

# A Comparison of Eating Disorder Symptomatology, Psychological Distress and Psychosocial Function Between Early and Later Onset Anorexia Nervosa

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## Research article

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# Abstract

**Objective:** Epidemiological studies suggest that the incidence of anorexia nervosa (AN) is increasing in younger populations, with some evidence that clinical differences occur between early onset (EO) and later onset (LO) AN, which may impact prognostic outcomes. The current study sought to compare eating disorder (ED) symptomatology, psychological distress and psychosocial function between EO- and LO-AN in a large sample of treatment-seeking patients with a diagnosis of AN.

**Methods:** Participants included 249 individuals with a diagnosis of AN who were assessed at an outpatient ED service. The sample was divided into two groups based on age of onset (AOO) using a median split (median AOO=16); those with an AOO  $\leq 16$  years ( $N=128$ ) were termed 'EO-AN' and those with an AOO of  $> 16$  years ( $N=121$ ) were termed 'LO-AN'. Comparisons were made between AOO groups on assessments of ED symptomatology, psychological distress and psychosocial function.

**Results:** EO-AN patients reported a significantly longer illness duration ( $p<.001$ ), significantly higher ED symptomatology ( $p=0.005$ ), dysmorphic concern ( $p=0.02$ ), stress ( $p=0.011$ ), anxiety ( $p=0.023$ ), and cognitive inflexibility ( $p=0.042$ ), compared to the LO-AN group.

**Discussion:** These findings suggest that clinical differences do occur according to AOO in AN whereby EO-AN may represent a more severe form of illness. Treatment strategies which specifically address patients with EO-AN may improve long term health outcomes and recovery.

## Plain English Summary

Presentations of anorexia nervosa (AN) are increasing in young populations. There is some evidence that there are differences in clinical features between those who have an early age of onset of AN and those who have a later age of onset. The current study compared individuals with early and later onset AN on eating disorder (ED) symptoms, psychological distress and psychosocial function in a large sample of treatment-seeking patients. Individuals with an early onset AN demonstrated a longer illness duration, higher ED symptoms, depression, stress and cognitive inflexibility than those with later onset AN. Treatment strategies for individuals with early onset AN should incorporate environmental and developmental factors that may contribute to the development and maintenance of AN.

Anorexia nervosa (AN) is a severe illness that has an approximate lifetime prevalence of 0.3% (1), is associated with significant psychiatric comorbidity (2), and demonstrates the highest mortality rate of any psychiatric disorder (3). The typical age of onset (AOO) for AN is between 15–19 years old (1), however population based studies suggest there has been an increased incidence of eating disorders (EDs) in the high risk group of girls aged between 15–19 (4), with individuals also presenting with AN at an earlier age (5). AOO has been demonstrated as a clinically significant feature in various psychiatric illnesses including affective disorders (6, 7), psychotic disorders (8) and anxiety disorders (9, 10) and may have important prognostic implications (11). Accordingly, exploration of clinical features in early

onset AN (EO-AN) versus later onset AN (LO-AN) may allow demarcation of symptom presentation and inform treatment prognosis.

Previous investigations into AOO in AN are inconclusive, with conflicting evidence surrounding the impact of AOO on ED severity, prognostic implications and psychological profile. Evidence for increased ED severity and poorer prognostic outcomes in EO-AN (as compared to LO-AN) have been demonstrated including; more rapid weight loss (12, 13), poorer long-term outcomes of low body weight and psychiatric comorbidity (14), and a longer duration of illness (15). However, other studies have found no difference in severity of weight loss between EO- and LO-AN (16), fewer cases of extremely low weight in those with EO-AN compared to LO-AN (17), and a positive association between low body mass index (BMI) and increased AOO (18). Assessments of the impact of AOO on psychological profile in individuals with AN also provide contrasting evidence. Whereas one study reported better self-esteem in those with EO-AN (19), others have reported that individuals with EO-AN demonstrate higher maturity fear, impulsivity and asceticism (interpreted as greater character fragility) than those with LO-AN (20).

A contributing factor to the discordant evidence to date may be the lack of consensus for what age constitutes 'EO' and 'LO' AN. EO-AN has previously been depicted as an AOO of < 14 years in some studies (17, 19, 21), < 16 years (20) and < 25 years in others (16), while others still have used puberty and menarche to demarcate AOO groups (22).

