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Research Paper

Does the cortisol: CRP ratio inform the measurement of individual burden of illness for depression in community samples? ☆

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ABSTRACT

Background: Individual Burden of Illness for Depression (IBI-D) represents a method for assessing the degree to which depressive symptomatology reduces functioning. Although the IBI-D has been shown to provide more information than measures of depressive symptomatology alone, previous studies have relied upon participant self-reports, and have not included an objective measure of physiological functioning. Such an index might add to the validity and informational value of IBI-D data.

Methods: Responses to scales measuring depressive symptoms, functional impairment due to mental and physical health, and saliva samples were collected from 111 community volunteers from rural Australia. Saliva was assayed for cortisol and C-Reactive Protein concentrations, and the ratio of these was used as an indicator of the balance between the Hypothalamic-Pituitary-Adrenal axis and the inflammatory response from the immune system.

Results: Principal Components Analysis (PCA) produced two- and three-factor solutions from the psychological and biological data, and were used to form weighted models of two IBI-D equations. Stepwise regression analysis indicated that the addition of the biological index to the second IBI-D made a significant extra contribution to variance in depression score.

Limitations: No longitudinal data were collected, participants were from a single geo-cultural region, and were self-selecting. Clinician interviews might augment participant self-reports.

Conclusions: Valid assessment of the self-reported symptoms of depression provides one aspect of diagnostic information, but the addition of biological information can further inform clinicians and researchers about the effect that these symptoms have upon individual patient functioning.

1. Introduction

As well as being the leading cause of ill health and disability worldwide (WHO, 2017), depression also has profound effects on individuals who suffer from it. In clinical practice, it is relevant to estimate the degree to which a patient's overall functioning is decreased by depression. This concept is sometimes referred to as the "Individual Burden of Illness for Depression" (IBI-D) (Cohen et al., 2013; IsHak et al., 2011) because it focusses on the individual rather than the national or global cost of depression, such as the Quality of Life Adjusted Years (Zeckhauser and Shepard, 1976) and Disability Adjusted Years (Murray, 1994).

The IBI-D includes measures of (a) depressive symptoms, (b) functional impairment, and (c) quality of life, and compares the relative contribution that each of those factors makes to an individual's depressive state. IsHak et al. (2011) used Principal Components Analysis (PCA) of three standardized scales which measured Major Depressive Disorder (MDD) symptoms, functional impairment, and quality of life satisfaction respectively, weighted each of these according to the PCA outcomes, and formed a combined index of the burden that depression placed upon each individual. By applying their model to data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D), IsHak and colleagues were able to "capture the full burden of illness in depression…(and) offer a more accurate metric of recovery" (Cohen et al., 2013, p. 343).

This kind of measurement of depression and its effects might be valuable to researchers and clinicians by providing more information than just symptom severity (as is the case with most self-report scales or clinical interviews of depression), allowing for more comprehensive treat-

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ment planning based upon the extent of functional impairment and overall satisfaction with life in addition to depressive symptoms. As well as being better clinical practice, such an approach is congruent with the development of "individualized", "personalized" or "precision" medicine which has been recommended as a major research and treatment goal for depression (Insel, 2013; Kapur et al., 2012; NIMH, 2008).

However, in their IBI-D, IsHak et al. (2011) relied solely upon patient-reported data from clinically-diagnosed and healthy samples, and the exploration of the IBI-D in community samples has not been reported, which limits the applicability of the construct in everyday community settings where formal diagnosis may yet to be conducted. Additionally, it may be that inclusion of some more objective information might increase the validity of such an IBI-D procedure, and that information might include biological factors such as hormones and inflammation.

