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Appetite loss as a clinical marker of loss of function during ageing

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Abstract

Recent literature has shown that appetite loss during ageing can lead to negative health outcomes in older adults, particularly malnutrition and mortality. However, its association with functional decline and the mechanisms driving this relationship are not well explored. This review summarises the current evidence regarding the potential effects of appetite loss on frailty and functional outcomes. Despite the limitations due to heterogeneous methodologies, including study designs, population characteristics and appetite assessments, most studies indicate that older adults with poor appetite tended to exhibit poor physical performance and increased functional limitations. Furthermore, the simultaneous weight loss in individuals experiencing appetite loss was associated with a higher risk of functional impairments. Finally, emerging evidence connects reduced appetite to biomarkers of ageing, including epigenetic alterations, chronic inflammation and the upregulation of GDF-15. Therefore, loss of appetite is a potential earlier marker of loss of function that deserves further investigation. Adopting a geroscience perspective may enhance our understanding of appetite loss during ageing and foster the development of effective interventions.

Introduction

Appetite loss during ageing is a common condition among older adults, affecting approximately 15% to 30% of the community-based population and even at higher rates in individuals in hospitals and nursing homes[1,2]. Extensive evidence has demonstrated the association between appetite loss and adverse outcomes in older people, particularly malnutrition and mortality[2]. Despite the high prevalence and potential prognostic value, appetite loss remains understudied and overlooked in real-life environments, constituting an unmet clinical need for many older individuals. Recent publications from the International Conference on Frailty and Sarcopenia Research (ICFSR) Task Force have elaborated on the factors contributing to appetite loss during ageing, the available assessment tools and potential approaches for clinical management[3,4]. However, the association between reduced appetite and functional decline and the mechanisms driving this relationship are still underexplored.

The aim of this review is to highlight the potential role of appetite loss as a marker of loss of function and frailty in older adults. Three main aspects will be approached in this review: first, we summarise the current evidence about the effects of appetite loss on frailty and functional outcomes; second, we evaluate various appetite-related phenotypes among older adults, that is, experiencing appetite loss along with concomitant clinical conditions, such as weight loss; finally, we discuss the issue of age-related appetite loss under the perspective of geroscience and the central role of biological ageing.

Terminology

Prior studies used heterogeneous terminologies to define self-reported loss of appetite over a given period. In this review, we have unified the term 'appetite loss' throughout the text to avoid confusion. For studies that examined multiple aspects of eating-related problems in older adults, rather than focusing solely on appetite, we will specify their definitions in the description. Definitions and assessment methods of appetite loss used in the original papers are listed in Table 1, which summarises the study characteristics and main results of each study.

The terms 'cachexia' and 'sarcopenia' will be mentioned several times as common consequences of appetite loss. According to the prior papers[5,6], cachexia is defined as involuntary body weight loss of >5% in the past six months or of >2% when body mass index (BMI) <20 kg/m^2 (definition often used in the context of cancer). 'Sarcopenia', a condition characterised by the loss of muscle mass and function, is diagnosed or assessed using established criteria (e.g., EWGSOP2 guidelines[7]) or questionnaires (e.g., the 5-item SARC-F questionnaire[8]; higher scores indicate a greater risk of sarcopenia).

Table 1. Characteristics and main results of studies investigating the associations between appetite loss, functional outcomes and frailty

Author; year; country	Study design (length of follow-up)	Sample size and population characteristics;mean (SD) age; % female	Exposure; assessment method; prevalence	Outcomes	Covariates	Main findings
Landi et al.; 2010; Italy	Longitudinal (2 years)	364 community-dwelling adults aged ≥80; 85.8 (4.8); 67.0%	Presence of loss of appetite and/or lower food intake; self-reported; 20.3%	SPPB (including 4-metre walking speed, balance, chair stand tests), handgrip strength, incident ADL disability assessed with the MDS-HC instrument	Age, sex, BMI, number of diseases, depression, congestive heart failure, lung diseases	Individuals with appetite loss and/or lower food intake showed significantly lower SPPB scores (adjusted mean [SE] = 5.83 [0.42] vs. 6.81 [0.20]; $p = 0.03$), slower walking speeds (0.38 [0.03] vs. 0.50 [0.01]; $p = 0.001$) and weaker handgrip strength (27.96 [1.50] vs. 30.84 [0.74]; $p = 0.03$) compared to those without the condition. Furthermore, Individuals with appetite loss and/or lower food intake had a higher risk of developing ADL disability over 2 years (Model adjusted for age and sex: OR [95% CI] = 2.22 [1.13 to 4.36]; Model adjusted for all covariates: OR [95% CI] = 1.98 [0.99 to 4.02]).
Reijnierse et al.; 2015; Netherlands	Cross-sectional	185 geriatric outpatients; 82.0 (7.3); 60.0%	Presence of loss of appetite in the last month; One item in the Short Nutritional Assessment Questionnaire; 27.6%	Handgrip strength, walking speed	Age, body mass, height	Loss of appetite was associated with lower handgrip strength after adjustment for age and body mass (β [SE] = −0.36 [0.16]; $p = 0.026$) and with slower walking speed after adjustment for age (β [SE] = − 0.40 [0.18]; $p = 0.031$). These associations became weaker after additional adjustment for height (handgrip strength: β [SE] = − 0.31 [0.16]; $p = 0.051$; walking speed: β [SE] = − 0.37 [0.19]; $p = 0.052$).
Chang et al.; 2021; Iceland	Cross-sectional	5764 community-dwelling older adults; 77.0 (5.9) for normal appetite /77.2 (5.8) for poor appetite; 57.7%	Illnesses or physical conditions affecting the appetite or ability to eat; self-reported; 13.9%	Knee extension strength, handgrip strength, 6-metre walking time, TUG test, ADL dependence (0–5 point)	Age, sex, fat-free mass or body-fat mass, height, physical activity level, smoking	Having illnesses or physical conditions that affect appetite or the ability to eat was associated with poor performance in all physical measures. After additionally adjusting for lifestyle and anthropometric covariates, individuals with poor appetite or eating ability performed worse on the 6-metre walk (β [95% CI] = 0.21 [0.05 to 0.38]; $p = 0.010$) and TUG tests (β = 0.65 [0.35 to 0.95]; $p < 0.001$), while no significant differences were found in knee extension (β = − 4.82 [− 12.70 to 3.07]; $p = 0.231$) or handgrip strength (β = − 6.08 [− 12.80 to 0.65]; $p = 0.076$) compared to those with normal appetite. Poor appetite or eating ability was also associated with increased dependence in ADL (β = 0.20 [0.12 to 0.29]; $p < 0.001$).
Tsutsumimoto et al.; 2017; Japan	Cross-sectional	4417 community-dwelling adults aged ≥70; 75.8 (4.3); 52.7%	Appetite loss, defined as SNAQ score ≤13; SNAQ; 10.6%	Fried's frailty phenotype and components	Age, sex, education, BMI, number of medications, presence of chronic disease, alcohol use, smoking, blood total protein and albumin, self-rated health, depressive symptoms, cognitive function	Individuals with appetite loss showed a higher likelihood of prefrailty (OR [95% CI] = 1.59 [1.25 to 2.02]; $p = 0.001$) and frailty (OR = 1.86 [1.39 to 2.49]; $p = 0.001$). Independent associations were found between appetite loss and slowness (OR [95% CI] = 1.42 [1.14 to 1.75]; $p = 0.002$),

