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Endpoints in clinical trials in cancer cachexia: where to start?

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Title: Endpoints in clinical trials in cancer cachexia: where to start?

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Abstract

Purpose of review: The lack of agreement and knowledge of optimal endpoints in cachexia trials have impeded progress in finding interventions counteracting the devastating effects cancer cachexia has on morbidity and mortality. An endpoint should both be sensitive enough to detect change and specific enough not to be influenced by other conditions or treatments.

Recent findings: There is a wealth of potential and applied endpoints in trials investigating cachexia. As of today, there is no generally acknowledged consensus, but assessments of key factors such as body composition should continue to be applied. However, the impact and effect size necessary to achieve clinical benefit using these endpoints are not clear. Further, the use of other endpoints assessing physical function, symptom evaluation and quality of life remains to be elucidated.

Summary: It is essential that endpoints are clinically relevant and further research is therefore needed to develop endpoints that are meaningful for patients with cachexia.

Keywords: cachexia, trials, endpoints

INTRODUCTION

Despite the advances in cancer cachexia research, the overall landscape in clinical cancer cachexia research remains somewhat depressing. At the time of publication of this review, there is no licensed treatment for cancer cachexia, and no standard of care. Indeed, lack of regulatory approval for the ghrelin agonist anamorelin (1), the monoclonal antibody targeting Interleukin-1α (MABp1) (2), and no further development planned of the selective androgen receptor modulator (SARM) enobosarm (3, 4), means that the pharmalogical armamentarium in cancer cachexia remains empty.

In the last decade, the number and quality of clinical trials in cachexia has increased and consequently the possibility of developing treatments has increased. Key to the improved quality has been the focus on reducing the heterogeneity of populations studied (e.g. stage, oncological treatments and focussing on cancers where cachexia is prevalent [e.g. lung, pancreatic]). Further recruiting patients in cachexia trials earlier in their disease trajectory has minimised the inherent problem of attrition while at the same time exploiting the anabolic potential afforded when cachexia interventions are delivered as early as possible. However, a major obstacle remains in determining the optimal endpoint in cachexia trials. So why might this be the case?

Key to this is defining cachexia; if the definition of something is not established then how can it be measured? The definition and classification of cancer cachexia, has been subject to much debate and the plethora of cachexia definitions proposed may therefore have impeded progress in standardising endpoints.(5-11) Nevertheless, most cachexia trials apply the key factors defining cachexia as endpoints, e.g. measurements of muscle mass or body weight, but often a wealth of other assessments are also applied as more or less predefined secondary or exploratory endpoints.

In an aim to progress this, there have been calls for improved guidance and consistency from regulatory authorities (Federal Drug Administration [FDA] and European Medicines

Agency [EMA]) as to what should constitute the optimal endpoint(s) in clinical trials in cancer cachexia.(12) It has been advocated that a clear clinical benefit needs to be added as a co-primary endpoint to muscle mass. Of the aforementioned pharmacological intervention trials, there were differences in the choice of co-primary endpoints and the resulting failure to meet these were critical factors in not gaining regulatory approval. It is therefore not surprising that the optimal endpoints in cachexia trials remain elusive, when the definition, classification and regulatory consensus is not firmly established.

The most allied cachexia definition provides a useful framework upon which to examine endpoints in cachexia trials: "a multifactorial syndrome characterized by loss of muscle mass (and loss of fat) that cannot be fully reversed by conventional nutritional support and leads to functional decline. Further, its pathophysiology was characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism."(10) This definition provides the opportunity for a wide variety of different endpoints, such as anthropometry measures, biomarkers describing the pathophysiology or different assessments of physical function or food intake. However, it could also be argued, as the ultimate consequence of cachexia is reduced survival, this could also be applied in cachexia trials. As patients with cachexia have increased morbidity and thus increased use of health services, also the use of health care resources and cost is important endpoints.

