Aging Clinical and Experimental Research

Enhancing the management of anorexia of ageing to counteract malnutrition: are physical activity guidelines optimal?

--Manuscript Draft--

Manuscript Number:	ACER-D-22-00699R1
Full Title:	Enhancing the management of anorexia of ageing to counteract malnutrition: are physical activity guidelines optimal?
Article Type:	Point of View
Funding Information:	
Corresponding Author:	Daniel Crabtree, PhD University of the Highlands and Islands Inverness, Highland UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	University of the Highlands and Islands
Corresponding Author's Secondary Institution:	
First Author:	Daniel R Crabtree, PhD
First Author Secondary Information:	
Order of Authors:	Daniel R Crabtree, PhD
	Natalie J. Cox, PhD
	Stephen E.R. Lim, PhD
	Adrian Holliday, PhD
Order of Authors Secondary Information:	
Author Comments:	Dear Editor, We hereby resubmit our manuscript, entitled “Enhancing the management of anorexia of ageing to counteract malnutrition: are physical activity guidelines optimal?”, for consideration by Aging Clinical and Experimental Research. On behalf of my co-authors and I, I wish to thank the Editor and the expert Reviewers for taking the time and effort to review our manuscript. I wish to also thank the Editor and the expert Reviewers for their positive feedback and constructive comments. We have made several amendments based on the recommendations provided. The comments that we received and the amendments that we have subsequently made have undoubtedly strengthened our manuscript. We would like to highlight that Reviewer 4 requested that an additional figure be added to the manuscript. We have subsequently created a new supplementary figure, currently entitled "Supplement 2 - Fig S1". The figure can be found within the manuscript and attached separately. We feel that the Reviewers recommendation enhances the quality of the manuscript and we would like to kindly request that the figure be included within the main body of text, as opposed to within the supplementary materials please. We are however aware that only one figure/table is permitted within this type of manuscript. Whatever the outcome, we will of course accept the decision of the Editor. We hope that you look favourably upon our work. Kind regards, Dr Daniel Crabtree and co-authors

Response to Reviewers:	Manuscript Number: ACER-D-22-00699 Title: Enhancing the management of anorexia of ageing to counteract malnutrition: are physical activity guidelines optimal? Dear Editor and Reviewers, On behalf of my co-authors and I, I wish to thank you for taking the time and effort to review our manuscript. We wish to also thank you for your positive feedback and constructive comments. We have made several amendments based on the recommendations provided. The comments that we received and the amendments that we have subsequently made have undoubtedly strengthened our manuscript. Please see below specific responses to each of the comments provided. Amendments to the manuscript are explained, with line numbers for reference. Amendments are highlighted in red colour in the manuscript itself. Thank you for your consideration of this manuscript. Kind regards, Dr Daniel Crabtree (Corresponding Author) Reviewer #1: In the manuscript "Enhancing the management of anorexia of ageing to counteract malnutrition: are physical activity guidelines optimal?" the aim is to understand if the UK's guidelines for physical activity are an effective tool to counteract malnutrition and control the anorexia of aging. The authors investigated the relationship between physical activity and level of appetite, energy intake and it resulted that the level corresponded to "moderate" activity might provide substantial benefits to appetite and energy intake. Indeed, further studies are needed for optimize the amount and nature of PA especially for elderly with anorexia, and taking into account the likely acute and chronic impact of PA on appetite. Comments: * The authors mention the problem of malnutrition in elderly, but it would be interesting know the etiology of this problem in this population. Thank you for raising this point. We agree that describing the aetiology of malnutrition in older adults would be of interest. However, unfortunately, we are restricted by the word limit of the opinion piece. Therefore, we have described the aetiology of malnutrition in older adults as multifactorial in nature and directed readers to a comprehensive overview by leading experts (lines 49-50). * It is mentioned that moderate activity levels might provide enhancing in appetite and energy intake but are not clarify the frequency or the criteria to define the physical activity as moderate instead of low, or very low. Thank you for your comment. In this manuscript we have referred to current UK physical activity recommendations, which do not define moderate physical activity by frequency but instead recommend that those over 65 years accumulate 150 minutes of moderate intensity activity each week. The UK physical activity guidelines also provide examples of moderate intensity activity, one of which we have now included within the manuscript (lines 60-61). Furthermore, the frequency and criteria for activity to increase appetite in ageing remains uncertain, as we discuss in page 6, line 168 onwards. * Physical activity seems to prevent anorexia, but this occur only because it increases the energy expenditure and consequentially the energy intake and the appetite, are other factors involved in this phenomenon? Thank you for your comment. In addition to the specific factors that we have discussed in our manuscript, there are a number of other factors that may contribute to the potential for physical activity to improve appetite and diet in older adults, for example,

executive functioning, social interaction and gut microbiome.