Table 1. (*Continued*)

						exhaustion (OR = 1.39 [1.11 to 1.74]; $p = 0.004$) and weight loss (OR = 1.37 [1.05 to 1.79]; $p = 0.019$), but not weakness or low physical activity.
de Lima et al.; 2022; Brazil	Cross-sectional	106 community-dwelling adults aged ≥60; 71.4 (8.0); 58.5%	Appetite loss using the continuous SNAQ score; SNAQ; 19.8% for SNAQ score ≤14	Frailty, using FRAIL-BR scale	Age, waist circumference, sarcopenia risk	A lower SNAQ score was associated with a greater likelihood of prefrailty (OR [95% CI] = 0.68 [0.50 to 0.92]; $p = 0.012$) and frailty (OR = 0.64 [0.45 to 0.90]; $p = 0.009$).
van Dronkelaar et al.; 2019; Netherlands	Longitudinal (from admission to three months post-discharge)	400 acutely hospitalised adults aged ≥70; 80.1 (6.7); 48.5%	Presence of decreased appetite in the last month or since hospital admission; One item in the Short Nutritional Assessment Questionnaire; 50.5% at admission	Handgrip strength, Morton Mobility Index, SPPB	Age, sex, cognitive impairment, fatigue, depression, comorbidity, skeletal muscle mass (only for handgrip strength), fear of falling (only for mobility index and SPPB)	Decreased appetite was longitudinally associated with reduced handgrip strength (β [95% CI] = − 1.09 [− 1.72 to − 0.46]; $p = 0.001$), lower SPPB scores ($\beta = -0.71$ [− 1.08 to − 0.33]; $p < 0.001$) and lower Morton Mobility Index ($\beta = -3.89$ [− 6.06 to − 1.73]; $p < 0.001$).
Sun et al.; 2023; Japan	Longitudinal (an average [SD] of 25.3 [25.0] months)	135 individuals (8 normal/6 SCD/ 121 MCI); 76.7 (6.4); 65.2%	Presence of appetite loss for at least 6 months; caregiver-reported; 9.6%	Diagnosed dementia	None	The presence of appetite loss was not associated with the onset of dementia, as indicated by Kaplan–Meier survival analysis (log-rank test, $p = 0.326$).
Ding et al.; 2024; China	Cross-sectional	1355 individuals aged ≥60 with type 2 diabetes; 67.8 (5.1); 45.5%	Appetite change in past 3 months (none, reduced, or severely reduced); self-reported; 7.5% for reduced appetite /1.2% for severely reduced appetite	Cognitive impairment, defined as MoCA < 26	Age, sex, education, diabetes duration, fasting blood glucose	Both reduced appetite (OR [95% CI] = 4.41 [2.67 to 7.29]; $p < 0.001$) and severely reduced appetite (OR = 9.63 [2.14 to 43.25]; $p = 0.003$) were associated with a high risk of cognitive impairment.
Gaussens et al.; 2024; France	Cross-sectional	14572 community-dwelling adults aged ≥60; 76.7 (8.8); 62.0%	Presence of appetite loss; self-reported; 14.0%	Potential IC domain impairments assessed by ICOPE screening tools: cognition, locomotion, psychology, vision, hearing	Age, sex, weight	Appetite loss was associated with positive screenings for the domains of cognition (OR [95% CI] = 2.16 [1.92 to 2.42]; $p < 0.001$), vision (OR = 1.39 [1.23 to 1.58]; $p < 0.001$), hearing (OR = 1.22 [1.09 to 1.38]; $p = 0.001$), psychology (OR = 4.24 [3.81 to 4.72]; $p < 0.001$) and locomotion (OR = 2.52 [2.27 to 2.81]; $p < 0.001$). People reporting both appetite and weight loss showed increased odds of psychological (OR = 5.33 [4.53 to 6.27]) and locomotion impairments (OR = 3.38 [2.88 to 3.98]).

(*Continued*)

Table 1. (*Continued*)

Author; year; country	Study design (length of follow-up)	Sample size and population characteristics;mean (SD) age; % female	Exposure; assessment method; prevalence	Outcomes	Covariates	Main findings
de Souto Barreto et al.; 2023; France	Longitudinal (an average [SD] of 6.5 [2.1] months for people with longitudinal data)	14358 community-dwelling adults aged ≥60; 76.7 (8.8); 62.0%	Presence of appetite loss; self-reported; 13.9%	Potential IC domain impairments assessed by ICOPE screening tools: cognition, locomotion, psychology, vision, hearing	Age, sex, weight	At baseline, individuals with appetite loss had a higher likelihood of potential impairment in all IC domains compared to those without the condition ($p < 0.05$ for all). Longitudinally, having appetite loss was associated with the incidence of potential impairment in cognition ($n = 1649$; OR [95% CI] = 1.83 [1.20 to 2.80]; $p = 0.005$), locomotion ($n = 985$; OR = 1.62 [1.00 to 2.61]; $p = 0.05$) and psychology ($n = 2527$; OR 1.73 [1.08 to 2.76]; $p = 0.02$).
Tsutsumimoto et al.; 2018; Japan	Longitudinal (2 years)	4393 community-dwelling adults aged ≥70; 75.9 (4.3); 52.7%	Appetite loss, defined as SNAQ score ≤13; SNAQ; 10.7%	Incident disability, based on the record in the public long-term care insurance system	Age, sex, education, BMI, polypharmacy, hypertension, diabetes, hyperlipidaemia, blood total protein and albumin, living alone, alcohol use, smoking, depressive symptoms, decline in physical and cognitive function	After adjusting for covariates (except for frailty status), having appetite loss was associated with a higher risk of incident disability (HR [95% CI] = 1.43 [1.04 to 1.95]; $p = 0.026$). However, appetite loss was not significantly associated with incident disability after additionally adjusting for frailty status (HR = 1.33 [0.96 to 1.80]; $p = 0.093$)
Vázquez-Valdez et al.; 2010; Mexico	Cross-sectional	1247 community-dwelling adults aged ≥60; 69.9 (7.8); 59.3%	Presence of eating less in the last 12 months due to loss of appetite; self-reported; 30.1%	Disability assessed with the Rosow-Breslau mobility scale, Lawton's IADL, Katz's ADL.	Age, sex, living alone, comorbidity, oral health, weight loss, BMI, depressive symptoms, cognitive function	The presence of eating less due to appetite loss was associated with all types of disability (mobility disability: OR [95% CI] = 2.20 (1.27 to 3.81), $p = 0.005$; IADL disability: OR = 2.58 [1.33 to 5.02], $p = 0.005$; ADL disability: OR = 1.62 [1.02 to 2.57], $p = 0.04$). The interaction between appetite loss and depressive symptoms was significant only in models using mobility and IADL disability as outcomes.