In a bid to establish the challenges faced to date and also potential way forward an appraisal of recent work is warranted. With this in mind, the overall aim of this narrative review is to discuss endpoints examined in clinical trials of cachexia, and to consider potential ways forward.

CONSIDERATIONS IN CHOICE OF ENDPOINTS IN CACHEXIA TRIALS

Endpoint(s) reflecting clinical benefit

Regulatory authorities have naturally advocated that achieving a clinical benefit is a key aim of studies in cancer cachexia. Loss of muscle mass can have a grossly negative influence patients physical function (13, 14), but improvements or stabilization of muscle mass in cachexic patients have not yet been univocally elated to improvements in physical function and/or quality of life. However, the relevance of these endpoints in terms of being meaningful for patients is less clear; instead endpoints which could be more valid include patient reported outcomes (PROs). The EMA and the FDA suggest PROs should be used "when measuring a concept best known to the patient or best measured from the patient perspective."(15)

Currently there is limited knowledge if stabilization or an increase of muscle mass is inevitably followed by a response in PROs such as fatigue, physical function or overall quality of life. Furthermore it is not known how much muscle, fat or weight is it necessary to gain, or lose to generate a change in PROs or even physical function. Nevertheless ensuring that endpoints should reflect clinical benefit is essential, and further research is therefore needed to ensure that commonly used endpoints actually have meaning for the patients suffering from cachexia.

Endpoint(s) reflecting the mechanism of action

Cachexia has a complex pathophysiology where multiple factors (e.g. decreased nutritional intake, catabolism, systemic inflammation) manifest phenotypically as reduced appetite, loss of weight and muscle mass, and decreased physical function. It might be unrealistic to expect single agents, acting through a specific mechanism, to influence all components of the cachexia phenotype. To illustrate, the ghrelin agonist anamorelin primary influences appetite, and as such this would seem a sensitive measure of efficacy. Although assessed as a secondary endpoint in recent trials, appetite was not chosen as a primary endpoint; rather effect on muscle mass and muscle strength was used.(1) A similar paradigm could be

applied to enobosarm whose primary effect on muscle mass was seen in phase III trials, yet the effect on the co-primary endpoint muscle function was not reached (4). It could be argued that in such trials the criteria for success is set too high and that trials should primarily adopt endpoints reflecting the mechanism of action rather than a plethora of endpoints pertaining to cachexia definitions. This change in endpoints might increase the possibility of studies reporting positive findings.

There are however several disadvantages in this approach, including an increased risk of bias if all studies continue to develop their own endpoints and the lack of possibility of comparing the efficacy of different cachexia interventions. Furthermore it could be argued that there are advantages of keeping cachexia together as a symptom complex and not dividing it into its different components, as many patients experience several symptoms simultaneously which will vary in intensity during their cachexia trajectory. A possible solution could be keeping the primary endpoint as derived from mechanism of action with secondary endpoints reflecting other basic cachexia parameters.

SPECIFIC ENDPOINTS

Figure 1 provides a summary of some examples of endpoints for use in clinical trials in cachexia.

Anthropometry and body composition

Historically measurement of weight has been the main outcome in cachexia trials, derived from early descriptions of cachexia where it was defined as a wasting disease most evident with loss of weight. However weight reflects all body compartments and can be influenced by other factors including ascites. Partly based on this, but also based on pathophysiology, muscle mass has now evolved as the main endpoint in cachexia.

There are several different methods assessing muscle mass and body composition, and it is important to acknowledge that the effect sizes of these different methods cannot necessary be used interchangeably.(16) Bio-impedance is now generally considered obsolete, and only useful in between group comparisons if there are no large alterations in body composition. An international consensus recommended cross sectional imaging (computed tomography (CT) or magnetic resonance) before dual energy x-ray imaging for measurements of body composition in cachexia trials.(17)

