Università Campus Bio-Medico di Roma

Corso di dottorato di ricerca in

Scienze e Ingegneria per l'Uomo e l'Ambiente

XXXIV ciclo a.a. 2018-2019.

Analysing weaknesses in undernutrition management in COPD patients: an excursus from the screening to the treatment.

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03 Novembre 2022

To my beloved grandmother

The perseverance, strength and hope
you taught me with your example
have led me this far.
I feel you by my side, always.

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GENERAL INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, complex and heterogeneous disease characterized by a persistent airflow limitation.

Whilst the negative impact of lung function impairment on patients' survival and symptom burden has been widely clarified, body weight and body composition abnormalities in COPD have attracted fewer attention, considered for years a consequence rather than an independent determinant of patients' survival.

Nowadays, evidence about the negative influence of undernutrition on the clinical disease course are increasing and it has been demonstrated that it is associated with worse quality of life, increased healthcare use and costs.

Undernutrition is primarily caused by an altered energy balance characterized by an insufficient intake of energy and nutrients therefore, the quantification of the balance of energy intake and expenditure should be warranted especially in COPD patients who have an increased resting energy expenditure (REE).

The clinical gold standard for the estimation of REE is the indirect calorimetry (IC) however, due to high cost and time requested for the exam, dieticians and pneumologists usually use predictive formulas, even though not validated in a COPD population.

This contributes to underestimate undernutrition in COPD patients.

Given that, it can be useful to identify clinical predictors of undernutrition collected during routine respiratory assessment in order to immediately recognize patients at risk of undernutrition that need to undergo full nutritional evaluation.

The management of undernutrition is a pathway that first forecasts dietary advices to ensure the correct intake of energy and macro and micronutrients and, for high risk individuals, they should be used alongside oral nutritional supplementation (ONS).

Despite guidelines strongly recommend ONS, evidence on this topic remains still controversial and no study evaluated ONS efficacy stratifying according to type of supplementation (macro or microsupplementation).

It is clear that, although the negative role of undernutrition in COPD patients is well established, it continues to be underestimated and under-recognized among healthcare professionals.

The aim of this thesis is to go through the management of undernutrition in COPD patients, highlighting weaknesses and pitfalls from the screening to the treatment, paying particular attention to:

- The accuracy of predictive formulas for the estimation of resting energy expenditure (chapter 2)
- The identification of clinical predictors for undernutrition (chapter 3)
- The role of nutritional supplements in improving pulmonary function, nutritional status, and quality of life (chapter 4)

In the following sections will be reported the studies developed during the PhD training on the previously reported topics.

1.1 CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Chronic Obstructive Pulmonary Disease (COPD) is a common, complex and heterogeneous disease characterized by persistent, often progressive respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases and influenced by host factors including abnormal lung development [1].

However, the disease is highly heterogeneous with a number of overlapping clinical phenotypes and pathophysiological processes that mainly consists of varying degrees of small airways disease and destruction of the gas-exchanging surface of the lung [2].

Emphysema and chronic bronchitis are the two main conditions that make up COPD. They can occur together and vary in severity. Emphysema is a lung condition that affects and destroys over time the air sacs (alveoli): damage to the walls of the air sacs causes the loss of their shape until they break creating one big air pocket hold air instead of many small ones. This condition leads to a reduction of the gas-exchanging surface area of the lungs that traps old air and prevents oxygen from getting into the bloodstream. Consequently, the lungs fill up slowly and cause the breathing to be more difficult [3].

Chronic bronchitis is long-term inflammation and irritation of the bronchial tubes (bronchi) that cause severe coughing spells, mucus hypersecretion, wheezing, chest pain and shortness of breath. The overproduction of mucus and the swelling of the bronchi make harder the exchange of oxygen and carbon dioxide [4].

COPD symptoms often appear when the lungs damage is already significant. The cardinal symptom is a chronic and progressive dyspnea that represents the major cause of disability associated with the disease [5]. Cough with wheeze and sputum production is present in up to 30% of people suffering from COPD. Other systemic symptoms, mainly common in patients with severe or very severe disease, can occur such fatigue, muscle weakness and reduction in muscle strength, reduced

exercise capacity that worsen the disease progression and prognosis [6,7]. People with COPD experience a day-to-day variation in symptoms that can also become worse (exacerbations).

