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REVIEW

Are the therapeutic strategies in anorexia of ageing effective on nutritional status? A systematic review with meta-analysis

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Abstract

Background: Anorexia of ageing (AA) may be considered as a risk factor for frailty and has an important impact on quality of life, morbidity and mortality.
Methods: A systematic review and a meta-analysis were performed to summarise the results from several trials on the effectiveness of treatments in AA, as associated with depression, sensory impairment of taste and smell, decreased appetite or early satiety, and disability. Eligible studies were required to report baseline and follow-up values, the mean change (Δ-change) from baseline, and/or the mean difference among intervention groups versus control group, concerning food intake (kcal/daily) and/or nutritional outcomes, such as body weight, body mass index, albumin and Mini Nutritional Assessment.
Results: The systematic review included 20 papers based on different therapeutic approaches concerning food intake and/or nutritional outcomes. The results of the meta-analysis indicate that the interventions for AA have an important impact on body weight [+1.59 kg; 95% confidence interval (CI) = 1.48–+1.71 kg; $P < 0.001$) and on energy intake (+56.09 kcal; 95% CI = −54.05 to +166.25 kcal; $P = 0.32$). Regarding secondary outcomes, it was not possible to meta-analyse the limited amount of data availab le.
Conclusions: The different variants of AA need to be defined because diverse therapeutic approaches are available. A more precise definition of the functional impairments associated with AA may allow a more correct decision about the most appropriate therapy to be prescribed. Moreover, this may allow for a more effective performance of the different therapeutic approaches once they are better targeted to the different scenarios of AA.

Introduction

A reduction of appetite and food intake, namely, anorexia of ageing (AA), is frequently observed in the elderly; it can be considered as a risk factor for frailty, and it has a relevant impact on quality of life, morbidity and mortality [(1–6)]. Indeed, several studies conducted in community-dwelling and institutionalised elderly subjects have indicated that AA and unintentional weight loss are dominant risk factors for protein-energy malnutrition, sarcopenia, physical frailty and mortality, independent of age, sex and other potential confounders [(7,8)]. A number of screening tools are available to identify subjects at risk of developing anorexia, including Functional Assessment of Anorexia/Cachexia Therapy; the Appetite, Hunger and Sensory Perception Questionnaire; and the Simplified

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Nutritional Assessment Questionnaire [9–12]. In clinical practice, AA can be diagnosed when, in the absence of alterations in the oral cavity that can affect the physiological act of eating and/or masticatory function, spontaneous food intake is significantly reduced (≤50% of the standard portion served or ≥25% of food left uneaten at two-thirds of meals for ≥3 days) [13–15].

The prevalence of AA is highly variable in the different epidemiological studies; it is approximately 30% in hospitalised subjects in acute care and rehabilitation wards and it decreases in free-living subjects; however, it remains at approximately 10% [7,16,17,18]. Anorexia should not be considered as an inevitable 'side effect' of ageing because many risk factors, such as disability, depression, sensory impairments, reduced chewing efficiency and a decline in gastrointestinal functions, can be identified and potentially corrected [19].

Macronutrient distribution can affect oral intake; a higher proportion of energy from fat appears to increase the satiety signal from glucagon-like peptide-1 and decrease hunger [20]. Protein intake moderately beyond the recommended dietary allowances in older adults appears to have a beneficial effect on muscle protein anabolism and appetite regulation, favouring the preservation of muscle mass at the same time as controlling body fat [20]. Different studies have confirmed the positive effects of oral nutritional supplements in malnourished older adults and different pharmaceutical approaches have been used in AA (e.g. megesterol, meclobemide, tetrahydrocannabinol, cyproheptadine, cholecystokinin antagonists), although the results are conflicting [21–25]. Improving the ambiance of dining rooms and assistance with meals (i.e. allowing adequate time for caregivers to feed subjects with disability or 'slow-eaters'), encouraging the relatives to be present during the mealtime and providing them with ethnically appropriate food choices may be helpful with respect to improving the nutritional status of free-living elderly subjects and nursing home residents [26–28].

Therefore, a systematic review and a meta-analysis were performed to summarise the findings from several trials on the effectiveness of treatments in AA.

Materials and methods

The present systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement [29].

