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The concept of anorexia of aging in late life depression: A cross-sectional analysis of a cohort study.

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ABSTRACT

Introduction: Anorexia of aging (AA) is classically associated with depression. However, robust evidence is lacking regarding general clinic populations. Our aim was to evaluate the association between AA and major depressive disorder (MDD) in geriatric outpatients from a middle-income country.

Methods: We conducted a cross-sectional analysis of a cohort study. MDD diagnosis was assessed with a psychiatric interview (SCID-5-CV) according to DSM-5 criteria. Depressive symptomatology was assessed by a 15-items Geriatric Depression Scale (GDS) and the PHQ-9 questionnaire. Appetite was measured with the Simple Nutrition Appetite Questionnaire (SNAQ), whereas AA was defined as a SNAQ score $\leq$13 points). Linear and logistic regression analysis adjusted for potential confounders were applied to assess the association between depressive symptomatology, MDD and AA.

Results: Of the total 339 participants, MDD was present in 65. AA was more frequent in patients with MDD compared to non-depressed patients (30.7 versus 7.7%; $p<0.001$). The SNAQ score was lower in depressed patients (14.5 vs. 16.6, $p<0.001$). Adjusted for confounding, linear and logistic regression showed a significant association between the GDS score, PHQ-9 score and MDD with the SNAQ score ($p<0.001$) and cut-off representing AA ($p<0.001$), respectively. Moreover, MDD and AA interacted significantly with their association with weight loss ($p<0.001$).

Conclusions: Depression scales (even without somatic complaints) and MDD were associated with AA in geriatric outpatients. AA is associated with weight loss in MDD. Prospective studies should expand these findings.

1. Introduction

Anorexia of aging (AA) is conceptualized as the loss of appetite and food intake due to a decrease in basal metabolic rate and proportion of lean body mass (Morley & Silver, 1988). Appetite involves sensations of hunger and satiation and in addition to the 'physiological' AA can also be affected by secondary causes such as acute or chronic diseases, disabilities and medications (Cox et al., 2020). Although AA is underreported in the literature, its prevalence is high across different settings, being around 22% in the population (Landi et al., 2013; van der Meij et al., 2017), approximately 30% in long-term care facilities (Donini et al., 2011) and 42% in a general hospital (Pilgrim et al., 2016). AA is a risk factor for malnutrition and weight loss (Wilson et al., 2005), culminating in poor outcomes such as sarcopenia, frailty, impaired physical function, disability and mortality (Landi et al., 2013; Malafarina, Uriz-Otano, Gil-Guerrero & Iniesta, 2013; Tsutsumimoto et al.,

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2017). Poor appetite and AA can be easily assessed using the Simplified Nutritional Appetite Questionnaire (SNAQ) (Wilson et al., 2005). Nonetheless, studies that evaluate AA due to secondary medical causes are scarce, especially among geriatric outpatients, in whom AA is probably highly prevalent.

Meta-analysis shows that 7.2% of older persons suffer from a depressive disorder and even 17.1% from clinically significant depressive symptoms (Luppa et al., 2012). Depression is also the most common mental disorders in the geriatric clinic (Hall et al., 2014). This is not surprisingly, as depression shares several pathophysiological mechanisms with other geriatric syndromes such as AA, sarcopenia and frailty, including chronic low-grade inflammation, autonomic nervous system dysfunction, and hypothalamic-pituitary-adrenal axis dysregulation (Krishnan & Nestler, 2008). Depression often manifests with reduced appetite and weight loss, classically accounting for 30% of the causes of weight loss among older outpatients (Wilson et al., 1998). In fact, alterations in appetite or weight is one of the nine criteria for a major depressive episode according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5). Several explanations can be put forward for the association between depression and anorexia. Appetite loss can be related to an increased release of ghrelin due to a higher concentration of corticotropin-releasing factor, a potent anorectic agent, and to increased concentrations of serotonin after the stimulation of serotonin 5-HT2B and 5-HT2C receptors in depressed individuals (Takeda et al., 2013). Clinically, constipation (leading to fullness), grief, loss of social network and psychosis (delusion being poisoned) can also contribute to anorexia.

