, K., Lasgaard, M., & Palic, S. (2012). Social support, coping and posttraumatic stress symptoms in young refugees. *Torture : Quarterly Journal on Rehabilitation of Torture Victims and Prevention of Torture, 22*(1), 11–23.

Eruyar, S., Huemer, J., & Vostanis, P. (2018). Review: How should child mental health services respond to the refugee crisis? *Child and Adolescent Mental Health, 23*(4), 303–312. https://doi.org/10.1111/camh.12252.

Eruyar, S., Maltby, J., & Vostanis, P. (2018). Mental health problems of Syrian refugee children: The role of parental factors. *European Child & Adolescent Psychiatry*, (0123456789)https://doi.org/10.1007/s00787-017-1101-0.

Eruyar, S., Maltby, J., & Vostanis, P. (2020). How do Syrian refugee children in Turkey perceive relational factors in the context of their mental health? *Clinical Child Psychology and Psychiatry, 25*(1), 260–272. https://doi.org/10.1177/1359104519882758.

Eurostat. (2020). *Asylum statistics explained. Retrieved April 14, 2020*. From https://ec.europa.eu/eurostat/statistics-explained/index.php/Asylum_statistics.

Fazel, M., & Betancourt, T. S. (2018). Preventive mental health interventions for refugee children and adolescents in high-income settings. *The Lancet Child and Adolescent Health, 2*(2), 121. https://doi.org/10.1016/S2352-4642(17)30147-5.

Fazel, M., Reed, R. V., Panter-Brick, C., & Stein, A. (2012). Mental health of displaced and refugee children resettled in high-income countries: Risk and protective factors. *The Lancet, 379*(9812), 266–282. https://doi.org/10.1016/S0140-6736(11)60051-2.

Flink, I. J. E., Restrepo, M. H., Blanco, D. P., Ortegon, M. M., Enriquez, C. L., Beirens, T. M. J., & Raat, H. (2013). Mental health of internally displaced preschool children: A cross-sectional study conducted in Bogota, Colombia. *Social Psychiatry and Psychiatric Epidemiology, 48*(6), 917–926. https://doi.org/10.1007/s00127-012-0611-9.

Giordano, F., Cipolla, A., Ragnoli, F., & Bruno, F. B. (2019). Transit migration and trauma: The detrimental effect of interpersonal trauma on Syrian children in transit in Italy. *Psychological Injury and Law, 12*(1, SI), 76–87.

Goosen, S., Stronks, K., & Kunst, A. E. (2014). Frequent relocations between asylum-seeker centres are associated with mental distress in asylum-seeking children: A longitudinal medical record study. *International Journal of Epidemiology, 43*(1), 94–104. https://doi.org/10.1093/ije/dyt233.

Gormez, V., Kılıç, H. N., Orengul, A. C., Demir, M. N., Demirlikan, Ş., Demirbaş, S., … Semerci, B. (2018). Psychopathology and associated risk factors among forcibly displaced Syrian children and adolescents. *Journal of Immigrant and Minority Health, 20*(3), 529–535. https://doi.org/10.1007/s10903-017-0680-7.

Hodes, M., & Vostanis, P. (2018). Practitioner Review: Mental health problems of refugee children and adolescents and their management. *Journal of Child Psychology and Psychiatry, 60*(7). https://doi.org/10.1111/jcpp.13002. jcpp.13002.

Jakobsen, M., DeMott, M. A. M., Wentzel-Larsen, T., & Heir, T. (2017). The impact of the asylum process on mental health: A longitudinal study of unaccompanied refugee minors in Norway. *BMJ Open, 7*, 015157. https://doi.org/10.1136/bmjopen-2016-015157.

Javanbakht, A., Rosenberg, D., Haddad, L., & Arfken, C. L. (2018). Mental health in Syrian refugee children resettling in the United States: War trauma, migration, and the role of parental stress. *Journal of the American Academy of Child and Adolescent Psychiatry, 57*(3), 209–211. e2 https://doi.org/10.1016/j.jaac.2018.01.013.

Jensen, T. K., Skar, A.-M. S., Andersson, E. S., & Birkeland, M. S. (2019). Long-term mental health in unaccompanied refugee minors: Pre- and post-flight predictors. *European Child & Adolescent Psychiatry*, 1–12. https://doi.org/10.1007/s00787-019-01340-6.

Jensen, T. K., Skårdalsmo, E. M., & Fjermestad, K. W. (2014). Development of mental health problems - a follow-up study of unaccompanied refugee minors. *Child and Adolescent Psychiatry and Mental Health, 8*(1), 29. https://doi.org/10.1186/1753-2000-8-29.

Karam, E. G., Fayyad, J. A., Farhat, C., Pluess, M., Haddad, Y. C., Tabet, C. C., … Kessler, R. C. (2019). Role of childhood adversities and environmental sensitivity in the development of post-traumatic stress disorder in war-exposed Syrian refugee children and adolescents. *The British Journal of Psychiatry, 214*(06), 354–360. https://doi.org/10.1192/bjp.2018.272.

Keles, S., Friborg, O., Idsøe, T., Sirin, S., & Oppedal, B. (2016a). Depression among unaccompanied minor refugees: The relative contribution of general and acculturation-specific daily hassles. *Ethnicity and Health, 21*(3), 300–317. https://doi.org/10.1080/13557858.2015.1065310.

Keles, S., Friborg, O., Idsøe, T., Sirin, S., & Oppedal, B. (2016b). Resilience and acculturation among unaccompanied refugee minors. *International Journal of Behavioral Development, 42*(1), 52–63. https://doi.org/10.1177/0165025416658136.

Khamis, V. (2019). Posttraumatic stress disorder and emotion dysregulation among Syrian refugee children and adolescents resettled in Lebanon and Jordan. *Child Abuse and Neglect, 89*, 29–39. https://doi.org/10.1016/j.chiabu.2018.12.013.

Khawaja, N. G., Ibrahim, O., & Schweitzer, R. D. (2017). Mental wellbeing of students from refugee and migrant backgrounds: The mediating role of resilience. *School Mental Health, 9*(3), 284–293. https://doi.org/10.1007/s12310-017-9215-6.

Kien, C., Sommer, I., Faustmann, A., Gibson, L., Schneider, M., Krczal, E., … Gartlehner, G. (2019). Prevalence of mental disorders in young refugees and asylum seekers in European Countries: a systematic review. *European Child & Adolescent Psychiatry*. https://doi.org/10.1007/s00787-018-1215-z.

Kim, Y. J., Cho, Y.-A., & Kim, H. A. (2015). A mediation effect of Ego resiliency between stresses and mental health of north Korean refugee youth in South Korea. *Child and Adolescent Social Work Journal, 32*(5), 481–490. https://doi.org/10.1007/s10560-015-0385-5.

Lambert, J. E., Holzer, J., & Hasbun, A. (2014). Association between Parents' PTSD severity and Children's psychological distress: A meta-analysis. *Journal of Traumatic Stress, 27*, 9–17. https://doi.org/10.1002/jts.21891.

Lau, W., Silove, D., Edwards, B., Forbes, D., Bryant, R., McFarlane, A., … O'Donnell, M. (2018). Adjustment of refugee children and adolescents in Australia: Outcomes from wave three of the building a new life in Australia study. *BMC Medicine, 16*(157). https://doi.org/10.1186/s12916-018-1124-5.

Lee, M., Lee, E.-S., Jun, J. Y., & Park, S. (2020). The effect of early trauma on north Korean refugee youths' mental health: Moderating effect of emotional regulation strategies. *Psychiatry Research, 287*. https://doi.org/10.1016/j.psychres.2019.112707.

Li, S. S. Y., Liddell, B. J., & Nickerson, A. (2016). The relationship between Post-migration stress and psychological disorders in refugees and asylum seekers. *Current Psychiatry Reports, 18*, 1–9. https://doi.org/10.1007/s11920-016-0723-0.

Lincoln, A. K., Lazarevic, V., White, M. T., & Ellis, B. H. (2016). The impact of acculturation style and acculturative hassles on the mental health of Somali adolescent refugees. *Journal of Immigrant and Minority Health, 18*(4), 771–778. https://doi.org/10.1007/s10903-015-0232-y.

Lustig, S. L., Kia-Keating, M., Knight, W. G., Geltman, P., Ellis, H., Kinzie, J. D., … N. (2004). Review of child and adolescent refugee mental health. *Journal of the American Academy of Child and Adolescent Psychiatry, 43*(1), 24–36. https://doi.org/10.1097/00004583-200401000-00012.

Luthar, S. S., Cicchetti, D., & Becker, B. (2001). The construct of resilience: A critical evaluation and guidelines for future work. *Child Development, 71*(3), 543–562. https://doi.org/10.1038/jid.2014.371.

Mace, A. O., Mulheron, S., Jones, C., & Cherian, S. (2014). Educational, developmental and psychological outcomes of resettled refugee children in Western Australia: A review of School of Special Educational Needs: Medical and Mental Health input. *Journal of Paediatrics and Child Health, 50*(12). https://doi.org/10.1111/jpc.12674.

MacLean, S. A., Agyeman, P. O., Walther, J., Singer, E. K., Baranowski, K. A., & Katz, C. L. (2019). Mental health of children held at a United States immigration detention center. *Social Science & Medicine, 230*, 303–308. https://doi.org/10.1016/J.SOCSCIMED.2019.04.013.

McGregor, L. S., Melvin, G. A., & Newman, L. K. (2015). Familial separations, coping styles, and PTSD symptomatology in resettled refugee youth. *Journal of Nervous and Mental Disease, 203*(6), 431–438. https://doi.org/10.1097/NMD.0000000000000312.

McLeod, B. D., Weisz, J. R., & Wood, J. J. (2007). Examining the association between parenting and childhood depression: A meta-analysis. *Clinical Psychology Review, 27*(8), 986–1003. https://doi.org/10.1016/j.cpr.2007.03.001.

Meyer, S., Steinhaus, M., Bangirana, C., Onyango-Mangen, P., & Stark, L (2017). The influence of caregiver depression on adolescent mental health outcomes: Findings from refugee settlements in Uganda. *BMC Psychiatry, 17*(1), 1–10. https://doi.org/10.1186/s12888-017-1566-x.

Meyer, S., Yu, G., Hermosilla, S., & Stark, L. (2017). Latent class analysis of violence against adolescents and psychosocial outcomes in refugee settings in Uganda and Rwanda. *Global Mental Health, 4*, e19. https://doi.org/10.1017/gmh.2017.17.

Meyer, S., Yu, G., Rieders, E., & Stark, L. (2020). Child labor, sex and mental health outcomes amongst adolescent refugees. *Journal of Adolescence, 81*, 52–60. https://doi.org/10.1016/j.adolescence.2020.04.002.

Miller, K. E., & Rasmussen, A. (2010). War exposure, daily stressors, and mental health in conflict and post-conflict settings: Bridging the divide between trauma-focused and psychosocial frameworks. *Social Science & Medicine, 70*(1), 7–16. https://doi.org/10.1016/j.socscimed.2009.09.029.

Mitra, R., & Hodes, M. (2019). Prevention of psychological distress and promotion of resilience amongst unaccompanied refugee minors in resettlement countries. *Child: Care, Health and Development, 45*(2), 198–215. https://doi.org/10.1111/cch.12640.

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine, 6*(7). https://doi.org/10.1371/journal.pmed.1000097.

Mohwinkel, L.-M., Nowak, A. C., Kasper, A., & Razum, O. (2018). Gender differences in the mental health of unaccompanied refugee minors in Europe: A systematic review. *BMJ Open, 8*(7), Article e022389. https://doi.org/10.1136/bmjopen-2018-022389.

Müller, L. R. F., Büter, K. P., Rosner, R., & Unterhitzenberger, J. (2019). Mental health and associated stress factors in accompanied and unaccompanied refugee minors resettled in Germany: A cross-sectional study. *Child and Adolescent Psychiatry and Mental Health, 13*(1), 1–13. https://doi.org/10.1186/s13034-019-0268-1.

Müller, L. R. F., Gossmann, K., Hartmann, F., Büter, K. P., Rosner, R., & Unterhitzenberger, J. (2019). 1-year follow-up of the mental health and stress factors in asylum-seeking children and adolescents resettled in Germany. *BMC Public Health, 19*(1), 908. https://doi.org/10.1186/s12889-019-7263-6.

Nasıroğlu, S., & Çeri, V. (2016). Posttraumatic stress and depression in Yazidi refugees. *Neuropsychiatric Disease and Treatment, 12*, 2941–2948. https://doi.org/10.2147/NDT.S119506.

Nasıroğlu, S., Çeri, V., Erkorkmaz, Ü., & Semerci, B. (2018). Determinants of psychiatric disorders in children refugees in Turkey's Yazidi refugee camp. *Psychiatry and Clinical Psychopharmacology, 28*(3), 291–299. https://doi.org/10.1080/24750573.2017.1422958.

Neuner, F., Schauer, M., Karunakara, U., Klaschik, C., Robert, C., & Elbert, T. (2004). Psychological trauma and evidence for enhanced vulnerability for posttraumatic stress disorder through previous trauma among West Nile refugees. *BMC Psychiatry, 4*, 34. https://doi.org/10.1186/1471-244X-4-34.

Nicolai, S., & Triplehorn, C. (2003). *The role of education in protecting children in conflict.* London: Humanitarian Practice Network.

O'Higgins, A., Ott, E. M., & Shea, M. W. (2018). What is the impact of placement type on educational and health outcomes of unaccompanied refugee minors? A systematic review of the evidence. *Clinical Child and Family Psychology Review, 21*(3), 354–365. https://doi.org/10.1007/s10567-018-0256-7.

Oppedal, B., & Idsoe, T. (2012). Conduct problems and depression among unaccompanied refugees: The association with pre-migration trauma and acculturation. *Anales de Psicologia, 28*(3), 683–694. https://doi.org/10.6018/analesps.28.3.155981.

Oppedal, B., & Idsoe, T. (2015). The role of social support in the acculturation and mental health of unaccompanied minor asylum seekers. *Scandinavian Journal of Psychology, 56*(2), 203–211. https://doi.org/10.1111/sjop.12194.

Oppedal, B., Özer, S., & Şirin, S. R. (2018). Traumatic events, social support and depression: Syrian refugee children in Turkish camps. *Vulnerable Children and Youth Studies, 13*(1), 46–59. https://doi.org/10.1080/17450128.2017.1372653.

Park, S., Kim, S. Y., Lee, E.-S., & Jun, J. Y. (2019). Factors related to change in depression among north Korean refugee youths in South Korea. *International Journal of Environmental Research and Public Health, 16*(23).

Park, S., Lee, M., & Jeon, J. Y. (2017). Factors affecting depressive symptoms among north korean adolescent refugees residing in South Korea. *International Journal of Environmental Research and Public Health, 14*(8). https://doi.org/10.3390/ijerph14080912.

Reavell, J., & Fazil, Q. (2017). The epidemiology of PTSD and depression in refugee minors who have resettled in developed countries. *Journal of Mental Health, 26*(1), 74–83. https://doi.org/10.1080/09638237.2016.1222065.

Reed, R. V., Fazel, M., Jones, L., Panter-Brick, C., & Stein, A. (2012). Mental health of displaced and refugee children resettled in low-income and middle-income countries: Risk and protective factors. *The Lancet, 379*(9812), 250–265. https://doi.org/10.1016/S0140-6736(11)60050-0.

Ross, L. E., Grigoriadis, S., Mamisashvili, L., Koren, G., Steiner, M., Dennis, C.-L., … Mousmanis, P. (2011). Quality assessment of observational studies in psychiatry: An example from perinatal psychiatric research. *International Journal of Methods in Psychiatric Research, 20*(4), 224–234. https://doi.org/10.1002/mpr.356.

Ruf, M., Schauer, M., Neuner, F., Catani, C., Schauer, E., & Elbert, T. (2010). Narrative exposure therapy for 7- to 16-year-olds: A randomized controlled trial with traumatized refugee children. *Journal of Traumatic Stress, 23*(4), 437–445. https://doi.org/10.1002/jts.20548.

Samara, M., El Asam, A., Khadaroo, A., & Hammuda, S. (2019). Examining the psychological well-being of refugee children and the role of friendship and bullying. *The British Journal of Educational Psychology*. https://doi.org/10.1111/bjep.12282.

Sapmaz, Ş. Y., Tanrıverdi, B. U., Öztürk, M., Gözaçanlar, Ö., Ülker, G. Y., & Özkan, Y. (2017). Immigration-related mental health disorders in refugees 5–18 years old living in Turkey. *Neuropsychiatric Disease and Treatment, 13*, 2813–2821. https://doi.org/10.2147/NDT.S150592.

Sierau, S., Schneider, E., Nesterko, Y., & Glaesmer, H. (2018). Alone, but protected? Effects of social support on mental health of unaccompanied refugee minors. *European Child & Adolescent Psychiatry, 28*(6), 769–780. https://doi.org/10.1007/s00787-018-1246-5.

Silove, D., Ventevogel, P., & Rees, S. (2017). The contemporary refugee crisis: An overview of mental health challenges. *World Psychiatry, 16*(2), 130–139. https://doi.org/10.1002/wps.20438.

Sim, A., Bowes, L., & Gardner, F. (2018). Modeling the effects of war exposure and daily stressors on maternal mental health, parenting, and child psychosocial adjustment: A cross-sectional study with Syrian refugees in Lebanon. *Global Mental Health, 5*. https://doi.org/10.1017/gmh.2018.33.

Sleijpen, M., van der Aa, N., Mooren, T., Laban, C. J., & Kleber, R. J. (2019). The moderating role of individual resilience in refugee and Dutch adolescents after trauma. *Psychological Trauma: Theory, Research, Practice, and Policy*. https://doi.org/10.1037/tra0000450.

Smetana, J. G., & Ahmad, I. (2018). Heterogeneity in perceptions of parenting among Arab refugee adolescents in Jordan. *Child Development, 89*(5), 1786–1802. https://doi.org/10.1111/cdev.12844.

Smid, G. E., Lensvelt-Mulders, G. J. L. M., Knipscheer, J. W., Gersons, B. P. R., & Kleber, R. J. (2011). Late-onset PTSD in unaccompanied refugee minors: Exploring the predictive utility of depression and anxiety symptoms. *Journal of Clinical Child & Adolescent Psychology, 40*(5), 742–755. https://doi.org/10.1080/15374416.2011.597083.

Tam, S. Y., Houlihan, S., & Melendez-Torres, G. J. (2017). A systematic review of longitudinal risk and protective factors and correlates for posttraumatic stress and its natural history in forcibly displaced children. *Trauma, Violence & Abuse, 18*(4), 377–395. https://doi.org/10.1177/1524838015622437.

Tozer, M., Khawaja, N. G., & Schweitzer, R. (2018). Protective factors contributing to wellbeing among refugee youth in Australia. *Journal of Psychologists and Counsellors in Schools, 28*(1), 66–83. https://doi.org/10.1017/jgc.2016.31.

UNHCR. (2019). *Global trends: Forced displacement in 2018*. Geneva: United Nations High Commissioner for Refugees.

Unterhitzenberger, J., Wintersohl, S., Lang, M., König, J., & Rosner, R. (2019). Providing manualized individual trauma-focused CBT to unaccompanied refugee minors with uncertain residence status: A pilot study. *Child and Adolescent Psychiatry and Mental Health, 13*(1). https://doi.org/10.1186/s13034-019-0282-3.

Vervliet, M., Lammertyn, J., Broekaert, E., & Derluyn, I. (2014). Longitudinal follow-up of the mental health of unaccompanied refugee minors. *European Child & Adolescent Psychiatry, 23*(5), 337–346. https://doi.org/10.1007/s00787-013-0463-1.

Vervliet, M., Meyer Demott, M. A., Jakobsen, M., Broekaert, E., Heir, T., & Derluyn, I. (2014). The mental health of unaccompanied refugee minors on arrival in the host country. *Scandinavian Journal of Psychology, 55*(1), 33–37. https://doi.org/10.1111/sjop.12094.

Vossoughi, N., Jackson, Y., Gusler, S., & Stone, K. (2018). Mental health outcomes for youth living in refugee camps. *Trauma, Violence & Abuse, 19*(5), 528–542. https://doi.org/10.1177/1524838016673602.