COPD develops gradually over time and it is often caused by a mixture of risk factors combined with a variety of host factors including genetics, airway hyper-responsiveness and poor lung growth during childhood [1].

Cigarette smoking has been recognized as COPD most important causative factor worldwide both from active or passive exposure to second-hand smoke. More and more evidences addressing this issue demonstrated that if smokers continue smoking lifelong, they have at least a one in two chances of developing COPD [8]. Other risk factors implicated in the development of COPD include indoor air pollution (biomass fuel), outdoor air pollution, industrial fumes and dust, chronic asthma, lung growth and development or infection occurred during childhood and ageing.
Regarding genetic factors, the best known genetic factor linked to COPD is a deficiency of alpha-1 antitrypsin (AATD) that have also been related to a decline in lung function or risk to develop COPD [9]. As people age, there is an increased COPD prevalence, morbidity, and mortality because lung function, physiologically, starts to decline in the third and fourth decades of life [10,11].

Heterogeneity due to diagnostic criteria and different methodologies used for establishment of disease prevalence, make it difficult to produce accurate estimates of COPD prevalence worldwide. Indeed, there is a widespread under-recognition and under-diagnosis of COPD globally.
Despite that, Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) and Burden of Obstructive Lung Disease (BOLD) studies used the same methodology (post-bronchodilator lung function) to assess prevalence of disease burden obtaining estimates with a large variability [12,13].
For example, the PLATINO study investigated the prevalence of COPD among person > 40 years in five Latin American countries, showing an overall prevalence ranging from a low of 7.8 in

Mexico to 19.7% in Uruguay. In each country, the prevalence of COPD increased with age and it was higher in men than in women.

Results reported in BOLD study, based on 12 international sites, showed worse lung function than previous studies with an overall prevalence of GOLD stage II or higher in people aged 40 and over is 10% (11.8% for men and 8.5% for women) with a steady increase with age for men and women in every site [14].

Considering that a larger proportion of the global population lives longer and the increasing prevalence of smoking, the prevalence of COPD and the socio-economic burden associated will increase in years to come.

Nowadays, COPD represents a major public health challenge and is currently the third leading cause of death worldwide [5].

The management of COPD patients has a significant impact on healthcare system. The European Global Impact of Respiratory Disease reported that the direct cost of COPD is 6% of total healthcare spending in the European Union and accounts for 56% of the total cost of treating respiratory diseases [15].

A recent systematic review and meta-analysis reported data about cost of management in different European Countries including Italy: annual per patient direct medical cost in Italy is $ 8203, annual per patient hospital admission cost is $ 5798, mean annual per patient medication cost is $ 1546 and annual per patient outpatient consultation cost is $ 1002 [16].

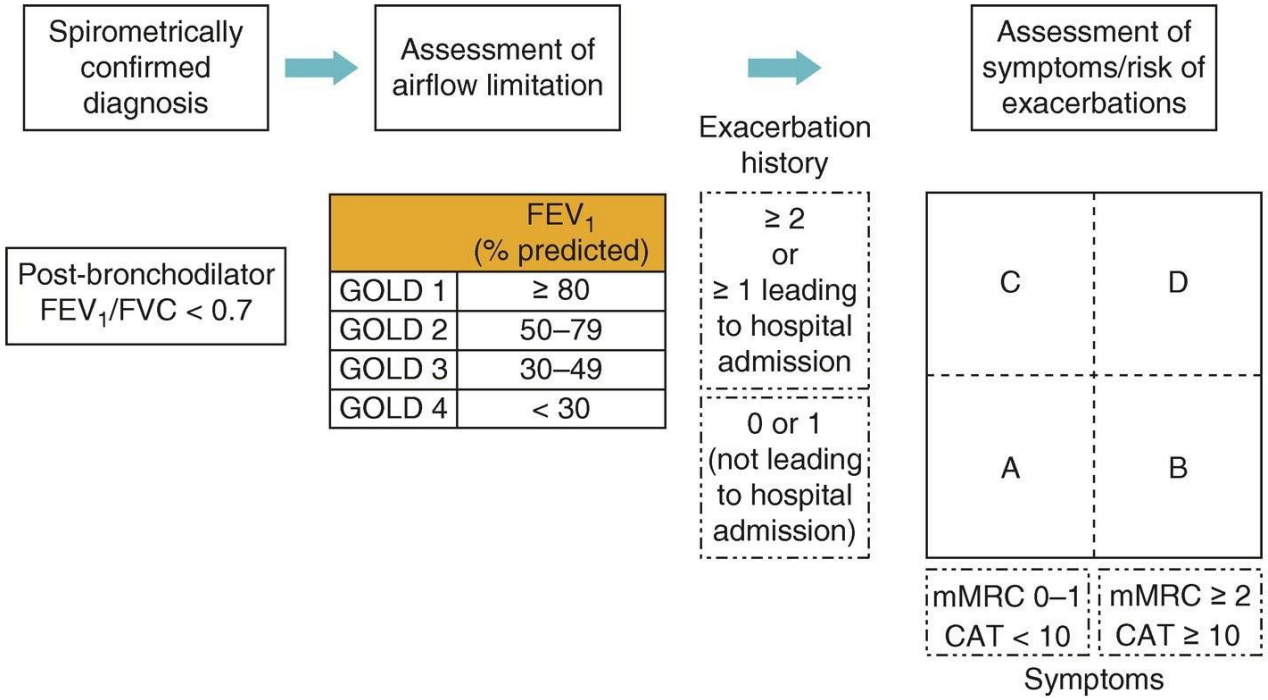
Most of the costs depend on inpatient hospitalisation and exacerbations that are directly proportional to disease severity.