To date, there is a paucity of studies that compare levels of psychological distress, such as depression and anxiety and psychosocial functioning across different AOO groups in AN. Moreover, the majority of investigations into AOO in ED populations have utilised inpatient samples or retrospective healthcare records, with fewer investigations into outcomes in community and out-patient ED groups.

The current study aims to compare clinical presentation across AOO groups in individuals with a diagnosis of AN in a large sample of treatment-seeking adults at an out-patient ED service. Specifically, measures of ED symptomatology, psychological distress and psychosocial function will be compared across EO-AN and LO-AN groups. It is anticipated that those with EO-AN will exhibit increased ED symptomatology, psychological distress and more impaired psychosocial functioning than those with LO-AN.

## Methods

### Participants and Procedure

Data from 269 patients with a diagnosis of AN who were assessed for treatment at the Body Image and Eating Disorders Recovery Service (BETRS) at St. Vincent's Hospital, Melbourne Australia between 2012–2019 were included in this study. The service provided at BETRS includes outpatient and day patient programs and is described elsewhere (23). Diagnosis of AN was determined through a comprehensive assessment by specialist clinicians under the guidance of consultant psychiatrists in accordance with DSM-5 (24). Data were collected upon initial presentation as part of a larger assessment protocol. The

study was granted ethics approval from the Human Research Ethics Committee at St Vincent's Hospital, Melbourne and all procedures were in line with the Declaration of Helsinki. Informed consent was obtained from all participants.

## Measures

Demographic and clinical information:

- Information relating to education, employment status, partnered status, age of illness onset, duration of illness.

Eating disorder symptomatology:

- BMI: Height and weight were assessed using calibrated instruments. The participant's BMI was calculated by dividing their weight (kg) by the square of their height (m).
- The Eating Disorder Examination Questionnaire (EDE-Q) (25) is a 28-item self-report measure of psychological domains relevant to individuals with eating disorders. The questionnaire asks individuals to report on items in relation to the past 28 days and provides subscales of eating restraint, eating concern, weight concern, shape concern and global score, with higher scores on the EDE-Q indicate greater levels of disordered eating.
- Dysmorphic Concern: The Dysmorphic Concern Questionnaire (DCQ) is an assessment of levels of dysmorphic concern (26) and has gained support as a brief screening measure for BDD (27). It is a self-report questionnaire has 7 items rated on a 4-point Likert scale from 0 = "Not at all" to 3 = "Much more than most people".
- Motivation to change: The Anorexia Nervosa Stages of Change Questionnaire (ANSOCQ) is an assessment of readiness and motivation for change specific to AN (28).
- Dominant feature: During the assessment process and evaluation of ED diagnosis, clinicians at BETRS reported the dominant feature as restraint or purging for each participant.

Psychological distress and psychosocial assessment:

- The Depression Anxiety Stress Scale (DASS-21) (29) is a 21-item self-report instrument designed to measure the three related negative emotional states of depression, anxiety and tension/stress over the past week. Individual subscale scores representing depression, anxiety and stress were used here.
- Self-efficacy: The General Self-Efficacy Scale (GSES) provides a measure of optimistic sense of personal competence (30).
- Cognitive flexibility: The Cognitive Flexibility Scale (CFS) measures a person's awareness of communication alternatives, willingness to adapt to challenging situations and self-efficacy in being flexible (31).

- Quality of Life: The Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF) is a 16-item self-report measure of QOL (32). Responses are scored on a 5-point Likert scale, with higher scores indicating greater enjoyment and satisfaction with life. The Q-LES-Q-SF measures enjoyment and satisfaction with overall well-being including physical health, mood, social and occupation functioning, relationships and daily functioning. The overall Q-LES-Q-SF score was used here.
- Disability: The Brief Disability Questionnaire (BDQ) is an assessment of overall perceived physical and mental disability (33).

## Statistical Analyses

Given the lack of official criterion to classify EO- and LO-AN, we used a data-driven approach to dichotomise the sample into AOO groups. A median split of AOO (median AOO = 16) was conducted to group the patients into EO-AN (AOO of  $\leq 16$ ) or LO-AN (AOO of ED of  $> 16$ ). The use of a median-split has been demonstrated to be a robust method of analysis (34) and pertinent to our research design. The large sample size utilised in the current study negates the potential issue of Type II error and experimental power that may arise when conducting a median-split (35).