Wiegersma, P. A., Stellinga-Boelen, A. A. M., & Reijneveld, S. A. (2011). Psychosocial problems in asylum seekers' children: The parent, child, and teacher perspective using the strengths and difficulties questionnaire. *Journal of Nervous and Mental Disease, 199*(2), 85–90. https://doi.org/10.1097/NMD.0b013e31820446d2.

World Bank. (2019). *World development indicators dataset. Washington, D.C.*

Yaylaci, F. T. (2018). Trauma and resilient functioning among Syrian refugee children. *Development and Psychopathology, 30*(5), 1923–1936. https://doi.org/10.1017/S0954579418001293.

Zevulun, D., Post, W. J., Zijlstra, A. E., Kalverboer, M. E., & Knorth, E. J. (2018). Migrant and asylum-seeker children returned to Kosovo and Albania: Predictive factors for social–emotional wellbeing after return. *Journal of Ethnic and Migration Studies, 44*(11), 1774–1796. https://doi.org/10.1080/1369183X.2017.1391076.

Zwi, K., Mares, S., Nathanson, D., Tay, A. K., & Silove, D. (2018). The impact of detention on the social–emotional wellbeing of children seeking asylum: A comparison with community-based children. *European Child & Adolescent Psychiatry, 27*(4), 411–422. https://doi.org/10.1007/s00787-017-1082-z.

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Review Article

A Narrative Review of the Assessment of Depression in Chronic Pain

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ABSTRACT

Objectives: This narrative review sought to explore the main critical issues in the assessment of depression in chronic pain and to identify self-report tools that can be reliably used for measuring it.
Design: Narrative review of the literature.
Methods: Articles were obtained through a search of three databases and a hand search of the references of full-text papers. Key results within the retrieved articles were summarized and integrated to address the review objectives.
Results: Criterion contamination, different ways to define and evaluate pain and depression across studies, variability in chronic pain samples and settings, pitfalls of diagnostic systems and self-reports, and reluctance to address (or difficulty of recognizing) depression in patients and healthcare providers emerged as main critical issues. The Beck Depression Inventory seems to be the more accurate tool to evaluate depression in chronic pain patients, while other instruments such as the Patient Health Questionnaire could be recommended for a rapid screening.
Conclusions: Assessment of depression comorbidity in chronic pain represents a challenge in both research and clinical practice; the choice and use of tests, as well as the score interpretation, require clinical reasoning.
Nursing Practice Implications: Nurses play an important role in screening for depression. Cognitive contents of depression should be carefully evaluated since somatic symptoms may be confusing in the chronic pain context. Some self-reports may be useful for rapid screening. It is also advisable to consider other relevant patient information in evaluating depression.

Chronic pain occurs in 19% of adult Europeans (Breivik et al., 2006) and in 20.4% of U.S. adults (Dahlhamer et al., 2018), and depression is a frequently associated comorbidity (Banks & Kerns, 1996). Epidemiological studies suggest that depression rates are higher among persons with chronic pain than those without chronic pain (Velly & Mohit, 2018). While in the adult general population the prevalence of depression is 7% in Europe (Eurostat, 2020) and 7.1 % in the U.S. (Substance Abuse & Mental Health Data Archive, 2017), an extensive European survey found a 21% prevalence rate of self-reported depression associated with chronic pain (Breivik et al., 2006), and a study on a representative U.S. community sample found that approximately 35% of participants with chronic pain also had comorbid depression (Miller & Cano, 2009). Moreover, evidence suggests that a larger proportion of chronic pain patients (CPPs) may develop a Major Depressive Disorder (MDD) compared to patients with various other chronic medical conditions (Banks & Kerns, 1996).

Comparing individuals with both major depression and chronic pain to those with major depression only, researchers have found that comorbid patients with both diseases reported longer duration of depression and more symptoms (Ohayon, 2004). Depression was also associated with higher levels of reported pain, increased functional impairment (Arnow et al., 2006), larger use of medical services (Wörz, 2003), other psychological factors such as anxiety and alexithymia (Castelnuovo et al., 2016), and less successful treatment outcomes (Burns et al., 1998). Particularly, depression, together with other psychological factors such as anxiety, anger, low self-efficacy, and catastrophizing, may predict worse outcomes of multidisciplinary, surgical, physical, and psychological treatment of pain (Castelnuovo et al., 2016). Finally, depression has been shown to predict disability better than pain intensity and duration (Rudy et al., 1988) and to predict chronicity when assessed during early presentation of pain (Burton et al., 1995; Castelnuovo et al., 2016).

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The Relationship Between Depression and Chronic Pain

Several studies investigated the frequent coexistence of depression and chronic pain to identify the nature of their relationship. From a biological perspective, depression and pain share neurobiological pathways (e.g., norepinephrine pathway, hypothalamo-pituitary-adrenal axis), neurotransmitters (5-HT), hormones (e.g., growth hormone), neurotrophic factors (e.g., nerve growth factor), and immune modulators (e.g., pro-inflammatory cytokines), which are implicated in the development of both conditions (Blackburn-Munro & Blackburn-Munro, 2001; Han & Pae, 2015). From a psychological perspective, several factors contribute to making depression so frequent in chronic pain: (1) personal vulnerabilities (e.g., negative processing biases) to the multiple stressors provided by chronic pain; (2) an increase of inactivity and avoidance behaviors together with a decrease of self-efficacy and positive external reinforcement; (3) learned helplessness or hopelessness derived from the perception of chronic pain as an incomprehensible, inescapable, and nonrelievable experience (Agüera et al., 2010; Banks & Kerns, 1996).

As observed by Fishbain et al. (1997), in many studies the direction of the relationship was from pain to depression, although in some cases episodes of depression occurred before the onset of pain. Other studies suggested a bidirectional association, such that each disease occurring first may increase the risk of the other subsequently (Chang et al., 2015; Gureje et al., 2001).

Given the non-negligible prevalence of depression comorbidity in chronic pain and its serious consequences for the prognosis of both conditions and patients' quality of life, an accurate evaluation of this condition is crucial. However, assessing depression in CPPs is complex and presents several critical aspects. For example, a review by Banks and Kerns (1996) observed that the reported prevalence of depression among CPPs varied widely, from 10% up to 100%, due to a variability in the definition and assessment of depression across studies. It was also observed that underlying mood disorders such as MDD are often unrecognized and thus not evaluated in CPPs (Agüera et al., 2010; Lee et al., 2018). Other authors (Pincus & Williams, 1999) observed that some measures of depression are "contaminated" by somatic symptoms reflecting the effect of pain itself rather than depressed mood. Therefore, although most studies on comorbidity of depression in chronic pain disregard the critical aspects of its evaluation, addressing this issue is necessary to reliably assess this clinical condition. In fact, this is a premise for being able to identify appropriate tools for measuring depression in CPPs. It is noteworthy that, despite depression representing a core symptom domain that should be evaluated in all chronic pain treatment trials (Dworkin et al., 2005) and in clinical practice (e.g., Hooten et al., 2013), there is little agreement on which tool should be used to measure it in chronic pain (Boomershine, 2012).

Objectives

The main objective of this literature review was to identify critical aspects in the assessment of depression in chronic pain. The most relevant aspects are summarized to highlight implications for clinicians looking for ways to screen for depression in CPPs, and suggestions for interpretation of results are given.

A secondary objective was to describe the self-report tools most frequently used to measure comorbid depression in the retrieved studies.

Methods

A systematic search strategy would have offered a more comprehensive literature coverage; however, the literature search was based on a narrative approach to provide a descriptive summary of studies that raised issues related to assessing comorbidity of depression in chronic pain (Newton et al., 2013).

The Results section has been organized into two parts. The first part synthetizes the main critical issues on assessing depression comorbidity in chronic pain that emerged from the retrieved studies. The second part reports some considerations on the principal self-report tools used in the retrieved studies to assess depression in chronic pain.

Search Strategy

The first and the last authors independently conducted a search for all listed publications, with no time limits, on PubMed, Scopus, and Google Scholar; the results of the search were then discussed with the second author. The following keywords in the title were used: "depress*" AND "chronic pain" OR "fibromyalgia" OR "migraine" OR "headache" OR musculoskeletal" OR "arthritis" AND "assess*" OR "measur*" OR "evaluat*". Additional relevant studies were identified from the reference lists of the retrieved papers.

Inclusion and Exclusion Criteria

Only articles published or in press in peer-reviewed journals, in the English language, and accessible in full text were considered. Additional inclusion criteria were studies conducted in adult populations focusing on critical issues related to the assessment of depression in chronic pain, or which investigated the psychometric characteristics of self-report tools to assess depression in chronic pain considering the critical issues of such assessment.

Exclusion criteria were dissertations, conference papers, commentaries and editorials, and other publications other than journal articles; studies on healthy people, children, adolescents, or elders; studies investigating chronic pain secondary to other diseases (e.g., cancer, respiratory disease, HIV, spinal cord injury), the efficacy of a given treatment, the association of depression and chronic pain with other variables; neurobiological, neurological, or genetic studies; studies on animal models.

Methods for Identifying Critical Issue and Self-Report Tools

The first and last authors independently scrutinized the selected articles to take note of the critical issues outlined by their authors, and they then identified relevant categories to group together articles that raised or discussed similar issues. The results of this process were discussed with the second author. The self-report tools used for assessing depression in each included study were also identified in order to address the secondary objective of this review.

Results

From the search conducted, a total of 2,463 studies were retrieved. After the removal of duplicates across databases, 2,180 studies were excluded by title based on inclusion/exclusion criteria. Subsequently, 39 studies were excluded by abstract, and the remaining 244 were evaluated in full text. Fifty-five studies were considered to satisfy the inclusion/exclusion criteria and were included in the review. An additional 11 studies were identified through hand-searching the reference lists of the included studies. This process resulted in a total of 66 relevant studies for inclusion in the review. The complete list of retrieved studies with a

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Table 1
Summary of Main Critical Issues Emerged From the Retrieved Papers

Critical issues	Studies addressing the issue
Variability in the definition and evaluation of depression and pain	Turner & Romano (1985); Abdel-Nasser et al. (1998); Frank et al. (1988); Williams (1998); Dersh, Polatin & Gatchel (2002); Dickens, McGowan, Clark-Carter, & Creed (2002); Sardá, Nicholas, Pimenta, & Asghari (2008); Matcham, Rayner, Steer, & Hotopf (2013); Amoozegar et al. (2017)
Variability in chronic pain samples and settings	Robinson, Hernandez, Dick, & Buchanan (1977); Romano & Turner (1985); Callahan, Kaplan, & Pincus (1991); Burckhardt, O'Reilly, Wiens, Clark, Campbell, & Bennett (1994); Dersh, Polatin, & Gatchel (2002); Dickens, McGowan, Clark-Carter, & Creed (2002); Morley, Williams, & Black (2002), Sardá, Nicholas, Pimenta, & Asghari (2008); Wong, Chen, Yap, Mak, Tam, & Fielding (2011); Matcham, Rayner, Steer, & Hotopf (2013); Scheidt et al. (2014); Amoozegar et al. (2017)
Reluctance to address or difficulty of recognizing depression	Robinson, Hernandez, Dick, & Buchanan (1977); Turner & Romano (1984); Romano & Turner (1985); Alarcon & Glover (1994); Ruoff (1996); Krug, Woods, & Mahowald (1997); Fuller-Thomson, Nimigon-Young, & Brennenstuhl (2012); Cocksedge, Shankar, & Simon (2016); Whiters, Gonzales, & Karpouzas (2017); Beebe & Utley (2018); Lee, Choi, Nahm, Yoon, & Lee (2018)
Criterion contamination	Romano & Turner (1985); Crisson, Keefe, Wilkins, Cook, & Muhlbaier (1986); Frank et al. (1988); Blalock, DeVellis, Brown, & Wallston (1989); Peck, Smith, & Ward (1989); Kaiser, Middaugh, Kee, Levin, & Berndt (1990); Callahan, Kaplan, & Pincus (1991); Pincus & Callahan (1993); Alarcon & Glover (1994); Burckhardt, O'Reilly, Wiens, Clark, Campbell, & Bennett (1994); Chibnall & Tait (1994); Holm, Penzien, Holroyd, & Brown (1994); Turk & Okifuji (1994); Novy, Nelson, Berry, & Averill (1995); Pincus, Griffith, Pearce, & Isenberg (1996); Geisser, Roth, & Robinson (1997); Krug, Woods, & Mahowald (1997); Suárez-Mendoza, Cardiel, Caballero-Uribe, Ortega-Soto, & Márquez-Marín (1997); Abdel-Nasser et al. (1998); Williams (1998); Pincus & Williams (1999); Wesley, Gatchel, Garofalo, & Polatin (1999); Rhee et al. (1999); Miles, McManus, Feinmann, Glover, Harrison, & Pearce (2001); Wilson, Mikail, D'Eon, & Minns (2001); Dersh, Polatin, & Gatchel (2002); Martens, Parker, Smarr, Hewett, Slaughter, & Walker (2003); Pincus, Williams, Vogel, & Field (2004); Taylor, Lovibond, Nicholas, Cayley, & Wilson (2005); Martens et al. (2006); Poole, Bramwell, & Murphy (2006); Harris & D'Eon (2008); Lee, Lin, Hsu, Cing-Chi, Yang, & Wen (2008); Sardá, Nicholas, Pimenta, & Asghari (2008); Pincus, Hassett, & Callahan (2009); Poole, Bramwell, & Murphy (2009); Poole, White, Blacke, Murphy, & Bramwell (2009); Corbière et al. (2011); Holmes, Christelis, & Arnold (2013); Lopez, Pierce, Gardner, & Hanson (2013); Matcham, Rayner, Steer, & Hotopf (2013); Surah, Baranidharan, & Morley (2014); Knaster, Estlander, Karlsson, Kaprio, & Kalso (2016); Masood, Salim, Nasim, Khalid, & Afzal (2017); Englbrecht et al. (2017); Fu et al. (2017); Whiters, Gonzales, & Karpouzas (2017)
Difficulty in differentiating between clinical depression and other pathological conditions or normal reactions to chronic pain	Haythornthwaite, Sieber, & Kerns (1991); Krug, Woods, & Mahowald (1997); Matcham, Rayner, Steer, & Hotopf (2013); Knaster, Estlander, Karlsson, Kaprio, & Kalso (2016); Rusu, Santos, & Pincus (2016)
Pitfalls of classification and diagnostic systems applied to chronic pain	Frank, Chaney, Clay, & Kay (1991); Williams & Richardson (1993); Estlander, Takala, & Verkasalo (1995); Williams (1998); Knaster, Estlander, Karlsson, Kaprio, & Kalso (2016)
Pitfalls related to the use of self-report tools	Kaiser, Middaugh, Kee, Levin, & Berndt (1990); Williams (1998); Pincus, Williams, Vogel, & Field (2004); Wong, Chen, Yap, Mak, Tam, & Fielding (2011); Lopez, Pierce, Gardner, & Hanson (2013); Hu & Ward (2017); Hitchon et al., 2020

description of their main objectives, critical issues addressed, and self-report tools used for assessing depression is provided as Supplementary Material (S1).

Critical Issues in the Assessment of Comorbid Depression

Seven main critical issues emerged from the retrieved papers. A summary is presented in Table 1.

Variability in the definition and evaluation of depression and pain

There was a high variability in the definition of depression and in methods used to evaluate it. A meta-analysis studies of rheumatoid arthritis found 40 different definitions of depression (Matcham et al., 2013). The term "depression" was used differently across studies to refer to a mood status that includes other affective symptoms, a symptomatology, or a syndrome, i.e., a condition of varying severity (Romano & Turner, 1985). Comorbid depression was assessed with different strategies, from structured clinical interviews to self-report instruments (Abdel-Nasser et al., 1998). The studies using structured interviews reported different subtypes of depression (from Major Depressive Disorder to Dysthymic Disorder), while those using self-reports defined depression using a variety of instruments and thresholds (Matcham et al., 2013).

The evaluation of a patient's pain condition and the different methods used, such as visual analogue scales, numerical rating scales, multidimensional questionnaires, or physical examinations, also influenced the assessment of pain-depression comorbidity (Romano & Turner, 1985). As a result, the extent to which clinically significant chronic pain complaints were associated with depression was not always adequately addressed.

Variability in chronic pain samples and settings

The heterogeneity of both the patients evaluated (e.g., with a single pain site, widespread pain, or specific syndromes) and the treatment settings considered (e.g., pain clinics or psychiatric services) was another source of variability in the evaluation of comorbid depression (Dersh et al., 2002). Different populations presented different chronic pain syndromes. For example, fibromyalgia was more frequent in the female population, and rheumatoid arthritis in older female adults. Particular types of medication used for chronic pain were found to affect depression prevalence levels (Matcham et al., 2013). Small sample sizes of studies and a failure to control for covariates such as pain intensity resulted in imprecision and variability of the prevalence estimates (Scheidt et al., 2014). Cultural differences across populations were also found to influence the assessment of comorbid depression. For example, it has been suggested that Asian populations tend to avoid extremes and select options from the midpoints of self-report scales in order to adhere to cultural virtues of moderation and nonjudgementalism (Wong et al., 2011). Moreover, the assessment of pain-depression comorbidity was influenced by different sociodemographic characteristics across samples, such as work status, level of education, and marital status, which affected the self-report measurement of depression (Callahan et al., 1991).

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Reluctance to address or difficulty of recognizing depression

The assessment of comorbid depression may be affected by a reluctance to address depression or an inability to recognize it, in both patients and healthcare providers. On the patient's side, conformity to the role of good patient and fear of being labelled "hypochondriac" or having psychological problems and being stigmatized or disbelieved about their account of pain may lead patients to minimize or even deny depressive and other psychological symptoms. Other patients have difficulty recognizing and verbally expressing emotional states such as depression or may tend to express them via somatic complaints (Alarcon & Glover, 1994). Patients may also be reluctant to introduce the issue with the physician because of time constraints, lack of provider continuity in public settings, or the limited availability of psychotherapy services in public settings, or because they believe that psychological concerns should be discussed with other providers. Ethnic or underserved populations may encounter additional barriers such as language (Romano & Turner, 1985; Withers et al., 2017). On the healthcare provider's side, further obstacles can include time constraints, inadequate referral services, and a lack of training or confidence in dealing with mental health issues (Withers et al., 2017).

Criterion contamination

A major problem in research and clinical practice is so-called "criterion contamination," an overlap of symptoms between chronic pain and depression to the point that it may not be possible to clearly differentiate them (Callahan et al., 1991). Chronic pain is associated with a range of somatic symptoms very similar to those included in contemporary diagnostic criteria for depression. For example, sleep disturbance, fatigue, and difficulty in concentrating had the greatest degree of overlap and were reported by 34%-53% of non-MDD patients with chronic pain (Wilson et al., 2001). Practical implications of such overlap of symptoms are not clear. Some have argued that the inclusion of somatic symptoms in questionnaires can inflate estimates of depression when screening for depression among CPPs (e.g., Williams & Richardson, 1993), while others have suggested that their inclusion is not confusing (Geisser et al., 1997). More recently, Englebrecht and colleagues (2017) stated that the overlap between chronic pain and somatic symptoms of depression neither interferes with nor contradicts the use of self-report tools to screen for depression in clinical practice. To handle the problem of contamination criteria, different approaches have been proposed, especially when depression is evaluated with questionnaires that allow to separately measure its multiple dimensions (Table 2).

Difficulty differentiating clinical depression from normal reactions to chronic pain

Criterion contamination might be also due to causes other than the overlap of somatic symptoms between chronic pain and depression. On the one hand, CPPs can acquire a clinically significant score on most depression measures by endorsing somatic items (e.g., sleep problems, fatigue, reduced activity). On the other hand, the pattern of item endorsement seems to differentiate CPPs from other psychiatric patients. In particular, patients with comorbid depression and chronic pain can present different patterns of items from other clinically depressed patients, because although distressed by pain and its effects on their lives, they might have not developed a negative view of themselves as worthless or guilty persons (Pincus & Williams, 1999; Poole et al., 2006). For this reason, some authors suggest distinguishing between traditional clinical depression and "pain-related distress," a complex mixture of emotional suffering frequently experienced by CPPs (Rusu et al., 2016). The difficulty of differentiating between a psychopathological condition and a normal reaction to a chronic and debilitating disease has emerged as another critical issue. An alternative proposed to address this issue was to diagnose a chronic adjustment disorder with depressed mood to help in choosing the appropriate treatment (Krug et al., 1997).