On the other hand, COPD also has social implication. First of all, the affected individual often is not able to maintain his/her employment due to disease disability that reflects on productivity costs.

An international survey conducted on 2400 people showed that twenty-six per cent of the responders (n= 1690) had given up work because of their COPD [17].

In particular, severely disable patients need continuous home care that force a family member to leave the workplace. Hence, estimates of direct medical cost for home-based care are underrate because don't take into account the economic value of the care provided by a family member.
According to the authors of the Global Burden of Disease Study (GBD), that developed a method (Disability-Adjusted Life Years - DALY) to better estimates mortality and disability rate associated to major disease, in 2013 COPD was the fifth leading cause of DALYs lost across the world [18].
Since COPD is often underestimated, recognise risk factors and symptoms on time is useful to make an early diagnosis and avoid damage progression.
The diagnosis of COPD requires the presence of airflow limitation defined by a post-bronchodilator forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) ratio of less than 0.7, the presence of the above-mentioned symptoms and significant exposure to noxious stimuli. The gold standard to confirm the airflow obstruction is the spirometry [19].
After understanding that there is only a weak correlation between airflow limitation and patient's health status, the Global Initiative for Obstructive Lung Disease (GOLD) committee proposed a classification of airflow limitation severity which incorporates symptomatic assessment and risk of exacerbations with spirometric classification [1].
Figure 1 shows the "ABCD" assessment tool that combines spirometric grades, patient symptoms and history of exacerbations.

Figure 1. The refined ABCD assessment tool according to GOLD 2021.



Legend 1. FEV1: Forced expiratory volume in first second, FVC: Forced vital capacity, mMRC: Modified Medical Research Council , CAT : COPD Assessment Test).

1.2 MANAGEMENT OF STABLE COPD PATIENTS

COPD is a leading cause of morbidity and mortality worldwide [5].

Therefore, its underdiagnosis increases the burden of disease that can be managed by reducing the factors that influence disease development and progression and adopting an optimal preventive and therapeutic approach.

The goals of COPD management are to keep under control and improve symptoms, reduce frequency of exacerbations and hospitalization and improve the overall quality of life.

The recommended interventions to manage patients with stable COPD include preventive strategies and primary care such as vaccination and smooking cessation, non pharmacological treatments like pulmonary rehabilitation (PR) or pharmacological therapy [1].

Vaccination decreases the incidence of lower respiratory tract infections that often represents the trigger for COPD exacerbations.

Influenza and pneumococcal vaccinations are recommended for COPD patients.

Findings from a population-based case-cohort study suggested that patient with influenza vaccination had a decreased risk of respiratory failure in comparison to those without vaccination [20].

Similarly, a recent study that evaluated the effectiveness of influenza vaccination on hospitalizations showed that it was associated with a significant reduction of hospitalization among patients with COPD [21].

Cigarette smoking is the most common risk factor for COPD, therefore its cessation is an essential key in the management of COPD.

As early as 1970, Fletcher et al demonstrated that smokers with COPD who quit smoking reduce the rate of lung function decline to that of a non-smoker [22].