Several biological factors have been found to be involved with depression, including neurotrophic deficiency (Numakawa et al., 2014), hypothalamic-pituitary-adrenal (HPA) axis malfunction (Pariante and Lightman, 2008) and proinflammatory cytokines (Raison et al., 2006). HPA axis function is often measured by cortisol, and an index of inflammation is C-Reactive Protein (CRP). Although these two factors act in their own right, they also have a reciprocal relationship, reflecting the associations between the HPA axis (which is measured via cortisol) and the inflammatory system (e.g., Karlović et al., 2012; Lamers et al., 2013), which may be measured by CRP. The ratio between these two factors has been used to measure that reciprocal relationship and any imbalances in one direction or the other (i.e., dominant cortisol or dominant CRP) (Suarez and Sundy, 2017). It has been demonstrated that 'low' cortisol:CRP ratios (indicating low cortisol and elevated CRP) have been found among depressed women (Miller et al., 2005), but this ratio has not previously been used in studies of the IBI-D.

Therefore, the current study tested the effects of adding the cortisol:CRP ratio to psychological variables in an IBI-D model, using scores from standardized self-report instruments of depression, functional impairment, and quality of life. In order to test for the efficacy of this version of the IBI-D for community settings (rather than with diagnosed depressive cases), a volunteer community sample was recruited rather than comparing clinically depressed versus healthy cohorts, as this has been previously reported (IsHak et al., 2011). Additionally, because previous study of the IBI-D has been largely drawn from urban settings (IsHak et al., 2011), the current study focussed on recruiting participants from a rural setting.

2. Methods

2.1. Participants

Volunteers were recruited from the New England region of New South Wales, Australia. The project was advertised by publicity and news media as "a study about mental health". Inclusion criteria stated that participants were to be at least 18 years of age. Exclusion criteria were the presence of an acute medical illness or current medication for a mental illness.

2.2. Instruments

2.2.1. Background questionnaire

Participants were asked to state their age (years), sex, and racial origin.

2.2.2. Depression

Depression was assessed by the 20-item Zung Self-rating Depression Scale (SDS) (Zung, 1965). The SDS is based on data from factor analytic studies of Major Depressive Disorder (MDD) (APA, 2000) and fits the most recent definitions of that disorder (APA, 2013). Respondents indicate the frequency of each of those 20 items by answering: "None or a little of the time", "Some of the time", "Good part of the time", or "Most or all of the time", which produce numerical scores of 1 to 4, providing total raw scores from 20 to 80. SDS raw scores of 40 or above indicate the presence of "clinically significant depression" (Zung, 1973, p. 335). The SDS has demonstrated split-half reliability of 0.81 (Zung, 1965), 0.79 (DeJonge and Baneke, 1989) and 0.94 (Gabrys and Peters, 1985). Internal consistency (Cronbach alpha) has been reported as 0.88 for depressed patients and 0.93 for non-depressed patients (Schaefer et al., 1985) and as 0.84 for a previous Australian sample (Sharpley et al., 2009). The SDS has been shown to possess higher validity than the MMPI Depression Scale or the Beck Depression Inventory for assessing depression in male psychiatric inpatients, referenced to psychiatric diagnoses (Schaefer et al., 1985). SDS raw scores were used in this study.

2.2.3. Daily functioning

Two multi-item indices (mental health, physical health) of daily functioning were drawn from the SF-36, a well-validated indicator of health status that is used in studies of health economics to contribute to the Quality-Adjusted Life Years measure. The SF-36 has satisfactory validity in recognizing patients with good and poor health, and also reliability (Cronbach alpha) of 0.85 (Brazier et al., 1992; Jenkinson et al., 1994). The SF-36 has eight subscales, measuring various 'domains' of a person's functioning in physical, social, and emotional areas, plus mental health and pain. From these subscales, three items were developed to measure (i) global mental health on a five-point scale (excellent, very good, good, fair, poor), (ii) whether participant's mental health had influenced their daily functioning by impeding the time they had spent on activities, their success on those activities, or the care they had taken with those activities, and (iii) whether their mental health had impeded their social activities (all 'yes' vs. 'no' responses). The same questions were repeated for physical health to clarify the relative contributions of both aspects of health and functioning. The mental health functioning scale was called MHFS, and the physical health functioning scale was named PHMS.