Pitfalls of classification and diagnostic systems applied to chronic pain

Another critical issue in the assessment of depression comorbidity in chronic pain is related to pitfalls of classification and diagnostic systems. One of the first psychiatric approaches applied to chronic pain was based on Kraepelin's dichotomic model, in which, in the absence of organic findings, both somatic and depressive symptoms were taken as indicative of an underlying mood disorder. This approach came to be considered unsatisfactory, with critics noting that it was theoretically defective, lacking in explanatory power, and patient-blaming (Williams, 1998). Although the DSM-5 system was redesigned to permit comorbidity, its criteria for depression continue to exclude somatic symptoms that are clearly and fully attributable to a general medical condition. However, the complex nature of chronic pain makes the decision difficult or even impossible, and the diagnosis often relies only on the examiner's clinical judgement (Knaster et al., 2016). In general, diagnostic systems tend to maximize discriminant validity, but chronic pain and depression seem to be related more dimensionally than hierarchically (Williams, 1998). Further, some authors note that even diagnostic manuals such as the DSM incorporate somatic symptoms as diagnostic criteria for depression, and hence their use reveals the same problem of criterion contamination encountered with self-report scales (Knaster et al., 2016; Williams & Richardson, 1993). In addition, the DSM-5 allows a wide combination of symptoms within MDD, and almost all symptoms have the same weight in guiding diagnostic decisions, so the clinical picture of depression may be heterogeneous and a diagnosis of MDD plausible even in the presence of very few cognitive symptoms (Frank et al., 1991; Knaster et al., 2016; Williams & Richardson, 1993).

Pitfalls related to the use of self-report tools

The assessment of depression comorbidity may be influenced also by some pitfalls related to the use of self-report tools in CPPs. First, there are very few depression measures and standardized norms specifically designed for chronic pain populations (Lopez et al., 2013; Pincus et al., 2004; Williams, 1998). Second, the response options of self-reports used for assessing depression in CPPs vary from neutral in mood to deeply depressed, with no positive dimensions specifically aimed at evaluating a positive outlook, which may be an important outcome of treatment for those without severe depression (Pincus et al., 2004). Third, items of questionnaires may not be equally specific indicators of depression in all persons. For example, Hu and Ward (2017) found that individuals with arthritis responded to items on the Center for Epidemiological Studies Depression Scale and of the Patient Health Questionnaire-9 similarly to persons without arthritis, despite the inclusion of somatic items in these scales. Fourth, there is little consensus on the optimal cutoff points for depression for each self-report used, and different studies reported different cutoff points using the same measure (Matcham et al., 2013). Some authors have suggested that adjustments to the cutoff points of screening instruments are required when these scales are applied to populations with specific chronic health conditions (Hitchon et al., 2020; Poole et al., 2009a). Other authors have noted that the optimal cutoffs may also depend on the setting and goals of the assessment. For example, Wong et al. (2011) found that lower cutoffs were more appropriate for patients of orthopedic services than those of pain clinics. Amoozegar et al. (2017) noted that a lower cutoff point may be more appropriate if the goal is to identify most depressed

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Table 2
Different Approaches Proposed to Handle the "Criterion Contamination" Problem

Approach	Limits of the approach and clinical considerations
Excluding somatic items from depression questionnaires (exclusive approach)	Some authors suggest it does not improve the accuracy in the identification of MDD and could even decrease it (Turk & Okifuji, 1994; Geisser et al., 1997; Wilson et al., 2001). The inclusion of somatic items is expected to lead to an overestimation of depression; excluding their contribution may lead to the opposite problem, i.e. an underestimation of depression (Wilson et al., 2001; Knaster et al., 2016). Although false-positive and false-negative diagnoses could be viewed as statistically comparable errors, they may have different clinical consequences. A false positive might result in the stigma of a diagnostic label and risks, side effects, and drawbacks of undergoing unnecessary treatment. On the other hand, a false negative may lead to patients with a potentially treatable episode of depression not receiving appropriate treatments. Hence for some authors the risks associated with a false negative diagnosis of MDD might outweigh that associated with a false positive diagnosis (Wilson et al., 2001; Knaster et al., 2016).
Including all items regardless of the possible confounding influence on pain followed by an accurate qualitative interpretation of them (inclusive approach)	Many overlapping symptoms between pain and depression (e.g., insomnia, difficulty concentrating) seem to maintain a discriminatory value because they occurred at much higher rates among CPPs with MDD (Wilson et al., 2011). It is thus important to analyze all dimensions of depression questionnaires, identifying the contribution of each dimension to the total score (Williams & Richardson, 1993; Poole et al. 2006; Corbière et al., 2011; Miles et al., 2001). Given the greater loading that somatic items may have on the total score of most depression questionnaires, it has been suggested to discriminate between symptoms caused by depression and those caused by pain or medication side effects (Corbière et al., 2011). However, the method used to determine the primary cause of symptoms (e.g. patients' attribution of causality, clinical judgement, direct physiological evidence) may influence the results (Wilson et al., 2001). Moreover, some authors suggest there is an intrinsic body/mind dualism in parsing the CPP's experience into independent parts attributable to psychological versus somatic causes. Lacking a clear medical origin, establishing that a somatic symptom has a psychological origin is problematic for the new DSM-5 as well (APA, 2013). The discussion of whether a somatic symptom has a medical or psychological origin resembles that of whether pain precedes depression or depression leads to pain, and cannot be solved with linear deterministic thinking (Wörz, 2003).
Substituting somatic items with nonsomatic alternatives (substitutive approach)	Some authors (Wilson et al., 2001) suggest using the alternative criteria proposed by Endicott (1984) for cancer patients. Changes in appetite or weight may be replaced by a fearfulness or depressed appearance in face or body posture, sleep disturbances by social withdrawal or decreased talkativeness, loss of energy or fatigue by brooding, self-pity, or pessimism, and diminished ability to concentrate or indecisiveness by a lack of reactivity to pleasant events. Notwithstanding, others (Taylor et al., 2005) have raised questions about the adequacy of this substitutive method because Endicott replaced some somatic items, but others may still be problematic. Moreover, this approach seems to identify much the same population as the inclusive approach (Wilson et al., 2001) and there is no consensus on which symptoms can be used as substitutes, nor the total number required (Holmes et al., 2013).
Aetiological approach	This approach requires judgement by the clinician as to whether symptoms are related to physical illness or depression. This method is supported by the DSM-5 approach, but has the disadvantage of reduced reliability implicit in making this judgement.
Raising the cutoff values	The optimal cutoff may vary depending on methodological and sample differences (e.g. diagnostic criteria used or pain duration; Wilson et al., 2001). For example, Wong et al. (2011) found low cutoff values more appropriate for patients of orthopedic services but not for pain clinic patients. Moreover, pain and depression are measured continuously rather than dichotomously in clinical practice. Under these circumstances, sensitivity/specificity indices and cutoffs have less clinical utility (Wong et al., 2011). Hence criterion contamination is a problem that cannot be solved solely by raising the cutoff values for depression questionnaires when used in CPPs (Williams & Richardson, 1993).

CPP = chronic pain patients; MDD = Major Depression Disorder

patients even at the cost of higher false positive cases, while a cutoff point with relatively equal sensitivity and specificity may be more appropriate if the goal is to identify a reasonable number of depression patients while avoiding a high number of false positive cases. Researchers also noted that pain and depression are measured continuously rather than dichotomously in clinical practice; hence, under these circumstances, sensitivity/specificity indices and cutoffs have less clinical utility and more clinical judgement is needed to interpret the results (Wong et al., 2011). Finally, Kaiser et al. (1990) observed that many self-report measures of depression dichotomously categorize patients as depressed or nondepressed, while an appropriate categorization should recognize a continuum of depressive symptomatology.

What Assessment Tools Could Be Reliably Used to Assess Comorbid Depression?

In the retrieved articles, the most-used tools for assessing depression included the Beck Depression Inventory (BDI; Beck et al., 1961; Beck et al., 1996; Beck et al., 2000; Beck & Beck, 1972; Burckhardt et al., 1994), the Center for Epidemiological Studies–Depression Scale (CES-D; Radloff, 1977), the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983), and the Patient Health Questionnaire-9 (PHQ-9; Kroenke, Spitzer & Williams, 2001), followed by occasional use of the Zung Self-Rating Depression Scale (ZSDS; Zung, 1965), the Depressive, Anxiety and Stress Scale (DASS; Lovibond & Lovibond, 1995), and the depression scale of the Minnesota Multiphasic Personality Inventory (MMPI; Colligan et al., 1983).

Beck Depression Inventory (BDI)

The BDI was developed by Beck et al. (1961) and revised (BDI-II) in response to changes introduced by the DSM-IV-TR to the diagnostic criteria of MDD (Beck et al., 1996) to self-report the severity of depressive symptomatology. It is the most used tool for assessing depression in the retrieved studies. Poole and colleagues (2009b) found that the concordance between the BDI-II and the Structured Clinical Interview (SCID; First et al., 1997) in identifying depressed patients in the chronic pain context was reasonably good (kappa = 0.60). Therefore, the authors suggested that, in situations where it is not possible to use the SCID (e.g., lack of time or trained personnel), the BDI-II may represent a good alternative. However, the validity of the BDI somatic items was often questioned, and the number of studies whose authors suggest excluding them when diagnosing depression in CPPs is almost the same as those against their exclusion (Callahan et al.,

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1991; Chibnall & Tait, 1994; Crisson et al., 1986; Geisser et al., 1997; Harris & D'Eon, 2008; Holm et al., 1994; Knaster et al., 2016; Lee et al., 2008; Miles et al., 2001; Peck et al., 1989; Suárez-Mendoza et al., 1997; Turk & Okifuji, 1994; Wesley et al., 1999; Williams & Richardson, 1993; Wilson et al., 2001). It has been suggested that BDI somatic items should be used with caution to assess depressive mood in CPPs because they may reflect difficulties caused by pain or related aspects such as pain medications. For example, items related to loss of energy, concentration difficulty or changes in sleep, appetite, and sexual desire may be influenced by the presence of pain or medications, rather than by a real mood deflection. Chronic pain may in fact impede refreshing sleep and result in daytime fatigue, which could be worsened by medications such as opioids and anticonvulsants. Item related to psychomotor retardation may reflect physical limitations in individuals' functioning, fear-avoidance beliefs, or the impact of pain or painkillers. Item related to anhedonia may be ambiguous since previously enjoyed activities may be more difficult for CPPs due to pain. Furthermore, pessimism can be related in CPPs to their feelings about pain and disability rather than to a negative view of life and the future typical of depression (Corbière et al., 2011; Poole et al., 2006; Taylor et al., 2005). Some authors (Poole et al., 2009) suggest a score of 22 to be the optimal cutoff for CPPs, providing 89% sensitivity, while others (Lopez et al., 2013) provide standardized scores to help clinicians interpreting CPPs' scores on the BDI-II. Beck and colleagues (2000) developed the Beck Depression Inventory-Fast Screen (BDI-FS), a seven-item tool derived from the original BDI-II to assess cognitive and affective dimensions of depression according to DSM-IV diagnostic criteria. The BDI-FS showed good psychometric properties, strong agreement with the BDI-II, and equal ability to detect clinical change in CPPs.

Center for epidemiological studies–depression scale (CES-D)

The CES-D is a 20-item self-report scale that emphasizes the affective component of depression, while the somatic component is under-represented. The CES-D items coincide only partially with the DSM criteria for MDD, with no items related to suicidal ideation, guilty feelings, agitation, or loss of interests. In studies of rheumatoid arthritis, the CES-D seemed to identify general psychological distress rather than depression (Martens et al., 2003; Rhee et al., 1999). Considerations across studies on the sensibility and specificity of the CES-D were contradictory. Turk and Okifuji (1994) considered the sensitivity and specificity of the CES-D in CPPs less than optimal. Geisser et al. (1997) found that the CES-D was able to discriminate CPPs with or without comorbid MDD as well as the BDI. However, better sensitivity of the CES-D was found compared to the BDI (81.8% vs. 68.2%), while the BDI showed better specificity (78.4% vs. 72.7%; Geisser et al., 1997). More recently (Wong et al. 2011), the CES-D demonstrated a higher specificity than the BDI, considering CPPs from an orthopedic clinic or from a pain clinic. The validity of the CES-D somatic items has also been questioned (Blalock et al., 1989; Callahan et al., 1991; Hu & Ward, 2017; Martens et al., 2003; Rhee et al., 1999; Turk & Okifuji, 1994). Some authors noted that in CPPs certain CES-D items, particularly those concerning appetite, fatigue, sleep, and energy, may reflect the presence of chronic pain regardless of psychological status (Pincus et al., 2009).

Hospital anxiety and depression scale (HADS)

The HADS was originally developed for the self-assessment of anxiety and depressive symptoms in nonpsychiatric hospitalized patients suffering from somatic pathologies (Zigmond & Snaith, 1983). To avoid criterion contamination, the HADS excludes any somatic indicator. Thus for depression it focuses on anhedonia and a lack of positive affectivity. As noted by Williams (1998), the HADS ignores somatic symptoms of depression but also some cognitive indicators, bringing into question to what extent it measures depression. According to Rusu and colleagues (2016), in the context of chronic pain, the HADS Depression scale could be more effective as a screening measure of general psychological distress rather than as a tool for the assessment of comorbid depression.

Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 (Kroenke et al., 2001) is a screening instrument for detecting MDD based on the DSM-IV diagnostic criteria. A shorter version including the first two items of the PHQ-9 was also developed (Kroenke et al., 2003). Amoozegar et al. (2017) found that the PHQ-9 performed well in migraine patients attending a headache clinic, while in a study of arthritis patients Hu and Ward (2017) reported that individuals with arthritis responded to the PHQ-9 items similarly to persons without arthritis, despite the inclusion of somatic items in this scale. In a study (Englbrecht et al., 2017) aimed to validate standard self-report questionnaires for the screening of depression in patients with rheumatoid arthritis, the PHQ-9 met most of the validity criteria, despite the BDI-II performed better and showed higher sensitivity and specificity.

Depressive, Anxiety, and Stress Scale (DASS)

The DASS (Lovibond & Lovibond, 1995) is a 42-item self-report questionnaire developed for assessing the core symptoms of depression, anxiety, and stress, excluding somatic items to address the criterion contamination issue. The Depression scale contains items that measure symptoms typically associated with dysphoric mood (e.g., sadness or worthlessness). A short version of this scale (DASS-21) was also developed (Lovibond & Lovibond, 1995). The DASS has been occasionally used to evaluate depressive symptomatology in the chronic pain context. A study by Taylor et al. (2005) suggested that, compared to the Zung Self-Rating Depression Scale, the DASS can give a more accurate assessment of depression severity in CPPs by avoiding the criterion contamination issue.

Zung Self-Rating Depression Scale (ZSDS)

The ZSDS is a short self-rated scale that assesses psychological and somatic symptoms of depression (Zung, 1965). The ZSDS has been occasionally used to evaluate depressive symptomatology in the retrieved studies. In the study by Turner and Romano (1984), the ZSDS showed good sensitivity and specificity in detecting major depression in CPPs. However, Estlander and colleagues (1995) suggested that items of increased heartbeats, losing weight, constipation, sleep problem, and fatigue were more related to the chronic pain experience than to depression. In addition, Taylor et al. (2005) found poor performance of the ZSDS somatic items and suggested that the DASS was better able to discriminate depressed from nondepressed patients in chronic pain populations.

Discussion

Based on this narrative review, the assessment of depression in chronic pain presents many critical issues, which emerged at various levels. It may be influenced or even hampered by certain patients' characteristics (e.g., fear of stigma) or by clinicians' characteristics (e.g., lack of confidence in dealing with mental health issues). The frequently reported reluctance of patients to reveal depression suggests that healthcare providers should actively seek to identify this condition rather than relying on the patient spontaneously reporting such information (Lee et al., 2018). Characteristics of the individual's pain condition, setting, or cultural context

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may be further influencing factors. Self-report tools used for assessing depression in chronic pain present pitfalls that make the assessment very complex. Depression questionnaires tend to have better sensitivity than specificity, and to give higher estimates than interview-based methods (Williams, 1998). However, some authors noted that the use of a standardized interview based on diagnostic criteria did not produce different results, since diagnostic systems share similar pitfalls to self-reports (Dickens et al., 2002). Trying to distinguish among discrete entities, many diagnostic systems poorly fit the chronic pain context (Williams, 1998). The DSM-5 approach recognizes that discrete narrow diagnostic categories are not able to capture clinical reality, symptom heterogeneity within disorders, or sharing of symptoms across disorders (American Psychiatric Association [APA], 2013). The DSM-5 represents an improvement on previous versions and other diagnostic systems; however, it still pathologizes what many consider a normal reaction or difficulty in adaptation to a persistent medical condition with dramatic effects on the individual's life (Williams & Schäfer, 2016). The difficulty of differentiating between clinical depression and other pathological conditions (e.g., adjustment sisorder, dysthymia) or normal reactions to a chronic and debilitating disease emerged as an issue also in the retrieved studies (Krug et al., 1997; Rusu et al., 2016; Wilson et al., 2001). However, a major challenge in the assessment of pain-depression comorbidity is so-called "criterion contamination." This problem is more studied in relation to self-reports (e.g., BDI), but it also affects the diagnostic systems since they similarly confound somatic and nonsomatic items (Williams & Richardson, 1993). Many approaches have been proposed to overcome criterion contamination (Table 3), but no one has clear advantages over the others (Holmes et al., 2013). To overcome the problem of symptom overlap, Knaster et al. (2016) proposed partly accepting the indistinct boundaries between chronic pain, distress, and depression.

The criterion contamination issue is frequently blamed in research, as it may lead to an overestimation of depression in CPPs. From a clinical viewpoint, it may have other consequences like influencing the understanding of what chronic pain is and what depression is by both patients and providers. For example, when depressive symptoms are not identified, the patient may mistakenly attribute their source to the pain disease (Whiters et al., 2017) and may look for inappropriate medical solutions. On the clinician's side, a physician—or even a psychologist—who believes that a chronic pain symptom is due to depression may cause the patient to feel disbelieved and stigmatized.

Finally, the criterion contamination issue recalls to us a common question in the literature on comorbidity between chronic pain and depression: that is, which disease occurs first. A number of hypotheses have been proposed, but a definitive answer remained elusive, and perhaps the dynamic and reinforcing interplay between pain and depression makes it useless to consider either condition independently of the other (Dersh et al., 2002). In a similar way, an excessive emphasis on criterion contamination (i.e., the effort to discern the primary root of a given symptom) might favor an unwarranted dualism, leading to the belief that pain and depression are two parallel conditions, while instead they meet on common ground. Trying to identify the primary root of a given symptom, following a categorical approach, therefore seems to be misleading. Another option would be trying to understand the degree to which a patient can be affected by pain and depression following a dimensional approach.

Regarding the measures for assessment of comorbid depression in chronic pain, the BDI, the CES-D, and the HADS are the tools most frequently used in the retrieved papers. Compared to the BDI, the CES-D does not measure suicide risk, and this may be an issue considering the high risk of suicide in chronic pain populations (Hooley et al., 2014). The number of items and the time required for administration and scoring are similar across CES-D and BDI-II; however, the CES-D seems to present some gender biases (Balsamo & Saggino, 2007) that are not reported for the BDI-II (Harris & D'Eon, 2008). As regards their sensitivity and specificity, in their study of a Western sample, Geisser et al. (1997) found the BDI-II to have greater specificity. Greater specificity is advisable as it allows to obtain fewer false positives in patients who may show greater levels of emotional distress because of pain and its consequences, rather than real depression. In addition, some authors considered the BDI useful as a screening measure to identify patients who might benefit from a cognitive-behavioral intervention (Poole et al., 2006). Finally, it is noteworthy that if BDI subscale scores are used in research rather than the total score, the high intercorrelation among them makes multicollinearity an issue (Novy et al., 1995).

The use of the HADS to evaluate depression in chronic pain seems to be only partially justified, since in CPPs it seems to be more appropriate as a measure of general psychological distress (Giusti et al., 2020; Pallant & Tennant, 2007; LoMartire et al., 2020; Luciano et al., 2014; Rusu et al., 2016).

