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Published in:
Handbook of Famine, Starvation, and Nutrient Deprivation

DOI:
10.1007/978-3-319-40007-5_50-1

Licence:
Other

Facing Page

Comparing characteristics of malnutrition, starvation, sarcopenia and cachexia in older adults

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Word count
8,104 Words
3 Tables
7 Figures
74 References
1,831 Words in references

Key words: (10-15)

Elderly, aged, malnutrition, starvation, sarcopenia, cachexia, prevalence, undernutrition, nutrition assessment, diagnosis

List of abbreviations

AIDS, Acquired Immune Deficiency Syndrome

AND, Academy of Nutrition & Dietetics

ASPEN, American Society for Parenteral and Enteral Nutrition

BIA, Bioimpedance Analysis

CT, Computed Tomography

DEXA, Dual-Energy X-Ray

ESPEN, European Society of Clinical Nutrition & Metabolism

EWGSOP, European Working Group on Sarcopenia in Older People

HPHE, High Protein-High Energy

HMB, β-hydroxy-β-methylbutyrate

ICD, International Statistical Classification of Diseases and Health Related Problems

IL, Interleukin

IWGS, International Working Group on Sarcopenia

MNA, Mini Nutritional Assessment

MRI, Magnetic Resonance Imaging

ONS, Oral Nutrition Support

PEM, Protein Energy Malnutrition

PG-SGA, Patient-Generated Subjective Global Assessment

SGA, Subjective Global Assessment

TNF, Tumor Necrosis Factor

UK, United Kindom

Definitions of words and terms

Acute disease or injury related malnutrition: protein energy malnutrition caused by factors related to acute disease or an injury in the presence of a high degree of inflammation.

Cachexia: a complex syndrome which presents with the loss of body weight, predominately skeletal muscle, as a result of metabolic abnormalities related to disease processes.

Disease related malnutrition: protein energy malnutrition caused by disease related processes in the presences of a mild to moderate degree of inflammation.

Protein energy malnutrition: a syndrome caused by the inadequate bioavailability of energy and/or protein over time, leading to the catabolism of lean tissues with or without loss of fat mass, occurring most frequently in older adults.

Sarcopenia: The loss of muscle mass, strength and function that occurs in ageing.

Starvation-related malnutrition: Protein energy malnutrition due to pure chronic starvation or anorexia nervosa; but is also affected by social, environmental, physical and psychological risk factors.

Summary points (5 – 15)

1. Protein-energy malnutrition, a syndrome caused by the inadequate bioavailability of energy and/or protein over time, leading to the catabolism of lean tissues with or without loss of fat mass, occurring most frequently in older adults.
2. Inadequate energy and protein intake in malnutrition can be caused by not consuming sufficient dietary sources of energy and protein to meet an individual's nutrient requirements, which is exacerbated in states of hypermetabolism, and/or not absorbing the energy or protein consumed. This is further impacted by psychological, environmental, social and economic risk factors.
3. Malnutrition causes systemic catabolism of fat mass and lean tissues, including vital organs of the liver, heart, respiratory system and skeletal muscle mass.
4. Simple starvation is a physiological state referring to the metabolic alterations, such as hypophosphatemia and the production of ketones as the primary energy source, which are activated in a state of food and nutrient deprivation, but when it causes physiological consequences it is clinically referred to as malnutrition.
5. Starvation-related malnutrition is due to pure chronic starvation or anorexia nervosa; but is also affected by social, environmental, physical and psychological risk factors.
6. During extended starvation, several organ systems modify their metabolism. Liver gluconeogenesis decreases the production of glucose and kidney production of glucose increases. Fat loss also occurs in starvation-related malnutrition which provides a more stable energy source than glucose produced by gluconeogenesis.
7. Sarcopenia is the loss of muscle mass, strength and function that occurs in ageing.
8. The aetiology of age-related sarcopenia is multifactorial. Declines in nutritional intake, malabsorption of nutrients, reduced physical activity levels, progressive and irreversible loss of motor neurons, although normal in ageing, result in loss of muscle mass and function.
9. Sarcopenia has a significant impact on the independence of older adults, and is also known to increase the risk of depression and type II diabetes.
10. Cachexia is a complex syndrome which presents with the loss of body weight, predominately skeletal muscle, as a result of metabolic abnormalities related to disease processes.
11. Conditions which predispose to cachexia and disease-related malnutrition are those that present with systemic inflammation including cancer, chronic infection, chronic kidney

disease, chronic obstructive pulmonary disease, acquired immune deficiency syndrome, rheumatoid arthritis, chronic heart failure and liver failure.

12. Cachexia also significantly increases the risk of death beyond the rate seen in standard protein-energy malnutrition, and is one of the primary causes of death in cancer.

Abstract

Wasting syndromes such as malnutrition, starvation, sarcopenia and cachexia have been increasingly recognised in healthcare and are the subject of significant research endeavours internationally. It is the purpose of this chapter to compare the characteristics (definitions and diagnosis, aetiology and outcomes) of each of these conditions in older adults. Protein-energy malnutrition, a syndrome caused by the inadequate bioavailability of energy and/or protein over time, leading to the catabolism of lean tissues with or without loss of fat mass, occurring most frequently in older adults. Malnutrition prevalence ranges from 10 – 50% depending on the setting. Simple starvation is a physiological state referring to the metabolic alterations, such as hypophosphatemia and the production of ketones as the primary energy source, which are activated in a state of food and nutrient deprivation, but when it causes physiological consequences it is clinically referred to as malnutrition. Starvation-related malnutrition is only diagnosed when protein energy malnutrition is caused by food and nutrient deprivation over a long period time in the absence of disease processes and inflammation. Sarcopenia is the loss of muscle mass, strength and function that occurs due to age-related changes in physiology, and ranges in prevalence from 10 – 50% depending on age group. Cachexia is a complex syndrome which presents with the loss of body weight, predominately skeletal muscle, as a result of metabolic abnormalities related to disease processes. Cachexia may be considered as a type of disease-related malnutrition, and ranges in prevalence from 10 – 50% depending on the underlying disease. Malnutrition, starvation, sarcopenia and cachexia result in the catabolism and resulting dysfunction of multiple organ systems and skeletal muscle, leading to poor patient outcomes such as physical dysfunction, hospitalisations, poor quality of life, and increased risk of death.