ADL, activities of daily living; BMI, body mass index; CI, confidence interval; HR, hazard ratio; ICOPE, Integrated Care for Older People; IADL, instrumental activities of daily living; IC, intrinsic capacity; MCI, mild cognitive impairment; MDS-HC, Minimum Data Set for Home Care Assessment Instrument; MoCA, Montreal Cognitive Assessment; OR, odds ratio; SCD, subjective cognitive decline; SE, standard error; SNAQ, Simplified Nutritional Appetite Questionnaire; SPPB, Short Physical Performance Battery; TUG, timed up-and-go.

Impacts of appetite loss on functional outcomes and frailty

Although the mechanistic link between appetite loss and negative outcomes remains unclear, it is widely believed that a decreased appetite leads to reduced food intake, resulting in insufficient energy and nutrients to meet metabolic demands[9,10]. In other words, appetite loss could be a prodromal state of malnutrition that increases vulnerability to stressors and unfavourable health outcomes.

Several studies have investigated the effects of appetite loss on physical function, primarily focusing on components related to frailty and sarcopenia such as lower grip strength and slower walking speed (Table 1). Landi and colleagues investigated 364 community-dwelling octogenarians and compared participants with appetite loss and/or reduced food intake to those without either condition[11]. They found that those with appetite loss and/or reduced food consumption performed significantly worse on Short Physical Performance Battery (SPPB) and handgrip strength than those without the condition. Moreover, participants with reduced appetite and/or food consumption demonstrated twice the risk of developing disability in basic activities of daily living (ADL) over two years compared to individuals without the condition; however, the association became insignificant after adjusting for BMI and comorbidity[11]. A study by Reijnierse et al. involving 185 geriatric outpatients (mean ± SD age = 82.0 ± 7.3 years) reported similar results[12]. They found that having appetite loss in the last month, assessed by an item in the Short Nutritional Assessment Questionnaire, was cross-sectionally associated with reduced handgrip strength and slower walking speed, but this association was no longer significant after additionally adjusting for body height (handgrip strength: β [SE] = −0.31 [0.16]; $p = 0.051$; walking speed: β [SE] = −0.37 [0.19]; $p = 0.052$)[12]. A cross-sectional study of 5764 community-dwelling older adults from the AGES-Reykjavik Study identified participants whose appetite or eating ability was affected by illnesses or somatic problems[13]. In that study, individuals with appetite loss or eating ability performed worse on the 6-metre walk (β [95% CI] = 0.21 [0.05 to 0.38]; $p = 0.010$) and timed up-and-go (TUG) tests ($\beta = 0.65$ [0.35 to 0.95]; $p < 0.001$), while no significant differences were found in knee extension ($\beta = -4.82$ [−12.70 to 3.07]; $p = 0.231$) or handgrip strength ($\beta = -6.08$ [−12.80 to 0.65]; $p = 0.076$) compared to those with normal appetite after adjusting for lifestyle and anthropometric covariates. Poor appetite or eating ability was also associated with increased dependence in ADL ($\beta = 0.20$ [0.12 to 0.29]; $p < 0.001$)[13]. Another cross-sectional study of 4417 community-dwelling Japanese aged ≥70 found that the likelihood of prefrailty and frailty was 1.6 and 1.9 times higher, respectively, among individuals with appetite loss, defined by a Simplified Nutritional Appetite Questionnaire (SNAQ) score ≤13, compared to those without appetite loss[14]. When analysing the components of frailty, loss of appetite was associated with slowness, exhaustion and weight loss, but not with weakness or low physical activity[14]. Further evidence from a Brazilian cohort of 106 adults aged ≥60 reported that the odds of being prefrail and frail increased by 32% and 36%, respectively, for every point decrease of the SNAQ score[15]. Finally, Van Dronkelaar et al. evaluated appetite loss in 400 acutely hospitalised older adults aged ≥70 using Short Nutritional Assessment Questionnaire from admission to three months post-discharge[16]. Decreased appetite was longitudinally associated with reduced handgrip strength (β [95% CI] = −1.09 [−1.72 to −0.46]; $p = 0.001$), lower SPPB scores ($\beta = -0.71$ [−1.08 to −0.33]; $p < 0.001$) and impaired mobility (evaluated by Morton Mobility Index; $\beta = -3.89$ [−6.06 to −1.73]; $p < 0.001$)[16].

Appetite loss is a major contributor to weight loss, which are known risk factors for cognitive impairment[17]. Moreover, appetite loss and weight loss were associated with poor cognitive performance and a higher risk of dementia in older adults with major depressive disorder[18,19]. Nevertheless, an observational study involving 135 older adults (mean ± SD age = 76.7 ± 6.4 years) with normal cognitive function, subjective cognitive decline, or mild cognitive impairment failed to demonstrate difference in the onset of dementia between individuals with and without appetite loss using the Kaplan-Meier survival analysis (a log-rank test: $p = 0.326$)[20]. It is important to note that this study had a relatively short follow-up period (an average of 25.3 months), and appetite changes were reported by caregivers rather than participants[20]. In another study focusing on 1355 individuals aged ≥60 living with type 2 diabetes, loss of appetite over the past three months was associated with a higher likelihood of cognitive impairment, defined as Montreal Cognitive Assessment (MoCA) <26; the odds ratio was 4.4 times higher for individuals reporting reduced appetite and 9.6 times higher for those with severely reduced appetite, compared to their stable-appetite counterparts[21].

Data derived from the Integrated Care for Older People (ICOPE) programme implementation in the Toulouse region (located in southwestern France)[22] showed that loss of appetite could predict potential functional impairments in older adults[23]. In brief, the World Health Organization (WHO) ICOPE programme is a function- and person-centred healthcare pathway to promote healthy ageing[24]. It centres on preserving intrinsic capacity (IC), a composite of physical and mental capacities, across six core domains: locomotion, cognition, psychology, vision, hearing and vitality (the domain related to nutritional status). In the ICOPE programme, appetite loss, along with weight loss, is used to evaluate the vitality domain at the basic assessment phase (i.e., ICOPE Step 1) to screen for malnutrition. From January 2020 to February 2022, the Toulouse ICOPE programme screened 14,572 older individuals (mean ± SD age = 76.7 ± 8.8 years) through health professionals in primary care settings, with 14.0% people reporting appetite loss. Individuals with appetite loss showed a higher probability of having deficits in the other five domains compared to those without appetite loss, after controlling for age, sex and body weight[23]. An analysis of more recent data and a larger sample size from the Toulouse ICOPE programme confirmed the same findings[4]. Moreover, in subgroup analyses among people with two consecutive visits, having appetite loss at the first visit was associated with future impairment in cognition (OR [95% CI] = 1.83 [1.20 to 2.80]; $p = 0.005$), locomotion (OR [95% CI] = 1.62 [1.00 to 2.61]; $p = 0.05$) and psychology (OR [95% CI] = 1.73 [1.08 to 2.76]; $p = 0.02$)[4].