Executive function is controlled by the frontal lobe, an area of the brain that undergoes accelerated decline during old age (Stuss & Alexander, 2000). There has been considerable scientific interest in poor executive functioning and its relationship with overeating, impulsivity and weight gain. However, poor executive function has also been associated with anorexia nervosa (Wilson & Wade, 2006). Therefore, goal-directed eating behaviour is not only important for those who are overweight but also for those who are underweight. It has been observed that high levels of self-reported physical activity are beneficial for executive performance in healthy older adults.

Eating alone has consistently been found to be associated with increased nutritional risk in older adults (Hetherington et al 2006). Increasing physical activity may have an indirect, positive effect on eating behaviour, by facilitating social interaction and the formation of social networks.

Finally, Cox et al (2021) observed that in community-dwelling adults aged ≥65 years, those with poor appetite had reduced species richness and diversity of their gut microbiome. Interestingly, exercise has been associated with potentially beneficial alterations in gut microbial composition (Monda et al 2017), though further research in older adult cohorts is required.

These factors are of great interest and require further investigation, however, unfortunately, they are outside the scope of this point of view manuscript and the word limit will not permit a detailed description of these factors.

* High intensity exercise training typically induces a transient suppression of appetite, so is it better to avoid this kind of training or not?

Several research studies have demonstrated that an acute bout of high intensity exercise transiently suppresses feelings of hunger in adults. However, these studies have been conducted with young and middle-aged adults. We do not currently know how a bout of high intensity exercise will affect the appetite of adults aged ≥65 years. Therefore, we cannot speculate as to whether it would be better for older adults to avoid this type of exercise, in the context of appetite control. However, evidence from Johnson et al. (2021) suggests that resistance exercise does not negatively impact upon acute energy intake in older adults. Hence, there is no rationale for older adults avoiding this kind of training, from a drive to eat perspective.

* Line 81 is mentioned that the difference between high energy and low energy preloads, how does this influence the energy intake? How is it possible to understand it, and why is it important?

This statement relates to the ability of more active people to adjust feeding in order to better achieve acute coupling between energy intake and energy needs, compared with less active people. This has been clarified with the addition of the sentence: “This indicates a tendency for more active people to adjust feeding to achieve an acute coupling of energy intake with energy needs.” (Lines 96-97).

* Lines 115-116 "Consequently, resting metabolic rate and hence drive to eat is expected to be lower", However, energy expenditure (EE) is not mentioned, is expected to be lower?

This sentence reflects the relationship between fat-free mass, resting metabolic rate and drive to eat: fat-free mass predicts drive to eat and energy intake, mediated by resting metabolic rate (outlined in lines 130-131). This has been explained a little more clearly in the sentence highlighted.

* Lines 145-146 "Many of these characteristics of low activity are also consequences of malnutrition (low mass, low functional capacity)". In my opinion these factors are not the consequences of malnutrition, but they are factors influencing each other.

Thank you for raising this important point. We have altered the text to reflect your comment (line 161).

* Lines 171-172 authors stated that "We suspect such a threshold to be below the current PA guidelines of 150 minutes of moderate intensity activity per week". Regarding this, why the threshold is below 150 minutes? How have they arrived at this result?

Upon reflexion, prompted by this comment, we accept that this statement is somewhat speculative at this stage. This sentence has been removed.

Reviewer #2: This opinion piece has interesting aspects but it is not easy to follow. Increased structure would be helpful.

1. I recommend an Introduction in which you state the objectives (what will be discussed).

Thank you for your comment. We have now added an introductory section to the manuscript (lines 27-34), which includes reference to what will be discussed.