While the association between depression and the concept of AA seems obvious, it still poses important clinical challenges. Loss of appetite and anorexia in late-life depression can represent a symptom of depression (secondary cause of AA), an independent comorbid condition (a patient with AA that becomes depressed), or both. Furthermore, many depressed patients report normal appetite (a problem of insight) despite losing weight during a depressive episode (Simmons et al., 2020). Previous studies consistently found an association between (proxies for) AA and depression. Nonetheless, these studies were conducted in the general population, used screening scales to detect depression, and/or evaluated weight loss or malnutrition instead of changes in appetite or anorexia (Cabrera, Mesas, Garcia & de Andrade, 2007; Kimura et al., 2012). To our knowledge, no study has examined AA and depressive disorder according to DSM criteria in a clinical sample of geriatric outpatients. So basic knowledge of the prevalence of AA in depressed and non-depressed geriatric outpatients is lacking, while such data is important to increase awareness of this clinical problem, guide development of prevention strategies and to overcome iatrogenic damage by unnecessary clinical examinations.

The aims of the present study were (1) to evaluate the prevalence of AA in depressed and non-depressed geriatric outpatients, (2) to investigate the association between major depressive disorder (MDD), depressive symptomatology and AA, and (3) to evaluate the interaction between MDD and AA and their association with weight loss.

2. Methods

2.1. Study design and procedures

In the present study, we conducted a cross-sectional analysis with baseline data of the Multimorbidity and Mental health Cohort Study in Frailty and Aging (MiMiCS-FRAIL). The overall aim of the MiMiCS-FRAIL cohort is to explore the understanding of the bidirectional association between multimorbidity, frailty and depression within a geriatric outpatient sample accompanied in a multidisciplinary geriatric clinic (Aprahamian et al., 2020). Recruitment for the MIMICS-FRAIL has started in January 2018 and is still ongoing. Patients were included until June 2020 for the present study. All participants received an extensive evaluation based on clinical and psychiatric consultation and a comprehensive geriatric assessment (CGA) at baseline by a well-trained team of geriatricians, psychiatrists, and physical and nutritional therapists. A multi-axis diagnosis was reached after a multidisciplinary consensus meeting. Baseline assessment included a geriatric assessment protocol (which included the CGA), a structured psychiatric diagnostic interview, and validated observer-based and self-report questionnaires. The study followed the ethical standards and recommendations established by the Brazilian National Council of Health and all procedures were conducted in accordance with the precepts of research with humans stipulated by the Helsinki Convention. The local ethical committee approved this study under the protocol CAAE-12535218.5.0000.0065. A written informed consent was obtained from all participants.

2.2. Participants

All new patient referrals (from general practitioners, other medical specialties, or our triage clinic) to a secondary care university-based geriatric outpatient clinic were considered as eligible participants. Inclusion criteria were: (a) $\geq$ 60 years, (b) adherence to clinical follow-up, including at least one visit every 12 months, and (c) signing of the informed consent.

Additionally, exclusion criteria were: (1) a clinical diagnosis of dementia; (2) refusal to participate; (3) bipolar disorder; (4) psychotic disorder; (5) delirium or hospitalization in the last month; (6) electroconvulsive therapy; (7) wheelchair dependent; (8) severe sensory impairment; (9) severe limb paresis due to stroke; (10) unstable clinical condition (e.g., decompensated heart failure, current infection); and (11) terminal illness.

2.3. Measurements

2.3.1. Major depression

The primary independent variable of our study was the diagnosis of MDD according to DSM-5 criteria as assessed with the Structured Clinical Interview clinical version for DSM-5 (SCID-5-CV) (First, Williams, Karg & Spitzer, 2016). Six researchers were previously trained to apply the SCID-5-CV. All participants were clinically evaluated for the exclusion of a bipolar disorder as well as a depressive syndrome secondary to a clinical (somatic) condition by two geriatric psychiatry specialists.

Secondary independent variables were the Patient Health Questionnaire (PHQ) 9-item version and the Geriatric Depression Scale 15-items (GDS-15) in order to measure the severity of depressive symptoms. Brazilian versions of both instruments have been validated (Almeida & Almeida, 1999; Santos et al., 2013). The PHQ-9 is composed by 9 items which correspond to the DSM-5 criteria for a depressive episode and have to be rated on a Likert scale ranging from 0 – 3 points corresponding to “not at all”, “several days”, “more than half the days” and “nearly every day”. A higher score indicates a higher severity; a score of 1 to 4 points is considered normal; whereas 5 to 9 as mild, 10 to 14 as moderate, 15 to 19 as moderately severe, and 20 to 27 as severe depression. The GDS-15 was developed as a depression screening tool and contains 15 items which have been rated in a dichotomous format (yes/no). Scores $\geq$ 5 points best discriminates between persons with and without major depressive disorder and represent the presence of clinically relevant depressive symptoms (Pocklington, Gilbody, Manea & McMillan, 2016). We used two common instruments to evaluate depressive symptomatology due to two main reasons: (1) a variable of loss of appetite or weight is present at PHQ-9 (item 5) but not in GDS-15; (2) the PHQ-9 has the same 9 symptoms considered in DSM-5 criteria for MDD and can be used as a measure of symptom severity.