It was performed using the steps:

- Formulation of the review question: 'anorexia of ageing: treatment procedures';
- Definition of participants: geriatric patients (≥65 years), both sexes, from all settings;
- Search strategy for the identification of relevant intervention studies on anorexia of ageing;
- Analysis of the data through the systematic review and meta-analysis.

Search strategy

English-written articles were identified by searching the Medline database [30], Scopus [31], ISI Web of Science [32] and Google Scholar [33].

The search strategy was based on the search terms: '*anorexia of aging*' AND '*sensory impairment*' OR '*taste impairment*' OR '*smell impairment*' OR '*swallowing impairment*' OR '*chewing impairment*' OR '*depression*' OR '*feeding*' OR '*oral supplement*' OR '*enriched meal*' OR' *exercise*' OR '*nutritional intervention*'. In a first stage, four individuals (SP, MR, LMD and EP) independently performed a systematic review of the literature, employing the same search strategy. In a second stage, duplicate records were removed and discrepant records were carefully investigated within these four individuals before selecting retrieved papers for full-text review.

Eligible studies were required to report baseline and follow-up values, the mean change (Δ-change) from baseline, and/or the mean difference among intervention groups versus control group, concerning food intake (kcal day^{-1}) and/or nutritional outcomes [such as body weight (BW), body mass index (BMI), plasma albumin levels, Mini Nutritional Assessment (MNA) score]. Studies in subjects with any cancers in the terminal phase, with good nutritional status (MNA > 23.5), with any acute diseases, uncertain life expectancy or undergoing artificial nutrition, palliative care or chemotherapy, were excluded.

Analysis of the data and presentation of the outcomes

Clinical trials investigating the effectiveness of dietary or pharmacological treatment in AA were included. For each study, the data specified were: the author, the name of the journal in which the study was published and the year of publication, the number and age of participants enrolled in the study, the drop-out rate, the study characteristics, and the therapeutic intervention, duration and outcomes. A meta-analysis for pooled estimate for aggregated data was performed.

Risk of bias in individual studies

The risk of bias of each study was assessed using the Cochrane Collaboration Risk of Bias tool [34] and, considering as factors contributing to the study quality, the generation of the allocation sequence, allocation concealment, blinding of outcome data, the presence of incomplete data and selective reporting. These factors were

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classified as low risk of bias, high risk of bias or an unclear risk of bias. Studies with a low risk of bias for at least three items were considered as good; studies with a low risk of bias for at least two items were considered as fair, and studies with a low risk for no item or only for one item were regarded as poor. Only randomised controlled trials were included in the meta-analysis.

Results

The literature search retrieved 322 papers via database searching and 84 papers were selected via full-text revision. Sixty-four studies were excluded. The 20 remaining studies (17 clinical trials, all presenting a control group and three observational studies) were selected for the present systematic review. The systematic review includes 20 studies with a total of 1515 adults aged 59–99 years. Of these 20, 12 randomised clinical trials were included in a meta-analysis. Figure 1 shows the study selection procedure.

The general data concerning the different studies are provided in the Supporting information (Table S1), as are the specific interventions and the results obtained (see Supporting information, Table S2). The duration of the studies was from 8 weeks to 24 months.

The inclusion criteria considered in the selected studies are very different, with a diverse combination of parameters: accidental weight loss, low BMI (<18, 21 or 25 kg m^{-2} in different studies), BW below 80% of ideal weight, reduced levels of albumin (<35 or 38 g L^{-1} in different studies), prealbumin serum levels < 0.18 g L^{-1}, MNA score below 23.5, the concurrence of acute illness or the presence of chronic illness or dementia, and the need for assistance during meals.