Fielding et al. suggested that the association between appetite loss and adverse outcomes could be either direct or mediated through secondary outcomes[2]. Indeed, Tsutsumimoto and colleagues followed 4393 community-dwelling individuals aged ≥70 for two years and found that appetite loss, as assessed by SNAQ, increased the risk of disability by 1.4 times[25]. However, this association became insignificant after adjusting for frailty status. Their structural equation modelling analysis further confirmed an indirect association between appetite loss and disability through frailty[25]. Furthermore, the relationship between appetite loss and functional disability may vary by stage. A cross-sectional study of 1247 community-dwelling Mexicans

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aged 60 and older revealed significant associations between self-reported appetite reduction and disability across multiple scales, including the Rosow-Breslau mobility scale, Lawton's instrumental ADL (IADL) and Katz's ADL[26]. The Rosow-Breslau scale measures the ability to perform three physical tasks: doing heavy work around the house, walking up and down stairs and walking a half mile without help. Lawton's IADLs cover eight complex tasks, including managing finances and medications, telephoning and using transportation. Katz's ADLs refer to six basic, daily self-care activities, such as bathing, dressing, eating and toileting. These three disability scales reflect different stages of disability, from early limitations in physical performance and doing complex tasks to more advanced impairments affecting basic self-care. Interestingly, a significant interaction between appetite loss and depressive symptoms was observed for mobility and IADL disability, but not for ADL disability. The authors thus suggested that appetite reduction had a more independent impact in the advanced stages of disability[26]. However, given the cross-sectional nature of the study design, reverse causation is also possible – that is, appetite loss may result from physical inactivity due to disability, rather than be a contributing factor.

Phenotypes of appetite loss during ageing

Current literature indicates that appetite loss is a geriatric condition with multifaceted causes[27,28]. Therefore, the population facing appetite loss represents a heterogeneous group, potentially comprising multiple phenotypes hosted under the term 'loss of appetite', but which might have their roots in different etiological factors. The multiple phenotypes of appetite loss may also coexist with different clinical conditions, such as involuntary weight loss, malnutrition, or frailty. Therefore, it is plausible to think that the different appetite phenotypes may have various prognoses and require distinct management. Findings from two separate studies – one involving patients with heart failure[29]and the other focusing on octogenarians[11] – revealed that individuals experiencing both appetite loss and involuntary weight loss exhibited worse physical performance, compared to those without appetite loss or those who had appetite loss alone. Another study on 2757 older adults receiving home care also identified a gradient of increasing all-cause mortality risk over a mean follow-up of 10 months, with the highest mortality risk found in people experiencing poor appetite or decreased food intake accompanied by weight loss[30]. Our data from the ICOPE implementation in Toulouse also observed similar findings. Individuals aged ≥60 who experienced both appetite loss and weight loss showed higher odds of potential psychological and locomotion impairments, as assessed by the ICOPE Step 1 screening tools, than those with only appetite loss or weight loss[23].

Appetite loss in the geroscience era

There has been an increasing interest on the understanding of the biological processes underpinning appetite loss during ageing in order to identify key biomarkers for the screening and assessment of this condition and to inform the development of potential therapeutic solutions[31,32]. Given the close association between ageing and reductions in food intake, experts have suggested that appetite loss in older adults might share biological underpinnings with the ageing process[4,33]. Biological ageing results from the complex interplay of numerous and only partially understood processes at the molecular, cellular, organ and system levels (i.e. the hallmarks of ageing)[34,35]. Under the geroscience principles, given the interplay between ageing biology and the biology of age-related diseases, the intervention on mechanisms involved in biological ageing would assist in the prevention or delay of chronic conditions[36]. But so far, the extent to which biological ageing processes determine appetite loss is still largely unknown[33].

Accumulating evidence points to appetite regulation mechanisms that might be altered along the ageing process and that might be potential targets for interventions[4]. The main source of inputs to the appetite-control regions in the brain are the stomach and the gut, with enteroendocrine cells detecting variations in dietary molecules and digestion products, leading to the secretion of appetite-regulation hormones into the bloodstream[37,38]. Together with reduced stomach compliance and delayed gastric emptying, the alteration of this complex neuroendocrine circuitry[27,39,40], might lead to the extended satiety times and the reduction in hunger feelings and food intakes observed with ageing.

Classical main anorexigenic hormones involved in nutrient-sensing appetite regulation include cholecystokinin (CKK), glucagon-like peptide-1 (GLP-1), gastric inhibitory polypeptide (GIP), leptin and peptide tyrosine tyrosine (PYY). Recently, a potent appetite-inhibitory role of growth differentiation factor 15 (GDF-15), a stress-signalling protein closely linked to ageing, has also been described[41]. CKK upregulation is observed in post-prandial states and mediates early satiating signals after food intake, whereas GLP-1 and PYY are involved in delayed appetite suppression at the lower GI system[42]. On the other hand, ghrelin, the only orexigenic hormone, is secreted in fasting situations by stomach mucosal cells and induces hunger and intake initiation, with levels drastically falling upon eating[43,44]. Some studies have investigated which alterations in appetite-regulating hormones are related to ageing. In a recent meta-analysis by Johnson et al., differences between healthy older adults compared to younger populations in appetite-related hormones have been described, namely increases in both fasted and post-prandial CKK and greater levels of PYY after food consumption, with no clear differences in ghrelin, GIP or GLP-1[45]. In addition, a recent work by Dagbasi et al. showed an increased GLP-1 and PYY activity after food consumption in older adults with appetite loss, compared to non-anorectic counterparts[46].

Beyond these nutrient-sensing-related hormones, other active processes related to energy homeostasis sensing, considered as part of the energy availability signalling system that is often modified during ageing, seem to play a role in appetite loss. A key anorexigenic circulating peptide is insulin, released from the pancreas in response to increased postprandial glucose levels in blood. The levels of the latter are well known to be elevated both in the fasted state and post-prandially in response to overproduction following peripheral insulin resistance that progressively develops with age[45,47]. Another key energy-related anorexigenic peptide, leptin, is mainly secreted by adipocytes and enterocytes of the small intestine and is believed to be a marker of energy storage in the form of fat. Increases in both fasted and post-prandial leptin[48–51] have been described in older adults. However, whether these elevated levels are secondary to an increase in the activity of *leptinergic* pathways or result from leptin resistance at old age, with no effect on appetite, is a current matter of discussion[52].

In the realms of the hallmarks of ageing, the bulk of research exploring associations between ageing-related biological mechanisms and appetite is restricted to the exploration of the role of low-grade chronic inflammation[53]. Ageing is associated with an increase in circulating inflammatory markers (interleukins 1 and 6 [IL-1 and IL-6], tumour necrosis factor alpha [TNF-α])[54,55]. These has been shown to suppress appetite at peripheral (by

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contributing to delayed gastric emptying and intestinal motility) and central (anorexigenic signal at the appetite control centre in the hypothalamus) levels[56,57], and to be associated with several of the consequences of appetite loss of ageing, such as sarcopenia, malnutrition and frailty[53,58].