2.3.2. Anorexia of aging

All participants were evaluated with the validated Brazilian version of the Simplified Nutritional Appetite Questionnaire (SNAQ) (Zukeran, Aprahamian, Vicente & Ribeiro, 2020). The SNAQ is a fast and simple

4-item Likert-type questionnaire (Wilson et al., 2005) as follows: 1) My appetite is a.very poor, b.poor, c.average, d.good, e.very good; 2). When I eat a.I feel full, after eating only a few mouthfuls, b.I feel full after eating about a third of a meal, c.I feel full after eating over half a meal, d. I feel full after eating most of the meal, e.I hardly ever feel full; 3) I feel hungry a.rarely, b.occasionally, c.some of the time, d.most of the time, e. all of the time; and 4) Food tastes a.very bad, b.bad, c.average, d.good, e. very good. Each question is answered by choosing one option among five possible alternatives (letters a through e, corresponding to 1 to 5 points, respectively). The total SNAQ score is the sum of each answer of the 4 items, ranging from 4 (worst) to 20 (best) points (secondary outcome parameter). The lower the SNAQ score, the worse the appetite is. AA, our primary outcome parameter, is identified if the score is 13 points or lower (Wilson et al., 2005).

2.3.3. Weight loss

Weight loss was included as a secondary outcome parameter, since weight loss is clinically important. We measured self-reported weight loss over a 12-month period before the day of the interview through a question to the participant: "in the last year, have you lost weight, that is, not due to dieting or exercise?"

2.4. Confounders

Characteristics associated with MDD and AA were considered as potential confounders. Based on current literature (Cox et al., 2020) and also taking account of potential confounders we included demographic as well as lifestyle characteristics as covariates such as age, female sex, years of education, living alone, number of diseases, presence of polypharmacy (5 or more prescribed medications), body mass index (BMI, as indicated by the weight (in kg) of the patient divided by its squared length in meter), cognitive performance (according of the 10-Cognitive Screener [Apolinario et al., 2016]), regular use of alcohol (how many drinks and type of beverage consumed per week), currently smoking (yes/no) and frailty according to a 35-item Frailty Index (FI) (based on a previous validated model [Clegg et al., 2016]) with the exclusion of the variable weight loss to avoid collinearity with the SNAQ.

2.5. Statistical analyses

All continuous variables had a non-parametric distribution after histogram analysis and Kolmogorov-Smirnov test, except for the BMI. Descriptive statistics were performed for the characterization of the sample using percentages for categorical variables and mean with standard deviation for continuous measures. Chi-square test and Mann-Whitney test were used to compare categorical and continuous variables, respectively, between non-depressed and MDD participants. Student's T-test was used to compare BMI between the groups and Fisher test instead of chi-square test for groups with ≤ 5 individuals. Multiple regression analyses were conducted to assess the association between depression (either operationalized as MDD, GDS-15 score, or PHQ-9 score as independent variable) and the SNAQ score (linear regression) or the SNAQ cut-off for AA (logistic regression) as dependent variable, respectively. The analyses on the association between presence of MDD and the presence of AA was considered the primary analyses. All analyses using any dimensional measure were considered sensitivity analyses. We present unadjusted results as well as results adjusted for all covariates described above, except frailty (Model 1). In model 2 we additionally included the FI score instead of multimorbidity and polypharmacy due to a potential association between multidimensional frailty and AA (Tsutsumimoto et al., 2017).

Finally, we evaluated the interaction between MDD and AA and their association with weight loss (dependent variable) by logistic regression analysis. P-values lower than 5% were considered statistically significant. Data were analysed using Statistical Package of the Social Sciences (SPSS), version 25.0.