2. The claim of widespread inadequacy in energy intake (EI) in older adults in Western countries seems implausible in view of how many elders are overweight and obese. Adding information on weight status as a function of aging would be important as would be pointing out whether obese older adults can be malnourished. Also adding information on usual physical activity levels of overweight/obese vs normal weight older adults would be helpful.

Thank you for your comment. This raises some interesting and important considerations that we have attempted to address as best as possible within the tight word limit of this piece.

We acknowledge that the prevalence of excess body mass is high in older adults, indeed increasing with age. However, this is a particularly heterogeneous population, with relatively higher proportion of the population at extreme ends of the bodyweight status spectrum: while many may be living with overweight and obesity, many are undernourished and underweight. Interestingly, being underweight and losing body mass are shown to be greater risk factors of mortality that being overweight or gaining body mass in those over 65 years (Winter et al. 2014; Javed et al. 2020). Given this, and the prevalence of low appetite and malnutrition described in the manuscript, we think addressing these issues is important. This argument is presented at the start of the second paragraph.

We acknowledge that it is important to describe the term ‘malnutrition’ and to clearly define how the term will be applied for the purposes of this manuscript. We have now included a description of the term ‘malnutrition’ and stated that, for the purposes of this manuscript, malnutrition refers to a lack of intake of nutritional requirements leading to loss of body mass and function (lines 41-43). While we agree that it is important to consider the impact of different physical activity levels and body composition types on appetite and diet in older adults, this point of view article focuses specifically on the potential effects of physical activity on appetite and diet in the context of anorexia of ageing.

3. A comment on the distinctions between anorexia of aging, low EI, and malnutrition and their relationships with weight status (or BMI) would be helpful.

Thank you for highlighting this. We strongly agree that distinguishing between these terms is important (despite challenges associated with a lack of agreement and consistency with definitions and classifications of anorexia of ageing and malnutrition). We feel that the addition of an introductory paragraph and the editing of the second paragraph have afforded us the opportunity to introduce and define anorexia of ageing and malnutrition more clearly, and in the context of low EI and consequent effects on body composition and frailty, which is also outlined now more clearly with the addition of Fig. S1, in the Supplementary Material.

4. Page 3, line 67 - In the section entitled: Relationship between physical activity and appetite control…" please indicate early in this section that most of the studies were

conducted in young adults. As currently written, it is hard to link the content of this section to the problem of anorexia of aging.

Thank you for your comment. We have now stated early within this section of the manuscript that the studies informing the development of the J-shaped curve have predominantly been conducted with adults aged <65 years (lines 91-92).

Reviewer #3: Your proposed distorted J-shaped relationship between habitual PA and EI in older adults is an intelligent explanation and the data quoted in your publication support it. During COVID19 pandemic new data emerged that clearly support the need to exercise in all humans. Adding PA to treatment of anorexia is strongly supported by COVID 19 pandemic related data and should be added to this paper as an additional argument.

Thank you for your positive feedback regarding our manuscript. We entirely agree that opportunities for physical activity should be promoted and available to all, and that COVID19 significantly impacted upon the global populations physical activity levels. However, we could not locate data supporting a relationship between the effects of COVID19 on physical activity levels and anorexia of ageing. Therefore, we have not referred to COVID19 within our manuscript. If the Reviewer feels that we have overlooked data supporting a connection between the effects of COVID19 on physical activity levels and anorexia of ageing, then we may reconsider our response.

Reviewer #4: Clarity of content and adequacy to scientific language was demonstrated throughout the manuscript. In addition, the manuscript is interesting, however it is necessary to make some considerations.
I suggest that the authors make a figure related to the following content
It is easy to see how a sudden reduction in PA (perhaps due to illness) and consequent acceleration in loss of lean mass could elicit a reduction in drive to eat and EI. This will further exacerbate lean mass loss, potentially impairing functional capacity, which in turn reduces PA.

Thank you very much for this suggestion. We agree that presenting this in figure form would be beneficial for the reader. The formatting guidelines allow for only one figure, and the current figure is critical to a key argument of our manuscript. However, we have included a figure in the Supplementary Material (Figure S1). This diagram, entitled “The Vicious Cycle of Anorexia, Malnutrition and Frailty”, depicts the relationship between loss of appetite, protein-energy malnutrition, fat-free mass loss, reduction in resting metabolic rate, and consequent further suppression of appetite. The diagram also highlights how this cycle can be accelerated with illness or fall, leading to reduced physical activity and immobilisation.