The link between inflammation and appetite suppression is mainly supported by evidence derived from disease models characterised by both high inflammatory levels and appetite loss, such as cancer and Crohn's disease. According to these observations, inflammation could reduce hunger feelings by upregulating nutrient sensing, impairing the secretory activity of enterocytes at the gut level with increases in PYY, CCK and GLP-1[59,60] and decreases in orexigenic peptides. Furthermore, the promotion of ghrelin resistance and upregulation of leptin-related pathways through the action of pro-inflammatory cytokines on glucose-sensitive neurons in the ventromedial hypothalamus in individuals with chronic disease may lead to an impaired response to peripheral energy deficit signalling[61].

An important role of micronutrient deficits in the link between inflammation and appetite loss has been recently suggested. Namely, low levels of selenium[62], zinc[63] and vitamin D[64] have been linked to increased inflammatory processes, which might in turn, lead to appetite loss[65].

More recently, increased activity of the GDF-15-GFRAL axis has been suggested as a core mechanism linking appetite loss and ageing[66]. GDF-15 is a stress-signalling protein elevated in ageing, inflammation and mitochondrial stress[67,68]. Given the tight connections between increased GDF-15 and both chronological[69,70] and biological[71] ageing, age-related conditions[72], physical and cognitive functions[73] and late-life adverse outcomes[74,75], GDF-15 has been suggested as a potential transversal biomarker in the geroscience field[76]. Furthermore, in relation to appetite, it has displayed a strong anorexigenic potential in animal models, to be elevated in older adults with appetite loss[53,77] and to be associated with appetite and weight loss in cancer cachexia[77,78]. Pharmacological manipulation of the GDF-15-GFRAL axis has shown promising perspectives to modulate appetite in cancer cachexia/obesity, with both inhibition and stimulation (respectively), showing potential to treat these conditions[79,80]. With regard to appetite stimulation, a recent phase-2 randomised clinical trial by Groarke et al., the pharmacological inhibition of GDF-15-GFRAL axis by means of a humanised monoclonal GDF-15 antibody was effective in increasing appetite and weight in patients with cancer and cachexia in a dose-response manner[6]. Importantly, treated patients also improved body composition, physical function and their quality of life, demonstrating a beneficial effect of GDF-15 beyond weight loss.

Worthy of mention is the potential involvement of dysbiosis, a recently incorporated hallmark of ageing, in the alteration of nutrient sensing at the gastrointestinal level. With ageing, there is a progressive decrease in gut microbiome diversity[31,81], which might lead to the derangement of intestinal barrier integrity, further alter nutrient sensing and promote the release of anorexigenic peptides, as well as foster chronic low-grade inflammation[82]. Unfortunately, given the limited number of studies and the complexity of the microbiome, findings around these topics need further research.

At present, it is almost impossible to discern whether the described mechanisms putatively associated with the development of appetite loss in ageing result solely from the ageing process or from sub-clinical/clinical changes secondary to disease. Cutting-edge studies, such as the one by Turesson et al.[83] are trying to shed light on this issue. Relying on recently incorporated biological ageing measures, such as epigenetic and inflammatory clocks that allow to compute a biological age of an individual, authors have tried to explore whether individuals across the entire adulthood spectrum (from 20 to 102 years old) with appetite loss were biologically older than their counterparts, independently of sociodemographic characteristics or diseases. They found that individuals reporting having appetite loss were biologically older than their healthy counterparts, according to the GrimAge epigenetic clock. Importantly, this clock is trained on key proteins related to appetite regulation, such as leptin and GDF-15, suggesting a critical role of these peptides as mediators of appetite loss during ageing.

In summary, given the tight link between ageing biology and appetite loss, it is possible that both processes could share biological underpinnings; therefore, addressing biological ageing might promote appetite retention in older adults, and the latter might in turn prevent further progression of the biological ageing process. Further research exploring links of biological ageing in both absence and presence of diseases with the development of appetite loss and other chronic conditions might open the venue for the development of ageing biology-targeted interventions[84] and the promotion of healthy ageing.

Final considerations and future directions

Available evidence supports the association of appetite loss in older adults with frailty and loss of function, particularly in physical performance. Most existing studies used cross-sectional designs and focused on various populations, spanning from community-dwelling individuals and geriatric outpatients to patients with specific diseases. Definitions and assessments of appetite loss also varied across studies (Table 1). While a single question may be easier applied during the regular screening (such as ICOPE Step 1), validated questionnaires like SNAQ have strengths in quantifying the overall appetite quality of an individual. Overall, these methodological differences may contribute to the inconsistencies observed in the findings. Given the limited number of studies investigating the relationship between appetite loss and cognitive or other IC domains, further research, especially longitudinal studies with sufficient follow-up periods, is required.

The presence of co-occurring conditions in individuals reporting appetite loss, such as unintentional weight loss, may reflect greater severity and complexity, resulting in an elevated risk of adverse outcomes such as mortality. Notably, data from the Toulouse ICOPE programme showed that appetite reduction was not only a marker of malnutrition but also related to deficits in other IC domains. The findings underscore the importance of appetite assessment and management at an early stage to enhance the overall functional ability of older individuals. Future approaches to managing appetite loss in older adults may benefit from personalised strategies tailored to their phenotypes and determinants (physiological, psychosocial, environmental, etc.) and should incorporate multidomain interventions that include both nutritional and non-nutritional components[4]. It is important to note that the extensive data on functional performance and ageing phenotypes from the Toulouse ICOPE programme can identify multiple appetite-related phenotypes, including concomitant malnutrition, frailty and depression, for which relevant evidence is currently lacking in the literature. The large population involved in the Toulouse ICOPE programme also allows for having sufficient participants in each appetite-related phenotype and for investigating more personalised management for specific subgroups.

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Randomised controlled trials specifically targeting older adults with appetite loss can also provide valuable insights into this issue. For example, the ongoing multi-centre plAnt Protein fibre and Physical activity solutions to address poor appEtite and prevenT undernutrITion in oldEr adults (APPETITE) study investigates the effects of plant protein fibre and physical activity on appetite in community-dwelling adults aged 65 and older[85]. With comprehensive data being collected on nutritional, functional and clinical outcomes, this study is expected to shed light on the relationship between appetite loss and functional status, and to help identify effective interventions that address both.

From a biological perspective, appetite loss during ageing is influenced by age-related changes in appetite-regulating molecules. Emerging evidence also indicates a link between reduced appetite and biological ageing, involving mechanisms such as epigenetic alterations, chronic inflammation and the upregulation of GDF-15. Future studies on appetite loss are encouraged to adopt a geroscience approach by investigating the interplay between appetite-regulating molecules and biological ageing, and examining whether interventions targeting the cellular and molecular pathways of ageing could prevent or attenuate the severity of appetite loss in older adults. For instance, the pharmacological agent targeting the GDF-15-GFRAL pathway has shown potential to improve cancer-related cachexia[6]. It is important to explore the effectiveness of GDF-15/GFRAL manipulation in disease-free ageing models as a therapeutic target for interventions aimed at stimulating feelings of hunger and increasing food intake in older adults with appetite loss. Furthermore, non-pharmacological approaches such as physical exercise have been shown to influence both appetite regulation and GDF-15 levels[86,87]. Evidence suggests that GDF-15 levels rise acutely during exercise but decrease with long-term physical activity[88]. Clinical trials, specifically focusing on older adults, are needed to evaluate whether exercise interventions can improve appetite and to determine whether this effect is mediated by changes in GDF-15[33].