Data analysis was performed using SPSS (IBM, SPSS Statistics Version 25). Means and standard deviations were calculated for continuous variables, and frequencies were measured for categorical variables. Given the cross-sectional design of the assessments, total frequencies that were collected for each measure are stated. For individuals with multiple assessments, only their first assessment data was used. Comparisons were made between EO-AN and LO-AN groups on demographic characteristics, measures of ED symptomatology, psychological distress and psychosocial function. Independent *t*-tests were used to compare EO-AN and LO-AN groups on continuous variables while between-group comparisons of categorical variables were conducted using chi-squared tests of association; Fisher's exact test was used to analyse categorical variables where cell counts were low ( $n < 5$ ). For all analyses, significance was set at  $p < 0.05$ . Missing values were excluded on a list wise basis.

## Results

The mean age of the sample ( $N = 269$ , %F) was  $27.04 \pm 9.44$  at the time of assessment, of which 51% ( $n = 128$ ) had an AOO of  $\leq 16$  and 49% ( $n = 121$ ) had an AOO of  $> 16$ . Participant characteristics and comparison between EO-AN and LO-AN groups are presented in Table 1.

Table 1  
Participant characteristics

<b>Measure</b>	<b>All AN</b> <b>M ± SD or N (%)</b> <b>N=269</b>	<b>EO-AN</b> <b>M ± SD or N (%)</b> <b>N=128</b>	<b>LO-AN</b> <b>M ± SD</b> <b>N=121</b>	<b>p-value*</b>
Age at assessment	27.04 ± 9.44	25.09 ± 8.68	28.35 ± 9.54	<b>0.005</b>
Age of onset	17.74 ± 6.05	14.05 ± 2.27	21.64 ± 6.35	<b>&lt;.001</b>
Duration of illness (years)	8.86 ± 9.00	10.71 ± 9.20	6.30 ± 2.73	<b>&lt;.001</b>
Gender				0.856
Male	15 (5.6%)	7 (5.5%)	6 (5.0%)	
Female	254 (94.4%)	121 (94.5%)	115 (95.0%)	
Ethnicity				0.624
Aboriginal & Torres Strait Islander	5 (1.9%)	2 (1.6%)	3 (2.5%)	
Caucasian	209 (77.7%)	106 (82.8%)	88 (72.7%)	
Asian	8 (3.0%)	4 (3.1%)	3 (2.5%)	
Other European	16 (5.9%)	5 (3.9%)	9 (7.4%)	
Other	6 (2.2%)	2 (1.6%)	3 (2.5%)	
Unknown/missing	25 (9.3%)	9 (7.0%)	15 (12.4%)	
Education				<b>0.001</b>
Secondary	79 (29.4%)	52 (40.7%)	23 (19.0%)	
Tertiary commenced/completed	161 (59.9%)	67 (52.4%)	81 (67.0%)	
Vocational	7 (2.6%)	3 (2.3%)	3 (2.5%)	
Unknown/missing	22 (8.1%)	6 (4.7%)	14 (11.6%)	
Employment				0.465
Student	90 (33.5%)	46 (35.9%)	39 (32.2%)	
Full-time employed	22 (8.2%)	7 (5.5%)	13 (10.7%)	
Part-time employed	49 (18.2%)	29 (22.7%)	18 (14.9%)	
Home duties	10 (3.7%)	4 (3.1%)	4 (3.3%)	

AN: anorexia nervosa; M: mean; SD: standard deviation; EO-AN: early-onset anorexia nervosa; LO-AN: later onset anorexia nervosa; \*comparison of EO-AN and LO-AN groups.