Nowadays, smoking cessation programmes are widely available as well as legislative smoking bans supported by healthcare professional counselling.

A recent systematic review on the effectiveness of smoking cessation interventions for smokers with chronic diseases showed that an intervention delivered by healthcare professionals based on an intensive schedule was more effective in inducing smoking cessation, compared with minimal counselling [23]. However, these findings suggest that greater efforts are needed to design innovative smoking cessation interventions especially for smokers with no intention to quit.

More invasive interventions involve use of nicotine replacement products or pharmacological products.

Nicotine gum, nasal spray, transdermal patch, sublingual tablet and increase smoking abstinence rates in long term [24,25].

The use of electronic nicotine delivery systems, including electronic cigarettes, was originally promoted as an effective way to reduce the harm for tobacco although the efficacy still remains controversial [26].

Polosa et al conducted a prospective study on the long-term benefits of the use of electronic cigarettes (ECs) in smokers with COPD prior to and over a 5-years follow-up period.

EC user group showed a significant reduction in COPD exacerbations and improvement in lung function, symptoms and functional ability compared to control group. The findings suggest that benefits achieved persist long term [27].

Pharmacological intervention for smoking cessation is useful in the long-term, but it should be used as a support to smoking intervention program [28].

Pulmonary rehabilitation (PR) is a comprehensive training programme based on patient-tailored interventions that should be considered part of integrated management [1].

A Cochrane review published in 2015 included data from 65 RCTs that compare the effects of pulmonary rehabilitation versus usual care on health-related quality of life and functional and maximal exercise capacity in persons with COPD [29].

Results showed that PR contributes to improve dyspnoea, fatigue, emotional function, and mastery as well as functional exercise and maximal exercise.

Although evidences are still poor and controversial, systematic reviews found similar benefis for postexacerbation rehabilitation on hospital admissions and health-related quality of life [30].

PR programs lasting 6 to 8 weeks allow to achieve the best results, but it is necessary to have a supervised training at least twice weakly.

It is also important to underline that in all case the pulmonary rehabilitation programme should offer an individualized intervention in order to maximize physiological, psychological and social outcomes and promote long-term adherence behaviour change [31].

Pharmacological therapy in COPD depends on disease grade, severity of symptoms and exacerbations therefore the choice of the appropriate treatment needs to be individualized.

It has been reported that pharmacological treatment has an impact on respiratory symptoms, quality of life, exercise capacity and preventing exacerbations or reduce severity and frequency.

Overall, the classes of medications used to treat COPD are: bronchodilators as $beta_2$-agonists, anticholinergics and methylxanthines, inhaled corticosteroids and mucolytic agents.

Drugs can be used as a single agent or in combination, however combination of two or three agents can be more effective than a single drug [32,33].

Given that CODP is a chronic disabling disease, patients are responsible for their own care for the majority of the time even if they regularly attend medical examination with their healthcare professionals.

Smoking cessation, exercise capabilities and limitations, nutritional health, psychological health status, correct use of pharmacological therapy, early recognition of exacerbations should be part of a self-management of disease.

A commonly definition of self-management includes having the confidence to deal not only with medical management, but also positively adapt their health behaviours and develop skills to better manage their disease [34].

Systematics reviews and meta-analysis showed that self-management improve outcomes in COPD.

Cannon et colleagues in their meta-analysis reported that self-management program significantly improves patients' quality of life, exercise level and some aspects of their self-efficacy as improving nutrition and breathing techniques [35].

Cochrane reviews on COPD self-management interventions including action plans for worsening symptoms and exacerbations showed a reduced probability of respiratory-related hospitalization and improvement in health-related quality of life [36].

There are no univocal data on the impact of self-management interventions on overall mortality.

COPD patients become able to self-manage their condition after a process of education delivered by healthcare professionals. This educational process is not based only on the transmission of knowledge, but on the enhancement of appropriate health behaviours, motivation and confidence.

1.3 MALNUTRITION IN COPD PATIENTS: FROM THE SCREENING TO THE TREATMENT

COPD primarily affects the lungs but the chronic systematic inflammation causes many extrapulmonary effects including physical and metabolic adaptations. Therefore, COPD patients often have reduced functional capacity, altered metabolic process, increased nutritional requirements that are not balanced by correct nutritional intake.