3. Results

Characteristics of the total sample and according to the presence of MDD are shown in Table 1. Women, sedentary behaviour, and self-referred weight loss were more frequent in MDD group. A lower mean value of the SNAQ score and a higher depressive symptomatology were also observed in MDD. Of the total sample, 41/339 (12.1%) presented AA. Fig. 1 shows the prevalence of AA according to depression status, where 20/65 (30.8%) MDD patients (30.8%) presented AA compared to 21/274 (7.7%) non-depressed individuals (Chi^2=26.4, p<0.001).

Linear and logistic regression analyses showed that MDD as well as depressive symptomatology measured by PHQ-9 and GDS-15 were significantly associated with both the SNAQ score and the SNAQ cut-off

Table 1
Characteristics of the total sample and according to major depression status (n = 339).

Characteristics		Total sample (n = 339)	Non-depressed (n = 274)	Major depressive disorder (n = 65)	*p-value*[1]
Age (years)	Median (IQR)	74.5 (14)	75.0 (15)	73.5 (10)	0.359
Female sex	n (%)	187 (55.2)	140 (51.1)	47 (72.3)	0.002
Education (years)	Median (IQR)	4.0 (5)	4.0 (5)	4.0 (4)	0.897
White (Caucasian)	n (%)	258 (76.1)	206 (75.2)	52 (80.0)	0.413
Married[a]	n (%)	191 (56.3)	154 (56.2)	37 (56.9)	0.916
Low income[b]	n (%)	288 (85.0)	233 (85.0)	55 (84.6)	0.932
Presence of a social network[c]	n (%)	92 (27.1)	197 (71.9)	50 (76.9)	0.413
Living alone	n (%)	34 (10.0)	25 (9.1)	9 (13.8)	0.255
Sedentary behaviour	n (%)	283 (83.5)	223 (81.4)	60 (92.3)	0.004[3]
Smoking	n (%)	15 (4.4)	13 (4.9)	2 (3.1)	0.744
Alcohol abuse	n (%)	31 (9.1)	26 (9.8)	5 (7.7)	0.649
Multimorbidity[d]	Median (IQR)	2.0 (2)	2.0 (2)	2.0 (2)	0.766
Polypharmacy[e]	n (%)	217 (64.0)	171 (62.4)	46 (70.8)	0.207
Cognitive functioning (10-CS score)	Median (IQR)	7.0 (5)	7.0 (4)	7.0 (4)	0.144
Self-referred weight loss[f]	n (%)	84 (24.8)	56 (20.5)	28 (43.1)	<0.001
BMI (kg/m^2)	Mean (SD)	26.6 (4.7)	26.6 (4.8)	27.2 (6.2)	0.342[2]
SNAQ score	Median (IQR)	17.0 (3)	17.0 (2)	15.0 (4)	<0.001
Frailty Index (35 items)	Median (IQR)	0.16 (0.14)	0.16 (0.11)	0.22 (0.14)	0.003
PHQ-9 score	Median (IQR)	5.0 (10)	3.0 (6)	15.0 (9)	<0.001
GDS score	Median (IQR)	5.0 (5)	4.0 (4)	8.0 (5)	<0.001

Note: IQR=interquartile range; SD=standard deviation.
[1] Mann-Whitney test for continuous variables or chi-square test for categorical variables.
[2] t-test.
[3] Fisher test.
[a] married marital status.
[b] 3 minimum wages (R$1045) or less.
[c] presence of at least two persons on whom the patient could count on helping with his care.
[d] number of medical (somatic) diseases.
[e] 5 medications or more in use.
[f] at least 5% weight loss in the last 6 months.