The definition of AA in the different studies was based on:

- Reduced dietary intake [not specifically quantified in six studies; objectively quantified (left more than 25% of their food uneaten at two-thirds of meals) in two studies; evaluating reduced dietary intake and sensory perceptions (olfactory sensitivity; appetite, hunger, sensory perception) in one study];

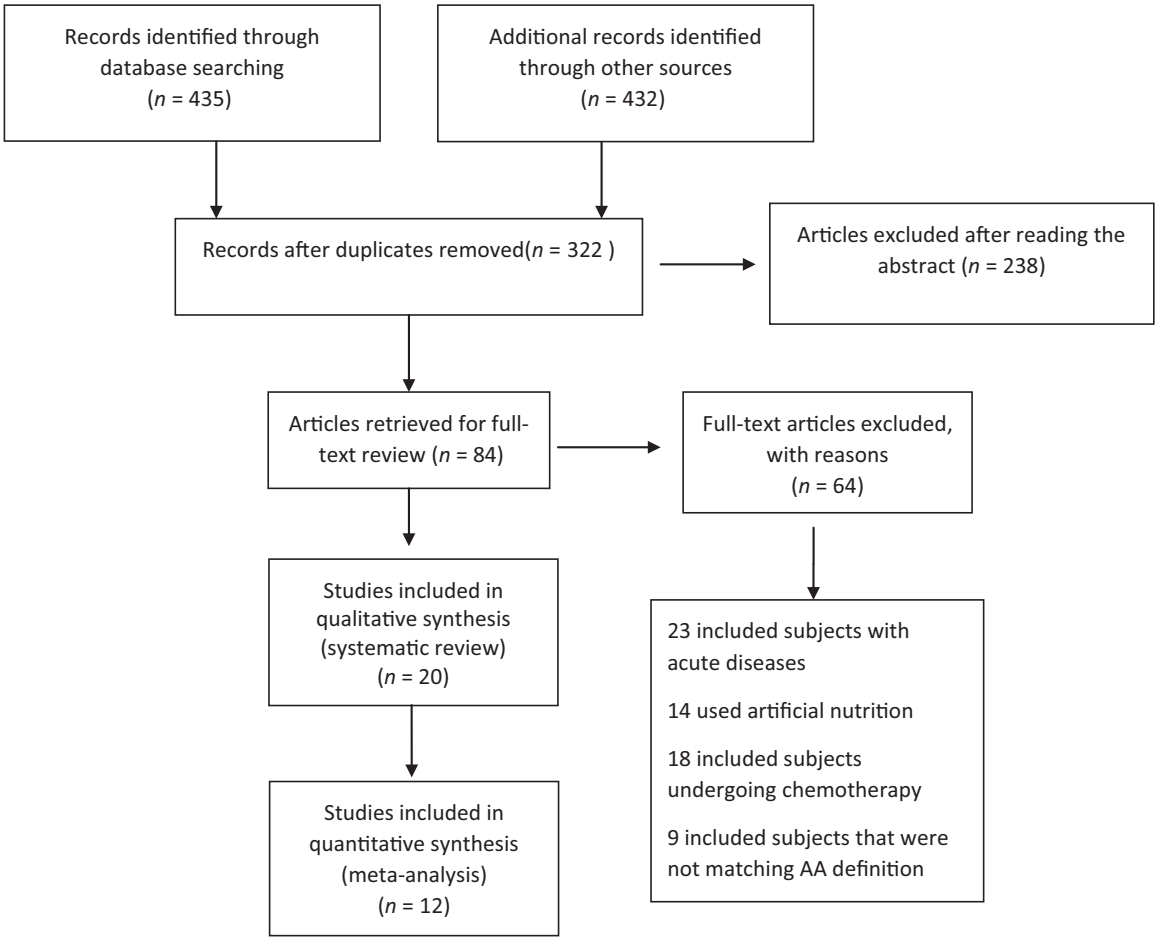

Figure 1 Flow diagram of the study.

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- Self-reported poor or fair appetite in one study;
- MNA score (considering the item aimed at assessing appetite in one study or the global score referring to the definition of 'at risk of malnutrition' in four studies);
- The presence of malnutrition (one study) or risk of undernutrition according to the physician judgment (two studies);
- The presence of disability that can affect eating in three studies.

The types of intervention were classified into five groups: pharmacological approaches [13,35,36], nutritional interventions or supplementation [37–46], flavour enhancement [47–49], assistance with meals [50–52], combination of nutritional intervention and exercise programme [53].