<b>Measure</b>	<b>All AN</b>	<b>EO-AN</b>	<b>LO-AN</b>	<b><i>p</i>-value*</b>
	<b>M ± SD or N (%)</b>	<b>M ± SD or N (%)</b>	<b>M ± SD</b>	
	<b><i>N</i>=269</b>	<b><i>N</i>=128</b>	<b><i>N</i>=121</b>	
Unemployed	24 (8.9%)	9 (7.0%)	11 (9.1%)	
Unable to work because of illness	60 (22.3%)	28 (21.9%)	29 (24.0%)	
Unknown/missing	14 (5.2%)	2 (1.6%)	7 (5.8%)	
<b>Marital Status</b>				<b>0.236</b>
Never married	198 (73.6%)	98 (76.6%)	89 (73.6%)	
Widowed	2 (0.7%)	-	1 (0.8%)	
Divorced/separated	14 (5.2%)	4 (3.1%)	9 (7.5%)	
Married/defacto	33 (12.3%)	15 (11.7%)	14 (11.6%)	
Unknown/missing	22 (8.2%)	11 (8.6%)	8 (6.6%)	
AN: anorexia nervosa; M: mean; SD: standard deviation; EO-AN: early-onset anorexia nervosa; LO-AN: later onset anorexia nervosa; *comparison of EO-AN and LO-AN groups.				

Individuals with EO-AN were significantly younger at assessment, had a significantly younger AOO and a longer duration of illness than those with LO-AN. The comparison of ED symptomatology, psychological distress and psychosocial functioning between EO-AN and LO-AN groups are presented in Table 2.

Table 2

Comparison of ED severity, psychological distress and psychosocial function between EO-AN and LO-AN.

Measure	EO-AN	LO-AN	<i>p</i> -value
	M ± SD	M ± SD	
	N = 128	N = 121	
	n = 122	n = 119	
BMI	16.94 ± 2.28	16.70 ± 2.73	0.461
	n = 99	n = 94	
EDE-Q (Restraint)	4.32 ± 1.58	3.74 ± 1.75	<b>0.017</b>
EDE-Q (Eating Concern)	4.07 ± 1.17	3.63 ± 1.59	<b>0.030</b>
EDE-Q (Shape Concern)	5.02 ± 1.11	4.47 ± 1.48	<b>0.004</b>
EDE-Q (Weight Concern)	4.72 ± 1.30	4.10 ± 1.58	<b>0.003</b>
EDE-Q (Total Score)	4.44 ± 1.25	3.87 ± 1.55	<b>0.005</b>
	n = 48	n = 45	
DCQ	12.63 ± 4.42	10.20 ± 5.43	<b>0.020</b>
ANSOCQ Stage	n = 47	n = 39	0.421
Pre-contemplation	2 (3.6%)	2 (3.1%)	
Contemplation	15 (27.3%)	20 (31.3%)	
Preparation	27 (49.1%)	21 (32.8%)	
Action	3 (5.5%)	6 (9.4%)	
Dominant Feature	n = 99	n = 98	0.191
Restraint	88 (91.0%)	93 (90.0%)	
Purging	11 (8.0%)	5 (8.0%)	
DASS-21	n = 117	n = 115	
Depression	26.43 ± 11.71	23.41 ± 12.93	0.064

AN: anorexia nervosa; M: mean; SD: standard deviation; EO-AN: early-onset anorexia nervosa; LO-AN: later onset anorexia nervosa; BMI: body mass index; EDE-Q: eating disorder examination questionnaire; DCQ: dysmorphic concern questionnaire; ANSOCQ: anorexia nervosa stages of change questionnaire; DASS-21: depression anxiety stress scale; GSES: general self-efficacy scale; CFS: cognitive flexibility scale; Q-LES-Q-SF: quality of life enjoyment and satisfaction questionnaire short form; BDQ: brief disability questionnaire.

#### Declarations

Measure	EO-AN	LO-AN	<i>p</i> -value
	M ± SD	M ± SD	
	N = 128	N = 121	
Anxiety	20.38 ± 11.07	16.96 ± 11.65	<b>0.023</b>
Stress	26.97 ± 8.93	23.55 ± 11.19	<b>0.011</b>
	n = 45	n = 43	
GSES	24.70 ± 5.20	25.36 ± 5.88	0.580
	n = 47	n = 46	
CFS	44.40 ± 8.38	48.00 ± 8.41	<b>0.042</b>
	n = 98	n = 91	
Q-LES-Q-SF	36.01 ± 9.83	36.98 ± 10.89	0.522
	n = 122	n = 115	
BDQ	11.57 ± 5.44	10.72 ± 5.56	0.239
AN: anorexia nervosa; M: mean; SD: standard deviation; EO-AN: early-onset anorexia nervosa; LO-AN: later onset anorexia nervosa; BMI: body mass index; EDE-Q: eating disorder examination questionnaire; DCQ: dysmorphic concern questionnaire; ANSOCQ: anorexia nervosa stages of change questionnaire; DASS-21: depression anxiety stress scale; GSES: general self-efficacy scale; CFS: cognitive flexibility scale; Q-LES-Q-SF: quality of life enjoyment and satisfaction questionnaire short form; BDQ: brief disability questionnaire.			
<b>Declarations</b>			