Given their shortness and good performance in CPPs, other tools such as the BDI-FS, the PHQ-9, the PHQ-2, and the DASS Depression subscale could be recommended for rapid screening of depression. The availability of a tool is another aspect to consider. Instruments such as the DASS or the PHQ-9 are available at no additional cost, while others such as the BDI usually requires payment of licensing fees.

Beyond the appropriateness of the tools available, further studies are needed to obtain self-report measures with good psychometric characteristics and optimal sensitivity and specificity for use with CPPs. In particular, the potential overlap between depressive symptoms and pain and disability levels should be addressed in the chronic pain context. For example, structural equation modeling techniques could be useful to better investigate the relationship between pain and depression and how they change over time.

Implications for Clinicians

The results of this narrative review have many implications for clinicians looking for ways to screen for depression in CPPs and to improve the evaluation process. The following suggestions may also be useful for nurses since they play an important role in the screening of depression (Van Daele et al., 2015).

1. Since somatic items are potentially confounding and may cause criterion contamination, it is advisable to score them separately from the other items, rather than excluding them, and to investigate their possible causes (Corbière et al., 2011; Williams & Richardson, 1993).
2. It might help to analyze separately each dimension of the questionnaire used, identifying its specific contribution to the total score, and paying attention to cognitive items that may have more weight in the chronic pain context (Corbière et al., 2011; Frank et al., 1991; Miles et al., 2001; Poole et al., 2006; Williams & Richardson, 1993).
3. From a clinical perspective, relevant information could be retrieved by evaluating the score assigned by patients to the individual items within each dimension. Indeed, the score obtained in each dimension may be the summative result of either extremely high scores in a few core symptoms or of low-to-moderate scores in several symptoms, which could indicate different depression profiles. For example, people with moderate or subthreshold depression are characterized by numerous symptoms and complaints of relatively low intensity (Faravelli, 2004).

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4. It is important to pay attention to those items of depression scales that are potentially confounding in the chronic pain context and may produce biased estimates. They include items referring to symptoms that could be due to pain-related discomfort, such as diminished interest in activities, insomnia, psychomotor agitation or retardation, fatigue, or diminished concentration (Wesley et al., 1999), or items related to appetite and loss of energy that could be influenced by medications, such as opioid and nonopioid analgesics (Corbière et al., 2011).
5. The patient's specific pain condition should be always taken into consideration (Matcham et al., 2013). For example, fatigue is a more typical symptom of fibromyalgia (Okifuji & Turk, 2003), while sexual difficulties are more frequent in painful conditions such as vulvodynia (Hallam-Jones et al., 2001).
6. Caregivers might consider assessing depression with more than one tool to develop a clearer picture of the patients' symptomatology by examining the coherence of their responses and the complementarity among items across questionnaires (Knaster et al., 2016; Rusu et al., 2016). For example, the administration of the depression scale of the DASS-21 in addition to the BDI-II may help in evaluating additional aspects of depression, such as the ability to experience positive feelings, which may help to evaluate treatment outcomes, since this ability is interpreted by patients as the return to normal level of psychological and vital functioning (Pincus et al., 2004; Zimmerman et al., 2006).
7. It is advisable to analyze information on depression together with all other relevant information, including medical diagnosis (Pincus et al., 2009); history and familiarity of depression (Holmes et al., 2013); other comorbidities (e.g., preexisting anxiety problems) and their severity; interpersonal difficulties (e.g., marital problems; Tomba & Fava, 2006); and other psychological factors related to pain, such as catastrophizing, which may add to the adverse effects of pain when present together with depression (Linton et al., 2011).

Finally, for an appropriate functional analysis, it is important to evaluate:

1. The consequences that depression may have on the individual's functioning in his or her various contexts of life (i.e., work, family, social relationships, leisure time, daily life, or autonomy), considering the difficulty in isolating the effect of depression from that of pain (Wörz, 2003).
2. The effects of the individual's contexts of life on depression, such as interpersonal and marital difficulties that may have a role in the onset or maintenance of depression (Cano et al., 2005).
3. The impact of depression on the individual's willingness to treat his or her pain, since the persistence of pain and the inadequacy of treatments may lead some people to think that "nothing more can be done" and persuade them not to treat their pain (Breivik et al., 2006).

Limitations

We acknowledge that this narrative review has several limitations. First, there may be significant and influential works that we have not included due to our search for keywords in the title. However, we meant to avoid locating large numbers of publications where these keywords might have been mentioned in the main text but not addressed in depth. Second, we limited the search to adults suffering from chronic pain, excluding children, adolescents, and elders because those populations can raise specific measurement issues in addressing comorbid depression. We encourage further reviews related to other age groups. Third, critical issues described in the first part were organized in seven different categories in order to summarize the results, but other authors could organize the issues in other ways. Fourth, the examination was limited to self-report instruments, which may present well-known limitations (Balsamo & Saggino, 2007). However, they are largely used in both research and clinical practice because they represent a quick and easy way to collect information from patients with assessed characteristics of validity and reliability. The self-reports described in the second part are tools used in the included studies, which are the ones that addressed critical issues related to the assessment of depression in chronic pain. Many other studies used the same or other tools, without focusing on the critical issues in the comorbidity assessment. Further and more in-depth analyses are thus needed to identify all the measures used to assess comorbid depression in CPPs and to review their accuracy in this population.

Conclusions

Assessment of depression comorbidity in chronic pain represents a challenge in both research and clinical practice, and the present review provides some information that might help improving this evaluation process.

Chronic pain represents a complex biopsychosocial experience, and its management requires a multidisciplinary approach that may provide an accurate evaluation of the different factors involved. Given its prevalence and consequences on pain experience and patients' quality of life, depressive symptoms should be evaluated in chronic pain as an essential part of the assessment process. Although the use of self-report measures can favor a rapid and standardized assessment of comorbid depression in chronic pain, especially in clinical settings, the choice of tests, as well as the interpretation of scores, should always be supported by a solid clinical reasoning, which allows going beyond the descriptive study of the patient's symptoms to get to a full understanding of his or her individual experience.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pmn.2021.03.009.

References

Abdel-Nasser, A. M., Abd El-Azim, S., Taal, E., El-Badawy, S. A., Rasker, J. J., & Valkenburg, H. A (1998). Depression and depressive symptoms in rheumatoid arthritis patients: an analysis of their occurrence and determinants. *British Journal of Rheumatology, 37*(4), 391–397.
Agüera, L., Failde, I., Cervilla, J. A., Díaz-Fernández, P., & Mico, J. A. (2010). Medically unexplained pain complaints are associated with underlying unrecognized mood disorders in primary care. *BMC Family Practice, 11*(1), 17.
Alarcon, R. D., & Glover, S. G. (1994). Assessment and management of depression in rheumatoid arthritis. *Physical Medicine and Rehabilitation Clinics of North America, 5*(4), 837–858.
American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). American Psychiatric Association.
Amoozegar, F., Patten, S. B., Becker, W. J., Bulloch, A. G., Fiest, K. M., Davenport, W. J., & Jette, N. (2017). The prevalence of depression and the accuracy of depression screening tools in migraine patients. *General Hospital Psychiatry, 48*, 25–31.
Arnow, B. A., Hunkeler, E. M., Blasey, C. M., Lee, J., Constantino, M. J., Fireman, B., & Hayward, C. (2006). Comorbid depression, chronic pain, and disability in primary care. *Psychosomatic Medicine, 68*(2), 262–268.
Balsamo, M., & Saggino, A. (2007). Test per l'assessment della depressione nel contesto italiano: un'analisi critica. *Psicoterapia Cognitiva e Comportamentale, 13*(2), 167–199.
Banks, S. M., & Kerns, R. D. (1996). Explaining high rates of depression in chronic pain: A diathesis-stress framework. *Psychological Bulletin, 119*(1), 95–110.
Beck, A. T., & Beck, R. W. (1972). Screening depressed patients in family practice. *Postgraduate Medicine, 52*, 81–85.

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Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Beck Depression Inventory-II*. San Antonio, Texas: The Psychological Corporation, Harcourt Brace & Co.
Beck, A. T., Steer, R. A., & Brown, G. K. (2000). *BDI-II fast screen for medical patients manual*. The Psychological Corporation.
Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry, 4*(6), 561–571.
Beebe, M., & Utley, R. (2018). Primary care depression screening: Relationship to chronic pain and gender. *The Journal for Nurse Practitioners, 14*(1), e13–e16.
Blackburn-Munro, G., & Blackburn-Munro, R. E. (2001). Chronic pain, chronic stress and depression: coincidence or consequence? *Journal of Neuroendocrinology, 13*(12), 1009–1023.
Blalock, S. J., Devellis, R. F., Brown, G. K., & Wallston, K. A. (1989). Validity of the Center for Epidemiological Studies Depression Scale in arthritis populations. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology, 32*(8), 991–997.
Boomershine, C. S. (2012). A comprehensive evaluation of standardized assessment tools in the diagnosis of fibromyalgia and in the assessment of fibromyalgia severity. *Pain Research and Treatment*, Article 653714. https://doi.org/10.1155/2012/653714.
Breivik, H., Collett, B., Ventafridda, V., Cohen, R., & Gallacher, D. (2006). Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment. *European Journal of Pain, 10*(4), 287 -287.
Burckhardt, C. S., O'Reilly, C. A., Wiens, A. N., Clark, S. R., Campbell, S. M., & Bennett, R. M (1994). Assessing depression in fibromyalgia patients. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology, 7*(1), 35–39.
Burns, J. W., Johnson, B. J., Mahoney, N., Devine, J., & Pawl, R. (1998). Cognitive and physical capacity process variables predict long-term outcome after treatment of chronic pain. *Journal of Consulting and Clinical Psychology, 66*(2), 434–439.
Burton, A. K., Tillotson, K. M., Main, C. J., & Hollis, S. (1995). Psychosocial predictors of outcome in acute and subchronic low back trouble. *Spine, 20*(6), 722–728.
Callahan, L. F., Kaplan, M. R., & Pincus, T. (1991). The Beck Depression Inventory, Center for Epidemiological Studies Depression Scale (CES-D), and general well-being schedule depression subscale in rheumatoid arthritis criterion contamination of responses. *Arthritis Care and Research, 4*(1), 3–11.
Cano, A., Johansen, A. B., Leonard, M. T., & Hanawalt, J. D. (2005). What are the marital problems of patients with chronic pain? *Current Pain and Headache Reports, 9*(2), 96–100.
Castelnuovo, G., Giusti, E. M., Manzoni, G. M., Saviola, D., Gatti, A., Gabrielli, S., & Corti, S. (2016). Psychological considerations in the assessment and treatment of pain in neurorehabilitation and psychological factors predictive of therapeutic response: Evidence and recommendations from the Italian consensus conference on pain in neurorehabilitation. *Frontiers in Psychology, 7*, 468.
Chang, M. H., Hsu, J. W., Huang, K. L., Su, T. P., Bai, Y. M., Li, C. T., & Chen, M. H. (2015). Bidirectional association between depression and fibromyalgia syndrome: a nationwide longitudinal study. *The Journal of Pain, 16*(9), 895–902.
Chibnall, J. T., & Tait, R. C. (1994). The short form of the Beck Depression Inventory: Validity issues with chronic pain patients. *Clinical Journal of Pain, 10*(4), 261–266.
Cocksedge, K., Shankar, R., & Simon, C. (2016). Depression and pain: The need for a new screening tool. *Progress in Neurology and Psychiatry, 20*(1), 26–32.
Colligan, R. C., Osborne, D., & Swenson, W. M. (1983). *The MMPI: A contemporary normative study*. Praeger Scientific.
Corbière, M., Bonneville-Roussy, A., Franche, R. L., Coutu, M. F., Choinière, M., Durand, M. J., & Boulanger, A. (2011). Further validation of the BDI-II among people with chronic pain originating from musculoskeletal disorders. *The Clinical Journal of Pain, 27*(1), 62–69.
Crisson, J., Keefe, F. J., Wilkins, R. H., Cook, W. A., & Muhlbaier, L. H. (1986). Self-report of depressive symptoms in low back pain patients. *Journal of Clinical Psychology, 42*(3), 425–430.
Dahlhamer, J., Lucas, J., Zelaya, C., Nahin, R., Mackey, S., DeBar, L., & Helmick, C. (2018). Prevalence of chronic pain and high-impact chronic pain among adults—United States, 2016. *Morbidity and Mortality Weekly Report, 67*(36), 1001–1006.
Dersh, J., Polatin, P. B., & Gatchel, R. J. (2002). Chronic pain and psychopathology: Research findings and theoretical considerations. *Psychosomatic Medicine, 64*(5), 773–786.
Dickens, C., McGowan, L., Clark-Carter, D., & Creed, F. (2002). Depression in rheumatoid arthritis: a systematic review of the literature with meta-analysis. *Psychosomatic Medicine, 64*(1), 52–60.
Dworkin, R. H., Turk, D. C., Farrar, J. T., Haythornthwaite, J. A., Jensen, M. P., Katz, N. P., & Carr, D. B. (2005). Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain, 113*(1), 9–19.
Endicott, J. (1984). Measurement of depression in patients with cancer. *Cancer, 53*, 2243–2248.
Englbrecht, M., Alten, R., Aringer, M., Baerwald, C. G., Burkhardt, H., Eby, N., & Kleinert, S. (2017). Validation of standardized questionnaires evaluating symptoms of depression in rheumatoid arthritis patients: Approaches to screening for a frequent yet underrated challenge. *Arthritis Care & Research, 69*(1), 58–66.
Estlander, A. M., Takala, E. P., & Verkasalo, M. (1995). Assessment of depression in chronic musculoskeletal pain patients. *The Clinical Journal of Pain, 11*(3), 194–200.
Eurostat. (2020). *Persons reporting a chronic disease, by disease, sex, age and educational attainment level* [hlth_ehis_cd1e] http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=hlth_ehis_cd1e&lang=en .
Faravelli, C. (2004). Assessment of psychopathology. *Psychotherapy and Psychosomatics, 73*(3), 139–141.
First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W (1997). *Structured clinical interview for DSM-IV Axis I disorders*. American Psychiatric Publishing.
Fishbain, D. A., Cutler, R., Rosomoff, H. L., & Rosomoff, R. S. (1997). Chronic pain-associated depression: antecedent or consequence of chronic pain? A review. *The Clinical Journal of Pain, 13*(2), 116–137.
Frank, R. G., Beck, N. C., Parker, J. C., Kashani, J. H., Elliott, T. R., Haut, A. E., & Kay, D. R. (1988). Depression in rheumatoid arthritis. *The Journal of Rheumatology, 15*(6), 920–925.
Frank, R. G., Chaney, J. M., Clay, D. L., & Kay, D. R. (1991). Depression in rheumatoid arthritis: A re-evaluation. *Rehabilitation Psychology, 36*(4), 219–230.
Fu, X., Li, Z. J., Yang, C. J., Feng, L., Sun, L., Yao, Y., & Huang, Y. T. (2017). The prevalence of depression in rheumatoid arthritis in China: A systematic review. *Oncotarget, 8*(32), 53623–53630.
Fuller-Thomson, E., Nimigon-Young, J., & Brennenstuhl, S. (2012). Individuals with fibromyalgia and depression: Findings from a nationally representative Canadian survey. *Rheumatology International, 32*(4), 853–862.
Geisser, M. E., Roth, R. S., & Robinson, M. E (1997). Assessing depression among persons with chronic pain using the Center for Epidemiological Studies-Depression Scale and the Beck Depression Inventory: A comparative analysis. *The Clinical Journal of Pain, 13*(2), 163–170.
Giusti, E. M., Jonkman, A., Manzoni, G. M., Castelnuovo, G., Terwee, C. B., Roorda, L. D., & Chiarotto, A. (2020). Proposal for Improvement of the Hospital Anxiety and Depression Scale for the Assessment of Emotional Distress in Patients With Chronic Musculoskeletal Pain: A Bifactor and Item Response Theory Analysis. *The journal of pain, 21*(3–4), 375–389. https://doi.org/10.1016/j.jpain.2019.08.003.
Gureje, O., Simon, G. E., & Von Korff, M (2001). A cross-national study of the course of persistent pain in primary care. *Pain, 92*(1-2), 195–200.
Hallam-Jones, R., Wylie, K. R., Osborne-Cribb, J., Harrington, C., & Walters, S (2001). Sexual difficulties within a group of patients with vulvodynia. *Sexual and Relationship Therapy, 16*(2), 113–126.
Han, C., & Pae, C. U. (2015). Pain and depression: A neurobiological perspective of their relationship. *Psychiatry investigation, 12*(1), 1–8.
Harris, C. A., & D'Eon, J. L (2008). Psychometric properties of the Beck Depression Inventory-(BDI-II) in individuals with chronic pain. *Pain, 137*(3), 609–622.
Haythornthwaite, J. A., Sieber, W. J., & Kerns, R. D. (1991). Depression and the chronic pain experience. *Pain, 46*(2), 177–184.
Hitchon, C. A., Zhang, L., Peschken, C. A., Lix, L. M., Graff, L. A., Fisk, J. D., … Marrie, R. A. (2020). The validity and reliability of screening measures for depression and anxiety disorders in rheumatoid arthritis. *Arthritis Care & Research, 72*(8), 1130–1139. https://doi.org/10.1002/acr.24011.
Holm, J. E., Penzien, D. B., Holroyd, K. A., & Brown, T. A. (1994). Headache and depression: confounding effects of transdiagnostic symptoms. *Headache: The Journal of Head and Face Pain, 34*(7), 418–423.
Holmes, A., Christelis, N., & Arnold, C. (2013). Depression and chronic pain. *The Medical Journal of Australia, 199*(6), S17–S20.
Hooley, J. M., Franklin, J. C., & Nock, M. K. (2014). Chronic pain and suicide: Understanding the association. *Current Pain and Headache Reports, 18*(8), 435.
Hooten, W. M., Timming, R., Belgrade, M., Gaul, J., Goertz, M., Haake, B., … Walker, N. (2013). *Health care guideline: Assessment and management of chronic pain*. Institute for Clinical Systems Improvement.
Hu, J., & Ward, M. M. (2017). Screening for depression in arthritis populations: an assessment of differential item functioning in three self-reported questionnaires. *Quality of Life Research, 26*(9), 2507–2517.
Kaiser, C. F., Middaugh, S. J., Kee, W. G., Levin, R. B., & Berndt, S. M. (1990). Self-reported depression profiles in chronic pain and family practice patients. *The Clinical Journal of Pain, 6*(4), 271–275.
Knaster, P., Estlander, A. M., Karlsson, H., Kaprio, J., & Kalso, E. (2016). Diagnosing depression in chronic pain patients: DSM-IV major depressive disorder vs. Beck Depression Inventory (BDI). *PloS One, 11*(3), Article e0151982.
Kroenke, K., Spitzer, R. L., & Williams, J. B. (2001). The PHQ-9: Validity of a brief depression severity measure. *Journal of General Internal Medicine, 16*(9), 606–613.
Kroenke, K., Spitzer, R. L., & Williams, J. B. (2003). The Patient Health Questionnaire-2: Validity of a two-item depression screener. *Medical Care*, 1284–1292.
Krug, H. E., Woods, S. R., & Mahowald, M. L. (1997). The importance of identifying depression in patients with rheumatoid arthritis: evaluation of the beck depression inventory. *Journal of Clinical Rheumatology, 3*(5), 248–257.
Lee, Y., Lin, P. Y., Hsu, S. T., Cing-Chi, Y., Yang, L. C., & Wen, J. K. (2008). Comparing the use of the Taiwanese Depression Questionnaire and Beck Depression Inventory for screening depression in patients with chronic pain. *Chang Gung Medical Journal, 31*(4), 369–377.
Lee, H. J., Choi, E. J., Nahm, F. S., Yoon, I. Y., & Lee, P. B. (2018). Prevalence of unrecognized depression in patients with chronic pain without a history of psychiatric diseases. *The Korean Journal of Pain, 31*(2), 116–124.
Linton, S. J., Nicholasl, M. K., MacDonaldl, S., Boersmal, K., Bergboml, S., Maherl, C., & Refshaugel, K. (2011). The role of depression and catastrophizing in musculoskeletal pain. *European Journal of Pain, 15*(4), 416–422.
LoMartire, R., Äng, B. O., Gerdle, B., & Vixner, L. (2020). Psychometric properties of Short Form-36 Health Survey, EuroQol 5-dimensions, and Hospital Anxiety and Depression Scale in patients with chronic pain. *Pain, 161*(1), 83–95.
Lopez, M. N., Pierce, R. S., Gardner, R. D., & Hanson, R. W. (2013). Standardized Beck Depression Inventory-II scores for male veterans coping with chronic pain. *Psychological Services, 10*(2), 257–263.