Results of interventions

Considering the different interventions

- *Pharmacological approaches*: antidepressants were effective with respect to increasing BW, MNA score and serum albumin levels significantly ($P < 0.05$) in subjects without dementia [35], whereas, in the study conducted by Wilson *et al.* [13] (using dronabinol), weight gain was not significant. Megestrol acetate was used in one randomised controlled trial conducted in 47 elderly subjects, recently discharged from an acute care hospital, with fair or poor appetite. Participants were randomised to four different intervention groups (placebo or megestrol acetate 200, 400 mg or 800 mg day^{-1}) for 9 weeks. No significant differences were found between treatment groups with respect to appetite and albumin levels, whereas prealbumin increased in a dose–response relationship [36].
- *Nutritional intervention or supplementation*: hot evening meal, protein and energy enriched soups and sauces or supplementation [with cookies or oral nutritional supplements (ONS)] were effective with respect to improving significantly ($P < 0.05$) nutritional parameters (energy intake, BW, BMI, albumin concentrations, MNA score) [37,39–43,45]. ONS were not effective only in the study conducted by Bos *et al.* [44], whereas a hot evening meal was not effective in the study conducted by Odlund *et al.* [38];
- *Flavour enhancement*: flavour enhancers and sauces added to the main dish were effective with respect to significantly increasing BW or energy intake in two studies [47,49], whereas they did not improve any nutritional parameters in the study by Essed *et al.* [48];
- *Meal assistance*: assistance with the meal was effective with respect to significantly increasing different nutritional parameters especially energy intake and MNA score ($P < 0.05$), whereas it did not affect BW or BMI [50–52];
- *Combination of nutritional intervention and exercise*: in the only study adopting this approach, this was not found to be effective with respect to improving BW, BMI, energy intake or albumin concentrations [53].

Considering the different nutritional outcomes:

- *Changes in body weight*: seven clinical trials [35,37,39,40,45–47] using different approaches, including antidepressants, hot evening meal, protein and energy enriched soups and sauces supplementation with cookies, flavour enhancers and ONS, demonstrated a statistically significant increase in intervention groups. BW varied from +0.73 to +2.4 kg depending on the study ($P < 0.05$). Five other trials using different approaches, such as assistance with the meal, flavour enhancers and other nutritional interventions or supplementation, found no significant weight gain [44] or registered a nonstatistically significant weight gain in the intervention groups compared to the control groups [38,42,43,50]. Finally, two observational studies reported contradictory observations: in the study conducted by Wilson *et al.* [13] (using dronabinol), the increase in BW was not significant, whereas, in the study by Cruz-Jentoft *et al.* [43], the use of ONS led to a significant increase in BW (+2.1 kg; $P < 0.0001$);

Changes in body mass index: in three randomised clinical trials based on nutritional interventions or supplementation [39,40,45], BMI increased significantly in intervention groups (BMI: +0.5, +0.8 and +1.3 kg/m^2, respectively; $P < 0.05$) compared to the control group, whereas the change in BMI was not significant in other studies using hot evening meals, feeding assistance or ONS [38,43,51];

- *Changes in albumin levels (in g L^{-1} and/or as a percentage)*: the three studies that evaluated the effects of interventions in terms of albumin levels produced contrasting results: both significant and nonsignificant increases or decreases. In a longitudinal study using antidepressants [35] albumin levels increased significantly (+1.78 g L^{-1}; $P < 0.05$) in subjects without dementia, whereas the increase in subjects with dementia was not statistically significant. In another study using ONS [39], a statistically significant decrease in albumin levels was observed in both intervention and control groups (−2.0 and −2.6%, respectively; $P < 0.05$). In a randomised clinical trial performed by Wouters-Wessling *et al.* [40] (using ONS), a nonsignificant increase in albumin levels was found in both intervention (+1.3 g L^{-1}) and control groups (+1.4 g L^{-1});
- *Changes in Mini Nutritional Assessment score*: three randomised controlled trials [42,45,50] and one observational study [43] using nutritional intervention/supplementation and assistance with meal showed a significant increase in MNA score in intervention groups (+3.6, +3, +1 and +2.5 points, respectively; $P < 0.05$).The results of the study conducted by Thomas *et al.* [35] (based on

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antidepressant therapy) showed a significant increase in MNA score (+0.76 points; $P < 0.05$) in subjects without dementia, whereas, in subjects with dementia, the increase was not significant;

- *Changes in energy intake*: four studies [41,49,50,52] (using different approaches: dronabinol, nutritional intervention or supplementation, assistance with a meal) showed a statistically significant increase in energy intake in intervention groups (energy intake variation: from +115 to +341 kcal day; $P < 0.05$). By contrast, two studies [48,53] (using assistance with a meal and a combination of nutritional intervention and exercise programme, respectively), found no significant variation in energy intake in the intervention groups.