As a result, disease-related malnutrition is a common consequence in patients suffer from COPD and it has been demonstrated that it is associated with worse quality of life, increased healthcare use and costs [37,38].

The term malnutrition can refer to undernutrition or overnutrition.

Undernutrition is characterized by a lack of intake of nutrition that leads to altered body composition (decreased fat free mass) and body cell mass ending in a diminished physical and mental function and impaired clinical outcomes.

Overnutrition arises from an excessive intake of nutrients, leading to accumulation of body fat that impairs health.

According to the latest data on malnutrition prevalence among COPD patients, around 1in 3 inpatients and 1 in 5 outpatients are at risk of malnutrition and about 20% are undernourished [39,40].

The exact casual link between undernutrition and COPD is still poorly understood and it seems to be bidirectional, with undernutrition both a cause and consequence of disease.

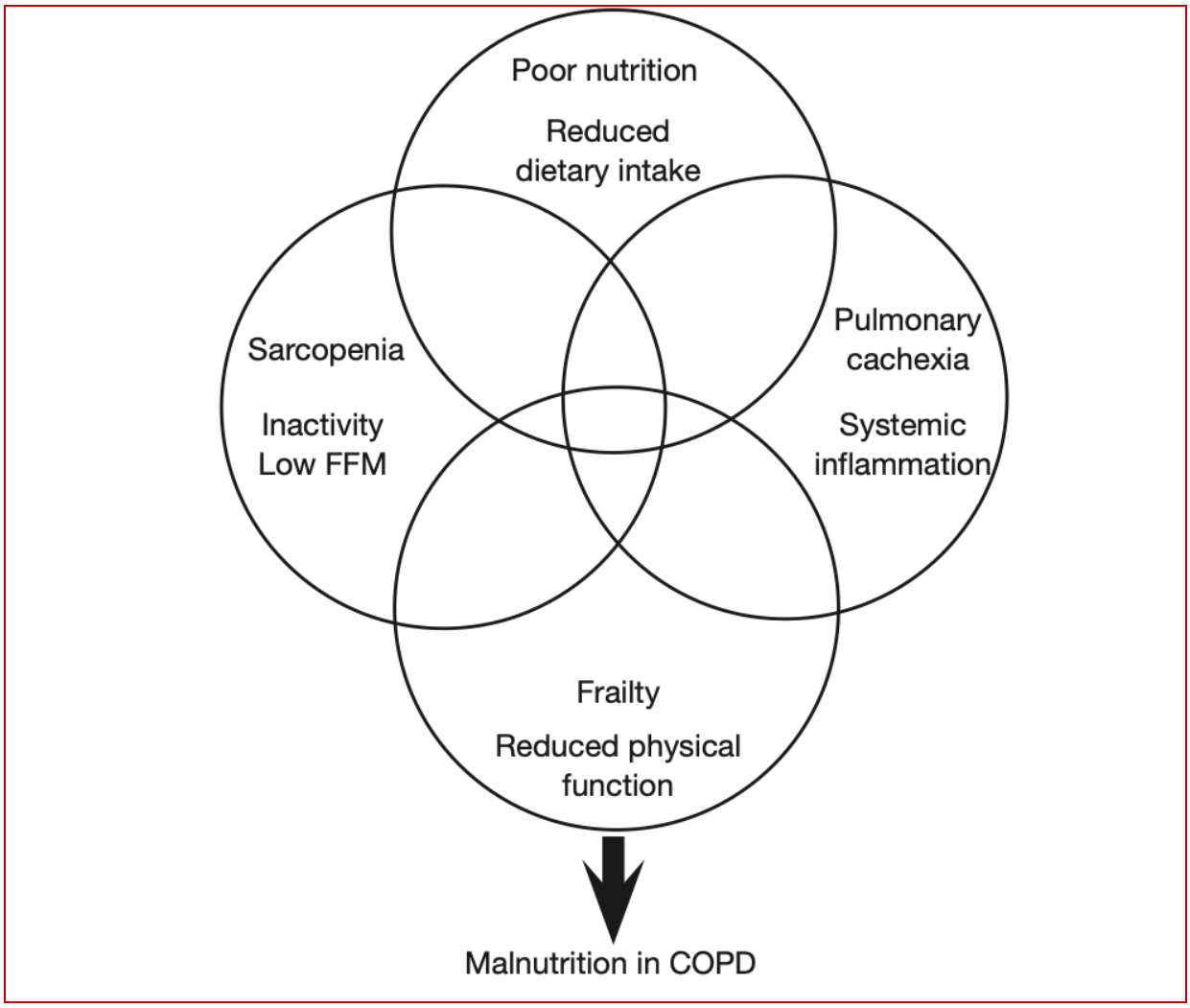
For example, the impact of undernutrition on the respiratory system investigated in patients with anorexia nervosa and severe nutritional depletion showed a significant weakness of respiratory muscles which progressively worsened with the duration of disease [41].