2.2.4. Cortisol extraction

Cortisol in saliva was measured using a specific salivary cortisol ELISA kit from Abnova Corporation (KA1885, Taipei, Taiwan). This is a solid-phase ELISA using a polyclonal rabbit antibody directed against cortisol. The assay is based on the principle of competitive binding, and endogenous cortisol in the sample competes with a cortisol-horseradish peroxidase conjugate for binding to the antibody. This ELISA has an intra-assay variability of 8.27% and inter-assay variability of 8.33%, with a spiking recovery of 100% and calibration range of 0.1 to 30 ng/ml. Salivary cortisol was assayed according to the manufacturer's instructions. Briefly, 50 µl of neat saliva from participants or cortisol standards (0.1–30 ng/ml) were transferred to the appropriate wells of a 96-well microtitre plate. Fifty µl enzyme-conjugate was dispensed into each well with thorough mixing. The plate was incubated at room temperature with gentle rocking for 60 min. The contents of each well were aspirated, followed by four rinses with 300 µl wash solution. Substrate (200 µl) was added to each well and the plate was incubated at room temperature for 30 min. The reaction was stopped with the addition of 50 µl stop solution and absorbance was read at 450 nm immediately. All standards, controls and samples were assayed in duplicate and results were calculated using a 4-parameter logistics curve fit.

2.2.5. CRP assays

Blood samples were collected and centrifuged at 1000 g for 15 min. The sera were frozen at −80 °C until analysis of C-reactive protein. Serum concentrations of CRP were determined using a Siemens Dimension XPand Plus Autoanalyser (Siemens, Newark, USA), using the CRP extended range (RCRP) Flex reagent cartridge (Siemens Dimension, Newark, USA) according to the manufacturer's instructions. This assay is based on the particle-enhanced turbidimetric immunoassay (PETIA) technique, where synthetic particles coated with anti-CRP antibodies

aggregate in the presence of CRP, increasing turbidity in proportion to CRP concentration. Concentrations are reported in mg/L.

2.2.6. Procedure

From a list of 20,000 random names and addresses (balanced for equal numbers of males and females) supplied by the Australian Electoral Commission, sufficient participants were recruited to exceed the sample size required for Principal Components Analysis (as used by IsHak et al., 2011). Recommendations for the ratio of participants to components range from 5:1 to 20:1 (Tabachnik and Fidell, 2013), and the latter ratio was adopted here, so that there were at least 80 participants to test a four-factor solution. Additionally, the rule of thumb of 8 M + 50 participants for regression analysis (where M = the number of variables entered into the regression equation) was followed so that, with four variables, the required sample size was 82 participants.

Using the list of 20,000 names, selection was made based on random number tables to contact approximately twice the required sample size (i.e., 170 persons were contacted). Equal numbers of males and females were contacted via this process, and a random distribution of age was incorporated. These contactees received a link to an online portal or a copy of the questionnaire booklet containing an explanatory statement and consent form, plus the background questionnaire and the SDS, MHFS and PHFS, and a small container (Salivette) and written instructions for collection of morning cortisol saliva (about 45 min after waking in the morning and without eating or drinking before sampling), which represents the apex concentration in the diurnal rhythm (DR) of cortisol (Pruessner et al., 1997), and which may be used as an indicator of the overall cortisol-related stress level of the individual (Fries et al., 2009). Although a large study of 1693 men and women found that there was evidence of flattening of the daily curve in cortisol production according to age, socioeconomic and gender factors, the timing of the peak at 45 min after waking was "broadly consistent across demographic groups" and "consistent with previous studies that have found no effect of gender or age on the timing of the morning cortisol peak" (Karlamangla et al., 2013). Similarly, although some studies have made repeated collections of salivary cortisol for reliability reasons, a review of 14 studies of repeated saliva collections concluded that this was unnecessary and placed an undue research burden on research participants (Sharpley et al., 2016).

Participants were asked to freeze their saliva samples until they came to the researchers' lab a few days later to provide a blood sample for the CRP assay. CRP is relatively stable over time and shows no DR (Suarez and Sundy, 2017). The project was approved by the University of New England Human Research Ethics Committee (approval no. HE14–010). All participants gave written consent to the study.