Meta-analysed data

The meta-analysed mean differences for random effects (MD) showed a significantly greater increase in BW (MD = −1.59 kg; range = 1.47 to 1.71; $P < 0.01$) (Fig. 2) and in energy intake (MD = 56.09 kcal; range = −54.05 to 166.24; $P = 0.32$) regardless of the approach adopted to treat AA (Fig. 3).

In the five studies [40,42,47,48,50] (242 subjects in the intervention groups and 232 subjects in the control groups) that considered BW as an outcome variable, there was a significant increase (Fig. 2) when comparing the results of the intervention groups with those of the control groups. The test for heterogeneity indicated that the treatment effect was not significantly different between the considered studies ($P < 0.93$) with I^2 values = 0%. Mean differences of random effects showed a change in BW of −0.8 (−7.68, +6.08) kg, −0.0 (−6.8, +6.8) kg, −0.90 (−7.75, +5.95) kg [48], +1.51 (+0.09, +2.93) kg [42], +1.40 (+0.69, +2.11) kg [47], +1.60 (+1.48, +1.72) kg [50], +2.2 (+0.41, +3.99) kg [40] between groups, as shown in Fig. 2 as mean difference IV random effects.

In four studies [41,48,50,53] considering the energy intake as the outcome variable (634 subjects in the intervention groups and 265 subjects in the control groups), there was no significant increase in energy intake (Fig. 3) when comparing the results of the intervention groups to the control groups. However, the tests for heterogeneity indicated that the treatment effect was significantly different between the different studies ($P < 0.001$) with $I^2 = 96\%$. Mean differences of random effects between groups showed changes in energy intake of +36 (−67, +139) [41], 0 (−171, +171), +141 (−52, +335), +119 (−75, +314) [53], −20 (−85, +45), −16 (−70, +37), −5 (−61, +51) [48] and +215 (+202, +228) [50] kcal, as shown in Fig. 3 as mean difference IV random effects.

Risk of bias

Figure 4 shows the methodological quality of the studies. Only nine studies were suitable for all the five items considered for the methodological quality assessment (six studies were blinded for the variables considered). In summary, no studies were rated as appropriate in random sequence generation and in allocation concealment, 75% of the studies were rated as appropriate in blinding of participants and personnel, 75% of the studies were adequate in blinding of the outcome assessment, 80% reported incomplete outcome data, 90% gave only a selective reporting, and 75% showed other bias.