Ezzell et al demonstrated that undernourished patients with COPD have greater hyperinflation, poorer lung diffusing capacity and reduced exercise tolerance when compared to non-malnourished patients with the disease [42].

On the other hand, several factors related to disease such as increased resting energy expenditure (REE) as a consequence of increased work of breathing and hypermetabolism due to systemic inflammation, decreased dietary intake because of appetite loss, reduction of physical activity and medication use can contribute to the development of undernutrition.

Hence, the aetiology of malnutrition related to COPD is multifactorial because it includes different factors and pathophysiological mechanisms such as disease effects (systematic inflammation, pulmonary cachexia), age-related factors (frailty, reduced physical function, inactivity) and unbalanced nutritional intake (reduced dietary intake, loss of appetite) [43] (figure 2).

Figure 2. Aetiology of malnutrition in COPD. (Collins et al, 2019)



Legend 2. FFM: fat free mass; COPD: chronic obstructive pulmonary disease.

Psychological and social aspects are also important in the development and management of malnutrition: loneliness, lack of practical support, depression and poor motivation have been associated to worse prognosis and higher risk of exacerbations and hospitalization in COPD patients [44,45]. In particular, a recent narrative review showed that psychiatric comorbidity like depression and anxiety are associated with reduced adherence to treatment, reduced physical activity and overall reduction in quality of life leading to more frequent exacerbations and increased mortality [46].

Undernutrition in COPD patients contributes to the impairment of respiratory function, progression and severity of the disease; therefore it is associated with worse patient outcomes and increased healthcare costs [47].

It has been demonstrated [48, 49] that COPD patients with low body weight, low body mass index (BMI) and/or low fat-free mass index (FFMI) have a worse prognosis and quality of life (QoL) when compared with patients with a similar severity of disease but without undernutriton [50].

Body weight and body composition abnormalities represent an independent risk factor for increased health-care utilization and mortality in COPD too [51–53], particularly in the older patients.

Although disease-related malnutrition is an important problem in COPD, it is usually overlooked during the management of patients and under-treated between healthcare professionals maybe due to the misconception that it is an integral part of the disease progression [54].

The ways used to identify malnutrition are different, National Institute for Health and Care Excellence (NICE) guidelines recommend body mass index (BMI) is calculated in all patients with COPD and that attention should be paid to unintentional weight loss particularly in older people [47]. Moreover, the unintentional weight and muscle mass loss are often masked by a normal BMI so this latter will not identify all patients at risk of malnutrition.

Hence, a validated nutritional screening (e.g. Malnutrition Universal Screening Tool) should be performed in all patients on first contact with healthcare services and the subject identified as at risk need to undergo nutritional assessment [55].

Once a patient is identified as at risk of undernutrition, NICE guidelines recommend applying the following strategies for the management of malnutrition in stable COPD patients [47]:

- Increase body weight and fat free mass eating small frequent meals with high energy and protein;
- Provide dietary advice in order to ensure that all the requirements of macro and micronutrients are met;
- Give attention to the requirements of vitamin D and calcium as patients with COPD are often at high risk of osteoporosis;
- For patients with a low BMI (BMI<20 kg/m^2) or unplanned weight loss >10% over 3-6 months, an oral nutritional supplementation (ONS) should be prescribed;
- Review the progress after 1-3 months.

Over the years, several researchers tried to estimate the daily calorie intake in patients with COPD. The formula that seems to be more appropriate for calculating the daily energy intake in this population is equal to 30 kcal/Kg/body weight [56].

Regarding amino acids/protein intake there are no specific indications, but in order to prevent sarcopenia, NICE COPD guidelines estimate an amount of 0.8-1.5 g/kg/body weight for not at risk/ no malnourished patients and up to 1.5 g/kg of body weight in the patient with overt sarcopenia [47].