I suggest that the authors add information about the need to practice resistance training in older adults. Thus, there may be an increase in muscle mass, with a consequent increase in energy expenditure at rest. This could influence the increase in appetite in this population.

This is indeed an important consideration to highlight. Effort was made in the original submitted manuscript to make this point, with the following two sentences at the end of the penultimate paragraph:

“Secondly, the benefits of resistance exercise for older adults with regards maintaining lean mass and physical capacity are well-established. Such benefits are also important for maintaining drive to eat. In addition, while high-intensity exercise typically induces a transient suppression of appetite, resistance exercise has been shown not to negatively impact short-term EI in older adults [12]. Therefore, there may be an argument for resistance exercise to be a more prominent component of PA recommendations for older adults with low appetite; it may be beneficial, from an appetite and EI perspective, to exceed the current guidelines of completing resistance exercise on two days per week.” (Lines 188-196).

This section has been edited to add greater explanation and emphasis.

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We once again would like to thank the Editor and the expert Reviewers for their time, efforts and expertise.

Enhancing the management of anorexia of ageing to counteract malnutrition: are physical activity guidelines optimal?

Short running title:

Enhancing the management of anorexia of ageing.

Daniel R. Crabtree [1], Natalie J. Cox [2,3], Stephen E.R. Lim [2,3, 4,5], Adrian Holliday [6]

[1] Institute of Health Research and Innovation, Division of Biomedical Sciences, University of the Highlands and Islands, Old Perth Road, Inverness, UK.

[2] Academic Geriatric Medicine, Faculty of Medicine, University of Southampton, Tremona Road, Southampton, UK.

[3] NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Tremona Road, Southampton, UK.

[4] NIHR Applied Research Collaboration Wessex, Southampton, UK.

[5]University Hospital Southampton NHS Foundation Trust, Tremona Road, Southampton, UK

[6] Human Nutrition Research Centre, Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, UK.

Corresponding author:

Dr Daniel R. Crabtree, Institute of Health Research and Innovation, Division of Biomedical Sciences, University of the Highlands and Islands, Centre for Health Science, Old Perth Road, Inverness IV2 3JH, Scotland, UK; E-mail: daniel.crabtree@uhi.ac.uk; Telephone: +44(0)1463 279405.

Introduction

Poor appetite in later life – termed "anorexia of ageing" - is acknowledged as a key determinant of age-related malnutrition. While physical activity (PA) is often recommended for increasing drive to eat, these recommendations are not well-evidenced in the older population. In this opinion piece we outline limitations to physical activity recommendations in anorexic older adults. We then discuss current evidence for the relationship between physical activity and appetite amongst younger adults and postulate how this relationship may change in later life, with implications regarding future recommendations and research.

Malnutrition and anorexia in later life

The older adult population is particularly heterogeneous. Somewhat paradoxically those aged 65-75 years in the United Kingdom (UK) are at greater risk of both excess body mass and low body mass, compared with young- and mid-life adults [1]. However, it is low body mass and a loss of mass, rather than excess body mass or gains in mass, that pose the greatest risk of mortality in older adults [2,3]. As such, malnutrition – in this context referring to a lack of intake of nutritional requirements leading to loss of body mass and function – is a major healthcare challenge in older people, contributing to negative health outcomes, including sarcopenia and frailty, and adversely affecting independence and quality of life, to large healthcare cost [4]. It is estimated that around 27% of community dwelling older adults and up to 50% of those in healthcare settings are at risk of malnutrition [5]. The management of malnutrition in older adults, such as promotion of higher protein intake, has progressed over recent years. However, knowledge regarding optimal approaches to prevent or delay its onset and to slow its progression are less well established [4]. The aetiology of malnutrition in older people is multifactorial (see Volkert et al. [6] for a comprehensive overview) but one key determinant is loss of appetite, which is highly prevalent across settings, affecting 20% of community dwelling older adults and rising to over 40% in hospitalised populations [4,7]. Anorexia can be due to effects of comorbidity or medications but can also be a consequence of the ageing process itself acting to reduce overall energy intake (EI) and negatively alter dietary pattern [7]. Stimulating appetite and thus EI is an important potential strategy to prevent onset or reduce progression of malnutrition.