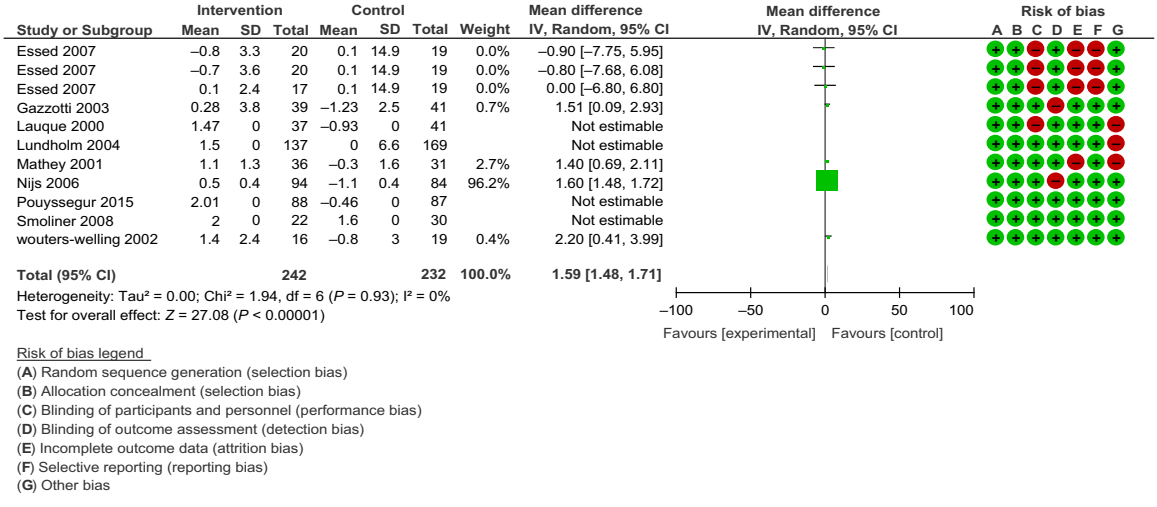

Figure 2 Effectiveness of treatments on body weight in the randomised controlled clinical trials included in the meta-analysis. CI, confidence interval.

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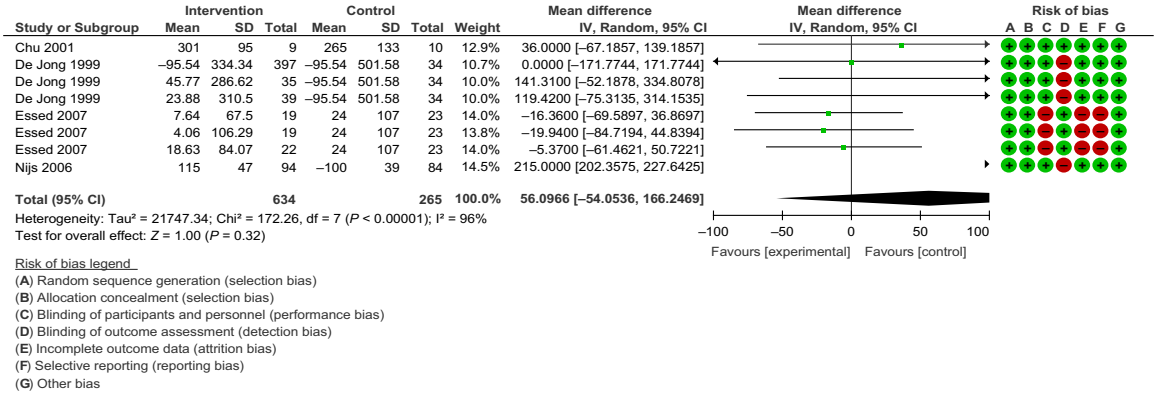

Figure 3 Effectiveness of treatments on energy intake in the randomised controlled clinical trials included in the meta-analysis. CI, confidence interval.

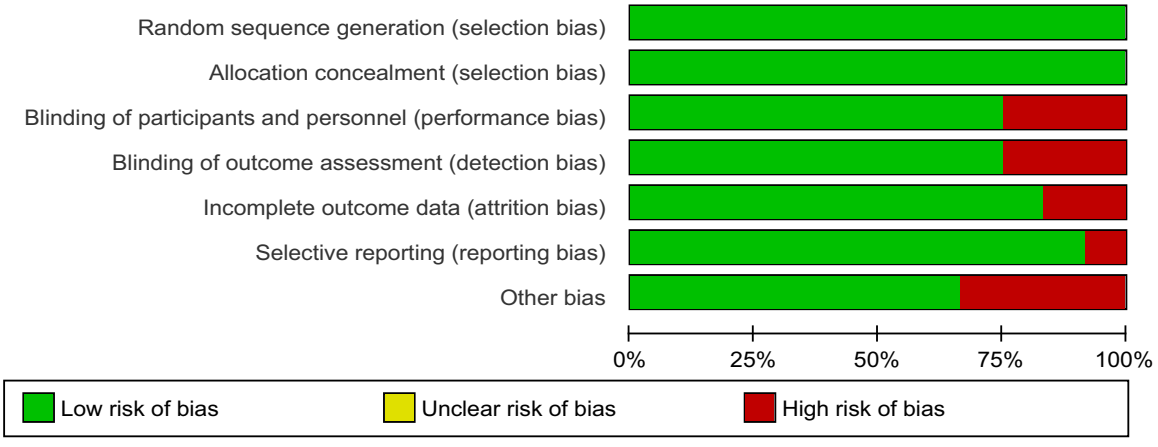

Figure 4 Summary of bias in either outcome considered: body weight and energy intake.