The EO-AN group demonstrated significantly higher levels of ED symptoms in all subscales (restraint, eating concern, shape concern and weight concern) and global score of the EDE-Q, compared to the LO-AN group. The EO-AN group also reported significantly higher levels of dysmorphic concern than the LO-AN group. Individuals with EO-AN had significantly higher levels of anxiety and stress and significantly lower scores of cognitive flexibility, compared to the LO-AN group. There were no significant differences between groups on other variables.

## Discussion

The current study utilised a large sample of treatment-seeking adults at an out-patient ED service to investigate ED symptomatology, psychological distress and psychosocial function between EO-AN and LO-AN patients. Our hypotheses that those with EO-AN would demonstrate increased ED symptomatology, psychological distress and more impaired psychosocial function than those with LO-AN were partly support. Increased ED symptomatology in EO-AN was demonstrated by a longer illness duration, measures of ED symptomatology (EDE-Q) and of dysmorphic concern. However, there was no

difference in BMI, motivation to change or dominant feature between the two groups. The EO-AN group reported significantly increased psychological distress in symptoms of anxiety and stress, but not depression. Finally, the EO-AN group reported impaired psychosocial function through significantly decreased cognitive flexibility but the groups did not differ on self-efficacy, quality of life or perceived disability.

In accordance with prior research, our observations that patients with EO-AN reported a longer illness duration, higher ED symptomatology and dysmorphic concern indicate that EO-AN may present with a more severe form of illness (20, 36). The increased severity in ED symptomatology demonstrated by the EO-AN group was consistent across all domains of the EDE-Q, which includes restraint, eating concern, shape concern and weight concern, as well as the overall global score. This supports previous findings of more severe ED behaviours, such as complete refusal of oral intake and more severe restriction, in patients with EO-AN. Similarly, distorted self-perception of body image, a key feature of AN (24, 37), was significantly higher in those with EO-AN compared to LO-AN, consistent with previous findings (20). Contributing factors to the increased ED psychopathology seen in the EO-AN group may include various biological and environmental factors, which differ across development. These include pressures experienced by younger patients, such as changes related to puberty and external negative influences on body image perception and idealisation (38). It has been postulated that onset of AN prior to puberty may intensify perceived body image ideals (39), whereby the associated increase in adipose tissue and widening of the hips in adolescent females during puberty may exacerbate cognitions related to thin body ideal (13). Moreover, experience of body change in the EO-AN group may also be substantially influenced by social media ideals, peer relationships and the emergence of gender roles (40, 41) which may also contribute to the heightened stress and anxiety seen in the current study. The importance of physical attractiveness and the consolidation of sexuality have been demonstrated to influence self-concept and psychological profile at this stage of development (42). Moreover, rates of teasing and bullying have been demonstrated to be higher in EO-AN than LO-AN (16), supportive of the theory that early developmental trauma may contribute to increased levels of psychological distress as well as enduring patterns of body image disturbance (43, 44).

Another feature that is widely associated with AN is cognitive inflexibility (45, 46), which involves deficits in the ability to adapt thinking or attention to shifting goals or environmental stimuli (47). The current study demonstrated significantly lower levels of cognitive flexibility in patients with EO-AN compared to LO-AN, supportive of previous findings of lower metacognitive abilities in patients with EO-AN (48). Decreased cognitive flexibility, as demonstrated in the EO-AN group, may manifest in heightened rigidity in thinking and be reflected in more severe ED cognitions (49) and result in behaviours such as categorisation of food and calorie counting (50). Moreover, cognitive inflexibility may also lead to problems in finding solutions to managing difficulties and distress, therefore maintaining maladaptive thoughts and behaviours in AN (50), contributing to the challenges faced in psychotherapeutic interventions in this patient group. Specifically, diminished cognitive flexibility may be a limiting factor in cognitive behaviour therapy interventions, whereby a lack of communication of alternatives may lead to poor engagement with treatment and suboptimal outcomes of therapy. Indeed, cognitive inflexibility and

obsessional thinking have been shown to predate the onset of AN, persist over the course of the illness and contribute to later relapses in adulthood (51, 52).