The uncertainty regarding the extent to which biological ageing processes determine appetite loss might result from the fact that appetite control is a complex and multifaceted process, in particular in older adulthood, involving hedonic inputs comprising societal, behavioural, endocrine, neural and physiological cues[89,90] that remain far from being fully understood. Notably, if the focus is on appetite loss during ageing, it is crucial to distinguish those physiological factors directly related to the condition from other conditions that might limit food intake (dysphagia, loneliness, poor economic status, or functional disability) in the absence of overt reductions in appetite. Also, to better understand the intersection of ageing biology and appetite dysregulation, it is essential to understand central and peripheral physiological changes occurring as a result of biological ageing processes, dissociating them from those resulting from pathological processes.

Conclusions

This review explores how appetite loss may serve as an early indicator of functional impairment and frailty. Distinct appetite-related phenotypes, associated with varying risks for adverse outcomes, have been identified among community-dwelling older adults. Emerging evidence linking reduced appetite to biomarkers of ageing reinforces the need to investigate how appetite-regulating molecules interplay with the biology of ageing. Adopting a geroscience perspective may enhance our understanding of appetite loss and foster the development of effective interventions.

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References

1. Dericioglu D, Methven L, Clegg ME (2024) Understanding age-related changes: exploring the interplay of protein intake, physical activity and appetite in the ageing population. *Proc Nutr Soc* 1–13.
2. Fielding RA, Landi F, Smoyer KE, *et al.* (2023) Association of anorexia/appetite loss with malnutrition and mortality in older populations: a systematic literature review. *J Cachexia, Sarcopenia and Muscle*. **14**, 706–29.
3. de Souto Barreto P, Cesari M, Morley JE, *et al.* (2022) Appetite loss and anorexia of aging in clinical care: an ICFSR task force report. *J Frailty Aging* **11**, 129–34. doi: 10.14283/jfa.2022.14.
4. de Souto Barreto P, Cesari M, Morley JE, *et al.* (2023) Assessment and management of appetite loss in older adults: an ICFSR task force report. *J Frailty Aging* **12**, 1–6.
5. Fearon K, Strasser F, Anker SD, *et al.* (2011) Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* **12**, 489–95.
6. Groarke JD, Crawford J, Collins SM, *et al.* (2024) Ponsegromab for the treatment of cancer cachexia. *New England J Med* **391**, 2291–303.
7 Cruz-Jentoft AJ, Bahat G, Bauer J, *et al.* (2019) Sarcopenia: revised European consensus on definition and diagnosis. *Age and Ageing* **48**, 16–31.
8. Malmstrom TK, Miller DK, Simonsick EM, *et al.* (2016) SARC-F: a symptom score to predict persons with sarcopenia at risk for poor functional outcomes. *J Cachexia, Sarcopenia and Muscle* **7**, 28–36.
9. Picca A, Calvani R, Coelho-Júnior HJ, *et al.* (2022) Anorexia of aging: metabolic changes and biomarker discovery. *Clin Interv Aging* **17**, 1761–7.
10. Cox NJ, Lim SE. (2024) The anorexia of ageing and risk of mortality: more than a story of malnutrition? *J Nutr Health and Aging*. **28**, 100173.
11. Landi F, Russo A, Liperoti R, *et al.* (2010) Anorexia, physical function, and incident disability among the frail elderly population: Results from the ilSIRENTE study. *J Am Med Dir Assoc* **11**, 268–74.
12. Reijnierse EM, Trappenburg MC, Leter MJ, *et al.* (2015) The association between parameters of malnutrition and diagnostic measures of sarcopenia in geriatric outpatients. *PLoS ONE* **10**, doi: 10.1371/journal.pone.0135933.
13. Chang M, Geirsdottir OG, Launer LJ, *et al.* (2021) A poor appetite or ability to eat and its association with physical function amongst community-dwelling older adults: age, gene/environment susceptibility-Reykjavik study. *European J Ageing* **18**, 405–15.
14. Tsutsumimoto K, Doi T, Makizako H, *et al.* (2017) The association between anorexia of aging and physical frailty: results from the national center for geriatrics and gerontology's study of geriatric syndromes. *Maturitas* **97**, 32–7.
15. de Lima ES, Zukeran MS, Valentini Neto J, *et al.* (2022) Factors related to malnutrition and their association with frailty in community-dwelling older adults registered at a geriatric clinic. *Exp Gerontol* **165**, 111865. doi: 10.1016/j.exger.2022.111865.
16. Van Dronkelaar C, Tieland M, Aarden JJ, *et al.* (2019) Decreased appetite is associated with sarcopenia-related outcomes in acute hospitalized older adults. *Nutrients* **11**, doi: 10.3390/NU11040932.
17. Alhurani RE, Vassilaki M, Aakre JA, *et al.* (2016) Decline in weight and incident mild cognitive impairment Mayo Clinic study of aging. *JAMA Neurol* **73**, 439–46.
18. Potter GG, McQuoid DR, Steffens DC (2015) Appetite loss and neurocognitive deficits in late-life depression. *Int J Geriatr Psychiatry* **30**, 647–54.
19. Saha S, Hatch DJ, Hayden KM, *et al.* (2016) Appetite and weight loss symptoms in late-life depression predict dementia outcomes. *Am J Geriatr Psychiatry* **24**, 870–8.

https://doi.org/10.1017/S0029665125101778 Published online by Cambridge University Press