2.3. Statistical analyses

Data were tested for normality. Pearson correlation coefficients were calculated to test for any significant age effects on the DVs, and gender was also tested for its effect via MANOVA. The cortisol:CRP ratio was derived by dividing cortisol concentration by the CRP value as described by Suarez et al. (2017, 2015). Z-scores were calculated for the SDS, MHFS, PHFS, and the cortisol:CRP ratio to reduce the possibility of a confound due to the influence of one of the measures above the others. These were then entered into PCA, firstly without the cortisol:CRP ratio, and then with it included, to create two versions of the IBI-D based upon the component loadings from the PCA. Hierarchical regression was used to determine which of these two versions of the IBI-D contributed most strongly to the SDS raw score.

3. Results

3.1. Data

A total of 111 participants (41 males, 36.9% of the sample) provided usable data on all measures in response to the contact process described above. None of these participants identified as Aboriginal or Torres Strait Islander, and all stated that their racial background was white or Anglo-Saxon. Table 1 presents the mean (SD), 5% mean and ranges for age and the SDS, MHFS, PHFS, and cortisol:CRP ratio. The 5% means were very close to the actual means, suggesting that effects from outliers were minimal. Inspection of the histograms, normal Q-Q plots and the detrended Q-Q plots indicated that all the self-report variables were within normal parameters; the cortisol:CRP data were not skewed but were centrally grouped about the mean. The internal consistency (Cronbach alpha) of the SDS was 0.878, acceptable for further analysis; and the 'functional' items for mental and physical health (i.e., those which related to participants' time, care, success at daily activities and social activities) were also acceptable for research purposes (MHFS = 0.717, PHFS = 0.798) (Tabachnik and Fidell, 2013).

3.2. Associations between variables before forming IBI-D indices

The Pearson correlation coefficients between the raw scores of the four variables indicated that the two functional impairment measures were significantly related with each other ($r = 0.366$, $p < .001$), and that the SDS was significantly correlated with the measure of the impact of mental health upon daily functioning ($r = 0.404$, $p < .001$) but not with the measure of the impact of physical health upon daily functioning ($r = 0.134$, $p = .120$). There were no significant correlations between the cortisol:CRP ratio and SDS ($r = 0.040$, $p = .673$), mental health ($r = -0.029$, $p = .764$), or physical health ($r = -0.116$, $p = .226$). None of those coefficients reached the level (i.e., > 0.7) that indicated communality of variables which could have affected the validity of the following statistical analyses (Tabachnik and Fidell, 2013).

3.3. Calculation of IBI-D indices

Z scores were calculated to reduce the influence of any variable's score upon the total IBI-D value. These z scores were then entered into two PCAs using direct oblimin rotation. All correlation coefficients were > 0.3, the Kaiser-Meyer-Olkin measures of sampling adequacy were greater than the recommended level of 0.6, and Bartlett's Test of Sphericity was significant for each PCA. Inspection of the eigenvalues, scree plots and parallel analysis indicated that a two-factor solution best fitted the first PCA, and a three-factor solution best fitted the second PCA (Table 2).

The following formulas were used to obtain each IBI-D index as per the method described by IsHak et al. (2011) by weighing the three scales by their respective component loadings, adding these weighted values together, and dividing the total by the standard deviation of the respective IBI-D. These formulas are shown below.

$$\text{IBI} - \text{D Index 1} := [0.944 \times (\text{zSDS}) + 0.815\,(\text{zMHFS}) + .765 \times (\text{zPHMS})]/1.485$$

$$\text{IBI} - \text{D Index 2} := [0.706 \times (\text{zSDS}) + 0.779 \times (\text{zMHFS}) + .792 \times (\text{zPHMS}) + .717 \times (\text{zcortisol} : \text{CRP ratio})]/1.473$$

Table 3 presents the descriptive statistics for these two IBI-D indices. IBI-D (2) was slightly more peaked for those participants whose scores were immediately to the left of zero, and IBI-D (1) was more homogeneous than IBI-D (2). There were no significant sex differences in either IBI-D index, nor any significant correlations with age.

3.4. Associations between IBI-D and depression

This study was designed to decide if a combinatory IBI for depression would provide more information about participants than the SDS scores alone. That is, did functional data (mental health, physical health, HPA-axis, inflammatory data) add to a measure of frequency and severity of

Table 1
Descriptive variables.