Chapter

Introduction

In1974 Dr Charles Edwin Butterworth Jr's put the first spotlight on wasting syndromes in older adults when he published "The Skeleton in the Hospital Closet" (Butterworth Jr, 1974). Since then, wasting syndromes such as malnutrition, sarcopenia and cachexia have been increasingly recognised in healthcare and are the subject of significant research endeavours internationally (Krumdieck, 1998). However, despite over 40 years of research aimed at improving the nutritional status of older adults, malnutrition, sarcopenia and cachexia remain highly prevalent worldwide in the community, hospitals and residential aged care (Watterson et al., 2009). In addition, there is significant confusion in the literature and in clinical practice between malnutrition, starvation, sarcopenia and cachexia (Tzankoff and Norris, 1978). Therefore, it is the purpose of this chapter to explore the current evidence regarding the definition and diagnosis, aetiology, and outcomes of each of these conditions in older adults.

Malnutrition in older adults

Definition and diagnosis

The term "malnutrition" traditionally refers to any state of an individual resulting from the inadequate and/or excessive intake of nutrients. Each nutrient has a range of intake that is required for optimal health, and an intake below or above this is associated with impaired physical function (2005). However, overtime the term "malnutrition" has come to be frequently used to refer to "protein-energy malnutrition" (PEM), a syndrome caused by the inadequate bioavailability of energy and/or protein over time, leading to the catabolism of lean tissues with or without loss of fat mass, occurring most frequently in older adults (2008). Other nutrients may also be deficient; however, the lack of sufficient energy and/or protein is the defining aetiological characteristic of PEM (2015). However, there is no international consensus on the definition of PEM, nor even its name, as it is also referred to as "protein-energy undernutrition" or "protein-calorie malnutrition". The loss of lean tissues (comprising 35 – 50% of total body weight) with or without fat mass presents clinically as decreased body weight, evidence of muscle wasting and compromised homeostasis in organ function, blood cells and immune cells (Pleuss, 2005).

Reflecting this variable clinical presentation, there is no single measure able to diagnose PEM. Instead, a diagnosis is reached through a global examination by a highly-trained health professional of an individual's medical status, anthropometry, biochemistry, dietary intake, nutrition-related symptoms and a physical examination. To support this process, health professionals frequently use a "nutrition assessment tool" to gather the required information and to guide interpretation. Although not all clinicians and researchers utilise a nutrition assessment tool to make a diagnosis of PEM, it is considered best-practice to do so, and is increasingly required in health care facilities (Watterson et al., 2009). There are three nutrition assessment tools which are validated for use in older adults, these are the Mini Nutritional Assessment (MNA) (Guigoz and Vellas, 1997), the Subjective Global Assessment (SGA) (Detsky et al., 1987) and Scored Patient-Generated Subjective Global Assessment (PG-SGA) (Marshall et al., 2016b).

Protein-energy malnutrition may also be defined and diagnosed by its severity and cause. Reflecting the amount of body weight lost and/or severity of muscle wasting in a certain time-frame, PEM an individual may be categorised as "mildly malnourished", "moderately malnourished" or "severely malnourished". However, there is also no consensus as to how each of these categories is defined, and usually is based upon the nutrition assessment tool utilised or the amount of weight lost in a certain period.

In 2012, the Academy of Nutrition & Dietetics (AND) and the American Society for Parenteral and Enteral Nutrition (ASPEN) reached a consensus on the set of aetiology-based diagnostic characteristics for PEM (White et al., 2012). There were three aetiology-based diagnostic criterion agreed upon, which are outlined in Figure 1. Beyond these three categories, the consensus definition also categorises PEM as severe or nonsevere (moderate), based on the degree of inadequate energy intake, weight loss, fat loss, muscle wasting, fluid accumulation and grip strength (White et al., 2012).

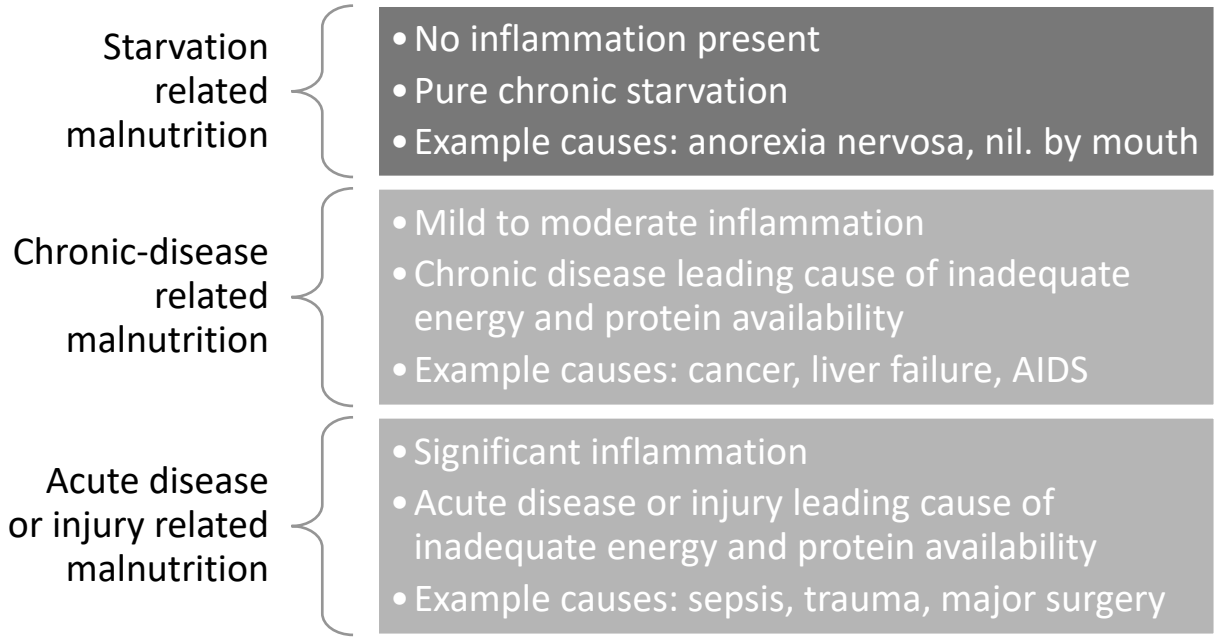

Figure 1: Consesus aetiology-based protein-energy malnutriton definitions (adapted from (White et al., 2012)).

Legend: The characteristics of the three sub-types of protein-energy malnutrition, which differ primarily on the cause of malnutrition. AIDS, acquired immune deficiency syndrome.