Discussion

This systematic review was able to select only a limited number of papers based on different therapeutic approaches, yielding contrasting results. The recent systematic review conducted by Malafarina *et al.* [54] concluded that these treatments were not effective for AA because they were not able to modify significantly the concentration of peptides involved in appetite control.

The results of this meta-analysis indicate that the interventions for AA have an important impact on BW (+1.59 kg, $P < 0.001$), whereas the effects on energy intake (+56.09 kcal, $P = 0.32$) do not appear to be statistically significant. With regard to secondary outcomes, such as albumin levels, MNA score and BMI changes, it was not possible to meta-analyse the data as a result of the limited amount of data available.

Although numerous studies suggest different approaches for managing AA, evidence based on randomised controlled clinical trials is scarce. It is important to note that following a nutritional support could be difficult for this population as a result of the coexistence of many factors: loss of appetite, inactivity, sensory impairment, early satiation, psychological disorders and mental impairments. Furthermore, AA treatment requires a multidimensional approach, including food manipulation (improvement of flavour, food texture and palatability, increasing dietary variety, and feeding assistance), correction of environmental threat (preventing social isolation and improving conviviality, particularly in nursing home residents, providing adequate individual feeding assistance, changing the mealtime routine, modifying the dining environment, and staff training), reduction of pharmacological risk factors (a certain number of cardiovascular, psychiatric and anti-rheumatic drugs may reduce appetite) and treatment of underlying medical causes (swallowing disorders, dyspepsia, malabsorption syndromes, neurological causes, endocrine and psychiatric disorders, respiratory diseases and cardiovascular diseases), as recommended in mumerous studies [26,55–59].

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Special attention should be also given to the nutritional screening tools, which constitute the primary intervention in the treatment of AA. MNA-Short Form and MNA-Long Form are considered among the best screening questionnaires, with a high accuracy for the prediction of malnourished elderly subjects, although the most recent versions of Nutritional Risk Screening also show good results in terms of compliance of subsequent nutritional treatments in younger residents of multiple healthcare sites, and perhaps this result could be significant also for older adults [60,61]. Additionally, the use of body composition and functional assessment techniques has become more frequent in the evaluation of nutritional status, with an improvement of the health outcomes of subjects, although clinical practice should evolve even more in this area, moving beyond current approaches [62].

Pharmacological approaches to AA have focused on research trials, in particular on interventions that try to modify neuropeptide regulation (administration of ghrelin, cholecystokinin and Melanocortin 4 receptor antagonists, drugs blocking protein catabolism) [51]. Thomas *et al.* [35] examined the effects of antidepressant therapy (mainly serotonin reuptake inhibitors; SSRIs) in AA associated with depression. Antidepressants were effective with respect to increasing BW, MNA score and albumin concentrations both in subjects with or without dementia. Previously, a study by Hilas *et al.* [57] involving mirtazapine assessed its favourable effects on appetite and weight in adults compared to placebo and other antidepressants. Mirtazapine may have multiple effects in subjects with weight loss because it relieves symptoms associated with depression, it regulates the gastrointestinal motor or sensory functions, and it significantly increases BW (mainly as a result of growth of visceral fat) [63]. Another study [64], comparing the effects of older tricyclic antidepressants (TCAs) and newer SSRIs in relation to weight gain in nursing home residents showed that TCAs do not contribute to weight gain more than other antidepressants.

In studies that considered subjects with AA combined with decreased appetite [13,37–43] or with early satiety [44,45,53], interventions focused on nutritional interventions characterised by providing an additional intake of cookies with high protein/energy density, liquid oral supplements enriched with micronutrients, a hot evening meal or adding flavour enhancers to the main dish. The results obtained in most of these studies, where decreased appetite was involved, showed an increase in BW and energy intake, whereas ONS combined with an exercise programme was not effective in the studies where AA was combined with early satiety [65,66]. A recent systematic review of the literature suggests that increasing energy/nutrients density of food intake may increase energy intake in older adults with anorexia [67]. It should be emphasised, as suggested by Yeomans *et al.* [68], that ONS preloads (mainly maltodextrin) may reduce the general desire to eat, whereas the administration of dietary supplements between meals is more effective with respect to increasing energy consumption [69].