Although weight has been less commonly used as an endpoint the recent years, it represents a meaningful and simple measure for patients and clinicians, and in combination with degree of weight loss and body mass index (BMI) it has proven prognostic value.(18) However weight does take into account fat mass, which in itself may influence outcomes in terms of ratio of muscle to fat and also distribution of lipophilic anti-cancer therapies (the latter influencing efficacy of these).(19)

To complicate matters further, it is also necessary to decide upon how each of the aforementioned endpoints should be evaluated. For example, there are a wealth of different possibilities on how to employ weight as an endpoint in clinical trials. It could be evaluated with % weight loss, absolute weight loss in kg, stabilistation of weight loss from previous observations, change in slope of weight loss curve or change in body mass index (BMI).(20) The lack of agreement naturally causes challenges in comparing results from different studies, and consensus should be reached.

Appetite and food intake

Reduced appetite and food intake are central characteristics of the cachexia syndrome and as such potential endpoint candidates. Various methods for assessing appetite have been used in cachexia trials, such as Visual Analogue Scales (VAS) scales (21, 22), anorexia-

cachexia scale from Functional Assessment of Anorexia/Cachexia Treatment (FAACT) questionnaire (23) and anorexia domains from the EORTC QLQ-C30 questionnaire.(2) Several different methods can also be used to assess nutritional intake, either as diet intake forms, food frequency questionnaires, dietary recalls or food records for various defined time periods.(24) There is no gold standard as which method that is most sensitive and responsive, neither for assessments of appetite nor nutritional intake in this, often frail, patient population.

A drug designed to improve appetite, should in theory also improve nutritional intake in order to have clinical benefit. Therefore, choosing endpoints measuring food intake should be included during the testing and development of such drugs, however partly due to feasibility of assessments this is not always done. Two early phase II studies investigating ghrelin assessed both caloric intake and appetite (using a VAS score).(21, 22) Daily intake of calories was calculated by weighing each dish before and after every meal. One study found that both caloric intake and appetite was gradually reduced in both arms, but significantly less in the ghrelin arm.(21) The other study estimated daily nutritional intake for two weeks by weighing each meal and taking photos before and after each patient ate. They reported no differences in energy intake between ghrelin and placebo neither during the day nor the meal eaten just after intravenous administration of ghrelin.(22) Pleasantness of the meal, perceived appetite, and perception of amount of food intake were also measured after lunch on infusion day, and there were no difference between the treatment arms compared to baseline.(22) The results from these studies indicates uncertainties whether ghrelin can lead to increased energy intake, and also if the increased intake that some might achieve is of relevance as the majority of patients seems to have an intake below what is needed to maintain energy balance. The recent anamorelin trials showed improvements in anorexia-cachexia scales (23), but did not assess food intake or caloric intake, thus limiting the inferences about anamorelin's effect on food intake.

In cachexia trials where appetite and energy intake is a relevant endpoint, methods for assessing food intake should represent normal intake over time in patients with a food intake that can vary considerably from day to day due to e.g. symptoms and side-effects of anti-neoplastic treatment.(21)

Physical function

By definition cachexia should lead to physical decline, and methods for assessing various dimensions of physical function are consequently needed to measure the effects of anti-cachexia treatments.(10) However, there is a lack of feasible, sensitive and validated methods, as well as in-depth knowledge of different aspects of physical function sensitive enough to reflect everyday functioning for this patient population.(25, 26) Physical function can also refer to several different outcomes describing the patients' physical performance in everyday life activities, physical strength and/or physical endurance. It can thus be assessed by methods measuring patient's own perception of function (e.g self-report from quality of life questionnaires), by health providers' perception of what the patient can do (e.g. Karnofsky Performance Score), by measurements of what the patients actually can do at one point in time (e.g. hand grip strength or walk tests), or measurements of what the patient is actually doing in everyday life (e.g. activity monitors such as ActivPAL).