20. Sun W, Matsuoka T, Imai A, *et al.* (2023) Relationship between eating problems and the risk of dementia: A retrospective study. *Psychogeriatrics* **23**, 1043–50.
21. Ding G, Lu M, Li J (2024) BMI, weight change, appetite reduction and cognitive impairment of elderly patients with diabetes. *Sci Rep* **14**, 1–7.
22. Tavassoli N, de Souto Barreto P, Berbon C, *et al.* (2022) Implementation of the WHO integrated care for older people (ICOPE) programme in clinical practice: a prospective study. *Lancet Healthy Longevity* **3**, e394–404.
23. Gaussens L, González-Bautista E, Bonnefoy M, *et al.* (2023) Associations between vitality/nutrition and the other domains of intrinsic capacity based on data from the INSPIRE ICOPE-care program. *Nutrients* **15**, 1567.
24. World Health Organization, Geneva Switzerland. (2024) Integrated care for older people (ICOPE): Guidance for person-centred assessment and pathways in primary care. https://www.who.int/publications/i/item/9789240103726 (accessed April 24, 2025).
25. Tsutsumimoto K, Doi T, Makizako H, *et al.* (2018) Aging-related anorexia and its association with disability and frailty. *J Cachexia, Sarcopenia and Muscle* **9**, 834–43.
26. Vázquez-Valdez OE, Aguilar-Navarro S, Ávila-Funes JA (2010) Association between anorexia of aging and disability in older community-dwelling Mexicans. *Journal of the American Geriatrics Society*. **58**, 2044–6.
27. Malafarina V, Uriz-Otano F, Gil-Guerrero L, *et al.* (2013) The anorexia of ageing: Physiopathology, prevalence, associated comorbidity and mortality. A systematic review. *Maturitas* **74**, 293–302.
28. Cox NJ, Morrison L, Ibrahim K, *et al.* New horizons in appetite and the anorexia of ageing. *Age and Ageing*. 2020; **49**: 526–34.
29. Saitoh M, dos Santos MR, Emami A, *et al.* (2017) Anorexia, functional capacity, and clinical outcome in patients with chronic heart failure: results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF). *ESC Heart Failure* **4**, 448–57.
30. Landi F, Liperoti R, Lattanzio F, *et al.* (2012) Effects of anorexia on mortality among older adults receiving home care: an observational study. *J Nutr Health and Aging* **16**, 79–83.
31. Cox NJ, Morrison L, Robinson SM, *et al.* (2021) Older individual's perceptions of appetite, its loss, influencing factors and adaptions to poor appetite. A qualitative study. *Appetite* **167**, 105609.
32. Cox NJ, Ibrahim K, Sayer AA, *et al.* (2019) Assessment and treatment of the anorexia of aging: a systematic review. *Nutrients* **11**, 144.
33. de Souto Barreto P (2022) Poor appetite & aging: the role of physical activity under a geroscience perspective. *J Nutr Health Aging*. **26**, 907–8.
34. López-Otín C, Blasco MA, Partridge L, *et al.* (2023) Hallmarks of aging: an expanding universe. *Cell* **186**, 243–78.
35. López-Otín C, Blasco MA, Partridge L, *et al.* (2013) The hallmarks of aging. *Cell* **153**, 1194.
36. de Souto Barreto P, Guyonnet S, Ader I, *et al.* (2021) The inspire research initiative: a program for geroscience and healthy aging research going from animal models to humans and the healthcare system. *J Frailty & Aging* **10**, 86–93.
37. Gribble FM, Reimann F. (2019) Function and mechanisms of enteroendocrine cells and gut hormones in metabolism. *Nat Rev Endocrinol* **15**, 226–37.
38. Gribble FM, Reimann F. (2016) Enteroendocrine cells: chemosensors in the intestinal epithelium. *Annual Rev Physiol* **78**, 277–99.
39. Sturm K, Parker B, Wishart J, *et al.* (2004) Energy intake and appetite are related to antral area in healthy young and older subjects. *Am J Clin Nutr* **80**, 656–67.
40. Clarkston WK, Pantano MM, Morley JE, *et al.* (1997) Evidence for the anorexia of aging: Gastrointestinal transit and hunger in healthy elderly versus young adults. *Am J Physiol Regul Integr Comp Physiol* **272**. doi: 10.1152/AJPREGU.1997.272.1.R243.
41. Conte M, Martucci M, Mosconi G, *et al.* (2020) GDF15 plasma level is inversely associated with level of physical activity and correlates with markers of inflammation and muscle weakness. *Front Immunol* **11**, 915. doi: 10.3389/fimmu.2020.00915.
42. Woods SC. Gastrointestinal Satiety Signals (2004) I. An overview of gastrointestinal signals that influence food intake. *Am J Physiol Gastrointestinal and Liver Physiol* **286**, G7–13. doi: 10.1152/AJPGI.00448.2003.
43. Pradhan G, Samson SL, Sun Y. (2013) Ghrelin: Much more than a hunger hormone. *Current Opinion Clin Nutrition and Metabolic Care* **16**, 619–24.
44. Holliday A, Horner K, Johnson KO, *et al.* (2025) Appetite-related gut hormone responses to feeding across the life course. *J Endocr Soc* **9**, bvae223. doi: 10.1210/JENDSO/BVAE223.
45. Johnson KO, Shannon OM, Matu J, *et al.* (2020) Differences in circulating appetite-related hormone concentrations between younger and older adults: a systematic review and meta-analysis. *Aging Clin Exper Res* **32**, 1233–44.
46. Dagbasi A, Warner J, Catterall V, *et al.* (2024) Augmented gut hormone response to feeding in older adults exhibiting low appetite. Appetite 201. doi: 10.1016/j.appet.2024.107415.
47. Kmiec Z (2011) Aging and peptide control of food intake. *Current Protein & Peptide Sci* **12**, 271–9.
48. Dent E, Hoogendijk EO, Wright ORL (2019) New insights into the anorexia of ageing: from prevention to treatment. *Current Opinion Clin Nutr Metab Care* **22**, 44–51.
49. Landi F, Picca A, Calvani R, *et al.* (2017) Anorexia of aging: assessment and management. *Clin Geriatric Med* **33**, 315–23.
50. Di Francesco V, Zamboni M, Zoico E, *et al.* Unbalanced serum leptin and ghrelin dynamics prolong postprandial satiety and inhibit hunger in healthy elderly: another reason for the 'anorexia of aging'. *Am J Clin Nutr* 2006; **83**, 1149–52.
51. Balaskó M, Soós S, Székely M, *et al.* (2014) Leptin and aging: review and questions with particular emphasis on its role in the central regulation of energy balance. *J Chem Neuroanat* **61–62**, 248–55.
52. Yanik T, Durhan ST (2023) Neuroendocrinological and clinical aspects of leptin. *Mini-Rev Med Chem* **24**, 886–94.
53. Sánchez-Sánchez JL, Guyonnet S, Lucas A, *et al.* (2023) Plasma inflammatory biomarkers and anorexia of ageing among community-dwelling older adults: an exploratory analysis of the MAPT study. *J Nutr Health Aging* **27**, 1127–31.
54. Franceschi C, Garagnani P, Parini P, *et al.* (2018) Inflammaging: a new immune–metabolic viewpoint for age-related diseases. *Nature Rev Endocrinol* **14**, 576–90.
55. Fulop T, Larbi A, Pawelec G, *et al.* (2023) Immunology of aging: the birth of inflammaging. *Clin Rev Allergy Immunol* **64**, 109–22.
56. Yeh SS, Blackwood K, Schuster MW. (2008) The cytokine basis of cachexia and its treatment: are they ready for prime time? *J Am Med Direct Assoc* **9**, 219–36.
57. Laviano A, Meguid MM, Inui A, *et al.* (2005) Therapy insight: cancer anorexia-cachexia syndrome—When all you can eat is yourself. *Nat Clin Practice Oncol* **2**, 158–65.
58. Morley JE (2017) Anorexia of ageing: a key component in the pathogenesis of both sarcopenia and cachexia. *J Cachexia, Sarcopenia Muscle* **8**, 523–6.
59. Dagbasi A, Fuller A, Hanyaloglu AC, *et al.* (2024) The role of nutrient sensing dysregulation in anorexia of ageing: the little we know and the much we don't. *Appetite* **203**, 107718.
60. Wysokiński A, Sobów T, Kłoszewska I, *et al.* (2015) Mechanisms of the anorexia of aging—a review. *Age* **37**, 81.
61. Braun TP, Marks DL (2010) Pathophysiology and treatment of inflammatory anorexia in chronic disease. *J Cachexia, Sarcopenia and Muscle*. **1**, 135–45.
62. García-Esquinas E, Carballo-Casla A, Ortolá R, *et al.* (2023) Blood selenium concentrations are inversely associated with the risk of undernutrition in older adults. *Nutrients* **15**, 4750.
63. Schulz MT, Rink L (2025) Zinc deficiency as possible link between immunosenescence and age-related diseases. *Immun Ageing* **22**, 19.
64. Coperchini F, Greco A, Teliti M, *et al.* (2025) Inflamm-ageing: how cytokines and nutrition shape the trajectory of ageing. *Cytokine Growth Factor Rev* **82**, 31–42.
65. Hara LM, Freiria CN, Silva GM, *et al.* (2019) Anorexia of aging associated with nutrients intake in brazilian elderly. *J Nutr Health Aging* **23**, 606–13.
66. Iglesias P, Silvestre RA, Díez JJ (2023) Growth differentiation factor 15 (GDF-15) in endocrinology. *Endocrine* **81**, 419–31.
67. Chang JY, Hong HJ, Kang SG, *et al.* (2020) The role of growth differentiation factor 15 in energy metabolism. *Diabet Metab J* **44**, 363–71.
68. Lerner L, Hayes TG, Tao N, *et al.* (2015) Plasma growth differentiation factor 15 is associated with weight loss and mortality in cancer patients. *J Cachexia, Sarcopenia and Muscle* **6**, 317–24.