Aetiology

Protein-energy malnutrition is a condition that develops over time, with a latency period ranging from days to years depending on the initial nutritional state of the individual and the severity of malnutrition-causing symptoms and environments. Inadequate energy and protein can be caused by: 1) not consuming sufficient dietary sources of energy and protein to meet an individual's nutrient requirements, which is exacerbated in states of hypermetabolism, or 2) not absorbing the energy or protein consumed. Additionally, it should be highlighted that in any one person, there may be one or many contributing causes.

There are innumerable causes of inadequate energy and protein dietary intake, examples of which are shown in figure 2. When hypermetabolism is present, the bodies demand for energy and protein increases significantly, and may in some cases double (Marshall, 2017, 2005). This is often confounded by a low level of nutrition knowledge, where older adults may fail to recognise increased nutrient requirements or the types of foods required to prevent malnutrition (Marshall et al., 2016a). Similarly, not absorbing the consumed energy and protein also has diverse causes, including:

1. Diseases related to maldigestion and malabsorption. Examples are short bowel syndrome, gastrointestinal catabolism as a result of malnutrition, gastritis, inflammatory bowel syndrome, cystic fibrosis, pancreatic and liver diseases, and bariatric surgery.
2. Diseases related to excessive nutrient losses. Examples are diarrhoea, steatorrhoea, vomiting, protein losing enteropathy, surgical drains, stomas, fistulae, haemodialysis and blood loss.

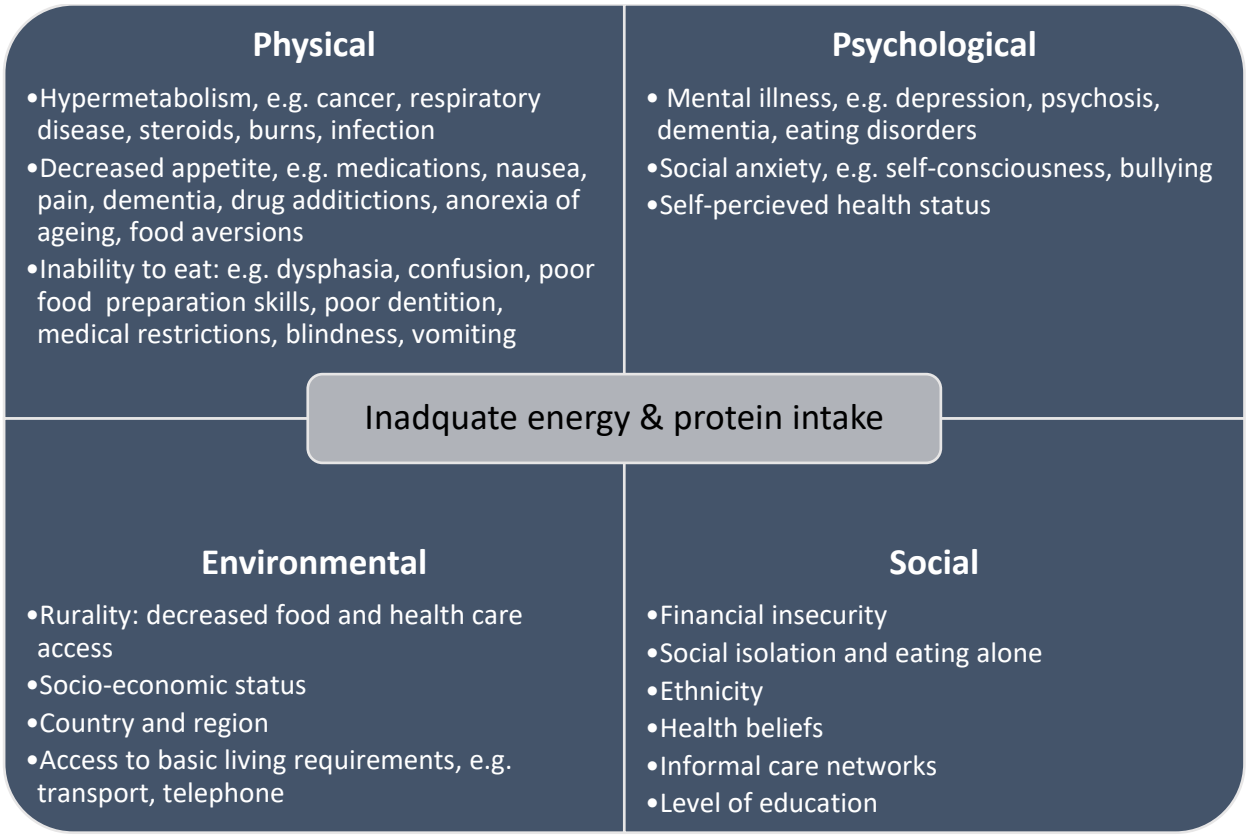

Figure 2: Social, environmental, physical and psychological factors which decrease a person's ability to consume adequate energy and protein (Marshall, 2017).

Legend: These are diverse and overlapping risk factors which increase the chances that an older adult will consume less energy and protein in their food, which in turn increases the chances they will become malnourished.

Prevalence

The prevalence of PEM varies widely according to the setting and the geographical location; but also varies according to the age group of a sample as well as the diagnostic tool used. Cereda and associates recently published a meta-analysis of PEM prevalence, diagnosed by the MNA, in older adults (>60 years) according to healthcare setting (Cereda et al., 2016). The highest prevalence was found in long-term care (29%; n=23 studies) and rehabilitation and sub-acute care (29%, n=15 studies), followed by acute care (22%, n=66 studies) and nursing homes (18%, n=44 studies), then home care services (9%, n=15 studies), out-patients (6%, n=37 studies) and the community (3%, n=58 studies) (Cereda et al., 2016). Additionally, this meta-analysis found that the prevalence of PEM, according to the MNA, was consistently and significantly higher in European countries as opposed to Asian countries across all settings, although other geographical locations were not described for comparison (Cereda et al., 2016).

However, reviews and diagnostic studies have found that the MNA considers fewer patients as malnourished than other tools including the SGA, PG-SGA and ICD, and therefore true PEM prevalence may be higher (Marshall, 2016, Marshall et al., 2016b).

The impact of rurality on the prevalence of malnutrition has not been evaluated in a meta-analysis; however, a review in the rehabilitation and sub-acute setting found that the highest prevalence was found to in be rural settings (53-65% in rural Australia; 32 – 49% in urban Australia; all measured using the SGA)(Marshall, 2016).