Variable	Mean (SD)	5% mean	Minimal	Maximum
Age (yr)	51.93 (17.01)	50.38	18	85
SDS total score	38.53 (7.25)	38.44	24	57
Mental Health & Function (MHFS)	9.56 (1.51)	9.51	6.00	14.00
Physical Health & Function (PHMS)	11.71	11.69	7.00	16.00
Cortisol:CRP ratio	4.41	2.68	−173.24	279.07

Table 2
PCA outcomes from two IBI-D models.

IBI-D Index	KMO	Bartlett's Test	Eigenvalues (% variance)	Scree plots
IBI-D (1)	.682	11.249 (3), p = .010	Factor 1: 1.306 (43.53) Factor 2: 1.012 (33.747)	
IBI-D (2)	.656	13.586 (6), p = .035	Factor 1: 1.315 (32.882) Factor 2: 1.085 (27.131) Factor 3: 0.948 (23.697)	

Table 3
Descriptive statistics for two individual burden of illness-depression indices.

	IBI-D (1)	IBI-D (2)
Mean	.0133	.0198
Median	−0.0639	−0.0968
Standard Deviation	1.511	1.571
Minimum	−0.299	−0.618
Maximum	4.18	4.15
Skewness	.400	−0.151
Kurtosis	−0.223	1.468

depression symptoms? To answer that question, stepwise regression was performed on these data, using SDS as the target variable and the two IBI-D values as the contributor variables. The overall regression equation was significant R square = 0.578, $F(1110) = 74.042$, $p < .001$. IBI-D (1) was entered first, and explained 47.3% of the variance in SDS scores F for change (1109) = 97.43, $p < .011$, and IBI-D (2) contributed an extra 10.5% (i.e., total variance 57.8%) to the variance in SDS score F for change (1108) = 26.883, $p < .001$. When divided into two subsamples on the basis of the SDS cutoff for presence of clinically significant depression, there was no difference in the direction of the statistical outcomes of the regression analyses on the IBI-D results between the depressed versus non-depressed participants, although the p values reduced to $p = .007$ for the IBI-D (2) in the non-depressed subsample and to $p = .002$ in the depressed sample.

To test the validity of using the combined measure of cortisol and CRP (i.e., the cortisol:CRP ratio) rather than cortisol or CRP separately, a final regression analysis was performed on SDS scores using cortisol, CRP, the cortisol:CRP ratio, and the two IBI-D indices. There was a significant effect for the overall equation $F(5110) = 94.831$, $p < .001$, and both IBI-D indices made significant contributions to SDS score ($p < .001$ each). The cortisol:CRP ratio also significantly contributed to the variance in SDS score $t = 11.721$, $p < .001$, but cortisol alone $t = 0.577$, $p = .565$, and CRP alone $t = 1.847$, $p = .068$, did not make significant contributions to the variance in SDS scores.

4. Discussion

4.1. Overall findings

The addition of an index of the impact of depression upon daily functioning is a logical and valuable pathway to more informed assessment of depression's overall effect upon individuals who may present in community settings. Combining this index with depression symptom scores provides a more comprehensive analysis of the overall state of presenting patients, which may be of assistance in identifying the severity of depression and its effect on the patient's lifestyle. It can also assist in planning treatments and the resolution of depressive symptoms. As previously commented by IsHak and colleagues (2011), this combination of symptoms and functioning is more informative than using the same measures but not including them in a single metric (e.g., Molenaar et al., 2007; Waern et al., 2002). By combining a weighted model of depressive symptoms plus daily functioning, more targeted treatments can be offered and then evaluated for change following treatment, rather than simply relying upon depression symptom reduction alone, which may not reflect changes in the ability of depressed persons to conduct their lives as they wish.