The amount of carbohydrates should be less than 200 g/die in favour of lipids because the production of CO2 is greater by carbohydrates. An higher production of CO2 leads to an increase in alveolar ventilation with a further negative impact on the respiratory system. Several studies showed that diet rich in lipids is more advantageous for the patient with COPD than a diet with higher carbohydrates for ventilatory exchange, as a reduced calorie intake of carbohydrates resulted in a better general well-being of patients with chronic respiratory insufficiency [57].

Hence, the diet should contain a percentage of lipids of about 55% of total energy expenditure with omega-3 fatty acids well represented.

In the dietary management of COPD, micronutrients supplementation has a significant role. For example, vitamin D value lower than 20 ng/mL increase the number of exacerbations therefore patients should monitor blood levels of vitamin D and assume adequate integration if necessary [56].

In general, in order to ensure the correct requirements of energy and macro and micronutrients and prevent undernutrition, the recommended dietary pattern for stable COPD patients should provide higher percentage of lipids (up to 50 %) and lower amount od carbohydrates (about 30%) with a well represented protein content depending on the presence of sarcopenia.

The presence of antioxidants, omega-3 fatty acids and fiber must be covered by the use of extra virgin olive oil, nuts, fruits and vegetables and whole grains.

As previously said, in presence of BMI<20 kg/m^2 or unplanned weight loss >10%, a ONS should be prescribed.

ONS provides high energy protein and micronutrients amounts in a small volume in order to manage patients with early satiety.

NICE guidelines recommend an average of 2/day ONS in addition to oral intake for at least 12 weeks duration [47].

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ENERGY EXPENDITURE AND INTAKE IN COPD: THE EXTENT OF UNNOTICED UNBALANCE BY PREDICTING REE

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Respir Med. 2022 Sep;201:106951. doi: 10.1016/j.rmed.2022.106951.

2.1 ABSTRACT

Body weight and body composition abnormalities represent an independent risk factor for increased health-care utilization and mortality in chronic obstructive pulmonary disease (COPD). Loss of body weight occurs when energy expenditure exceeds the energy intake. Despite several studies have demonstrated that resting energy expenditure (REE) of COPD patients is increased in comparison to healthy subjects, no formula has so far been developed for its calculation in COPD, compelling dieticians and pulmonologists to use formulas, such as the Harris-Benedict, developed in healthy subjects and therefore not validated in a COPD population. This study aimed at quantify the error of REE predicting formulas and at investigate to which extent these errors affect the identification of an energy unbalance in COPD patients. Forty-nine participants with a diagnosis of stable COPD underwent a multidimensional assessment including the indirect calorimetry (IC) for the estimation of REE. Participants with REE higher than energy intake (Kcal) measured using the EPIC questionnaire were defined as negatively unbalanced. The 24% of participants had a negative energy balance when REE was measured with IC, 10% when predicted with Harris-Benedict (HB) (p-value 0.01) and 31 %with Angelillo-Moore (AM) (p-value 0.01), respectively. Using REE HB predicting formula, 1 patient with a balance between energy intake and REE was classified as negatively unbalanced and 8 negatively unbalanced patients were classified as balanced, with an accuracy of 82%, a sensitivity of 33% and a specificity of 97%. Using REE AM estimating formula, 6 balanced patient were classified as negatively unbalanced and 3 negatively unbalanced patients were classified as balanced, with an accuracy of 82%, a sensitivity of 75% and a specificity of 84%.

In conclusion, the high variability makes the predicted REE unreliable, with HB unable to capture 66% and AM 25% of negatively unbalanced patients.

2.2 INTRODUCTION

Body weight and body composition abnormalities represent an independent risk factor for increased health-care utilization and mortality in chronic obstructive pulmonary disease (COPD) [1–3], particularly in the older patients. An energy- and protein-enriched diet is effective in improving body weight, fat-free mass (FFM), respiratory muscle strength and quality of life [4] and is recommended in undernourished COPD patients.

Undernourishment is promoted by an energy expenditure exceeding the energy intake, hence a precise quantification of both is crucial. This is particularly true in COPD patients, who have an increased resting energy expenditure (REE) [5]. Indirect Calorimetry (IC) represents the clinical gold standard for the estimation of REE, however, due to the high costs and the need of trained technicians, it is commonly replaced by REE predicting formulas, like the Harris-Benedict (HB) and the Angelillo-Moore (AM). Although the HB has been demonstrated to underestimate and the AM to overestimate on average REE [6, 7], no study has considered the high variance of these formulas and investigated to which extent COPD patients with an unbalance between energy expenditure and intake go unnoticed.