There are few well evidenced strategies to stimulate appetite in anorexic older adults [7]. Popular belief, alongside guidance from ageing charities and health agencies such as the National Health Service (NHS) in the UK, advocate increasing PA as a method to improve appetite in later life [8]. Current UK PA recommendations for those over 65 years include daily activity to accumulate 150 minutes of moderate intensity activity (such as brisk walking) a week and resistance activity on at least 2 days a week [9]. Higher levels of habitual PA have been proposed to increase the drive to eat and improve matching of energy intake with energy expenditure. However, evidence for this relationship stems from observations on adults aged under 65 years, while the nature of this association in older populations is largely unexplored.

Inadequate PA is a ubiquitous problem. A study which included data from 358 surveys across 168 countries (n=1.9 million) showed a global prevalence of insufficient PA of 23.3% [10]. Engagement in PA differs between older and mid-life adults, with a trend towards reduction in PA with advancing years. A survey conducted in England in 2016 showed that more than 60% of men and women aged between 45-54 years met the recommended aerobic activity guidelines [11]. In contrast, only 35% of men and 24% of women aged over 75 years met these guidelines [11].

Given the differences in PA between older and mid-life adults, it is questionable whether current guidance to follow recommended PA levels as a means to stimulate appetite for older adults is informed by sufficient strength of evidence. It is therefore important to interrogate potential differences in the relationship between habitual PA and appetite control for mid and later adult life to guide future research. This would provide evidenced PA recommendations with a view to stimulate appetite in older adults with anorexia and at risk of malnutrition.

The relationship between physical activity and appetite control: The J-shaped curve theory

It has been proposed that being physically active enhances the sensitivity of appetite control and is associated with improved coupling of EI with energy expenditure (EE). Seminal work by Mayer et al. [12] examined the relationship between caloric intake and habitual PA in a group of 213 mill workers, whose daily activities were categorized and ranged from sedentary to very hard physical labour. Mayer et al. [12] found that those workers with high PA increased daily EI to match EE, while at lower PA energy coupling appeared dysregulated and instead of

observing a proportional decrease in daily EI to accompany a reduction in EE, EI was found to increase.

This seemingly J-shaped relationship between habitual PA and EI has been substantiated and developed since the initial findings of Mayer et al. [12]. More recent studies, predominantly conducted with adults aged <65 years, have found that active individuals reported elevated feelings of hunger and greater EI in comparison with inactive individuals. Furthermore, it has been demonstrated that those who regularly engage in moderate-to-vigorous PA reduce EI after high energy vs low energy preloads, while those who are less active do not adjust subsequent EI to compensate for preload energy content. This indicates a tendency for more active people to adjust feeding to achieve an acute coupling of energy intake with energy needs. Thus, as individuals progress along the continuum of habitual PA towards higher levels of activity, the drive to eat increases (to offset the increase in physical activity energy expenditure (PAEE)) and postprandial satiety signalling strengthens. In contrast, those with lower levels of PA are perhaps more inclined to engage in non-homeostatic feeding behaviours, attributed to excess adiposity weakening satiety signalling [13]. In 2011, Professor John Blundell insightfully proposed the concept of appetite control zones in relation to the J-shaped curve theory. Blundell [14] purported that inactive individuals occupy a "non-regulated zone" of appetite control, in which satiety signalling is blunted, causing overeating and consequential weight gain. Conversely, a sustained increase in PA improves physiological regulation of energy balance, shifting those who are more active into what Blundell [14] termed the "regulated zone" of appetite control. Here, tonic appetite and EI is driven predominantly by the energy demand of resting metabolic rate (RMR) and PAEE, with active people demonstrating largely effective energy coupling.

The J-shaped model was most recently revised by Beaulieu et al. [15] to include the relationship between habitual PA and food reward. Beaulieu et al. [15] observed an association between low PA and greater liking and wanting for high-fat foods, while higher PA appeared to be associated with a reduced wanting for high-fat foods and a greater liking for low-fat foods. Therefore, although increasing PA may concomitantly increase the orexigenic drive to eat, PA-induced changes to the hedonic processing of food cues could stimulate healthier food choices, thereby promoting more effective weight management.

Physical activity and appetite control in later life: A distorted J-shaped relationship?