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Lovibond, P. F., & Lovibond, S. H. (1995). The structure of negative emotional states: Comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. *Behaviour Research and Therapy, 33*(3), 335–343.
Luciano, J. V., Barrada, J. R., Aguado, J., Osma, J., & García-Campayo, J. (2014). Bifactor analysis and construct validity of the HADS: A cross-sectional and longitudinal study in fibromyalgia patients. *Psychological Assessment, 26*(2), 395–406.
Masood, A., Salim, B., Nasim, A., Khalid, Z., & Afzal, A. (2017). Are we missing the diagnosis of depression in patients with rheumatoid arthritis at a tertiary care facility? *Pakistan Journal of Medical Sciences, 33*(2), 300–305.
Martens, M. P., Parker, J. C., Smarr, K. L., Hewett, J. E., Slaughter, J. R., & Walker, S. E. (2003). Assessment of depression in rheumatoid arthritis: A modified version of the center for epidemiologic studies depression scale. *Arthritis Care & Research: Official Journal of the American College of Rheumatology, 49*(4), 549–555.
Martens, M. P., Parker, J. C., Smarr, K. L., Hewett, J. E., Ge, B., Slaughter, J. R., & Walker, S. E. (2006). Development of a shortened Center for Epidemiological Studies Depression scale for assessment of depression in rheumatoid arthritis. *Rehabilitation Psychology, 51*(2), 135–139.
Matcham, F., Rayner, L., Steer, S., & Hotopf, M. (2013). The prevalence of depression in rheumatoid arthritis: A systematic review and meta-analysis. *Rheumatology, 52*(12), 2136–2148.
Miles, A., McManus, C., Feinmann, C., Glover, L., Harrison, S., & Pearce, S. (2001). The factor structure of the BDI in facial pain and other chronic pain patients: A comparison of two models using confirmatory factor analysis. *British Journal of Health Psychology, 6*(2), 179–196.
Miller, L. R., & Cano, A. (2009). Comorbid chronic pain and depression: who is at risk? *The Journal of Pain, 10*(6), 619–627.
Morley, S., Williams, A. C. D. C., & Black, S (2002). A confirmatory factor analysis of the Beck Depression Inventory in chronic pain. *Pain, 99*(1-2), 289–298.
Newton, B. J., Southall, J. L., Raphael, J. H., Ashford, R. L., & LeMarchand, K. (2013). A narrative review of the impact of disbelief in chronic pain. *Pain Management Nursing, 14*(3), 161–171.
Novy, D. M., Nelson, D. V., Berry, L. A., & Averill, P. M. (1995). What does the Beck Depression Inventory measure in chronic pain?: A reappraisal. *Pain, 61*(2), 261–270.
Ohayon, M. M. (2004). Specific characteristics of the pain/depression association in the general population. *The Journal of Clinical Psychiatry, 65*, 5–9.
Okifuji, A., & Turk, D. C. (2003). Fibromyalgia syndrome: Prevalent and perplexing. *Pain Clinical Updates, 11*(3), 1–4.
Pallant, J. F., & Tennant, A. (2007). An introduction to the Rasch measurement model: An example using the Hospital Anxiety and Depression Scale (HADS). *British Journal of Clinical Psychology, 46*(1), 1–18.
Peck, J. R., Smith, T. W., Ward, J. R., & Milano, R. (1989). Disability and depression in rheumatoid arthritis: A multi-trait, multi-method investigation. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology, 32*(9), 1100–1106.
Pincus, T., & Callahan, L. F. (1993). Depression scales in rheumatoid arthritis: Criterion contamination in interpretation of patient responses. *Patient Education and Counseling, 20*(2-3), 133–143.
Pincus, T., Griffith, J., Pearce, S., & Isenberg, D. (1996). Prevalence of self-reported depression in patients with rheumatoid arthritis. *Rheumatology, 35*(9), 879–883.
Pincus, T., Hassett, A. L., & Callahan, L. F. (2009). Criterion contamination of depression scales in patients with rheumatoid arthritis: The need for interpretation of patient questionnaires (as all clinical measures) in the context of all information about the patient. *Rheumatic Disease Clinics, 35*(4), 861–864.
Pincus, T., & Williams, A. (1999). Models and measurements of depression in chronic pain. *Journal of Psychosomatic Research, 47*(3), 211–219.
Pincus, T., Williams, A. C. D. C., Vogel, S., & Field, A (2004). The development and testing of the depression, anxiety, and positive outlook scale (DAPOS). *Pain, 109*(1-2), 181–188.
Poole, H., Bramwell, R., & Murphy, P. (2006). Factor structure of the Beck Depression Inventory-II in patients with chronic pain. *The Clinical Journal of Pain, 22*(9), 790–798.
Poole, H., Bramwell, R., & Murphy, P. (2009a). The utility of the Beck Depression Inventory Fast Screen (BDI-FS) in a pain clinic population. *European Journal of Pain, 13*(8), 865–869.
Poole, H., White, S., Blake, C., Murphy, P., & Bramwell, R. (2009b). Depression in chronic pain patients: prevalence and measurement. *Pain Practice, 9*(3), 173–180.
Radloff, L. S. (1977). The CES-D scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement, 1*(3), 385–401.
Rhee, S. H., Petroski, G. F., Parker, J. C., Smarr, K. L., Wright, G. E., Multon, K. D., & Komatireddy, G. R. (1999). A confirmatory factor analysis of the center for epidemiologic studies depression scale in rheumatoid arthritis patients: Additional evidence for a four-factor model. *Arthritis Care & Research, 12*(6), 392–400.
Robinson, E. T., Hernandez, L. A., Dick, W. C., & Buchanan, W. W. (1977). Depression in rheumatoid arthritis. *The Journal of the Royal College of General Practitioners, 27*(180), 423–427.
Romano, J. M., & Turner, J. A. (1985). Chronic pain and depression: Does the evidence support a relationship? *Psychological Bulletin, 97*(1), 18–34.
Rudy, T. E., Kerns, R. D., & Turk, D. C. (1988). Chronic pain and depression: Toward a cognitive-behavioral mediation model. *Pain, 35*(2), 129–140.
Ruoff, G. E. (1996). Depression in the patient with chronic pain. *Journal of Family Practice, 43*(6 Suppl), S25–S34.
Rusu, A. C., Santos, R., & Pincus, T. (2016). Pain-related distress and clinical depression in chronic pain: A comparison between two measures. *Scandinavian Journal of Pain, 12*(1), 62–67.
Sardá, J., Jr, Nicholas, M. K., Pimenta, C. A., & Asghari, A. (2008). Psychometric properties of the DASS-Depression scale among a Brazilian population with chronic pain. *Journal of Psychosomatic Research, 64*(1), 25–31.
Scheidt, C. E., Mueller-Becsangèle, J., Hiller, K., Hartmann, A., Goldacker, S., Vaith, P., & Lacour, M. (2014). Self-reported symptoms of pain and depression in primary fibromyalgia syndrome and rheumatoid arthritis. *Nordic Journal of Psychiatry, 68*(2), 88–92.
Suárez-Mendoza, A. A., Cardiel, M. H., Caballero-Uribe, C. V., Ortega-Soto, H. A., & Márquez-Marin, M. (1997). Measurement of depression in Mexican patients with rheumatoid arthritis: Validity of the Beck Depression Inventory. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology, 10*(3), 194–199.
Substance Abuse & Mental Health Data Archive (SAMHDA). (2017). National Survey on Drug Use and Health, 2017 (NSDUH-2017-DS0001). Retrieved April 1, 2020, from https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHDetailedTabs2017/NSDUHDetailedTabs2017.htm#tab8-56A
Surah, A., Baranidharan, G., & Morley, S. (2014). Chronic pain and depression. *Continuing Education in Anaesthesia. Critical Care & Pain, 14*(2), 85–89.
Taylor, R., Lovibond, P. F., Nicholas, M. K., Cayley, C., & Wilson, P. H. (2005). The utility of somatic items in the assessment of depression in patients with chronic pain: a comparison of the Zung Self-Rating Depression Scale and the Depression Anxiety Stress Scales in chronic pain and clinical and community samples. *The Clinical Journal of Pain, 21*(1), 91–100.
Tomba, E., & Fava, G. A. (2006). L'approccio clinimetrico in psicologia clinica. *Rivista di Psicologia Clinica, 2*(3), 141–151.
Turk, D. C., & Okifuji, A. (1994). Detecting depression in chronic pain patients: Adequacy of self-reports. *Behaviour Research and Therapy, 32*(1), 9–16.
Turner, J. A., & Romano, J. M. (1984). Self-report screening measures for depression in chronic pain patients. *Journal of Clinical Psychology, 40*(4), 909–913.
Van Daele, T., Vansteenwegen, D., Hermans, D., Van den Bergh, O., & Van Audenhove, C. (2015). Home nurses and patient depression: Attitudes, competences and the effects of a minimal intervention. *Journal of Advanced Nursing, 71*(1), 126–135.
Velly, A. M., & Mohit, S. (2018). Epidemiology of pain and relation to psychiatric disorders. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 87*(Part B), 159–167.
Wesley, A. L., Gatchel, R. J., Garofalo, J. P., & Polatin, P. B. (1999). Toward more accurate use of the Beck Depression Inventory with chronic back pain patients. *The Clinical Journal of Pain, 15*(2), 117–121.
Williams, A. C. D. C., & Richardson, P. H (1993). What does the BDI measure in chronic pain? *Pain, 55*(2), 259–266.
Williams, A. C. D. C (1998). Depression in chronic pain: Mistaken models, missed opportunities. *Behaviour Therapy, 27*(2), 61–80. https://doi.org/10.1080/02845719808408497.
Williams, A. C. D. C., & Schäfer, G (2016). How do we understand depression in people with persistent pain? *Journal of Contemporary Psychotherapy, 46*(3), 149–157.
Wilson, K. G., Mikail, S. F., Joyce, L. D., & Minns, J. E. (2001). Alternative diagnostic criteria for major depressive disorder in patients with chronic pain. *Pain, 91*(3), 227–234.
Withers, M. H., Gonzalez, L. T., & Karpouzas, G. A. (2017). Identification and treatment optimization of comorbid depression in rheumatoid arthritis. *Rheumatology and Therapy, 4*(2), 281–291.
Wong, W. S., Chen, P. P., Yap, J., Mak, K. H., Tam, B. K. H., & Fielding, R (2011). Assessing depression in patients with chronic pain: a comparison of three rating scales. *Journal of Affective Disorders, 133*(1-2), 179–187.
Wörz, R. (2003). Pain in depression–depression in pain. *Pain: Clinical Updates, 11*(5), 1–4.
Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica, 67*(6), 361–370.
Zimmerman, M., McGlinchey, J. B., Posternak, M. A., Friedman, M., Attiullah, N., & Boerescu, D. (2006). How should remission from depression be defined? The depressed patient's perspective. *American Journal of Psychiatry, 163*(1), 148–150.
Zung, W. W. (1965). A self-rating depression scale. *Archives of General Psychiatry, 12*(1), 63–70.

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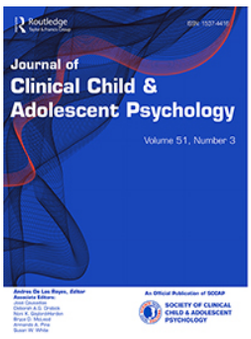

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Targeting the Proximal Mechanisms of Stress Adaptation in Early Adolescence to Prevent Mental Health Problems in Youth in Poverty

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ABSTRACT

Objective: This study used a randomized clinical trial design to evaluate the success with which The Building a Strong Identity and Coping Skills intervention (BaSICS) engaged the proximal mechanisms of poverty-related stress's impact on the psychosocial functioning and mental health of young adolescents living in high poverty contexts.

Method: 129 youth from very low-income families were randomized to receive the 32-hour group-based intervention or no-treatment control – 16 of these families withdrew before the intervention groups began. The remaining 113 youth aged 11–12 (53% assigned to intervention; 54% female; 40% Hispanic, 63% Black, 20% White) participated in the study, which included four assessment waves: pretest, posttest, 6-month follow-up and 12-month follow-up assessments. Primary control, secondary control, and disengagement coping were assessed via a combination of parent and youth reports as well as via interviews and questionnaires. Hypothalamic-pituitary-adrenal axis (HPA) reactivity was assessed via salivary cortisol responses occurring during a lab-based stress induction (Trier Social Stress Test).

Results: Multilevel regression models with repeated measures nested within subjects revealed that in comparison to controls, intervention youth had sustained significant increases in their knowledge about primary control coping (e.g., problem solving, emotion modulation), knowledge and utilization of secondary control (e.g., cognitive restructuring) coping, as well as decreased reliance on disengagement coping. These were accompanied by decreased cortisol reactivity in intervention versus control youth.

Conclusions: These findings support that BaSICS engages several proximal mechanisms of poverty-related stress' impact on early adolescent mental health – coping skills and HPA reactivity – during the neurodevelopmentally plastic pubertal period.

Abundant longitudinal research has shown that exposure to chronic adversity such as poverty and its accompanying stressful events (poverty-related stress; PRS; Wadsworth & Berger, 2006) is robustly associated with both internalizing and externalizing problems and disorders in children and adolescents (Grant et al., 2004; Wadsworth et al., 2016). As noted by Compas et al. (2017), stress exposure is a distal risk factor for the development of mental health problems, which operates through more proximal processes such as coping, self-regulation, and supportive social resources. Disengagement coping such as avoidance, for example, is generally associated with poorer mental health outcomes in the face of stressful conditions than is active, engagement coping such as problem solving. Importantly, economic hardship and poverty-related stress are, on average, positively associated with utilization of *typically maladaptive* disengagement coping and negatively associated with use of *typically adaptive* engagement coping (Cory et al., 2020; Santiago et al., 2012). In addition, the physiologic systems that support regulation during stress, such as the hypothalamic-pituitary-adrenal axis (HPA), also show atypical activation patterns in the face of poverty-related stress, which are associated with mental health problems (Duprey et al., 2021). Hence, "maladaptive" or what Wadsworth (2015) referred to as "stress-adapted" coping repertoires (reduced engagement and enhanced disengagement) and physiologic "dysregulations" (e.g., HPA) appear to constitute proximal mechanisms linking poverty and poverty-related stress to child and adolescent mental health problems over time. Despite the important role

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played by poverty and chronic stress in mental health, stress and its regulatory adaptations have received little attention in interventions for youth living with PRS (for an exception see, Grant et al., 2014). This is unfortunate because targeting mechanisms common to multiple health problems has the potential to prevent numerous health problems simultaneously (e.g., Raghavan et al., 2019).

Building on the Research Domain Criteria approach to understanding psychopathology (e.g., Cuthbert, 2015), the National Institute of Mental Health (NIMH) has articulated an experimental therapeutics approach to early-phase clinical trial research. This approach is characterized by identification and engagement of empirically and theoretically derived mechanistic intervention targets in the service of treating and/or preventing mental disorders (National Institute of Mental Health, 2015). The Building a Strong Identity and Coping Skills (BaSICS; Wadsworth et al., 2020) program uses the experimental therapeutics approach by targeting important mechanisms of poverty-related risk – stress, stress-adapted coping, diminished coping resources, and stress adapted HPA responsivity – in order to prevent the development of psychopathology in young adolescents living in high poverty contexts. This study reports results of tests of first the phase of experimental therapeutics – mechanism engagement – in a randomized control trial (RCT) of BaSICS in a sample of young adolescents living in poverty. Engagement of target mechanisms across multiple systems (biological, cognitive, and behavioral) is examined.

Adaptation to Poverty-Related Stress

Chronicity and uncontrollability, which characterize PRS for many children and youth, are the two dimensions of stress most robustly linked with negative outcomes such as depression and self-regulation problems (e.g., Landis et al., 2007), as well as damage to and dysregulation of the physiologic stress response (e.g., HPA; Koss & Gunnar, 2018). Chronic and uncontrollable stressors are also particularly challenging for children because these stressors simultaneously demand ongoing coping behaviors while also reducing adult support and coping assistance (e.g., Reife et al., 2020). Studies have consistently found higher levels of cognitive and behavioral avoidance in samples of low-income children (e.g., Kim et al., 2016). Importantly, a number of studies have found that avoidant coping in absence of adult support (Reife et al., 2020) or in the context of highly uncontrollable stressors such as community violence exposure, is not associated with mental health problems, at least in the short-term (Cory et al., 2020; Santiago & Wadsworth, 2009).

Children facing PRS also report using less primary control coping (active attempts to problem solve and manage emotions), a type of coping typically associated with better functioning. Research has suggested that the chronic and uncontrollable nature of PRS makes it difficult for children to identify active coping solutions – a phenomenon common to uncontrollable stress (e.g., Newman et al., 2011). Secondary control coping (efforts to accommodate oneself to stress via acceptance, cognitive reframing, and distraction) tends to be more helpful in coping with uncontrollable stress, but children facing PRS report using less of this type of coping as well (Wadsworth & Berger, 2006).

Primary reliance on disengagement coping, while potentially and at least temporarily helpful in the face of PRS (e.g., Cory et al., 2020), will not necessarily equip children to cope with stressors across multiple domains such as school and peers and can instead leave them vulnerable to the development of mental health problems (Kim et al., 2016). Hence findings suggest that living with chronic stress can constrain the development of and/or ability to use typically efficacious coping (Santiago et al., 2012) and instead promote disengagement coping. Therefore, the coping and self-regulation differences evident in poor youth do not necessarily reflect skill deficits, but rather adaptations that currently have (or once had) utility in coping with the volume, intensity, and uncontrollability of stressors that characterize life in poverty (e.g., Reife et al., 2020). Stress-adapted skills and reactivity nevertheless often have negative tradeoffs in other domains such as mental health (Ellis & Del Giudice, 2019; Wadsworth, 2015).

Paralleling the development of stress-adapted coping, the physiologic stress response system also adapts to chronic uncontrollable stress such as poverty. In its efforts to maintain homeostasis in the face of ongoing uncontrollable stress, the HPA adjusts its setpoints (e.g., Ellis & Del Giudice, 2019). The HPA's feedback mechanisms become sensitized over time, leading to an exaggerated response or what has been termed hyperactivation (increasingly easy to activate and increasingly difficult to down-regulate) and over time, theoretically eventuates in a hypo-active response (inability to mount a stress response; Booij et al., 2013). Stress-adapted HPA patterns are associated with psychopathology, especially internalizing problems (Ellis & Del Giudice, 2019)

As noted by Wadsworth (2015), stress-adapted coping is valuable and comes at a cost. The tradeoffs that come with stress adapted coping and regulation are not optimal and hence attention to how to lessen tradeoffs is

warranted. Given the variety and volume of conditions and events that comprise PRS, coping with poverty requires many different types of strategies; including those typically considered beneficial such as emotion regulation and problem solving as well as strategies typically considered detrimental such as avoidance and wishful thinking. In PRS affected youth, pervasive, repeated, and primary use of avoidance over time, for example, portends mental health problems, whereas strategic, periodic use of avoidance along with active coping strategies does not (Edlynn et al., 2008; Santiago & Wadsworth, 2009). This suggests that stress-adapted coping repertoires do not need to be replaced, but rather expanded and honed to meet the heightened demands of PRS.

Why Early Adolescence?

Appropriately timed interventions occurring during periods of enhanced neuroplasticity represent opportunities for making meaningful, qualitative shifts in development that can change a child's life trajectory. Puberty represents one such period, marked by neural plasticity, substantial maturation and reorganization of physiologic stress response systems, and rapid growth of cognitive, emotional, and behavioral abilities, including coping (Skinner & Zimmer-Gembeck, 2007). The early adolescent period is also when youth begin spending substantially more time out of the home without parents and are likely to encounter a wider variety of stressful exposures in multiple settings that they must increasingly navigate independently (Farahmand et al., 2011). The middle school years therefore represent a particularly important developmental period for intervention with stress-exposed youth in which stressful exposures are increasing, coping abilities are expanding, and the brain has enhanced plasticity (e.g., Gunnar et al., 2019).