4.2. Use of a biological variable in the IBI-D

The current study added an indicator of the physiological balance between two major systems to the kind of self-report data on MDD and functioning used in previous studies. An IBI-D that includes this kind of biological variable thus offers two advantages to clinical settings over those that rely solely upon self-reports of psychological or functional variables. First, it extends the range of information (i.e., by inclusion of a biological variable) and second, it also reduces reliance upon participants' self-reports. Although previous attempts to incorporate biological markers of depression via genetic analyses have not been successful so far (Border et al., 2019), the consideration of hormonal and inflammatory variables has been more forthcoming (Bhagwagar et al., 2003; Wysokinski et al., 2015). It is noteworthy that, while the cortisol:CRP ratio made a significant contribution to SDS score variance, cortisol and CRP alone did not, thereby arguing for the continued investigation of this combination variable. The current findings support the inclusion of hormonal and inflammatory variables, and suggest that the combination of biological and psychological variables in a single metric may be a direction worthy of further research.

4.3. Clinical and research applications

The IBI-D can be applied in clinical settings as well as in research studies, to identify the profile of depression's impact upon individual patients as well as the associations between other (predictor) variables and

depression impact and severity in large-scale studies. IBI-D with combined psychological and biological variables might also provide valuable information regarding the way that various anti-depression treatments effect individual patients. That is, not only can the kind of IBI-D used in the first version developed here identify whether MDD symptoms have decreased, but also whether that effect has generalised to the daily functioning of patients receiving the treatment. That process can also be further extended by adding a biological variable. Finally (and using the current model of IBI-D (2)), physiological aspects of functioning that are related to depression probably represent a valuable therapy informant that can be an adjunct to self-reports alone, in addition to not being vulnerable to any patient bias. Physiological variables may represent a more difficult therapy target because, while patient attitudes may change relatively quickly when the effects of the Therapeutic Alliance have strengthened the therapist-patient 'Bond' (Martin et al., 2000), therapy activities may require longer to change the way that physiological systems such as the HPA-axis and inflammatory systems function. However, those changes are also likely to have more long-lasting effects on overall health than patient self-reports alone, for the same reason.

4.4. Limitations

As expected, there are some limitations upon the generalizability of these results. First, data were collected at a single point in time and no implication can be made beyond that time point. Second, although there was a biological variable in IBI-D (2), three of the four measures were self-reports, open to participant bias and inaccuracy. Although self-reports of depression are common in research settings, clinical interviews for depression are the 'gold standard' and might provide more enlightening data. Third, the participants were from a single geographical area of several hundred square kilometres and different towns and cities within that area; additionally, they were all rural residents and, although this was intentional, no comment can be made regarding the applicability of these results to urban residents, nor how this selectivity may have influenced the calculation of the two IBI-D indices. Participants self-selected from a postal survey and IBI-D Index data on non-responders are not available, nor are data regarding the reason for non-participation. The choice of scales was based upon the criteria of validity and reliability, but other instruments might be substituted in future studies. Strengths of this study were the sample size being in excess of that required for adequate statistical power, use of a well-standardised measure of depression and selection of items from the SF-36, inclusion of biological data from two influential physiological systems, and testing for effects due to age, sex, and depression status. As a final note, the inclusion of the measure of physical health functioning was to replicate the original IBI-D procedures reported by (IsHak et al., 2011). However, the lack of a significant correlation between the physical health measure and the SDS score reported here may argue for the deletion of that factor in future studies of the IBI-D.

5. Conclusion

The results of this study provide the first published information on (i) the ways that an IBI-D metric might be constructed and applied within clinical settings to include biological data as well as psychological data and information about daily functioning, (ii) the equations for two comparative IBI-D metrics, and (iii) the amount of extra information that those metrics provided beyond that from a scale of depression alone or from depressive symptoms and daily functioning data. These findings suggest that evaluating a patient's depression might be based upon symptoms alone, the addition of self-reports upon daily functioning, or by both of those plus inclusion of a biological variable. In the ongoing search for effective clinically-relevant indices of depression and its effects upon patient ability to function in their daily life settings, the IBI-D could be implemented in daily mental health practice to provide a more focused and informative metric for understanding how much depression influences a patient's daily life, the potential need for augmenting patients' coping with medication and/or behavior-based therapies, and the efficacy of those treatments at an individual patient level.

Declaration of Competing Interest

None of the authors has a conflict of interest to report.

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Data availability

Data are available from the first author on request.

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