There are many social, cultural, economic and physical changes that occur in ageing, which increases the risk of protein-energy malnutrition; where many of the risk factors outlined in Figure 2 are more likely to occur in older adults. Research has consistently found age to be a risk factor for increasing risk of malnutrition (Agarwal et al., 2012). In Europe (n=15,043 participants, n=325 hospitals, n=25 countries), every 10 years of life was found to increase risk of PEM by 14% (OR:1.14 [95%CI:1.09-1.19]; $P<0.0001$).

Outcomes

The physiological and psychosocial consequences of malnutrition are significant and diverse (Agarwal et al., 2016). Confusion, fatigue and weakness, common symptoms of malnutrition, are often attributed to other conditions leading to frequent misdiagnosis and under-recognition of malnutrition (Wellman and Kamp, 2008). Malnutrition causes systemic catabolism of fat mass and lean tissues, including vital organs of the liver, heart, respiratory system and skeletal muscle mass (Figures 3, 4 and 5). Catabolism of these lean tissues cause a disruption in homeostasis in nearly all physiological systems, leading to diverse health outcomes (Figures 3, 4 and 5). In

addition to those shown in Figures 3, 4 and 5, malnutrition also causes fluid and electrolyte imbalances which may further affect kidney and cardiac function. The combination of decreasing physical function in multiple organ systems as a result of malnutrition increases risk of mortality. Malnutrition has been found to be an independent risk factor for death, with studies finding the risk of death doubled in hospital (RR: 2.63 [95%CI: 1.55-5.27] $P<0.05$) (Correia and Waitzberg, 2003) (OR: 1.92 [95%CI: 1.09-3.34] $P=0.023$) (Agarwal et al., 2013) and more than tripled in the year following discharge (HR: 3.41 [95%CI: 1.07-10.87] $P=0.038$) (Charlton et al., 2012).

As would be expected with such significant poor health outcomes, individuals who are malnourished may experience a lower quality of life, apathy, depression, self-neglect, hypochondriasis, poor self-efficacy, poor body image, confusion, decreased interest in food, loss of libido and engage less frequently in social activities (2006, Bottone et al., 2012, Marshall et al., 2014). Additionally, these poor health outcomes caused by malnutrition contribute a significant economic burden, where the cost of treating a patient with malnutrition in the UK is more than double the cost of treating a well-nourished patient due to the increase use of health-related resources (Guest et al., 2011). Using data on healthcare utilisation by people with malnutrition, it was recently estimated that the cost of treating the health problems associated with malnutrition in the UK is in excess of £13 billion (AUD$23 billion) per year (Elia and Stratton, 2005). In the USA, disease-related malnutrition in the community setting was found to have an annual burden of USD$156.7 billion (AUD$214.7 billion) to society, the large majority of which was due to medical complications associated with malnutrition (Snider et al., 2014). In order to offset the great patient and economic burden, it is essential that the condition is addressed by a multidisciplinary team with the support of the health care system, the community and society in general.

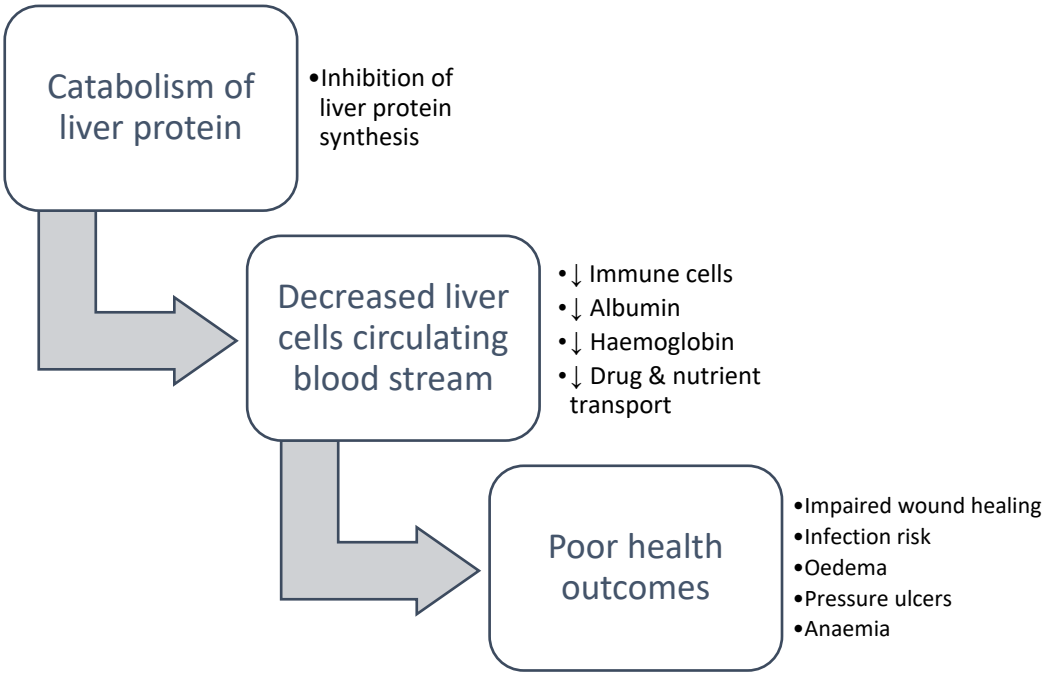

Figure 3: The physiological process and health outcomes related to liver catabolism as a consequence of protein-energy malnutrition (2006, Stratton et al., 2003, Pleuss, 2005, Ferreira et al., 2011, Martyn et al., 1998).

Legend: This figure describes how the breakdown of liver mass and function which occurs in malnutrition will have increased risk of impaired wound healing, infection, swelling, pressure sores and anaemia.