Investigations into psychological distress in the current study found that those with EO-AN reported significantly higher stress and anxiety, but not depression, than those with LO-AN. All scores in both groups were categorised as '*moderate to severe*', with the exception of anxiety in the EO-AN group being at '*extremely severe*' levels (29). Given that comorbid anxiety and depressive disorders are reported to occur in high rates (30–80%) across different AOO groups with AN (19, 36, 53–55), these results were anticipated. The increased stress and anxiety demonstrated in the EO-AN group may be due to the abovementioned developmental and environmental influences experienced by this group of patients. It has also been suggested that EO-AN is under stronger influence of biological processes such as pre-illness alterations in neural circuits (56), which may lead to higher expression of distress and anxiety symptoms. However, it remains unclear whether higher levels of distress are as a result of increased ED psychopathology or whether increased severity of ED precipitates higher levels of distress.

## Conclusion

The current study builds upon previous research and has demonstrated that a large community-based treatment-seeking sample of patients with EO-AN exhibit more severe ED pathology, higher levels of psychological distress and increased cognitive inflexibility, compared with LO-AN patients. The disparities between AOO groups have potential implications for prognostic and treatment outcomes. Indeed, knowledge of increased ED severity, psychological distress and decreased cognitive flexibility may enable clinicians to adopt more tailored interventions for this vulnerable group. Further investigation into understanding the developmental influences on illness manifestation could highlight unique targets of future interventions.

The limitations of the current study include the cross-sectional nature of assessment, with a lack of long-term follow up. Other limitations include the inclusion of self-report measures of ED symptomatology and psychological distress. Future research should investigate the long-term implications of AOO on ED duration and treatment outcomes. This will enable informed early detection and intervention with EO patients as well as targeted interventions.

## Abbreviations

AN  
anorexia nervosa  
EO  
early onset  
LA  
later onset  
ED

eating disorder  
A00  
age of onset  
BMI  
body mass index  
BETRS  
Body Image and Eating Disorders Recovery Service  
DSM-5  
Diagnostic and Statistical Manual of Mental Disorders, 5th Edition  
EDE-Q  
Eating Disorder Examination Questionnaire  
DCQ  
Dysmorphic Concern Questionnaire  
ANSOCQ  
Anorexia Nervosa Stages of Change Questionnaire  
DASS-21  
Depression Anxiety Stress Scale  
GSES  
General Self-Efficacy Scale  
CFS  
Cognitive Flexibility Scale  
Q-LES-Q-SF  
Quality of Life Enjoyment and Satisfaction Questionnaire Short Form  
BDQ  
Brief Disability Questionnaire  
SPSS  
Statistical Package for the Social Sciences

## **Declarations**

## **Ethics approval and consent to participate**

The study was granted ethics approval from the Human Research Ethics Committee at St Vincent's Hospital, Melbourne and all procedures were in line with the Declaration of Helsinki. Informed consent was obtained from all participants.

## **Consent for publication**

Not applicable

# Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## Competing interests

DJC has received grant monies for research from Eli Lilly, Janssen Cilag, Roche, Allergen, Bristol-Myers Squibb, Pfizer, Lundbeck, Astra Zeneca, Hospira; Travel Support and Honoraria for Talks and Consultancy from Eli Lilly, Bristol-Myers Squibb, Astra Zeneca, Lundbeck, Janssen Cilag, Pfizer, Organon, Sanofi-Aventis, Wyeth, Hospira, Servier, Seqirus; and is a current Advisory Board Member for Lu AA21004: Lundbeck; Varenicline: Pfizer; Asenapine: Lundbeck; Aripiprazole LAI: Lundbeck; Lisdexamfetamine: Shire; Lurasidone: Servier; Brexpiprazole: Lundbeck; Treatment Resistant Depression: LivaNova. He is founder of the Optimal Health Program, currently operating as Optimal Wellness. He is on the boards of both Mind Medicine Australia and The Mental health Foundation of Australia. He does not knowingly have stocks or shares in any pharmaceutical company. No other authors report any conflicts of interest.

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## Authors' contributions

All authors designed the project. ZMJ, LMC and LC drafted the manuscript. ZJ conducted the data analysis. All authors reviewed the final manuscript.

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