There is thus an abundance of tests that potentially can be used, but it is important to choose tests that are easy to perform, leave little room for errors, exclude a ceiling effect and can detect change in patients with different physical functions. In a feasibility trial of a multimodal intervention for cachexia, a 6-minute walk test was used as a performance test.(27) The results showed that patients at an early stage of their cachexia trajectory were able to walk much longer than anticipated (equally to a healthy population) without reaching a maximum level of performance. One might thus consider the possibility of a ceiling effect of the test and therefore would not be suited as a physical function endpoint.(27)

In an international consensus paper from 2011, measurement for hand grip strength was favored to strength testing of lower limb due to its feasibility.(10) Hand grip strength is used both for frail patients and athletes, and there is no ceiling effect. However, there are concerns if this test really reflects the total physical function in patients suffering from cachexia and is sensitive enough to detect functional decline or improvement in cachexia trials. Additionally, there is no consensus on measurement protocols for hand grip strength, which is important since several factors such as arm side, handle position and posture can impact measurements.(28) Furthermore, even though hand grip strength is shown to have a predictive potential regarding mortality and morbidity, it cannot replace measurements such as walking speed and lower muscle strength or evaluations of activities of daily living.(28) The recently published studies evaluating the effect of anamorelin were considered negative due to their failure to meet their co-primary endpoint as muscle mass was increased, but was unaccompanied by an increase in hand grip strength.(1)

A systematic review investigating physical performance measures for predicting outcome in cancer patients, described that the most commonly applied tests were Timed Up and Go (TUG), Short Physical Perfomance Battery (SPPB) and gait speed. All tests were associated with survival and treatment related complications, whereas TUG and SPPB also was associated with increased rate of functional decline.(29) However, it is not known whether more comprehensive tests such as TUG and SPPB, or more objective tests such as activity monitors will have a higher degree of sensitivity to change and be a more valid measurement of physical function in cachexia trial. One advantage of these monitors are that they register what the patient actually do at home and thus is a more inherent endpoint than e.g. hand grip strength.

Patient reported outcomes

The ultimate aim when treating patients is to improve survival and/or improve their health related quality of life (HRQoL); the latter cannot be assessed without asking patients. A systematic review investigating the use of HRQoL instruments in patients with cachexia, described that most studies applied generic cancer HRQoL instruments, and that only one cachexia-specific instrument was in use (Functional Assessment of Anorexia/Cachexia Therapy (FAACT)).(30) Since the FAACT questionnaire did not address important aspects such as psychosocial and relationship issues, the research group chose to design and validate a new cachexia specific HRQoL module, the European Organization for the Research and Treatment of Cancer (EORTC)–CAX24 questionnaire.(31) A further systematic review concluded that EORTC QLQ-C30 and FAACT were the HRQoL questionnaires most commonly in use, but that there was no evidence available to determine which of these instruments that were most responsive to changes in patients with cachexia.(32)

There are several challenges with the use of PROs, one is the lack of specificity in some of the scales (combining several symptoms and experiences) and thus accordingly reducing the ability to find specific changes after interventions.(32) Consequently, several trials used selected components of quality of life measurements (appetite loss, fatigue, physical function) that, at least when not pre-specified, can cause both challenges of multiple outcomes and reporting bias. Challenges do not alter the important factor that only the patient themselves can evaluate if they experience meaningful relief of their symptoms, and therefore patient reported outcomes is inevitable when clinical trials are conducted.

Healthcare utilization and cost

The prevalence of cachexia in an unselected cancer population has been shown to be 51% in inpatients and 22% in outpatients (33), but prevalence increases rapidly with the advancing cancer disease and in certain tumor types (e.g pancreatic cancer and lung cancer).

Based on the high prevalence and the detrimental consequences on morbidity it would seem reasonable to assume that treatment of cachexia may translate into reduced heath care costs, taking into account the costs of any intervention. As of today, few studies investigate economic consequences of interventions and those that do mostly report on experience from nutritional interventions. There are very few studies that have done broader and more rigorous assessments of cost effectiveness (32), e.g. intervention cost, use of health personnel, hospitalization and Quality-Adjusted Life-Year (QALYs). For most institutions and patients, there are limited economical resources, and resources available need to be allocated wisely to improve the quality of life for our patients. The focus on establishing cost effectiveness will thus most likely not diminish in the years to come. However, this will not be the primary objective in studies before the effectiveness of an intervention is established.