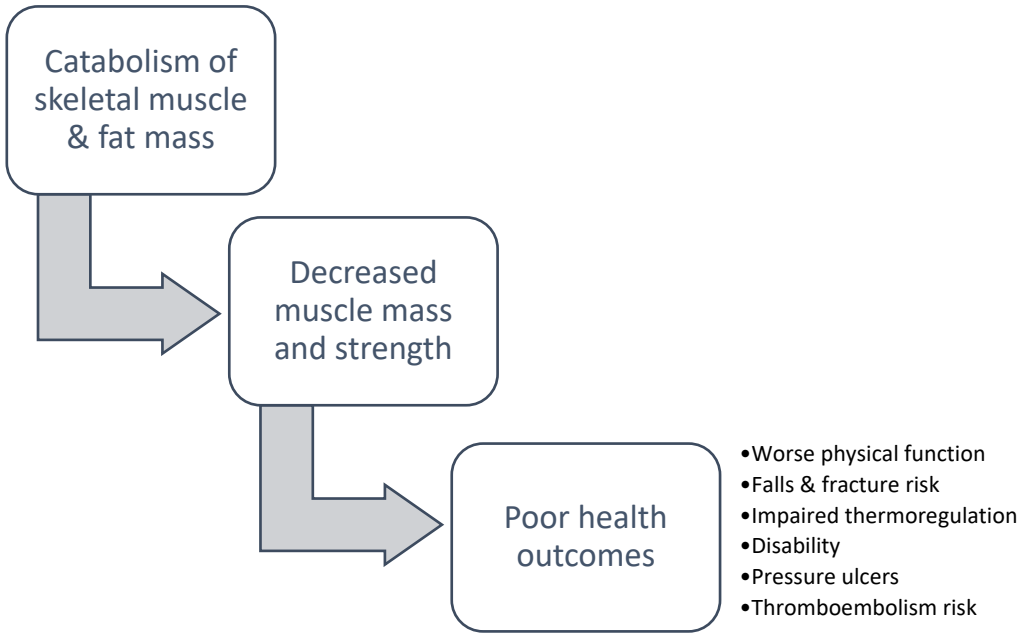

Figure 4: The physiological process and health outcomes related to skeletal muscle and fat mass catabolism as a consequence of protein-energy malnutrition (2006, Stratton et al., 2003, Pleuss, 2005, Ferreira et al., 2011, Martyn et al., 1998).

Legend: This figure describes how the breakdown of muscles and loss of fat which occurs in malnutrition will have increased risk of impaired physical function, falls and fractures, body temperature regulation, pressure sores and obstruction of blood flow.

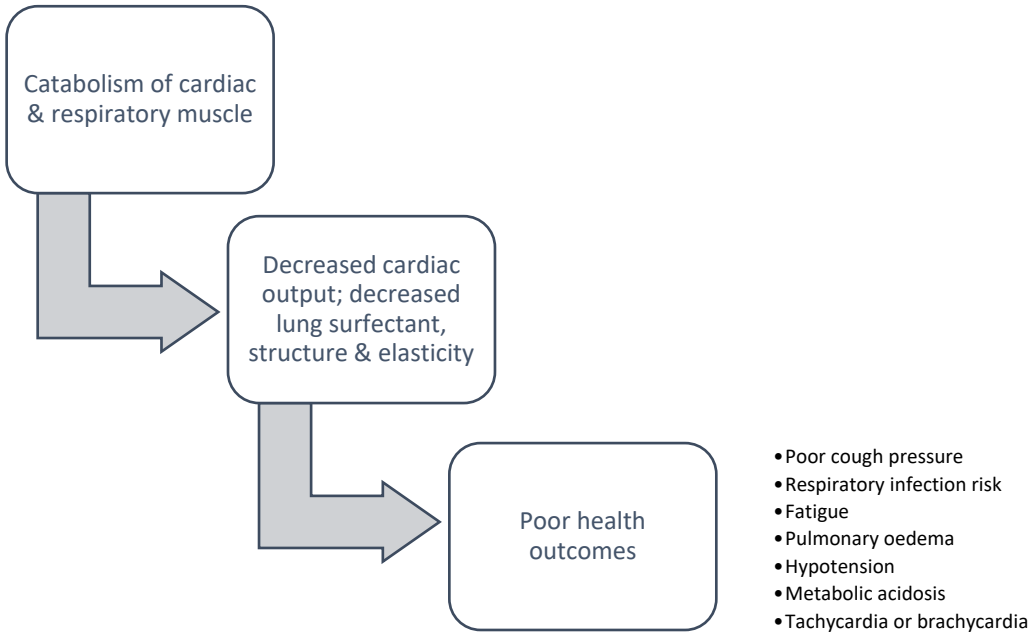

Figure 5: The physiological process and health outcomes related to respiratory and cardiac muslce catabolism as a consequence of protein-energy malnutrition (2006, Stratton et al., 2003, Pleuss, 2005, Ferreira et al., 2011, Martyn et al., 1998).

Legend: This figure describes how the breakdown of the heart and lungs which occurs in malnutrition will have increased risk of lung infections and water retention, fatigue, low blood pressure, poor coughing, and other heart problems.

Starvation in older adults

Definition and diagnosis

Simple starvation is a physiological state referring to the metabolic alterations, such as hypophosphatemia and the production of ketones as the primary energy source, which are activated in a state of food and nutrient deprivation, but when it causes physiological consequences it is clinically referred to as malnutrition (Gallagher, 2008, Litchford, 2008). Some definitions of starvation are analogous to PEM; that is, a chronic inadequate intake of protein and energy, causing a loss of both fat-mass and fat-free mass (Thomas, 2007); which is reflected in starvation being one of the aetiology-based definitions of PEM (Figure 1). Starvation-related malnutrition is only diagnosed when PEM is caused by food and nutrient deprivation over a long period time in the absence of disease processes and inflammation (White et al., 2012).

Extended periods of starvation may also lead to marasmus, another form of malnutrition also called adapted starvation defined as uncomplicated starvation without inflammation (Gallagher, 2008, Litchford, 2008). Again, this definition of marasmus, or adapted starvation, is analogous to starvation-related malnutrition. Starvation may also refer to the deprivation of particular nutrients, for example, the deprivation of protein when carbohydrate is regularly consumed may lead to kwashiorkor, which is also a form of malnutrition characterised by hypalbuminaemia (Gallagher, 2008). Overall, starvation may be an important component of malnutrition in some clinical situations, but starvation-related malnutrition should be used as a clinical diagnosis to enhance consistency in terminology across health care facilities and disciplines (White et al., 2012).