The J-shaped curve may not represent the association between habitual PA and EI in older adults. The impact of PA on appetite control has predominantly been studied in overweight and obese younger adults, and our understanding of how PA influences appetite and energy coupling within the context of ageing is limited. It should perhaps not be assumed that the relationship between PA and appetite control that has been demonstrated in young adults also applies to older adults. In fact, we postulate, with theoretical basis, a distorted J-shaped relationship (Fig 1) may be more representative. In the regulated zone, we propose a shallower curve, representing a somewhat attenuated increase in EI with increasing PA. Due to sarcopenic change and age-related anabolic resistance, physically active older adults likely possess less lean mass than equally active younger adults. Consequently, resting metabolic rate (the greatest determinant of which is fat-free mass), total energy expenditure, and hence drive to eat are expected to be lower. This may be exacerbated by inhibited orexigenic signalling via dysregulation of the ghrelin axis. Further, evidence points to augmented hormonal anorexigenic signalling with ageing, providing a mechanism by which older adults consume smaller intakes than younger adults, even when drive to eat is high. A recent meta-analysis by Johnson and colleagues [16] highlights greater fasted and postprandial circulating concentrations of the anorexigenic hormones leptin, insulin and cholecystokinin (CCK), and greater postprandial concentrations of peptide tyrosine tyrosine (PYY) in older adults, compared with younger adults. Such hormonal responses are associated with reduced appetite and EI.

At the other end of the PA spectrum, we hypothesise a non-regulated zone, but one in which EI is decreased at very low activity levels in older adults (Fig 1). This is in contrast to the high intakes seen with low activity in young and mid-life adults. There are several mechanisms by which we propose a differing response with ageing. Firstly, given that activity levels decline with age, a “low activity” older adult will likely be less active than a “low activity” younger adult. Very low activity, coupled with sarcopenia, likely renders inactive older adults with very low lean mass. Consequently, both RMR and PAEE will be extremely low, severely reducing the drive to eat. This again may be exacerbated by inhibited orexigenic signalling via dysregulation of the ghrelin axis. The non-regulated zone of the J-shaped curve is attributed, in part at least, to dysregulation in hormonal satiety signalling and increased hedonic drive associated with the increased adiposity of those of low activity level [13]; high adiposity “over-rides” the energy coupling mechanisms which prevail at higher activity and lower adiposity

levels. However, the age-related augmentation of hormonal satiety signalling is likely to mitigate any adiposity-related inhibition of hormonal satiety signalling. Further, hedonic inputs reduce with age due to weakening senses of taste and smell [4]. Add to this, possible declines in functional and cognitive capacity that can accompany ageing and frailty, which can limit capacity to access and prepare food [4] (essentially offering some degree of immunity to the Western obesogenic environment), and there are numerous potential reasons for malnutrition in low activity older adults.

Such a relationship between low PA and low EI would perpetuate a vicious cycle of malnutrition and frailty (see Fig S1 in Supplementary Material). Many characteristics of low activity are also closely related to malnutrition (low mass, low functional capacity). It is easy to see how a sudden reduction in PA (perhaps due to illness or injury) and consequent acceleration in loss of lean mass could elicit a reduction in drive to eat and EI. This will further exacerbate lean mass loss, potentially impairing functional capacity, which in turn reduces PA. Hence, this cycle can accelerate sharply, with severe reciprocal reductions in both PA and EI, and potentially catastrophic consequences for health and wellbeing.