Building a Strong Identity and Coping Skills

Guided by the Adaptation to Poverty Related Stress model (Wadsworth et al., 2018), the Building a Strong Identity and Coping Skills intervention (BaSICS) is a developmentally timed coping and empowerment program for middle schoolers that aims to foster growth in youth's individual and collaborative coping repertoires and improve youth's ability to regulate emotions and physiologic stress responses. The APRS model acknowledges that there are not universally beneficial or maladaptive coping strategies – coping strategies that are effective in resource-rich contexts may be less effective in resource-deprived contexts. A such, context-specific coping repertoires can confer protection in the face of poverty-related stress (PRS) and mitigate its effects on stress physiology and mental health problems. Hence the first module of BaSICS entails teaching about emotions, stress, and diverse coping strategies – building a strong core of fundamental knowledge and regulation abilities (Wadsworth & Berger, 2006; Wadsworth & Santiago, 2008). The second module of BaSICS targets cultural identity development as a coping resource, connecting youth with their supportive communities, fostering identification of one's own values and sense of self, and developing appreciation for their cultural roots (e.g., Spencer et al., 2003) – all in the service of preparing youth for collaborative coping (e.g., community social action). The final module of BaSICS targets collaborative problem-solving *vis á vis* collective social action to give youth tools for agentic and empowering ways to cope with PRS alongside others (Zimmerman et al., 2011). More details about the 32-hour curriculum can be found in Wadsworth et al. (2018).

Core Mechanisms of Action – Targets to Be Engaged

According to the APRS model, the BaSICS intervention will lead to improvements on a variety of coping skills, both increasing use of engagement coping such as cognitive reframing and emotion regulation and reducing primary reliance on avoidance and denial, for example. Other program elements such as cultural identity development are viewed as important resources to support the difficult work of coping with PRS but are not in themselves considered mechanisms of action. These are therefore not tested in this examination of core mechanisms. As children acquire a broader repertoire of coping and self-regulation skills, their ability to down-regulate their physiologic reactions in the face of stress should also improve. Hence, HPA axis hyper-responsivity should be reduced over time. Then, according to the APRS model, enhanced coping repertoires and better regulated stress reactivity will prevent the emergence of depression, anxiety, and post-traumatic stress symptoms – testing of this second experimental therapeutic goal will be addressed elsewhere.

After enrolling the first five cohorts of youth (N = 84), a proof-of-concept study was conducted to ensure that initial results suggested positive, non-iatrogenic effects on core mechanisms and psychological outcomes in

these highly vulnerable youth. Findings of that study's pretest-posttest analyses confirmed differential acquisition of engagement coping skill knowledge (e.g., problem solving steps and cognitive reframing), reductions in cortisol reactivity for intervention but not control youth, and reductions in parent and youth reported internalizing symptoms. Hence, these early findings suggested that BaSICS was safe and potentially efficacious (Wadsworth et al., 2020), but did not constitute a strong test of mechanism engagement, which the current study is designed to address.

The Current Study

The refinement and evaluation of the BaSICS intervention was supported by the NIMH (R21/61 mechanism) experimental therapeutics program. The current study builds on the promising proof-of-concept findings and was designed to evaluate the intervention's longer-term success in engaging the multiple mechanisms in the intended population of young adolescents living in chronically stressful high poverty contexts. The current study consists of a rigorous evaluation of engagement of target mechanisms across multiple systems over four timepoints, out to 12 month follow-up for the full sample of 129 intervention versus control youth. [Note that the COVID-19 pandemic precluded enrolling the final two cohorts of youth that would have resulted in a total N = 150.] Specifically, we hypothesized that across the 12 months of the study, (1) youth assigned to intervention would show increased knowledge about and use of active, engagement coping as compared to control youth, (2) intervention youth would show less reliance on disengagement coping after intervention, and (3) HPA reactivity would be reduced in intervention youth as compared to control youth. Prevention programs are generally expected to show differential change in *symptoms* over time wherein, for example, the control group's mental health worsens over time in comparison to the treatment group. Skill acquisition resulting from a prevention program, on the other hand, may not follow this type of linear change pattern. Continued growth of acquisition of skills after an intervention ends is not expected. Rather, acquisition of skills appearing at posttest or later and then being retained over time would be the logical predicted pattern of mechanism engagement. Hence, in this study, a differential linear change model is tested for thoroughness, but it was anticipated that a model of post-intervention change maintained over time would better represent the acquisition of skills and abilities targeted in BaSICS.

Methods

Study Procedures

All study components were approved by The Pennsylvania State University's institutional review board. Parents and guardians completed informed consent procedures, and youth completed assent to participate. Parent-child dyads were recruited from two adjacent low-income communities located in highly disadvantaged urban neighborhoods in a medium-sized city in Pennsylvania (Kind & Buckingham, 2018). The median household income (~$35,000), poverty level (~29%), and unemployment (~27%) rates are notably worse than the county average ($58.900, 12.7%, and 18.0%, respectively) in these "distressed" majority African American (~ 45%) and Latinx (~19%) communities (Distressed Communities Index, 2020). This city has very high homicide and violent crime rates (FBI Uniform Crime Report, 2020), its public schools are all designated Title I, and 87% of the students in the school district are classified as "economically disadvantaged" by the commonwealth (Pennsylvania Department of Education).

Dyads were recruited using flyers placed at community agencies and local schools, and in person at events through informational brochure and goody bag distribution at community and school events by staff who lived locally. Program events included parent-teacher events, religious and church-affiliated events, community festivals, block parties, recreational youth programs, and back to school programming, with a focus on events with high likelihood of parent attendance. The breadth of recruitment efforts used was employed to increase the generalizability of study findings. 65% of participating youth were recruited from the community and 35% of youth were recruited from middle schools.

Recruitment materials detailed the purpose of the study of investigating how BaSICS can improve a child's skillset in managing stress, which can, in turn, support greater physical and mental health. Families were apprised that participation in the study was voluntary and confidential, and that no information would be given to the child's school. Recruiters underwent training and demonstrated the ability to explain research protocol including monetary incentives, time commitments, and answer questions regarding the BaSICS intervention, randomization, and the evaluation components. Families who expressed interest were then contacted by program staff to begin checking for eligibility.

Youth aged 11 and 12 years were eligible if they did not demonstrate clinically significant levels of anxiety or depression that would require more intensive

intervention (i.e., treatment) or evidence of an autism spectrum disorder or intellectual disability, had families with an income of ≤ 200% FPL, and had at least one parent or guardian who was willing to complete the study. Figure 1 provides information about enrollment, randomization, and follow-up of participants. Of the 369 youths assessed for eligibility, 240 were excluded from the study. Of the 240 excluded youth, 81 were ineligible because they did not meet the full eligibility criteria as previously described and 159 youth declined to participate. Many families declined to participate due to time commitment issues or lack of interest in participation by the time they were contacted to schedule their pretest assessment. Of the 159 youth who declined to participate, 62% were recruited from the community and 38% from schools.

Eligible parent-youth dyads attended a three-hour pretest assessment appointment in which they consented for the study and to randomization. In-person pretest appointments occurred in either the youth's school or the project offices located in one of the communities between 4:00 pm and 7:00 pm. During these visits, participants were assessed using interviews, questionnaires, and the modified Trier Social Stress Task (TSST-M; Yim et al., 2010). Parent-youth dyads were assessed simultaneously, with parents independently completing measures on tablets while youth completed measures on tablets with the assistance of an examiner. Youth were then randomly assigned to either an intervention or control condition. Twenty-four sets of either 0 or 1 were printed out, placed in sealed envelopes, and given to children as generated by Research Randomizer (randomizer.org). The randomization ratio was 50:50 (I:C) for

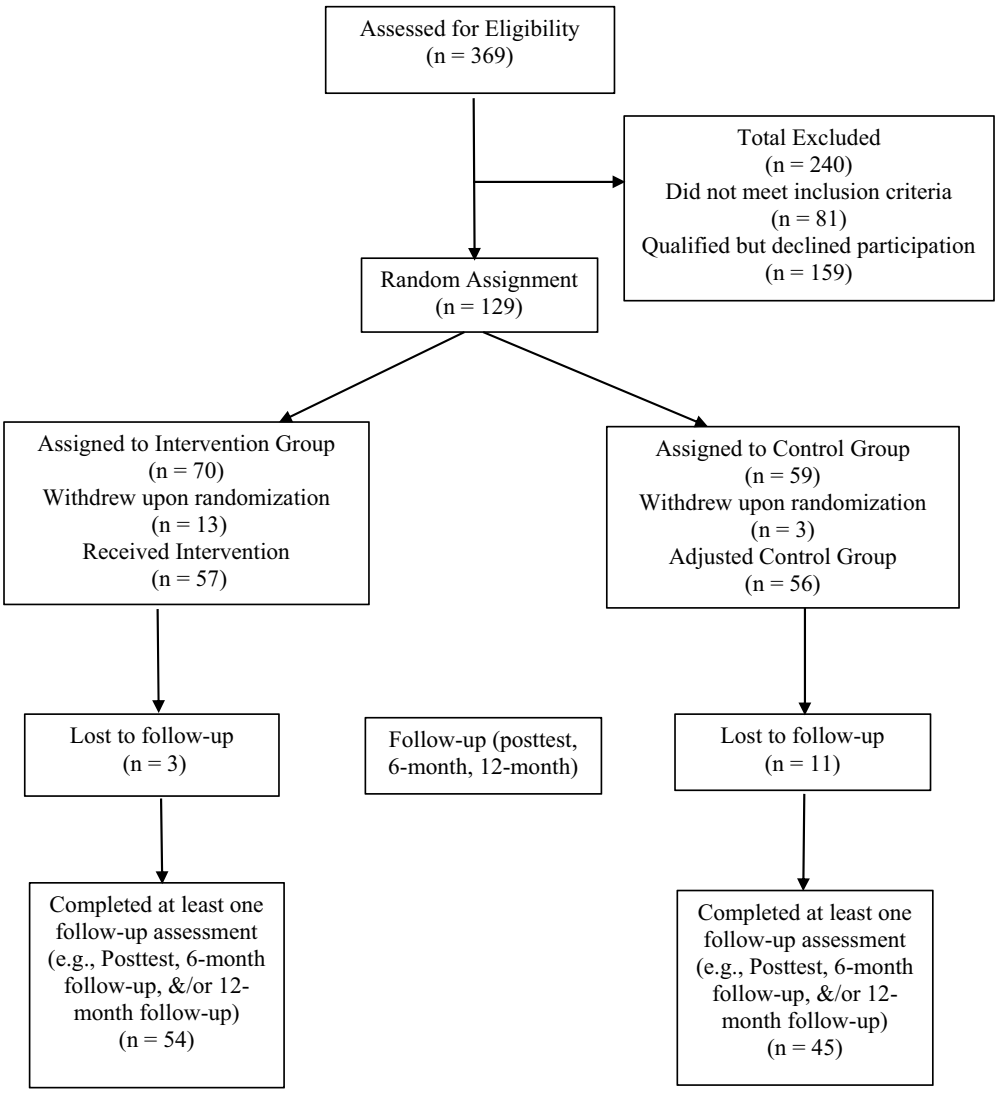

Figure 1. Consort table.

most cohorts but was adjusted to 60:40 (I:C) for cohorts 5 and 6 to adjust for differential withdrawal from the study by intervention recruits. Youth in the intervention participated in 16 sessions over the course of 8 weeks. Parents themselves did not participate in the intervention.

Participants and parents completed a posttest assessment two weeks after the final intervention session, ensuring 10–12 weeks between pre- and posttest assessment to minimize the practice effects of the TSST (Petrowski et al., 2012). Participants and parents then completed two additional follow-up assessments six and twelve months, respectively, after their posttest assessment. All post-intervention assessments were identical to pretest assessment. Families were compensated for completing assessments as follows: $40 pretest, $60 posttest, $80 six-month follow-up, and $100 twelve-month follow-up.

Participants

One hundred twenty-nine parent-child dyads (58% of children and 94% of caregivers were female) were recruited into the study, consented to the study, and completed pretest measures (Figure 1). Seventy youth were assigned to the intervention and 59 youth were assigned to the control group. Sixteen dyads withdrew from the study upon randomization but prior to the start of the intervention (13 had been randomized to the intervention group and 3 to the control group). Most parents of the 16 youth who withdrew from the study upon receiving their randomization assignment indicated that their or their child's schedules no longer permitted participation in biweekly intervention groups or were disappointed in their assignment. There were no significant differences between the withdrawn participants and those remaining in the study on demographic measures or variables of interest assessed at pretest except for parent report of child primary control (Supplementary Table 1). There were no significant differences between the intervention and control groups on the demographic or pretest variables of interest (Supplementary Table 2). All data reported in tables and text were restricted to the analysis sample.

On average, children were 11.82 years old (SD = 0.57) and were 43% Hispanic/Latino. Over half of the children identified as Non-Hispanic Black (59%), 15% identified as Non-Hispanic White, and 26% identified as Other/Multiracial. Parent age ranged from 26–63 years of age (M = 39.31, SD = 8.01), and parents were 34% Hispanic/Latino. About half of parents identified as Non-Hispanic Black (53%), 20% identified as Non-Hispanic White, and 27% identified as Other/Multiracial. Average household income was $23,102 ($SD$ = $31,608) with an average household size of 5.06 (SD = 1.97), which was below the 2017 federal poverty threshold for a family of five set at $28,780 (Fontenot et al., 2018). Most caregivers were employed (54%), 21% were unemployed, 15% received disability, and 10% were homemakers, full-time students, or retired. Thirty percent of parents did not complete high school, 27% had a high school diploma or GED, and 43% had schooling beyond high school. Many participating families received public assistance (41%) and reported food insecurity (70%). Lastly, 41% of parents were single, 15% were cohabitating, 22% were married, and 22% were widowed, separated, or divorced.

Sixteen dyads officially *withdrew* from the study upon receiving their assignment (prior to the commencement of any intervention sessions), stating they could no longer meet the requirements of the study due to various household and scheduling changes and were hence no longer eligible to be in the study. Fourteen additional dyads did not withdraw officially but did not return for any assessments following the pretest – these dyads are classified as *attrition*. Both withdrawn and attritted dyads are included in the analyses in order to adhere to strict Intent-to-Treat guidelines. Out of the 57 non-withdrawn participants who received the intervention assignment, 54 participants completed at least one follow-up assessment (retention rate of 95%), whereas 45 of the 56 non-withdrawn participants assigned to the control group completed at least one follow-up assessment (retention rate of 80%). The only significant differences between participants who completed at least one follow-up assessment and those who did not were child race, youth report of externalizing problems, and pubertal staging (Supplementary Table 3). As can be seen in Supplementary Table 3, participants who did not return for any follow-up sessions, were less likely to identify as Black, have lower level of externalizing problems, and more likely to have more advanced pubertal development.

Intervention

Eight cohorts with a mean of 7.3 children attended an average of 12.6 (mode = 16 sessions) sessions taught by two lead facilitators and one assistant facilitator. Groups met for two hours twice a week for 8 weeks. Sessions took place in the community health center and two middle schools within the targeted neighborhoods.

In the BaSICS curriculum, the first unit of content focuses on coping training over the course of 5 weeks. During this unit, youth are taught primary control coping skills (e.g., problem-solving), secondary control coping skills (e.g., distraction), and relaxation techniques

(e.g., progressive muscle relaxation). Throughout this unit and in subsequent units, strategies to help children learn to engage in primary and secondary control coping are implemented. The STEPS (Say the problem, Think of solutions, Examine each solution, Pick one and try it out, See if it worked) acronym is used to teach problem-solving action steps. The THINK (Think positively, Help from a friend, Identify the good things, Name a fun activity, Keep trying-don't give up) acronym is used to teach problem-solving, distraction, and positive thinking. The second unit of content focuses on positive identity development over the course of 6 weeks. During this unit, youth focus increasingly on social stressors – putting their personal experiences at home, school, and in their neighborhoods into a broader context. They learn about social justice, intersectionality, and community engagement and have opportunities to practice coping skills learned in unit 1 in an expanded range of situations. The third unit of the program entails working collaboratively with each other and with adults in the community to identify revitalization "opportunity zones" in their neighborhoods and to develop and implement a revitalization project in their neighborhood. Each week, parents are phoned by their child's group leader who gives them feedback about their child's participation in the intervention and share an overview of the content covered in the week's lessons.

Participant Satisfaction

At the end of each unit, participants completed surveys about their satisfaction with the sessions and the group facilitators. Participants were asked to rate BaSICS on several variables on a scale from (0 = not at all, 1 = a little bit, and 2 = very much). Participants were asked questions related to the content of each session, such as "*How much did you like the overall session?*" and *"How much did you like progressive muscle relaxation?"*

Measures

Demographics

Youth age, sex, race, and ethnicity were reported by parents. Parents also reported their own sex, race, ethnicity, immigrant status, marital status, annual household income, education level, and receipt of public assistance.

Coping Skills Knowledge Acquisition

Acquisition of knowledge about primary control (problem solving) and secondary control (distraction and positive thinking) coping was assessed using the Coping Skills Scale (CSS; Raviv & Wadsworth, 2010). The CSS assesses participants' ability to describe problem solving steps taught during the BaSICS intervention as well as steps necessary to engage in positive thinking and distraction. The CSS was administered orally, and responses were recorded on paper by research assistants. First, participants were asked to imagine stressful situations and identify potential solutions (e.g., "Imagine that your best friend is feeling very disappointed because her family cannot afford to go to the movies. What can your friend do to solve this problem? Think of as many solutions as you can."). Second, they were asked to list out the components of the STEPS acronym. Third, they were asked to identify ways in which cognitive restructuring could be used in these stressful situations. Fourth, they were asked to think of other coping strategies that could be used in these stressful situations. Fifth, they were asked to describe what the THINK acronym stands for.

Trained coders who were blind to participants' experimental conditions coded the recorded participant responses. Responses to the first item were coded based on whether a solution was proposed and the quality of solution (if it was logical, feasible, or realistic) on a scale from 1 (the solution proposed is no logical, feasible, or realistic) to 4 (the solution is highly developed, realistic, possible, and beneficial). Responses regarding the STEPS and THINK acronyms were coded based on youth's ability to accurately name each problem-solving step or way to think positively, respectively (0 = No, 1 = Yes). Questions targeting cognitive restructuring and other coping strategies were coded for each replacement thought the child provided and for each replacement activity that the child identified (0 = No, 1 = Yes). Coding was then checked for reliability (at least 80%) and two master coders coded 30% of responses to establish adequate inter-rater reliabilities for the primary control (κ = .70 – .90) and secondary control (κ = .86 – .94) sum scores. Primary control and secondary control sum scores were calculated.

Responses to Stress Questionnaire

Youth's use of primary control (e.g., problem solving, emotion regulation), secondary control (e.g., acceptance, distraction), disengagement coping (e.g., avoidance, wishful thinking), and involuntary responses to stress were assessed with parent- and self-report using the Family Stress version of the Responses to Stress Questionnaire (RSQ; Connor-Smith et al., 2000). In the RSQ, participants were first asked to report whether they had experienced any of 12 presented family stressors (e.g., "your parents arguing with each other," "your sibling(s) messing up, breaking, or taking your belongings") in their lifetime. Then, participants were asked to keep these selected family stressors in mind when

responding to 57 stress response items that each assessed the frequency with which participants used different coping strategies or endorsed different types of stress responses when they experienced family stress. Participants rated each of these 57 items on a Likert scale from 1 "*not at all*" to 4 "*a lot*."

The current study used primary control, secondary control, and disengagement coping factors. As recommended by Connor-Smith et al. (2000), proportion scores were calculated to control for response bias and individual differences in base rates of item endorsement, by dividing the total score for each factor by the total score for the entire Responses to Stress Questionnaire. For example, primary control coping is the ratio of one's endorsed primary control coping responses to total responses to stress. Primary control (α = .74; α = .84), secondary control (α = .76; α = .83), and disengagement coping (α = .76; α = .83) had adequate internal consistency at pre and post timepoints, respectively.

Puberty

Pubertal status was assessed using the Pubertal Development Scale (PDS; Petersen et al., 1988). Parents reported on youths' height, skin changes, and body hair growth. Girls' menarche and breast growth were also assessed; girls' average pretest PDS score was 2.42 (SD = 0.57; range 1.0–3.6). Boys' facial hair growth was assessed in addition to height, skin changes, and body hair; boys' average pretest PDS score was 1.76 (SD = 0.44; range 1.0–2.6).