Aetiology

Starvation-related malnutrition (Figure 1) is due to pure chronic starvation or anorexia nervosa (White et al., 2012). The social, environmental, physical and psychological factors which cause PEM (Figure 2), may also be the cause of starvation-related malnutrition. One of these physiological causes that occurs in older adults is referred to as the "anorexia of ageing", which refers to little to no dietary intake related to the decreased appetite which occurs as part of normal ageing (Visvanathan, 2003). Appetite is controlled by interactions between the cortex, limbic system and midbrain as well as peripheral inputs from the gut, adipose tissue and endocrine system (Visvanathan, 2003). These processes may work less efficiently with increasing age leading to consumption of a less varied and lower quality diet (Visvanathan, 2003). However, poor appetite leading to starvation and subsequently weight loss and/or malnutrition is not part of the normal ageing process and is preventable (Huffman, 2002).

Prevalence

There is no data regarding the prevalence of starvation-related malnutrition as opposed to PEM in general. However, starvation-related malnutrition may be more likely to be the type of PEM found in older adults living in the community, as malnutrition diagnosed in health care facilities is likely to be acute, disease or injury-related associated with the reasons for admission.

Outcomes

After several days of starvation, the gastrointestinal tract begins to atrophy, reducing its absorptive capacity; however, with recommencement of nutrient intake, absorptive capacity is returned within a few days (Beyer, 2008). During extended starvation, several organ systems modify their metabolism. Liver gluconeogenesis decreases the production of glucose and kidney production of glucose increases. The substrates used in liver gluconeogenesis originate from skeletal muscle, which releases glycogenic amino acids, pyruvate and lactate to be used for gluconeogenesis via the Cori cycle (Gallagher, 2008). In the renal gluconeogenesis, the glutamine released by skeletal muscle is deaminated to alpha-keoglutarate which is used to produce glucose (Gallagher, 2008).

Apart from catabolism of lean tissues such as skeletal muscle, fat loss also occurs in starvation-related malnutrition which provides a more stable energy source than glucose produced by gluconeogenesis (Gallagher, 2008). During starvation, low insulin levels allow fatty acids to be released from adipocytes and transported to the liver, where they form ketones. Ketones then enter the blood stream and are able to be used as an energy source (Gallagher, 2008).

These processes reveal the varying clinical presentation in starvation-related malnutrition as opposed to forms caused by injury or disease; where starvation-related malnutrition more typically presents with low fat and muscle mass, but other forms of malnutrition may occur with a the loss of lean tissues only (White et al., 2012).

In terms of poor health outcomes, these are the same for starvation-related malnutrition and PEM in general; excepting outcomes related to low fat mass such as increased fracture risk, may be more common {Stratton et al., 2003}.

Sarcopenia in older adults

Definition and diagnosis

The term "sarcopenia", derived from the Greek words 'sarx' (flesh) and 'penia' (loss), was coined by Professor Irwin Rosenberg in 1989 to describe age-related loss of muscle mass (Baumgartner et al., 1998). Eventually, with improved understanding of sarcopenia, loss of muscle quality, strength and function or 'dynapenia' were also linked with loss of muscle mass (Morley et al., 2014). Under the auspices of four international working groups, namely European Working Group on Sarcopenia in Older People (EWGSOP), the European Society for Clinical Nutrition and Metabolism Special Interest Groups (ESPEN-SIG), the International Working Group on Sarcopenia (IWGS), and the Society of Sarcopenia, Cachexia and Wasting Disorders, consensus definitions of sarcopenia were released (Table 1) (Cruz-Jentoft et al., 2010, Fielding et al., 2011, Morley et al., 2011, Muscaritoli et al., 2010). These consensus definitions led to sarcopenia being recently recognised as a disease entity in the International Classification of Diseases with its own unique ICD-10 code (Anker et al., 2016).

Table 1. Consensus definitions of Sarcopenia

Working group	Definition
European Working Group on Sarcopenia in Older People (EWGSOP) (Cruz-Jentoft et al., 2010)	The presence of: Low skeletal muscle mass AND Low muscle strength (e.g., handgrip) OR Low muscle performance assessed by walking speed or muscle power The presence of all three conditions indicates 'severe' sarcopenia.
International Working Group on Sarcopenia (IWGS) (Fielding et al., 2011)	The presence of Low skeletal muscle mass AND Low muscle function assessed by walking speed AND/OR Increased fat mass
Society of Sarcopenia, Cachexia and Wasting Disorders (Morley et al., 2011)	The presence of Loss of muscle mass AND Limited mobility in the absence of specific diseases of muscle, peripheral vascular disease, disorders of the central and peripheral nervous system, or cachexia.
European Society for Clinical Nutrition and Metabolism Special Interest Groups	The presence of: Low skeletal muscle mass AND Low muscle strength assessed by walking speed

(ESPEN-SIG) (Muscaritoli et al., 2010)	

Legend: There is no perfect or completely accepted definition of sarcopenia. These are the different recognised definitions put forth by various organisations. EWGSOP, European Working Group on Sarcopenia in Older People; ESPEN-SIG, European Society for Clinical Nutrition and Metabolism Special Interest Groups; IWGS, International Working Group on Sarcopenia.

All four definitions call for the quantification of muscle mass and muscle strength along with measuring deficits in muscle function (Scharf and Heineke, 2012). Currently, several parameters are available to measure age-related sarcopenia. A summary of available diagnostic methods along with advantages and limitations has been summarised in Table 2. With the development of its own unique disease classification code, it is extremely important for identifying the most suitable biomarker for correctly diagnosing, monitoring and treating sarcopenia (Scharf and Heineke, 2012).

Table 2. Diagnosis of sarcopenia (adapted from (Scharf and Heineke, 2012, Yu et al., 2016))

	Method	**Description**	**Advantages**	**Limitation**
Imaging-related quantification of muscle mass	Magnetic Resonance Imaging (MRI)	Calculates segmental and total muscle mass; assesses muscle quality through assessing fat infiltration in muscle; quantifies oedema and visceral organs	High quality image resolution; accurately quantifies and determines quality of whole-body and regional adipose tissue and skeletal muscle tissue; safe	Expensive; requires specialised setting, trained staff and specific software; time-intensive; non-portable
	Computed Tomography (CT)	Reconstructs image when x-ray attenuation through tissues is detected; identifies adipose tissue, skeletal muscle, bone, visceral organs and brain tissue	High quality image resolution; accurately quantifies and determines quality of body composition at tissue-organ level; identifies total and regional adipose tissue and skeletal muscle tissue	Expensive; requires specialised setting, trained staff and specific software; time-intensive; non-portable; considerable radiation
	Dual-energy X-ray absorptiometry (DEXA)	Using low radiation x-rays can differentiate between bone and soft tissue allowing for fat mass to be estimated from soft tissue; assesses bone mineral density	Determines fat, lean and bone tissue for whole body and specific regions; non-invasive, fast; accurate	Requires specialised setting, trained staff and specific software; hydration and thickness of tissue can influence measurements