CACHEXIA PROGNOSIS AND RESPONSE TO CANCER TREATMENT

Based on its suggested importance for survival, a clear aim of any treatment for cachexia will be to improve survival and this has been advocated as an endpoint by regulatory authorities. However, it has rarely been assessed as primary endpoint in trials to date.

Martin and co-workers' have established a BMI and weight loss grading system as a prognostic score (18) and McMillan and co-workers have proposed the Glasgow Prognostic Score (measuring CRP and albumin) as framework for cachexia investigation and treatment. (34) Both the Martin and McMillan frameworks have been extensively validated as having prognostic value, yet remain to be utilized in the cachexia clinical trial arena as a stratification factor and also in assessment of efficacy of therapies.

Cancer cachexia is estimated implicated in 20% of cancer related deaths (35), this is naturally a difficult estimate to make, as there are few studies investigating cause of death. Often tumor growth in combination with several consequences of cachexia co-coincide to early

demise such as reduced defense against infections, increased risk of cardiovascular incidences and reduced tolerance for oncological treatment.(36) In oncological studies targeting the tumor, there is often a need for very large sample sizes to demonstrate survival and partly to accommodate for this, but also to reduce the impact of other factors at play; surrogate markers such as progression free survival are frequently used. However, progression free survival would probably not be considered a reasonable endpoint for cachexia studies. The recently published anamorelin study reported increased body weight also in the control arm, and this could either be a placebo effect or a response to anti-neoplastic treatment, or both.(1) Reporting response to anti-neoplastic treatment should always be assessed as a confounder for cachexia effect and as an estimate of catabolic drive. So far curing cancer is the only cure for cachexia, and it is challenging to estimate effect of an intervention without also reporting on tumor growth, even though tumor treatment also has shown negative effects on key cachexia outcomes such as muscle mass.(36) As it stands today, in order to prove a principle of the effect of an intervention targeting cachexia, survival would probably not be a preferable primary endpoint. On the other hand, when there is an effective intervention targeting cachexia available, it will be very intriguing to see how this intervention will affect also patient survival and tolerance to oncological treatment.

CONCLUSION

A variety of different endpoints have been used in cachexia trials, and there is still no consensus on the optimal endpoints. An endpoint should both be sensitive enough to detect change and specific enough not to be influenced by other conditions or treatments. Since the key factor of cachexia is loss of weight and lean mass, these will continue to be important endpoints together with some aspect of physical function. Future studies will also need to demonstrate that any cachexia intervention impacts positively on QoL. Perhaps a final aim

would be to demonstrate that any cachexia intervention reduces health care costs and improved survival and tolerance to anti-cancer treatment. These aspirations may seem idealistic however this should not deter research targeting cachexia which in itself remains one of the most under-researched and impactful sequelae of cancer.

KEY POINTS

- The optimal endpoints in cachexia trials are not clear however measurements of lean mass and weight are important.
- Endpoints which assess physical functioning and quality of life are important for patients.
- The relationship between measures of lean mass and physical function is not clear.
- The optimal measures for assessing physical function remain to be defined.