Salivary Cortisol

Six saliva samples were taken via passive drool (Davis et al., 2002); immediately preceding the Trier Social Stress Test (TSST-M) (T1; 40 minutes post arrival at lab), immediately following TSST-M (T2; 15 minutes after T1), and at four 10-minute intervals thereafter (T3-T6). Given the 10- to 30-minute delay in cortisol's appearance in saliva, and as predicted, T3 represented the average peak cortisol level in the sample (Kirschbaum et al., 1993). To control for external factors that influence cortisol, participants were directed not eat a large meal, eat dairy products, brush their teeth, or drink sugary beverages an hour before their appointment. Saliva samples were stored in a biomedical grade freezer prior to the analysis at the CORE Biomarker Lab at Penn State University. Cortisol levels were determined using duplicates, with detection levels in the range of 0.003 to 3.0 Kg/dL (range, 0.08Y82.77 nmol/L) using a commercial expanded-range high-sensitivity enzyme immunosorbent assay kit (Lot #'s 1,410,510 and 1,502,503; Salimetrics, LLC, State College, PA). As per current best practices (e.g., Miller et al., 2018) T3 peak controlling for T1 baseline level was used to index reactivity.

Data Reduction and Preprocessing

Outliers more than 3 SD from the mean were winsorized to 3 SD (Smyth et al., 2013). In 6 saliva samples, insufficient saliva was collected for analysis (occurring randomly across participants). These 6 values were replaced with the mean cortisol value for the corresponding time point. Natural log (*ln*) transformation was used to normalize all salivary cortisol data (Smyth et al.).

Covariates

Because cortisol levels fluctuate with age, pubertal development, and by sex, it is recommended that these variables be accounted for in analyses capturing variability in cortisol levels (e.g., Shirtcliff et al., 2012). In addition, rates of internalizing and externalizing symptoms and disorders are known to vary according to race, ethnicity, and family structure in addition to age, sex, and pubertal maturation (e.g.,Natsuaki et al., 2009; Pomerantz et al., 2017; Shirtcliff et al., 2012). Hence, age in months, sex (0 = male, 1 = female), pubertal maturation, parental marital status (0 = not married, 1 = married), cohort (0 = cohorts 1–5, 1 = cohorts 6–8), Black race (0 = no, 1 = yes), White race (0 = no, 1 = yes), and Hispanic ethnicity (0 = no, 1 = yes) were therefore included in all statistical models.

Analytic Models

Study outcomes were analyzed with multilevel regression models to accommodate repeated measures nested within subjects, using SAS PROC MIXED. These models are well suited for this study as they allow for inclusion of incomplete data from respondents who did not provide measures in all waves or dropped out of the study. All 129 participants are included in the analytic models to meet criteria for Intent to Treat design. Random intercepts were specified to account for clustering due to repeated measures. Separate models were used for each outcome with the above covariates included. Child's age at time of assessment was also included as a predictor, centered at the last follow-up measurement period. We tested for inclusion of a random slope to represent variation in change over time across subjects. In all models, however, there was insufficient variance within subjects for both random intercepts and random slopes so the latter term was excluded in final models. Finally, we tested for but did not find evidence of quadratic effects in any of the models – hence these terms

were also excluded from the final models. We first implemented models that assessed overall group differences from posttest through both follow-up periods, controlling for the corresponding pretest score for the outcome. This model provides a statistical test of overall effects for group differences on average post-intervention across waves 2 through 4, regardless of change over time. Second, we implemented models examining differential change between groups from pretest through the 12-month follow-up assessment. In this second model a test of the interaction between time and intervention condition served as a test of whether differential change was occurring.

Results

Pretest, posttest, 6-month follow-up, and 12-month follow-up means and standard deviations by intervention group are presented in Table 1; correlations between study outcomes at pretest are presented in Table 2. Results from multilevel regression analyses are provided in Table 3. Results of the differential change models are presented in Supplemental Table 4. In general, the means reflect the modeling results. As indicated by the large effect sizes, scores on the CSS primary and secondary control skills increased dramatically for intervention youth from baseline to posttest and remained elevated in comparison to control youth out to the 12-month follow-up. Similar patterns but with a moderate effect size were found for parent report RSQ for secondary control coping, reflecting sustained increases in secondary control coping for intervention youth as compared to controls. Finally, disengagement coping responses and cortisol reactivity both showed declines over time for intervention youth but not controls, with small-to-moderate effect sizes. Sex was correlated with several coping variables as well as pubertal maturation.

Statistical differences between intervention and control groups were found for the overall effect models, controlling for the covariates listed above. For the observed CSS scores, the intervention participants demonstrated significantly higher coping skills than the control group for both primary and secondary control coping. No significant differences were found on parent or child report RSQ for primary control coping. However, statistical models indicated significant intervention effects for parent-reported coping for secondary

Table 1. Means and standard deviations of parent and adolescent reported coping and peak cortisol levels.

	Baseline		Posttest (3 Months)		6 Months		12 Months	
	Control	BaSICS	Control	BaSICS	Control	BaSICS	Control	BaSICS
Measure	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*
CSS-PCC	0.040 (0.19)	0.089 (0.28)	0.085 (0.37)	1.720 (1.88)	0.069 (0.37)	1.229 (1.66)	0.040 (0.20)	0.800 (1.11)
CSS-SCC	0.180 (0.43)	0.143 (0.35)	0.171 (0.45)	1.219 (1.26)	0.103 (0.30)	0.686 (0.99)	0.040 (0.20)	0.432 (0.85)
PRSQ-PCC	.188 (.044)	.190 (.045)	.185 (.032)	.200 (.038)	.191 (.039)	.194 (.047)	.183 (.037)	.207 (.044)
PRSQ-SCC	.252 (.045)	.246 (.041)	.237 (.039)	.242 (.034)	.225 (.036)	.250 (.047)	.227 (.049)	.254 (.039)
PRSQ-DC	.149 (.029)	.149 (.026)	.154 (.027)	.146 (.023)	.157 (.023)	.144 (.022)	.146 (.019)	.131 (.017)
CRSQ-PCC	.179 (.039)	.182 (.042)	.190 (.032)	.188 (.043)	.180 (.041)	.191 (.039)	.169 (.036)	.189 (.051)
CRSQ-SCC	.249 (.052)	.240 (.045)	.244 (.047)	.253 (.039)	.243 (.046)	.258 (.048)	.261 (.040)	.258 (.039)
CRSQ-DC	.152 (.030)	.151 (.028)	.158 (.024)	.147 (.026)	.161 (.030)	.147 (.029)	.143 (.028)	.141 (.025)
Peak Cortisol	.084 (.08)	.088 (.09)	.092(.09)	.067 (.05)	.078 (.07)	.062 (.04)	.080 (.06)	.065 (.04)

Note: CSS-PCC = Coping skills scale, primary control coping, CSS-SCC = Coping skills scale, secondary control coping. PRSQ = parent report RSQ, CRSQ = child report RSQ. RSQ scores are computed as proportion scores (i.e., PCC/Total RSQ score). Cortisol levels are µg/dL.

Table 2. Correlations among baseline parent and adolescent reported coping and peak cortisol levels.

	Sex	Age	Puberty	CSS-PCC	CSS-SCC	PRSQ-PCC	PRSQ-SCC	PRSQ-DC	CRSQ-PCC	CRSQ-SCC	CRSQ-DC	Peak Cortisol
Sex	–											
Age (months)	.089	–										
Puberty	.546***	.392***	–									
CSS-PCC	−.083	−.046	−.090	–								
CSS-SCC	.067	−.125	−.082	.196†	–							
PRSQ-PCC	.268**	.087	.123	−.087	−.137	–						
PRSQ-SCC	.057	.165	.001	.057	−.037	.400***	–					
PRSQ-DC	−.265**	−.009	−.086	−.078	.130	−.510***	−.249*	–				
CRSQ-PCC	.255**	−.013	−.012	.052	.012	.140	.006	−.088	–			
CRSQ-SCC	.048	.140	.062	−.045	.078	.113	.120	−.132	.285**	–		
CRSQ-DC	−.166	.067	.001	.051	−.156	−.256*	−.003	.187†	−.473***	−.324***	–	
Peak Cortisol *(ln)*	.068	−.122	.136	.056	−.104	−.021	.006	.032	.052	.095	−.040	–

† = p > .10, * = p < .05, ** = p < .01, *** = p < .001

Table 3. Multilevel regression models. Analytic results for study outcomes intervention effects (regression coefficients, standard errors, p-values, and effect sizes).

	Coping Skills Scale (observed)						Responses to Stress Questionnaire (parent report)								
	Primary control (STEPS)			Secondary control (THINK)			Primary control			Secondary control			Disengagement coping		
	b	Std.err	p-value	b	Std.err	p-value	b	Std.err	p-value	b	Std. err	p-value	b	Std. err	p-value
Intercept	0.002	0.472	.996	0.360	0.479	.455	0.633	0.407	.123	0.348	0.368	.348	−0.571	0.407	.165
Gender (female = 1)	0.443	0.237	.065	0.298	0.230	.200	−0.074	0.200	.712	−0.088	0.175	.618	0.113	0.189	.551
Race (black = 1)	−0.008	0.236	.973	0.058	0.225	.798	−0.178	0.189	.352	−0.072	0.167	.669	0.237	0.181	.196
Whether married	0.492	0.211	.021	0.290	0.213	.176	0.251	0.185	.177	−0.071	0.169	.675	−0.089	0.180	.622
Whether hispanic	−0.007	0.223	.976	−0.063	0.212	.769	−0.138	0.181	.450	−0.159	0.159	.323	−0.104	0.172	.549
Puberty status	−0.383	0.147	.010	−0.428	0.159	.008	−0.205	0.139	.144	−0.095	0.132	.473	0.172	0.141	.227
Cohort (later = 1)	−0.210	0.252	.407	−0.360	0.245	.146	−0.083	0.214	.701	−0.069	0.190	.716	0.044	0.203	.828
Outcome pretest score	0.268	0.091	.004	−0.023	0.098	.817	0.452	0.085	<.0001	0.536	0.076	<.0001	0.301	0.083	.001
Age	−0.371	0.114	.001	−0.292	0.126	.022	0.015	0.114	.896	0.208	0.107	.055	−0.302	0.115	.010
Condition	0.941	0.206	<.0001	0.935	0.194	<.0001	0.244	0.173	.163	0.350	0.147	.021	−0.408	0.162	.015
Condition Effect size:	0.90			0.84			–			0.41			0.45		

	Responses to Stress Questionnaire (child report)									Salivary cortisol		
	Primary control			Secondary control			Disengagement coping			Reactivity (logged)		
	b	Std.err.	p-value	b	Std.err.	p-value	b	Std.err.	p-value	b	Std. err.	p-value
Intercept	0.002	0.406	.996	0.215	0.386	.579	0.401	0.408	.328	0.557	0.469	.239
Gender (female = 1)	0.217	0.204	.290	−0.052	0.190	.784	−0.207	0.197	.297	−0.106	0.220	.631
Race (black = 1)	0.004	0.195	.984	−0.037	0.192	.846	−0.180	0.191	.348	0.177	0.216	.416
Whether married	−0.097	0.181	.594	−0.086	0.170	.613	0.084	0.179	.639	0.134	0.207	.519
Whether Hispanic	−0.466	0.186	.015	−0.186	0.180	.303	0.309	0.183	.096	−0.172	0.201	.395
Puberty status	−0.012	0.133	.926	0.011	0.122	.930	−0.062	0.133	.640	−0.127	0.152	.405
Cohort (later = 1)	−0.085	0.208	.686	0.006	0.200	.977	−0.043	0.205	.833	0.134	0.412	.746
Outcome pretest score	0.415	0.089	<.0001	0.550	0.081	<.0001	0.258	0.084	.003	0.417	0.090	<.0001
Age	−0.165	0.104	.116	0.055	0.095	.563	0.002	0.105	.982	0.097	0.134	.470
Condition	0.218	0.169	.200	0.020	0.165	.906	−0.308	0.165	.067	−0.378	0.186	.047
Condition Effect size:	–			–			0.34			0.41		

All models control for the pretest score for the outcome, gender, race (whether black), marital status (whether married), cohort (whether later cohort), whether Hispanic, and puberty status. Multilevel regressions include specified random intercept to accommodate repeated measures nested within subjects. Regression coefficients are standardized with respect to model outcomes (mean = 0, standard deviation = 1). Effect sizes represent standardized mean differences between Conditions (Cohen's D), calculated from model-adjusted means relative to model variance combined across levels.

control and disengagement coping. There was no significant difference on child-reported coping for secondary control, and a marginally non-significant result for child-reported disengagement coping. Finally, the analytic model examining group differences in measured salivary cortisol (log-transformed) showed that intervention children were significantly lower than the control group. Not shown in Table 3, the random intercept terms representing variation in the average outcome over time across respondents was found to have statistically significant variance in all models except for parent-reported secondary and disengagement coping. The pretest score significantly predicted the outcome in all models except for CSS-STEPS and CSS-THINK. Consistent with predictions, intervention group assignment was significant in many models, but differential change over time (time X group) was not significant for any of the models.

78% of participating youth reported liking the BaSICS program very much and none reported disliking it; 89% noticed positive changes in their own behavior; 95% reported that they had been better able to control their feelings since being in the program, and 92% stated that they would tell their friends they should participate in the program.

Discussion

This study tested the success of the BaSICS intervention in engaging its putative mechanisms of action, including acquisition of knowledge about how to apply primary and secondary control coping skills and demonstrated usage of these skills. Further, we examined the extent to which utilization of these active coping responses was accompanied by lessened reliance on disengagement coping responses such as avoidance and reduced HPA reactivity to the TSST-M. The findings suggest that

BaSICS was successful in engaging some, but not all of the proximal mechanisms of poverty-related stress' effects on young adolescent mental health set forth in the APRS theoretical model. Namely, medium and large (e.g., Cohen's d) treatment effects were found in salivary cortisol peaks, child-reported coping knowledge, and parent-reported child coping usage, showing hypothesized improvements for youth assigned to intervention versus control. The findings herein replicate the findings of the proof-of-concept study wherein the safety of the intervention was established and posttest improvements in STEPS, THINK, and cortisol reactivity were found. The current study also extended these initial findings in important ways, including establishing that the initial effects were sustained out to a year, revealing the emergence of several positive effects on the parent-report RSQ over time, and showing intervention-related changes across reporters and in stress biology.

As noted previously, skills and knowledge acquired in an intervention would be expected to be evident shortly after program completion and maintained over time. Additional acquisition of skills after an intervention ends would not be expected – for mental health problems, differential change is expected wherein control youth's mental health problems continue to worsen over time but intervention youth's mental health does not. The pattern of effects found in this study is therefore consistent with the expected model of skill acquisition change – post-intervention change maintained over time. A differential linear change model was tested for thoroughness (see Supplemental Table 4), but was not expected to adequately capture the acquisition and maintenance of skills and abilities targeted by BaSICS. The differential change models were also likely underpowered to detect small or medium interaction effects.

Coping Skill Knowledge Acquisition

Intervention youth were taught acronyms to help them learn and remember the steps involved in problem solving and in reframing one's cognitions. Borrowed with permission from the Families Coping with Economic Strain project (FaCES, Raviv & Wadsworth, 2010), the STEPS and THINK procedures were taught early in the intervention and used repeatedly throughout the 16 BaSICS sessions. Group facilitators were instructed to capitalize on interpersonal disputes and other difficulties that arose in the group setting as opportunities to practice using STEPS or THINK. Thus, early adolescents learned and practiced flexibly implementing problem solving and positive thinking on a regular basis using their own real-world problems. This developmentally appropriate "saturation" model of learning the planning, execution, and feedback procedures empirically linked to psychological adjustment (Cheng, Lau & Chan, 2014), appears to have been effective in teaching STEPS and THINK, as indicated by large effects. Problem solving and flexible thinking are fundamental skills needed for successfully engaging with the world, which make it possible for an individual to navigate an increasingly complex social world as they grow and develop. That the youth in the intervention were able to free recall both STEPS and THINK is indicative that they both learned how to use primary (STEPS) and secondary control (THINK) coping, and to distinguish between them.

Coping Skill Utilization

Both parents and youth completed the Responses to Stress Questionnaire (RSQ) to assess the relative use of primary control, secondary control, and disengagement coping in everyday life by youth participants across the four timepoints. Utilization of proportionally more secondary control coping skills and less disengagement coping was evident in parent reports of their child's coping. Children's reports on the RSQ did not show the increased utilization of secondary control coping that their parents' reports did. Parent-child cross-informant agreement on psychological constructs such as emotional and behavioral problems is generally low and is understood to reflect the unique perspectives of raters in context (De Los Reyes, 2011). Hence parents may have reported on improved coping that they observed in the home environment, whereas children's reports reflected their perceived coping across multiple domains. Both parents and youth reported reductions in disengagement coping following BaSICS, and while the youth reports failed to achieve statistical significance, the small-medium effect size (D = .34) of the youth-report effect suggests meaningful cross-informant convergence. Disengagement coping is likely more observable than the types of coping captured by secondary control such as acceptance and cognitive restructuring.

The pattern of findings across these measures and reporters suggests that intervention youth acquired knowledge about and increased their utilization of several cognitive, behavioral, and emotional coping skills, which were sustained across the 12 months of the study and were not evident in control youth. Avoidance, the defining feature of disengagement coping is, of course, a critical component of anxiety disorders and post-traumatic stress problems, and decreasing avoidance is a common goal of treatment. Coping is also prevalent in cognitive and behavioral models of depression, for

example, and acquisition of active coping skills and knowledge may be particularly critical to preventing the onset of depressive problems (Compas et al., 2010). Therefore, the concurrent reduction in disengagement coping and increases in active engagement coping knowledge and behavior show promise for preventing both anxiety and depressive problems (Compas et al., 2017).

Positive effects for usage of primary control strategies did not emerge in either child or parent RSQ reports. This may stem from the fact that the family stress domain includes many stressors over which a youth themself may have little control, such as arguments between parents and siblings taking or breaking one's belongings. The chronic and uncontrollable nature of PRS often makes it difficult for children to identify active coping solutions – a phenomenon common to uncontrollable stress (e.g., Cory et al., 2020). While primary control coping may be effective when youth face controllable stressors, it is not necessarily a good fit in cases where stressors are uncontrollable (Clarke, 2006; Jaser et al., 2005). Secondary control coping (efforts to accommodate oneself to stress through acceptance, cognitive reframing, distraction) tends to be more effective in coping with uncontrollable stress, but children facing toxic stressors like PRS often report using less of this type of coping as well (e.g., Wadsworth & Compas, 2002). The significant small-to-medium-sized effects for parent-reported secondary control coping and large effects of child-reported CSS-THINK also represent cross-informant evidence that low-income youth can learn to use these skills – which have enhanced utility for difficult-to-control stressors like PRS – in a culturally appropriate, developmentally timed intervention like BaSICS.

Still, it is important for youth to have ways to take action to respond to PRS and other large stressful burdens, which is why BaSICS strives to build up children's support networks and internal resources so that they can engage in collective actions with others. The family stress RSQ may not have picked up on youth's ability to engage in this active collaborative coping, which will be an important direction for future research. It is possible that, as with the secondary control and disengagement RSQ coping findings which were not evident at post but emerged after that, primary control effects could emerge over time when and if youth find more instances where problems can be solved collaboratively.

Cortisol Reactivity

It is encouraging that cortisol reactivity decreased significantly for intervention youth at the same time as and following the same pattern as improvements in several types of coping addressed in the intervention. A single small-to-medium finding of attenuated cortisol reactivity in intervention versus control youth does not in itself constitute evidence that the HPA has been changed or recalibrated. It is however promising, and certainly warrants additional attention as a possible outcome of psychosocial stress-focused prevention programs. As noted earlier, the pubertal period appears to be a neuroplastic window in which to intervene, especially on stress and stress responses. Across puberty, the HPA axis undergoes significant reorganization and change, and has been shown to be capable of what has been termed "pubertal recalibration," which is a normalizing of a "dysregulated" HPA response following an intervention or significant change in environmental context (DePasquale et al., 2019). The promise of interventions targeting stress and stress responses during puberty is therefore substantial.