	Bioelectrical impedance analysis (BIA)	Measures total body water to estimate fat- and fat-free mass	Portable, simple to use, inexpensive, no radiation exposure, quick	Hydration status and presence of oedema can distort results; limited use in those with BMI>34kg/m^2 as likely to underestimate fat mass
Functional Tests for muscle performance	EWGSOP algorithm	Measures gait speed and handgrip strength	Low cost; standardised test; simple to use	Results confounded by comorbidities (degenerative and inflammatory conditions); lacks validation studies; not useful in patients with arthritis in hand
	SARC-F questionnaire	Assesses 5 domains: strength, independence, rising from chair, climbing stairs and falls history	Rapid, cost-effective, no measurements required	Low sensitivity

Legend: There are various methods available to test if a patient has sarcopenia. This table outlines these, and summarises their benefits and limitations. BIA, Bioelectrical impedance analysis CT, Computed Tomography; DEXA, Dual-energy X-ray absorptiometry; EWGSOP; European working group on sarcopenia in older people; MRI, Magnetic Resonance Imaging. SARC-F has no full non-abbreviated title.

Aetiology

The aetiology of age-related sarcopenia is multifactorial. Declines in nutritional intake, malabsorption of nutrients, reduced physical activity levels, progressive and irreversible loss of motor neurons, although normal in ageing, result in loss of muscle mass and function (Cruz-Jentoft et al., 2010, Malafarina et al., 2012). Older adults confined to bed due to illness or trauma are highly prone to loss of muscle mass (Malafarina et al., 2012). Age-related loss of immunity causes an increase in inflammatory cytokines and are associated with reduction in muscle mass and strength in older adults (Malafarina et al., 2012). Deterioration in levels of hormones such as oestrogen, testosterone, and insulin-like growth factors also contribute to the development of sarcopenia (Malafarina et al., 2012). Coexisting conditions such as osteoporosis, obesity, and type 2 diabetes are also associated with sarcopenia in older adults (Cruz-Jentoft et al., 2010, Malafarina et al., 2012).

Prevalence

Ageing is associated with a 1% decline in muscle mass per decade from 30 years of age, accelerating to approximately 8% loss of muscle mass along with a 10-15% loss of leg strength per decade from the age of 40-70 years (Kim and Choi, 2013). After the age of 70 years, this escalates to 15% loss in muscle mass and 25-40% loss in leg strength per decade (Kim and Choi, 2013). Although age-related loss of muscle mass is greater in males, sarcopenia-related loss of function and increased disability is greater in women at three-fold versus males at two-fold (Kim and Choi, 2013). Sarcopenia has been identified in 1-30% of community-dwelling older adults, 14-33% of those living in aged care facilities, 10% of those in acute care, and in 50% of those aged over 80 years (Cruz-Jentoft et al., 2014). Prevalence of sarcopenia is also noticeably high in conditions such as stroke (53%) and hip fractures (71%) due to rapid muscle loss associated with denervation and inflammation respectively (Morley et al., 2014).

Outcomes

Almost 40% of the total body mass and 75% of the body's cell mass in comprised of skeletal muscle, which has a pivotal role in mobility and function (Lang et al., 2010a). Age-associated sarcopenia has major ramifications on health-related outcomes in older adults (Figure 6).

Figure 6. Consequences of Sarcopenia (Developed from (Lang et al., 2010b, Rolland et al., 2008)

Legend: These are the poor health outcomes which can be caused by having the condition of sarcopenia.

Cachexia in older adults

Definition and diagnosis

Cachexia is a complex syndrome which presents with the loss of body weight, predominately skeletal muscle, as a result of metabolic abnormalities related to disease processes (Evans et al., 2008). The 2008 consensus definition of cachexia is:

> *''Cachexia is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass. The prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) or growth failure in children (excluding endocrine disorders). Anorexia, inflammation, insulin resistance and increased muscle protein breakdown are frequently associated with cachexia. Cachexia is distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption and hyperthyroidism and is associated with increased morbidity."* (Evans et al., 2008)

Cachexia is further defined by consensus in the form of "cancer cachexia", the ongoing loss of skeletal muscle mass (with or without fat loss) which cannot be fully reversed by nutrition support and leads to progressive functional impairment. The loss of lean tissues in cancer cachexia is caused by inadequate dietary intake combined with abnormal metabolism (Fearon et al., 2011). Cachexia has been further staged into cachexia and pre-cachexia. The consensus diagnostic criteria and definition of pre-cachexia according to the 2015 ESPEN consensus paper (Muscaritoli et al., 2010) is shown in Figure 6. However, this ESPEN consensus paper did not provide diagnostic criteria for cachexia; therefore, the diagnostic criteria and definition of cachexia by a 2008 consensus paper is also shown in Figure 7 (Evans et al., 2008).

There is disagreement in the literature as to whether cachexia is a type of malnutrition (i.e. disease-related malnutrition), or is a separate condition. Some consensus publications state expert agreement that they are separate conditions, where not all malnourished patients are cachectic, but all cachectic patients are malnourished (Muscaritoli et al., 2010). However, this statement will still hold true with the acceptance that a cachexia is the same condition as disease-related malnutrition, as both are caused by disease in the presence of inflammation. This is reflected in a more recent consensus statement by ESPEN, which considers disease-related malnutrition and cachexia to be essentially the same condition due to the similarities in presentation and aetiology. However, it should be noted, that not all persons with chronic-disease related malnutrition may be diagnosed as having cachexia, and further clinical examination

should be undertaken to evaluate the level of inflammation in the individual (Cederholm et al., 2015).

Pre-cachexia (all criteria must be met)	**Cachexia** (weight loss and 3 of the 5 other criteria must be met)
• Underlying chronic disease • Unintentional weight loss ≤5% usual body weight during past 6-monhts • Chronic or recurrent systemic inflammatory response • Anorexia or anorexia-related symptoms	• Weight loss of ≥5% in 12-months (or BMI <20kg/m^2) • Decreased muscle strength • Fatigue • Anorexia • Low fat-free mass index • Abnormal biochemistry (increased inflammatory marekrs, anaemia or hypoalbuminurea)

Figure 7: The consensus definitions and diagnostic criteria of pre-cachexia according to Muscaritoli et. al. (Muscaritoli et al., 2010) and cachexia according to Evans et. al. (Evans et al., 2008).