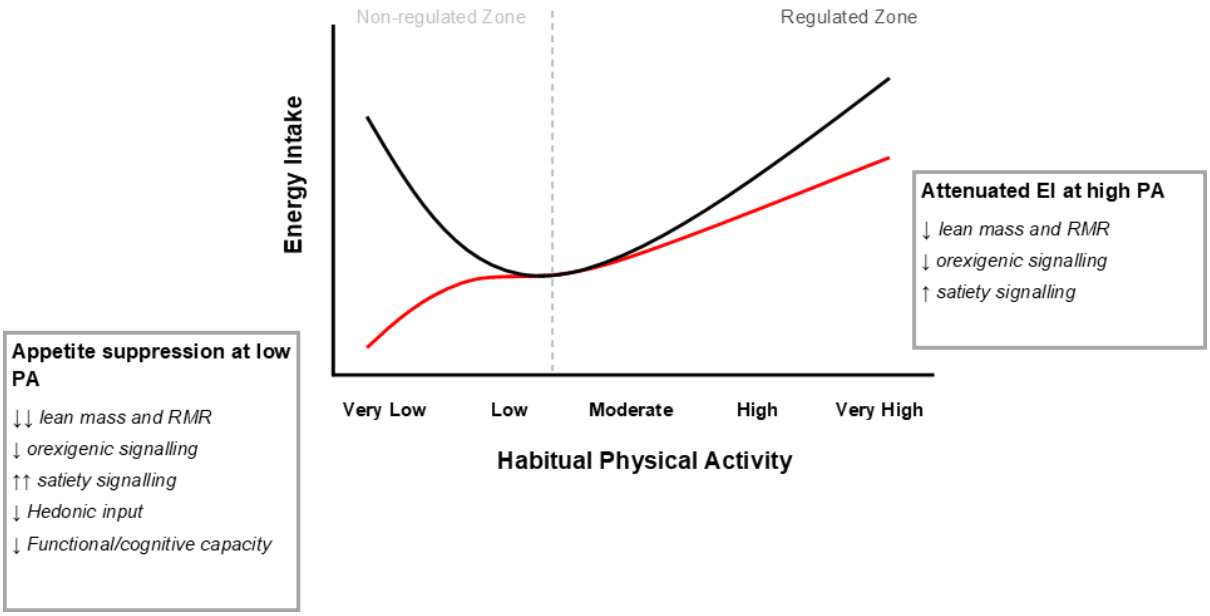

Fig 1. The well-established J-shaped relationship between habitual PA and EI in younger adults (black line), and the proposed distorted J-shaped relationship between habitual PA and EI in older adults (red line).

So, what next? Future research and potential implications

Studies are required to substantiate our hypothesised distorted J-shaped relationship between PA and EI in older adults. Cross-sectional data will be informative and is perhaps the first avenue to pursue for future research. Of particular importance, however, is understanding the impact of increasing PA on appetite and EI, and consequently on the risk of malnutrition. Our model suggests that moving undernourished older adults from "very low" or "low" activity levels to a "moderate" activity level might provide substantial benefits to appetite and EI.

As such, we propose that PA should form a fundamental component of treatment for anorexia of ageing. However, the lack of evidence-base to support current generic PA recommendations provided by health agencies with regards the effect of PA on appetite and EI in older adults limits PAs utility as a treatment option, rendering it potentially suboptimal for treating anorexia of ageing.

Studies are needed to inform and optimise the amount and nature of PA recommended for those with anorexia of ageing, with a consideration of the likely acute and chronic impact on appetite and energy balance. Firstly, fully elucidating the relationship between PA and EI in older adults may highlight a PA "threshold", at which those below suffer a marked reduction in appetite and EI. If this is the case, supporting older adults to exceed this PA "threshold" should be of paramount importance when treating anorexia of ageing. Secondly, the benefits of resistance exercise for older adults with regards maintaining lean mass and physical capacity are well-established. Maintaining, or even increasing lean mass, is also important for maintaining drive to eat, through a maintenance or increase in RMR. In addition, while high-intensity exercise typically induces a transient suppression of appetite, resistance exercise has been shown not to negatively impact short-term EI in older adults [17]. Therefore, there may be an argument for resistance exercise to be a more prominent component of PA recommendations for older adults with low appetite; it may be beneficial, from an appetite and EI perspective, to exceed the current guidelines of completing resistance exercise on two days per week.

Through further research and a greater understanding of the relationship between habitual PA and eating behaviour, we can progress to more effective, evidence-based practice in the management of anorexia of ageing.

Funding NJC and SERL receive funding from by The National Institute for Health Research (NIHR). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Declarations

Conflicting interests On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics approval Not applicable.

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Key references are listed below. The full reference list can be found in Supplement 1 of the Supplementary Material.