Conclusions

The patterns of findings reported in this study provide continued evidence of successful engagement of some of our theoretically and empirically derived target mechanisms, but not all of them – primary control coping did not emerge as an effect on either the child or parent RSQ. Primary control coping, as assessed by the CSS-STEPS measure did, however, show a large intervention effect, indicating that intervention youth do retain knowledge about primary control coping, even if it is not immediately evident in their behavior. It is certainly possible that the RSQ was not sensitive to changes in youth primary control coping – several coping focused interventions using the RSQ as a skill acquisition measure have consistently found smaller or nil effects for primary control coping in comparison to secondary control coping (e.g., Watson et al., 2014). It is also possible that transfer of knowledge (STEPS) to action (RSQ primary control coping) did not occur for the youth in this trial. It has already been noted that the context of poverty often limits opportunities for problem solving, which is why BaSICS includes action-oriented collaborative coping (social action) to equip youth with agentic ways to address PRS, which the family RSQ is not designed to measure. Further, parent and youth reports on relatively covert psychological constructs such as coping rarely show high convergence and this phenomenon is understood to arise from the fact that different informants have different vantage points from which they view a child's behavior (De Los Reyes, 2011). It is therefore promising that there was some concordance across reporters and in no case did parent and child reports show divergent effects.

Finally, the study findings are notable in several respects. Most of the enrolled youth were living in families with household incomes well below the federal poverty threshold in a community marked by concentrated economic disadvantage, high levels of crime and community violence, and failing schools. Yet, families signed on to participate in the complex, time consuming research. The youth assigned to the intervention came to 80% of the afterschool sessions on average (12.6 out of 16), participated in the activities, and learned many skills. Parents transported their children to assessments and intervention sessions, participated in assessments themselves, and noticed positive changes occurring in their children. Satisfaction ratings by the youth were uniformly high, but the burden of participating in an RCT was also high for families. Many parent-youth dyads who dropped out of the study after receiving the intervention condition indicated that the twice weekly after-school timing of the program conflicted with after school activities such as sports or with changing parental availability due to inconsistent work schedules. All of this suggests that BaSICS is an appealing intervention that families and youth are likely to want to participate in, especially once the intense constraints of a clinical trial are no longer required. In addition, alternative delivery modes should be considered to reduce parental burden and increase accessibility.

Limitations

The study is limited by the design and implementation of the RCT. First, the BaSICS RCT was unfortunately upended by the COVID-19 pandemic, limiting our final enrollment numbers and complicating follow-up assessments. This of course reduced our power to detect small effects, and precluded examining effects by race or sex, or testing various potential moderators of effects such as facilitator, dosage, and/or intervention location. That said, we included a wide variety of covariates known to be associated with effects of poverty on psychological adjustment, including race, ethnicity, sex, age, pubertal status, parental marital status.

Further, upon receiving their randomization assignment, 16 families decided that they were unable to make the time commitment of completing the study and withdrew. Recruitment staff on the project were trained to thoroughly explain the substantial time commitment involved in participating in the study and to obtain parent and child agreement to participate regardless of the eventual group assignment. Still, in a population where changes in employment, child-care, child extracurriculars, and residence can disrupt schedules, it was not surprising that 12% of families were unable to fulfill their commitment when the time came.

Third, the scope and sustainability of intervention youth's collaboration on a community action project was somewhat constrained by the relatively short time frame allotted for the after-school BaSICS groups to complete projects and plan for sustaining them. As a result, community projects were modest in scope and difficult to sustain over time. Future applications of BaSICS will likely benefit from integration into the ongoing work of community groups and organizations. In this way opportunities for youth to apply primary control coping skills to a collaborative action project and to see their positive contributions to community problem-solving can continue beyond the 8 weeks of the intervention.

Implications for Research, Policy and Practice

The next step in evaluating BaSICS using the experimental therapeutics approach will be to assess the extent to which engaging these mechanisms translates into lasting effects on psychological outcomes. As indicated in Wadsworth et al. (2020), initial treatment effects were evident at posttest for the first five RCT cohorts on internalizing and PTSD symptoms. Future studies will examine treatment effects over the course of a year and the mechanistic role of the skills, capacities, and stress responses evaluated in this study in transmitting positive mental health outcomes. It is certainly plausible to expect success in this regard, given the success of other interventions for youth facing chronic stress, wherein intervention-related increases in secondary control coping skills, for example, substantially mediated the association between the intervention and mental health benefits (e.g., Compas et al., 2010).

Finally, this BaSICS evaluation was an efficacy-effectiveness hybrid design by necessity. Practical and psychological barriers precluded conducting this RCT in a university lab. Hence, the research and intervention were all conducted in community settings, including schools, a community health center, and a research office rented in one of the primary recruitment neighborhoods. Therefore, the results of this study are particularly promising as we have already demonstrated that BaSICS can be successfully implemented and rigorously evaluated even in very disadvantaged community settings.

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References

Booij, S. H., Bouma, E. M. C., de Jonge, P., Ormel, J., & Oldehinkel, A. J. (2013). Chronicity of depressive problems and the cortisol response to psychosocial stress in adolescents: The TRAILS study. *Psychoneuroendocrinology*, *38*(5), 659–666. http://dx.doi.org/10.1016/j.psyneuen.2012.08.004

Cheng, C., Lau, H. B., & Chan, M. S. (2014). Coping flexibility and psychological adjustment to stressful life changes: A meta-analytic review. *Psychological Bulletin*, *140*(6), 1582–1607. http://dx.doi.org/10.1037/a0037913

Clarke, A. T. (2006). Coping with interpersonal stress and psychosocial health among children and adolescents: A meta-analysis. *Journal of Youth and Adolescence*, *35*(1), 11–24. http://dx.doi.org/10.1007/s10964-005-9001-x

Compas, B. E., Champion, J. E., Forehand, R., Cole, D. A., Reeslund, K. L., Fear, J., … Roberts, L. (2010). Coping and parenting: Mediators of 12-month outcomes of a family group cognitive–behavioral preventive intervention with families of depressed parents. *Journal of Consulting and Clinical Psychology*, *78*(5), 623–634. http://dx.doi.org/10.1037/a0020459

Compas, B. E., Jaser, S. S., Bettis, A. H., Watson, K. H., Gruhn, M. A., Dunbar, J. P., … Thigpen, J. C. (2017). Coping, emotion regulation, and psychopathology in childhood and adolescence: A meta-analysis and narrative review. *Psychological Bulletin*, *143*(9), 939–991. http://dx.doi.org/10.1037/bul0000110

Connor-Smith, J., Compas, B. E., Wadsworth, M. E., Thomsen, A. H., & Saltzman, H. (2000). Responses to stress in adolescence: Measurement of coping and involuntary stress responses. *Journal of Consulting and Clinical Psychology*, *68*(6), 976–992. https://doi.org/10.1037/0022-006X.68.6.976

Cory, M., Chen, A., DuBois, D., Smith Carter, J., & Grant, K. (2020). Overcoming exposure to complex stressors: An examination of protective coping mechanisms for low-income urban African American youth. *Children and Youth Services Review*, 112. https://doi.org/10.1016/j.childyouth.2020.104867

Cuthbert, B. N. (2015). Research domain criteria: Toward future psychiatric nosologies. *Dialogues in Clinical Neuroscience*, *17*(1), 89–97. https://doi.org/10.31887/DCNS.2015.17.1/bcuthbert

Davis, E. P., Bruce, J., & Gunnar, M. R. (2002). The anterior attention network: Associations with temperament and neuroendocrine activity in 6-year-old children. *Developmental Psychobiology*, *40*(1), 43–56.

De Los Reyes, A. (2011). Introduction to the special section: More than measurement error: Discovering meaning behind informant discrepancies in clinical assessments of children and adolescents. *Journal of Clinical Child and Adolescent Psychology*, *40*(1), 1–9. https://doi.org/10.1080/15374416.2011.533405

DePasquale, C. E., Donzella, B., & Gunnar, M. R. (2019). Pubertal recalibration of cortisol reactivity following early life stress: A cross-sectional analysis. *Journal of Child Psychology and Psychiatry*, *60*(5), 566–575. http://dx.doi.org/10.1111/jcpp.12992

Distressed Communities Index. (2020). https://eig.org/

Duprey, E. B., Oshri, A., Liu, S., Kogan, S. M., & Caughy, M. O. (2021). Physiological stress response reactivity mediates the link between emotional abuse and youth internalizing problems. *Child Psychiatry and Human Development*, *52*(3), 450–463. http://dx.doi.org/10.1007/s10578-020-01033-1

Edlynn, E. S., Gaylord-Harden, N., Richards, M. H., & Miller, S. A. (2008). African American inner-city youth exposed to violence: Coping skills as a moderator for anxiety. *American Journal of Orthopsychiatry*, *78*(2), 249–258. http://dx.doi.org/10.1037/a0013948

Ellis, B. J., & Del Giudice, M. (2019). Developmental adaptation to stress: An evolutionary perspective. *Annual Review of Psychology*, *70*(1), 111–139. http://dx.doi.org/10.1146/annurev-psych-122216-011732

Farahmand, F. K., Grant, K. E., Polo, A. J., Duffy, S. N., & DuBois, D. L. (2011). School-based mental health and behavioral programs for low-income, urban youth: A systematic and meta-analytic review. *Clinical Psychology: Science and Practice*, *18*(4), 372–390. http://dx.doi.org/10.1111/j.1468-2850.2011.01265.x

FBI Uniform Crime Report. (2020). www.fbi.gov/services/cjis/ucr

Fontenot, K., Semega, J., & Kollar, M. (2018). *Income and Poverty in the United States: 2017*. https://www2.census.gov/programs-surveys/cps/tables/time-series/historical-poverty-thresholds/thresh17.xls

Grant, K. E., Compas, B. E., Thurm, A. E., McMahon, S. D., & Gipson, P. Y. (2004). Stressors and child and adolescent psychopathology: Measurement issues and prospective effects. *Journal of Clinical Child and Adolescent Psychology*, *33*(2), 412–425. http://dx.doi.org/10.1207/s15374424jccp3302_23

Grant, K. E., Farahmand, F., Meyerson, D. A., Dubois, D. L., Tolan, P. H., Gaylord-Harden, N., … Duffy, S. (2014). Development of cities mentor project: An intervention to improve academic outcomes for low-income urban youth through instruction in effective coping supported by mentoring relationships and protective settings. *Journal of Prevention & Intervention in the Community*, *42*(3), 221–242. https://doi.org/10.1080/10852352.2014.916586

Gunnar, M. R., DePasquale, C. E., Reid, B. M., Donzella, B., & Miller, B. S. (2019). Pubertal stress recalibration reverses the effects of early life stress in postinstitutionalized children. *Proceedings of the National Academy of Sciences of the United States of America*, *116*(48), 23984–23988. https://doi.org/10.1073/pnas.1909699116

Jaser, S. S., Langrock, A. M., Keller, G., Merchant, M. J., Benson, M. A., Reeslund, K., … Compas, B. E. (2005). Coping with the stress of parental depression II: Adolescent and parent reports of coping and adjustment. *Journal of Clinical Child and Adolescent Psychology*, *34*(1), 193–205.

Kim, P., Neuendorf, C., Bianco, H., & Evans, G. W. (2016). Exposure to childhood poverty and mental health symptomatology in adolescence: A role of coping strategies. *Stress and Health: Journal of the International Society for the Investigation of Stress*, *32*(5), 494–502. http://dx.doi.org/10.1002/smi.2646

Kind, A. J. H., & Buckingham, W. R. (2018). Making neighborhood-disadvantage metrics accessible — The neighborhood Atlas. *New England Journal of Medicine*, *378*(26), 2456–2458. http://AND University of Wisconsin School of Medicine Public Health. (2018). Area Deprivation Index. https://www.neighborhoodatlas.medicine.wisc.edu/AND University of Wisconsin School of Medicine Public Health. (2018). Area Deprivation Index. . https://doi.org/10.1056/NEJMp1802313

Kirschbaum, C., Pirke, K., & Hellhammer, D. H. (1993). The "trier social stress test": A tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology*, *28*(1–2), 76–81.

Koss, K. J., & Gunnar, M. R. (2018). Annual research review: Early adversity, the hypothalamic–pituitary–adrenocortical axis, and child psychopathology. *Journal of Child Psychology and Psychiatry*, *59*(4), 327–346. http://dx.doi.org/10.1111/jcpp.12784

Landis, D., Gaylord-Harden, N., Malinowski, S. L., Grant, K. E., Carleton, R. A., & Ford, R. E. (2007). Urban adolescent stress and hopelessness. *Journal of Adolescence*, *30*(6), 1051–1070. http://dx.doi.org/10.1016/j.adolescence.2007.02.001

Miller, R., Wojtyniak, J., Weckesser, L. J., Alexander, N. C., Engert, V., & Lehr, T. (2018). How to disentangle psychobiological stress reactivity and recovery: A comparison of model-based and non-compartmental analyses of cortisol concentrations. *Psychoneuroendocrinology*, *90*, 194–210. http://dx.doi.org/10.1016/j.psyneuen.2017.12.019

National Institute of Mental Health. (2015). *Strategic plan for research*. http://www.nimh.nih.gov/about/strategic-planning-reports/index.shtml

Natsuaki, M. N., Klimes-Dougan, B., Ge, X., Shirtcliff, E. A., Hastings, P. D., & Zahn-Waxler, C. (2009). Early pubertal maturation and internalizing problems in adolescence: Sex differences in the role of cortisol reactivity to interpersonal stress. *Journal of Clinical Child and Adolescent Psychology*, *38*(4), 513–524. https://doi.org/10.1080/15374410902976320

Newman, M. L., Holden, G. W., & Delville, Y. (2011). Coping with the stress of being bullied: Consequences of coping strategies among college students. *Social Psychological and Personality Science*, *2*(2), 205–211. https://doi.org/10.1177/1948550610386388

Pennsylvania Department of Education. https://futureready pa.org/District/FastFacts

Petersen, A. C., Crockett, L., Richards, M., & Boxer, A. (1988). A self-report measure of pubertal status: Reliability, validity, and initial norms. *Journal of Youth and Adolescence*, *17*(2), 117–133. http://dx.doi.org/10.1007/BF01537962

Petrowski, K., Wintermann, G., & Siepmann, M. (2012). Cortisol response to repeated psychosocial stress. *Applied Psychophysiology and Biofeedback*, *37*(2), 103–107. http://dx.doi.org/10.1007/s10484-012-9183-4

Pomerantz, H., Parent, J., Forehand, R., Breslend, N. L., & Winer, J. P. (2017). Pubertal timing and youth internalizing psychopathology: The role of relational aggression. *Journal of Child and Family Studies*, *26*(2), 416–423. http://dx.doi.org/10.1007/s10826-016-0598-z

Raghavan, R., Munson, M. R., & Le, C. (2019). Toward an experimental therapeutics approach in human services research. *Psychiatric Services*, *70*(12), 1130–1137. http://dx.doi.org/10.1176/appi.ps.201800577

Raviv, T., & Wadsworth, M. E. (2010). The efficacy of a pilot prevention program for children and caregivers coping with economic strain. *Cognitive Therapy and Research*, *34*(3), 216–228. http://dx.doi.org/10.1007/s10608-009-9265-7

Reife, I., Duffy, S., & Grant, K. E. (2020). The impact of social support on adolescent coping in the context of urban poverty. *Cultural Diversity & Ethnic Minority Psychology*, *26*(2), 200–214. http://dx.doi.org/10.1037/cdp0000296

Santiago, C., & Wadsworth, M. E. (2009). Coping with family conflict: What's helpful and what's not for low-income adolescents. *Journal of Child and Family Studies*, *18*(2), 192–202. http://dx.doi.org/10.1007/s10826-008-9219-9

Santiago, C., Etter, E. M., Wadsworth, M. E., & Raviv, T. (2012). Predictors of responses to stress among families coping with poverty-related stress. *Anxiety, Stress & Coping: An International Journal*, *25*(3), 239–258. https://doi.org/10.1080/10615806.2011.583347

Shirtcliff, E. A., Allison, A. L., Armstrong, J. M., Slattery, M. J., Kalin, N. H., & Essex, M. J. (2012). Longitudinal stability and developmental properties of salivary cortisol levels and circadian rhythms from childhood to adolescence. *Developmental Psychobiology*, *54*(5), 493–502. http://dx.doi.org/10.1002/dev.20607

Skinner, E. A., & Zimmer-Gembeck, M. (2007). The development of coping. *Annual Review of Psychology*, *58*(1), 119–144. http://dx.doi.org/10.1146/annurev.psych.58.110405.085705

Smyth, N., Hucklebridge, F., Thorn, L., Evans, P., & Clow, A. (2013). Salivary cortisol as a biomarker in social science research. *Social and Personality Psychology Compass*, *7*(9), 605–625. http://dx.doi.org/10.1111/spc3.12057

Spencer, M. B., Fegley, S. G., & Harpalani, V. A. (2003). Theoretical and empirical examination of identity as coping: Linking coping resources to the self processes of African American youth. *Applied Developmental Science*, *7*(3), 181–188. https://doi.org/10.1207/S1532480XADS0703_9

Wadsworth, M. E., & Compas, B. E. (2002). Coping with family conflict and economic strain: The adolescent perspective. *Journal of Research on Adolescence*, *12*(2), 243–274. https://doi.org/10.1111/1532-7795.00033

Wadsworth, M. E., & Berger, L. E. (2006). Adolescents coping with poverty-related family stress: Prospective predictors of coping and psychological symptoms. *Journal of Youth and Adolescence*, *35*(1), 54–67. https://doi.org/10.1007/s10964-005-9022-5

Wadsworth, M. E., & Santiago, C. D. (2008). Risk and resiliency processes in ethnically diverse families in poverty. *Journal of Family Psychology*, *22*(3), 399–410. https://doi.org/10.1037/0893-3200.22.3.399

Wadsworth, M. E. (2015). Development of maladaptive coping: A functional adaptation to chronic, uncontrollable stress. *Child Development Perspectives*, *9*(2), 96–100. https://doi.org/10.1111/cdep.12112

Wadsworth, M. E., Evans, G. W., Grant, K., Carter, J. S., & Duffy, S. (2016). Poverty and the development of psychopathology. In D. Cicchetti (Ed.), *Developmental psychopathology: Risk, resilience, and intervention (vol. 4, 3rd ed.)* (3rd, pp. 136–179, Chapter xiii, 1137 Pages). John Wiley & Sons, Inc. https://doi.org/10.1002/9781119125556.devpsy404

Wadsworth, M. E., Ahlkvist, J. A., McDonald, A., & Tilghman-Osborne, E. M. (2018). Future directions in research and iIntervention with youths in poverty. *Journal of Clinical Child & Adolescent Psychology*, *47*(6), 1023–1038. https://doi.org/10.1080/15374416.2018.1485108

Wadsworth, M. E., McDonald, A., Joos, C. M., Ahlkvist, J. A., Perzow, S. E., Tilghman-Osborne, E. M., Creavey, K., & Brelsford, G. (2020). Reducing the biological and psychological toxicity of poverty-related stress: Building a strong identity and coping skills. *American Journal of Community Psychology*, *65*(3–4), 305–319. https://doi.org/10.1002/ajcp.12400

Watson, K. H., Dunbar, J. P., Thigpen, J., Reising, M. M., Hudson, K., McKee, L., … Compas, B. E. (2014). Observed parental responsiveness/warmth and children's coping: Cross-sectional and prospective relations in a family depression preventive intervention. *Journal of Family Psychology*, *28*(3), 278–286. http://dx.doi.org/10.1037/a0036672

Yim, I. S., Quas, J. A., Cahill, L., & Hayakawa, C. M. (2010). Children's and adults' salivary cortisol responses to an identical psychosocial laboratory stressor. *Psychoneuroendocrinology*, *35*(2), 241–248. http://dx.doi.org/10.1016/j.psyneuen.2009.06.014

Zimmerman, M. A., Stewart, S. E., Morrel-Samuels, S., Franzen, S., & Reischl, T. M. (2011). Youth empowerment solutions for peaceful communities: Combining theory and practice in a community-level violence prevention curriculum. *Health Promotion Practice*, *12*(3), 425–439. https://doi.org/10.1177/1524839909357316