https://doi.org/10.1017/S0029665125101778 Published online by Cambridge University Press

69. Tanaka T, Biancotto A, Moaddel R, *et al.* (2018) Plasma proteomic signature of age in healthy humans. *Aging Cell* **17**. doi: 10.1111/acel.12799.
70. Semba RD, Gonzalez-Freire M, Tanaka T, *et al.* (2020) Elevated plasma growth and differentiation factor 15 is associated with slower gait speed and lower physical performance in healthy community-dwelling adults. *J Gerontol—Series A Biol Sci Med Sci* **75**, 175–80.
71. Torrens-Mas M, Navas-Enamorado C, Galmes-Panades A, *et al.* (2025) GDF-15 as a proxy for epigenetic aging: associations with biological age markers, and physical function. *Biogerontology* **26**, 22. doi: 10.1007/S10522-024-10165-Z.
72. Li J, Hu X, Xie Z, *et al.* (2024) Overview of growth differentiation factor 15 (GDF15) in metabolic diseases. *Biomed and Pharma* **176**. doi: 10.1016/j.biopha.2024.116809.
73. Lu W-H, Guyonnet S, Martinez LO, *et al.* (2023) Association between aging-related biomarkers and longitudinal trajectories of intrinsic capacity in older adults. *GeroScience* **45**, 3409–18. 1–10.
74. Wiklund FE, Bennet AM, Magnusson PKE, *et al.* (2010) Macrophage inhibitory cytokine-1 (MIC-1/GDF15): a new marker of all-cause mortality. *Aging Cell* **9**, 1057–64.
75. Daniels LB, Clopton P, Laughlin GA, *et al.* (2011) Growth-differentiation factor-15 is a robust, independent predictor of 11-year mortality risk in community-dwelling older adults: the rancho bernardo study. *Circulation* **123**, 2101–10.
76. Justice JN, Ferrucci L, Newman AB, *et al.* (2018) A framework for selection of blood-based biomarkers for geroscience-guided clinical trials: report from the TAME Biomarkers Workgroup. *GeroScience* **40**, 419–36.
77. Johnen H, Lin S, Kuffner T, *et al.* (2007) Tumor-induced anorexia and weight loss are mediated by the TGF-β superfamily cytokine MIC-1. *Nat Med* **13**, 1333–40.
78. Patel MS, Lee J, Baz M, *et al.* (2016) Growth differentiation factor-15 is associated with muscle mass in chronic obstructive pulmonary disease and promotes muscle wasting in vivo. *J Cachexia, Sarcopenia and Muscle* **7**, 436–48.
79. Baek SJ, Eling T (2019) Growth differentiation factor 15 (GDF15): A survival protein with therapeutic potential in metabolic diseases. *Pharma Therap* **198**, 46–58.
80. Liu H, Huang Y, Lyu Y, *et al.* (2021) GDF15 as a biomarker of ageing. *Exp Gerontol* **146**, 111228. doi: 10.1016/j.exger.2021.111228.
81. Schoultz I, Claesson MJ, Dominguez-Bello MG, *et al.* (2025) Gut microbiota development across the lifespan: disease links and health-promoting interventions. *J Int Med* **297**, 560–83. doi: 10.1111/JOIM.20089.
82. Odamaki T, Kato K, Sugahara H, *et al.* (2016) Age-related changes in gut microbiota composition from newborn to centenarian: a cross-sectional study. *BMC Microbiol* **16**, doi: 10.1186/S12866-016-0708-5.
83. Turesson A, Koochek A, Nydahl M, *et al.* The associations between biological markers of aging and appetite loss across adulthood: retrospective case-control data from the INSPIRE-T study. *GeroScience* 2025; published online May 10. doi: 10.1007/s11357-025-01691-w.
84. Mandelblatt JS, Antoni MH, Bethea TN, *et al.* (2024) Gerotherapeutics: aging mechanism-based pharmaceutical and behavioral interventions to reduce cancer racial and ethnic disparities. JNCI: J Nat Cancer Inst 117. doi: 10.1093/JNCI/DJAE211.
85. Horner KM, Mullen B, Quinn A, *et al.* Plant protein, fibre and physical activity solutions to address poor appetite and prevent undernutrition in older adults: study protocol for the APPETITE randomised controlled trial. *British J Nutrition* 2024; **132**, 823.
86. Caruso L, Zauli E, Vaccarezza M (2023) Physical exercise and appetite regulation: new insights. *Biomolecules* **13**, 1170.
87. Klein AB, Kleinert M, Richter EA, *et al.* (2022) GDF15 in appetite and exercise: essential player or coincidental bystander? Endocrinology (United States) 163, 1–10.
88. Raffin J, Rolland Y, Parini A, *et al.* (2023) Association between physical activity, growth differentiation factor 15 and bodyweight in older adults: a longitudinal mediation analysis. *J Cachexia, Sarcopenia and Muscle* published online Jan 20. doi: 10.1002/jcsm.13152.
89. Sánchez-Sánchez JL, Rolland Y. (2023) Social isolation and loneliness: overlooked therapeutic targets of anorexia of aging? *J Nutrition, Health Aging* **27**, 794–96.
90. Bilman E, van Kleef E, van Trijp H. (2017) External cues challenging the internal appetite control system—overview and practical implications. *Critic Rev Food Sci Nutr* **57**, 2825–34.

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