Legend: These are the criteria which help define if a person has pre-cachexia or cachexia.

Aetiology

Conditions which predispose to caschexia and disease-related malnutrition are those that present with systemic inflammation including cancer, chronic infection, chronic kidney disease, chronic obstructive pulmonary disease, AIDS, rheumatoid arthritis, chronic heart failure and liver failure (Evans et al., 2008, Muscaritoli et al., 2010). In cachexia, the loss of skeletal muscle in cachexia is a result of increased resting energy expenditure mediated by elevated levels of proinflammatory cytokines (e.g. TNF-α, IL-1, IL-6) and decreased anti-inflammatory cytokines (e.g. IL-4, IL-12, IL-15) (Bauer et al., 2006, Muscaritoli et al., 2010). This systemic inflammation causes metabolic abnormalities including a prolonged acute phase protein response, increased muscle proteolysis and impaired lipid, carbohydrate and protein metabolism (Bauer et al., 2006, Muscaritoli et al., 2010). Therefore, cachexia is purported to not respond to typical dietary intervention which aims to provide a high protein-high energy diet, and instead other treatment approaches are being explored such as omega-3 fatty acids and mixtures of elemental amino acids (Dewey et al., 2007, Eley et al., 2007)., and states of malnutrition and sarcopenia have been described as a "pre-cachectic state", where nutritional intervention may have the most benefit (Evans et al., 2008). However, some research has shown that nutrition intervention may impact upon the pathogenesis of cachexia, although nutrition intervention alone is insufficient to treat the condition (Wilson and Morley, 2003, Evans et al., 2008, Isenring and Teleni, 2013).

Prevalence

The global prevalence of cachexia is estimated to be 1% of the patient population, which equates to approximately 9 million people (von Haehling and Anker, 2014). However, understanding the prevalence of cachexia is complicated by the lack of an overall accepted definition and diagnostic criteria, as well as most criteria being difficult to assess, such as the need for measurement of overall lean body mass (e.g. via DXA scans) and assessment of biochemistry (Tan and Fearon, 2008). Additionally, the prevalence of cachexia is expected to vastly differ according to the underlying disease process (e.g. cancer versus cardiac failure, or pancreatic cancer versus lung cancer) and population characteristics. Following a brief review of the literature, the prevalence of cachexia as reported in various studies is 10 – 50% (Table 3).

Table 3: The prevalence of cachexia in different disease states and populations.

Underlying disease	**Study**	**Population sample**	**Reported prevalence**
Cancer, all types	Von Haehling and Stefan, 2014 (von Haehling and Anker, 2014)	Estimated for entire European population.	30%
Unresectable pancreatic cancer	Tan and Fearon, 2008 (Tan and Fearon, 2008)	Unclear.	20%
Resectable pancreatic cancer	Bachmann et al. 2008 (Bachmann et al., 2008)	N=277, mean age 64-65 years, 35% female. Germany.	41%
Colorectal cancer	Thoresen et. al. 2013 (Thoresen et al., 2013)	N=77, mean age 63 years, 47% female. Norway & Canada.	28%
Chronic Obstructive Pulmonary Disease	Von Haehling and Stefan, 2014 (von Haehling and Anker, 2014)	Estimated for entire European population.	35%
Chronic Heart Failure	Von Haehling and Stefan, 2014 (von Haehling and Anker, 2014)	Estimated for entire European population.	10%

Chronic Heart Failure	Christensen et. al. 2013	N=238. Not further described.	11%
Chronic Heart Failure	Anker et. al. 1997 (Anker et al., 1997)	N=171, mean age 60 years, 11% female. United Kingdom.	16%
Severe rheumatoid arthritis	Von Haehling and Stefan, 2014 (von Haehling and Anker, 2014)	Estimated for entire European population.	10%
End stage chronic kidney disease	Von Haehling and Stefan, 2014 (von Haehling and Anker, 2014)	Estimated for entire European population.	50%

Legend: This table reports the prevalence of cachexia, as a percentage of various populations with other diseases as specified.

Outcomes

The loss of lean tissues in cachexia results in the dysfunction of multiple organ systems seen in malnutrition (Figures 4, 5 & 6). However, the weight loss in cachexia differs from the weight loss in malnutrition; although both are characterised by the loss of lean tissues, the loss of lean tissues compared to fat mass is accelerated in cachexia (Bauer et al., 2006). Cachexia also significantly increases the risk of death beyond the rate seen in standard protein-energy malnutrition, and is one of the primary causes of death in cancer (Bauer et al., 2006). The increased risk of death in cachexia may be due to the detrimental effect that decreased lean tissues has on the efficacy of medical treatment, such as increased risk of complications, and lower doses and duration of chemotherapy (Donohoe et al., 2011).

Policies and protocols

National and state-based health services in many countries have a nutrition care policy which aims to address geriatric wasting syndromes such as malnutrition, sarcopenia and cachexia. Policies for health services typically address nutrition screening and assessment, but may also address the provision of food and monitoring systems (2011). In recognition of the high burden of malnutrition, the United States of America has mandated compulsory nutrition screening upon admission to any health care facility (2017b). In the United Kingdom, although individual health services may have policies to manage malnutrition, there is no policy at the national level, and

instead there is a guidance document (England, 2015). Nutrition policies may also be supported by malnutrition pathways or nutrition care protocols, which guide clinicians to implementing best-practice, for example the Malnutrition Action Flowchart in Australia (Banks).

Outside of the health service, there is generally poor development and implementation of malnutrition policies in community and residential aged care settings, as each organisation is independent and managing malnutrition may not be part of accreditation standards. However, there are some facilities which are proactive in addressing this problem and many non-government organisations have arisen to support implementaiton of malnutrition policies and pathways, such as Managing Adult Malnutrition in the Community (Brotherton et al., 2012) and the UK and Canadian Malnutrition Task Force (2017c, 2017a).

Conclusion

There is ample evidence showing that weight and muscle loss seen in PEM, starvation, sarcopenia and cachexia are associated with frailty, loss of independence, poor prognosis and increased mortality. Although these conditions present with similar characteristics, differential diagnosis is important in the clinical setting so that the patient may be linked with the most appropriate treatment, and that new methods of management may be developed.

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