Sensory impairments in the elderly can lead to a reduced enjoyment of food and then to AA and, by this route, to a greater risk of frailty in community-dwelling elderly people [70]. A reduced ability to differentiate between various intensities or concentrations of taste and smell can result in anorexia [71]. With respect to the treatment of AA combined with sensory impairment of taste and smell, flavour enhancers or sauces added to the main dish were effective with respect to increasing BW or energy intakes in two studies [47,49], whereas they did not elicit any improvements in nutritional parameters in the study by Essed *et al.* [48]. In the literature, considering different groups of subjects, the results remain contradictory: a study conducted by Havermans *et al.* [72] found that flavour intensification did not alter sensory-specific satiety, whereas other studies suggest that the consumption of food with enhanced chemosensory properties could provide nutritional benefits and help to prevent weight loss. In particular, monosodium glutamate (MSG) appears to be effective with respect to improving both flavour enhancement and food intake [73]. However, in the study conducted by Essed *et al.* [48] MSG (0.5% and 2%) did not appear to be effective with respect to improving food intake in an elderly sample. In addition, a recent systematic review considering studies conducted in all age groups could not provide sufficient evidence to recommend zinc supplementation for improving taste perception or acuity in zinc deficiency-related or idiopathic dysgeusia [74,75].

The treatment of AA associated with disability is mainly characterised in the selected studies by assistance with meals and repeated measurement of BW [46,50–52]. In this category of subjects, the administration of fruits and high protein supplements, as suggested by Lauque *et al.* [46], appears to be effective. Moreover, an exercise programme may affect the regulation of energy balance through the stimulation of corticotrophin-releasing hormone (CRH) and neuropeptide Y (NPY). In particular, NPY, by producing orexigenic effects and reducing thermogenesis, tends to counterbalance the physiological effects of CRH and therefore overcomes the effects of exercise on energy loss [76]. Unfortunately, the only study considered in this systematic review using an exercise programme (focused on skill training, including strength, endurance, coordination and flexibility) [53] did not show beneficial effects: energy intake, BW and BMI were not positively affected by the intervention

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combining nutrient-dense products and an exercise programme.

Strength and limitations of the present study

The strength of this systematic review is represented by an attempt to analyse the practical interventions proposed for AA when considering diverse clinical scenarios based on its combination with different functional impairments. Indeed, AA combined with disability, for example, may be very different in clinical manifestations compared to AA combined with sensory impairment, depression or lack of appetite/early satiation. A limitation of the present study is therefore represented by the limited number of studies that were selected, or even available and appropriate for inclusion, especially for the meta-analysis that could consider only BW and energy intake as study outcome variables.

Conclusions

It is necessary to define the different variants of AA because diverse therapeutic approaches are available. A better definition of the functional impairments combined with AA may allow a more correct decision to be made about the most appropriate combination of therapies to be prescribed. Moreover, this may allow for a greater efficacy of the different therapeutic approaches once they are better targeted to the different clinical scenarios of AA. Finally, different treatments show a potentially favourable effect on BW (or BMI), energy intake, albumin levels and MNA score, suggesting the need for further research using long-term intervention studies in large study groups in with the aim of defining the best approach for the management of AA.

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported, that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained. The reporting of this work is compliant with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline.

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Conflict of interests, source of funding and authorship

The authors declare that they have no conflict of interests.

No funding.

SP, MR, LMD and EP designed the study and search strategy, and also performed primary and secondary searches, title and abstract screening, full-text screening, analysis, quality assessment, and wrote the draft and final manuscript. DS provided consultation on the study design and data collection and critically reviewed the draft and final manuscript. AL performed the full-text screening and quality assessment, and also contributed to the final manuscript. SP and MR supervised the study design and critically reviewed and contributed to the final manuscript. EP and LMD supervised the study design and analysis and critically reviewed the manuscript. All authors critically reviewed the manuscript and approved the final version submitted for publication.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. General characteristics of the studies considered.

Table S2. Therapeutic approach and results obtained in the studies considered.

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