Figure Legends

Figure 1 – examples of endpoints for cancer cachexia trials

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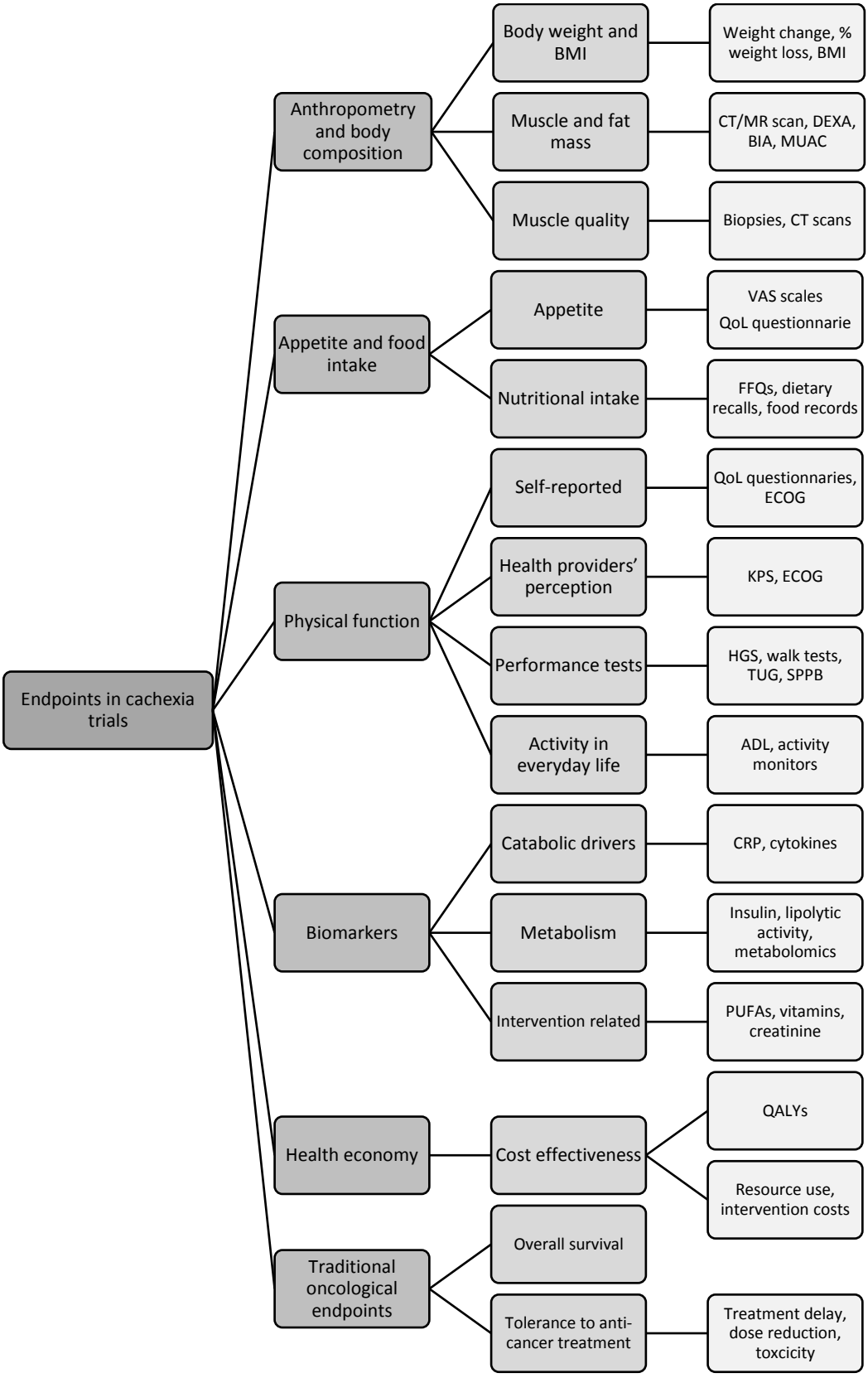

BMI-Body Mass Index; CT-computerise tomography; MR – magnetic Resonance; DEXA-dual x-ray absorpitometry; BIA-bioimpedance analysis; MUAC-mid upper arm circumference; VAS – visual analogue scales; QoL – quality of life; FFQ-food frequency questionnaire; ECOG-Eastern Cooperative Oncology Group; HGS – hand grip strength; TUG- timed up and go; SPPB – short physical performance battery; ADL – activities of daily living; CRP – C-reactive protein; PUFAs – poly unsaturated fatty acids; QALYs – Quality added life years.