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Supplementary Material

Supplement 1. Full Reference List

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Supplement 2 - Figure S1

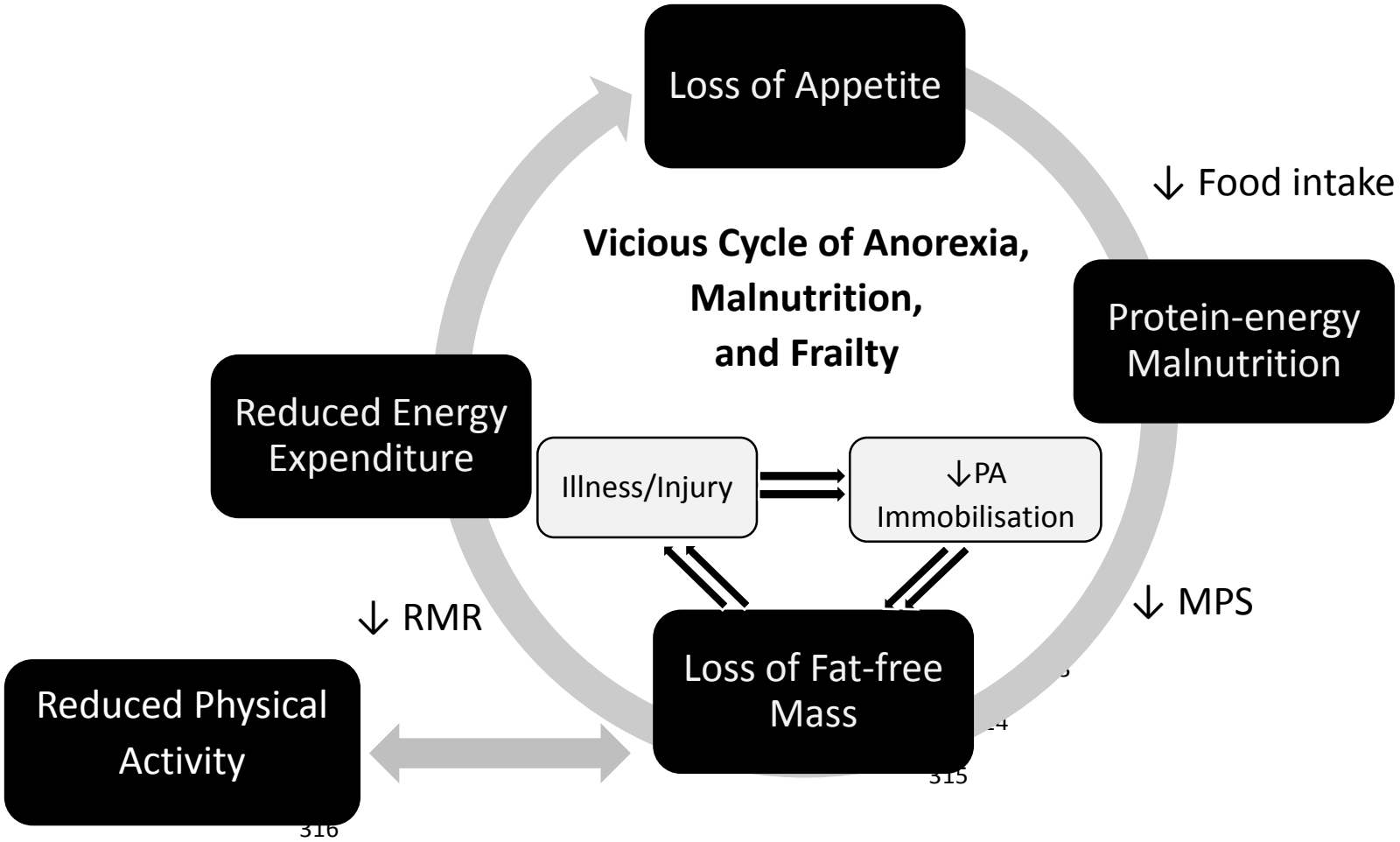

Figure S1. The vicious cycle of anorexia, malnutrition and frailty. A loss of appetite contributes to a cycle of reduced protein and energy intake, loss of fat-free mass and consequent reduction in resting metabolic rate (RMR). As energy expenditure, of which RMR is the greatest contributor, is the primary driver of appetite, this further reduces the drive to eat, perpetuating the cycle. The cycle is exacerbated by inactivity and accelerated by illness and injury which lead to immobilisation and a consequent augmented rate of fat-free mass loss. PA = physical activity; MPS = muscle protein synthesis.