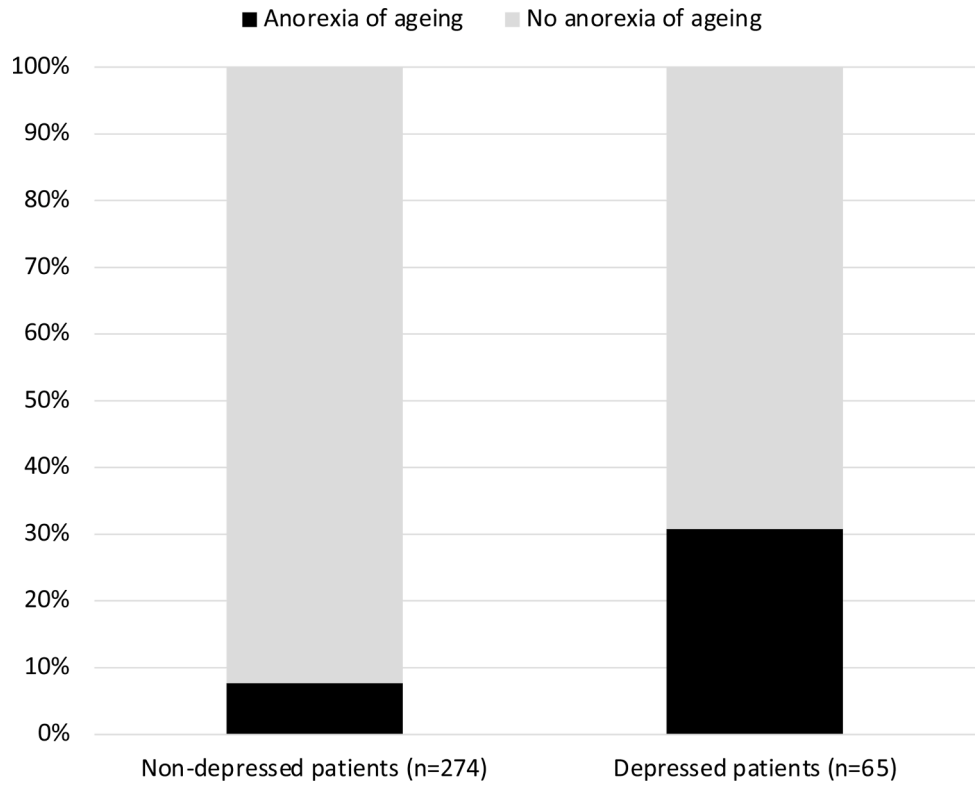

Fig. 1. Prevalence of anorexia of aging according to depression status (n = 339).

to AA (Table 2). Associations hardly changed after adjustment for potential confounders (models 1 and 2).

A shown in Fig. 2, self-referred weight loss was present in 28/65 (43.1%) depressed patients compared to 56/273 (20.5%) non-depressed patients (Chi^2=14.3, p<0.001). Among non-depressed patients, AA was observed in 13/56 (23.2%) of those who presented a self-referred weight loss and in only 7/217 (3.2%) of those without weight loss (Chi^2=26.2, p<0.001). On the other hand, a non-significant difference was observed among depressed patients, as 12/28 (42.9%) presented with AA and weight loss compared to 8/37 (21.6%) with AA without weight loss (Chi^2 =3.3, p = 0.066).

Logistic regression analyses showed a significant interaction between MDD and AA (unadjusted: p<0.001; adjusted for confounders (model 1): p<0.001) in their association with self-referred weight loss (at least 5%) in the last year. Table 3 shows the results stratified by depression and AA.

Table 2
Association between anorexia of aging, major depression and depressive symptomatology according to PHQ-9 and GDS-15.

	SNAQ score[a]	SNAQ cut-off[b]				
	B (SE)	Beta	p	OR	95%CI	p
Unadjusted						
PHQ-9 score	−0.16 (0.02)	−0.373	<0.001	1.17	1.10, 1.23	<0.001
GDS-15 score	−0.24 (0.04)	−0.311	<0.001	1.28	1.15, 1.42	<0.001
MDD	−1.65 (0.35)	−0.243	<0.001	5.79	2.85, 11.76	<0.001
Adjusted model 1*						
PHQ-9 score	−0.16 (0.02)	−0.373	<0.001	1.17	1.11, 1.24	<0.001
GDS-15 score	−0.25 (0.04)	−0.315	<0.001	1.33	1.19, 1.50	<0.001
MDD	−1.63 (0.36)	−0.251	<0.001	6.68	3.14, 14.19	<0.001
Adjusted model 2*						
PHQ-9 score	−0.16 (0.02)	−0.376	<0.001	1.17	1.10, 1.24	<0.001
GDS-15 score	−0.24 (0.04)	−0.314	<0.001	1.30	1.16, 1.46	<0.001
MDD	−1.60 (0.37)	−0.246	<0.001	6.07	2.80, 13.16	<0.001

Note:.
[a] linear regression.
[b] binary logistic regression.
* adjusted by age, female sex, education (years), living alone, number of diseases, polypharmacy, 10-CS score, smoking, and alcohol abuse.
** adjusted by age, female sex, education (years), living alone, 10-CS score, smoking, alcohol abuse, and the Frailty Index score.

4. Discussion

Among older patients visiting a geriatric outpatient clinic in a middle-income country, we found a 12.1% prevalence of AA. This prevalence was almost three times higher among MDD patients (30.7%). MDD and depressive symptomatology (with both PHQ-9 and GDS-15) remained significantly associated with AA and the SNAQ scoring after adjusting for multiple potential confounders. A distinction between AA and weight loss may be clinically important, as the majority of patients presenting with weight loss did not report AA. On the other hand, among patients with weight loss, AA should be a red flag for depression as only 3.2% of non-depressed older persons without weight loss reported AA in contrast to 21.6% of depressed patients without weight loss.

Previously, little is known about the true prevalence of AA and appetite dysfunction in older adults. Prevalence mostly ranged between 10 to 30% in different settings (Cox et al., 2020). This discrepancy may be related to different methods of evaluating AA, where most studies used BMI, weight measurement or single questions regarding appetite. Of our total sample, 12.1% presented AA, which was lower than expected to an outpatient population with a mean of 4.1 chronic diseases and high levels of polypharmacy (>60%). In another study conducted in

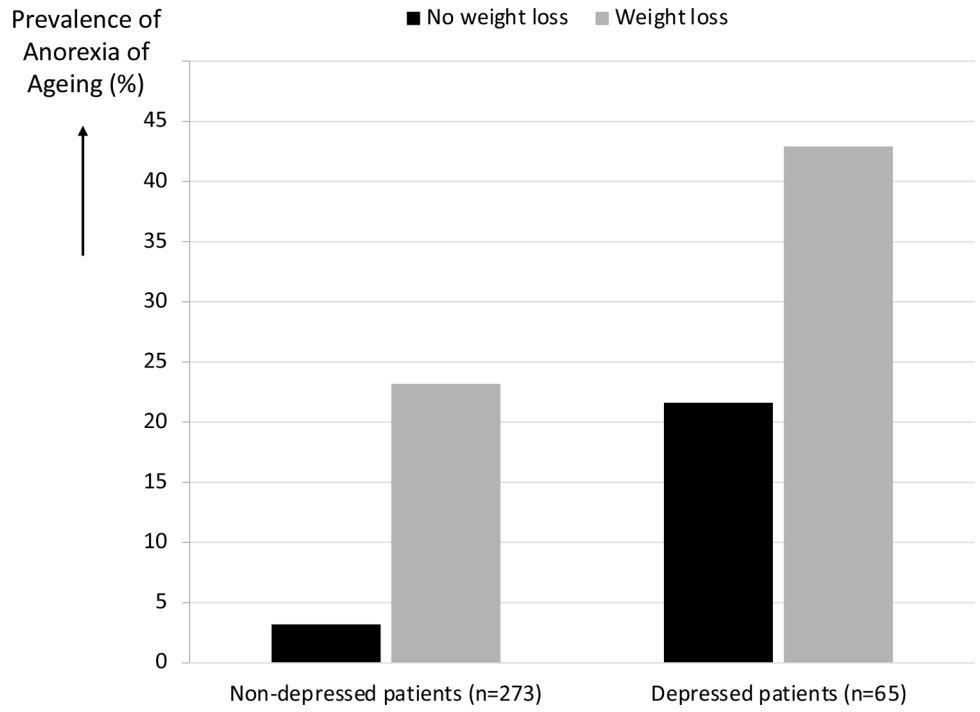

Fig. 2. Percentage of self-referred weight loss between depressed and non-depressed patients in the last year (n = 338).

Table 3
Interaction between depression and anorexia of aging in the association with subjective weight loss in the last 12 months.

	Odds Ratio (95% confidence interval) for Self-referred Weight Loss			
	Unadjusted Model	*p*	Adjusted Model*	*p*
No MDD or AA	1 (ref.)	–	1 (ref.)	–
No MDD, AA	8.11 (3.01–21.85)	<0.001	9.76 (3.29–29.07)	<0.001
MDD, no AA	2.63 (1.28–5.40)	0.008	3.48 (1.56–7.76)	<0.001
MDD and AA	7.10 (2.73–18.46)	<0.001	12.90 (4.35–38.20)	<0.001

Note: MDD=major depressive disorder; AA=anorexia of aging; interaction effect in binary logistic regression model.

* adjusted by age, female sex, education (years), living alone, number of diseases, polypharmacy, 10-CS score, smoking, and alcohol abuse.

an outpatient clinic in Brazil, the prevalence of AA was 27.7% using the SNAQ (Hara, Freiria, Silva, Fattori & Corona, 2019). This is surprising since we had a higher prevalence of MDD (19.1%), which could increase the frequency of anorexia. This discrepancy may also reflect different referral strategies of primary care physicians. In case of AA, primary care physicians can refer to a geriatric outpatient clinic for a comprehensive geriatric evaluation, including psychiatric disorders but also to a general internal medicine clinic to exclude a malignancy only. Referral strategies between primary care physicians may differ per catchment area. Further studies with different socioeconomically and geographically populations should be conducted.

Our study observed a prevalence of 30.7% of AA among MDD patients. Whereas geriatric depression is recognized as a major cause of AA, no systematic investigation of appetite and AA in geriatric depression has been published. Among adolescents, it has been reported that even 50% of MDD patients show lower appetite and 30% lose weight (Maxwell et al., 2009). In clinical practice appetite is less often evaluated compared to weight loss, whereas loss of appetite may be an important precursor of weight loss. This may especially count in case of geriatric depression, as we found that one in five depressed older patients reported AA without weight loss yet.

Neurochemical and functional neuroimaging studies show that change in appetite in depressed patients is highly linked to pathophysiological mechanisms of depressive subtypes (Simmons et al., 2020). Clinical studies have found that alterations in appetite and weight have the highest discriminative power in latent class analyses of depression subtypes (Ten Have et al., 2016). Recently, weight loss has also been associated with increased treatment resistance rates for SSRIs in depression (Zhang et al., 2020), which stresses the importance to prevent weight loss in depression. Prevention is also important as nutritional interventions become less effective in persons with higher risk for or at malnutrition or weight loss (Milne, Potter & Avenell, 2005). Moreover, AA is associated with several adverse outcomes such as frailty and weight loss (Wilson et al., 2005). Whether and how these outcomes will be present in depressed geriatric patients remains to be further investigated in prospective studies. Thus, monitoring appetite systematically and the consequent early identification of AA among depressed older adults might result in better outcomes. The interaction between depression and AA on explaining self-report weight loss, was due do the fact that among geriatric patients without weight loss, the prevalence of AA is very low among non-depressed geriatric patients (3.2%) and relatively high among depressed patients (21.6%). This means that in clinical practice, the presence of AA without weight loss may point to the presence of a depressive disorder.

Our study presents strengths and limitations that must be addressed. To the best of our knowledge, this is the first study to systematically evaluate the association between AA and MDD in a clinic sample of older adults. MDD was diagnosed using structured interview and specialized evaluation and AA was identified using the most recommended instrument. The most important limitation might be concerns about a spurious association between depression and AA due to overlapping criteria between AA assessed with the SNAQ and a depressive disorder of PHQ-9 sum score. Nonetheless, the GDS-15 does not screen for somatic symptoms of depression such as appetite or weight alterations and is the most widely used depression screening instrument in geriatric medicine. It is worth noting that the association between the GDS-15 and AA was similar to the association seen with the PHQ-9. In addition, our study has cross-sectional design, and no causality association can be drawn from our findings. Moreover, we did not include the effect of antidepressants as potential confounders to the association between MDD and AA. Our population has lower educational background and lower income, which

could prevent our findings from being extrapolated to other populations. Finally, weight loss was measured from self-report due to the cross-sectional design of our study.

5. Conclusions

In conclusion, AA is prevalent in older patients with MDD and depressive disorder is strongly associated with AA regardless of weight loss. Identifying appetite alteration in depressed patients can contribute with diagnosing depression subtypes, therapeutic response to treatment, and prevention of weight loss and adverse outcomes. Future studies should evaluate AA prospectively in this population and investigate anthropometric alterations potentially related to AA.

Brief summary

Depression screening instruments and major depression were associated with anorexia of aging. Anorexia were prevalent among depressed outpatients. The interaction between major depression and anorexia was significantly associated with weight loss.

Authors statement

IA and RCOV designed, analyzed the data and wrote the study. All authors critically appraised and contributed to manuscript revision, approved the final version of the paper, and agree to be accountable for all aspects of the work.

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Declaration of Competing Interest

None of the authors have any competing interests.

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