This study aimed at measuring at the same time the energy intake and the REE, through IC and predicting formulas, to quantify the error of REE predicting formulas and to investigate to which extent these errors affect the identification of an energy unbalance in COPD patients.

2.3 MATERIALS AND METHODS

This is a secondary analysis of a mono-center and longitudinal study aimed at investigating whether a multidimensional assessment might help to recognize distinctive traits of COPD. Individuals with a diagnosis of COPD, according to the current guidelines [8], without symptom worsening and/or changes in pharmacological therapy in the previous three months were included. Exclusion criteria were the inability to perform the multidimensional assessment, a diagnosis of active cancer, chronic heart failure in stage NYHA III or IV and chronic lung diseases other than COPD. The study protocol conforms to the principles outlined in the Declaration of Helsinki and it was approved by the Campus Bio-Medico Ethical Committee (30/15 PAR CMB). All participants provided written informed consent.

Participants underwent a multidimensional assessment comprehensive of medical history, functional status, pulmonary function tests, bio-impedance analysis, European Prospective Investigation into Cancer and Nutrition (EPIC) questionnaire and IC. Bio-impedance analysis was performed using the BIA 101 (Akern, Firenze, Italy). FFM was considered abnormally low when below the age-, sex- and BMI-adjusted 10^{th} percentile [4, 9]. The EPIC questionnaire provided information about energy intake and nutrient composition (macro- and micro-nutrients) in the previous year [10]. IC was performed using the Quark CPET device (COSMED, Albano Laziale, Italy) in the early morning, after an overnight fast, under standardized conditions, with the person lying awake and emotionally undisturbed, completely at rest, comfortably supine on a bed, with the mask perfectly adherent to face, in a thermally neutral environment, and after at least 8 hours of sleep. Only measurements of respiratory gas samples from steady states were considered for the analysis. The calorimeter was calibrated each day before the test according to the manufacturer's instructions.

Participants' characteristics were reported using descriptive statistics: median and 25^{th}-75^{th} percentile or mean and standard deviation (SD) for continuous variables and frequency and

percentage (%) for categorical variables. REE measured by IC and REE predicted using HB and AM formula were represented using boxplots and compared using Wilcoxon rank-sum test. The limits of agreement of the predicted REE and measured REE were determined by plotting the mean measurement difference ± 2 SD as described by Bland and Altman. Participants with REE higher than energy intake (Kcal) measured using the EPIC questionnaire were defined as negatively unbalanced. The percentage of negatively unbalanced obtained using REE predicting formulas was compared with that obtained measuring REE with IC (gold standard) using chi-squared test. All the analyses were performed using R version 4.0.2 (The R Foundation for Statistical Computing, Vienna, Austria, 2020).

2.4 RESULTS

Forty-nine participants were included in the analysis: the mean age was 73 (SD 7), 76% were males, 40% had 2 or more comorbidities. 49% had an impairment in at least one Lawton instrumental activity of daily living, 14% in at least one Katz basic activity of daily living. mMRC score was higher than one in 67% of the population, 8% were frequent exacerbators. According to GOLD classification 65% of participants were in stage GOLD B, 27% in stage GOLD A, 6% in stage GOLD C and 2% in stage GOLD D. There were no statistically significant differences with individuals excluded because of the lack of data about energy intake or expenditure in terms of age, sex, BMI and GOLD severity.

The mean BMI was 28 (SD 6) Kg/m^2, with only one participant having a BMI < 20 Kg/m^2 and with nine having a BMI > 30 Kg/m^2. The mean FFM was 56.2 Kg (SD:10), with 7 (14%) having a FFM lower than the age, sex and BMI-corrected cut-off. The median energy intake was 1974 Kcal (1659-2453), with 54% of energy coming from carbohydrates. The median measured REE was 1632 Kcal (1464-1892) using IC, 1482 Kcal (1290-1619) using HB and 1803 Kcal (1676-1906) using AM. The comparison between HB, AM and IC REE is provided in Figure 1.

Twelve participants (24%) had a negative energy balance when REE was measured with IC, 5 (10%) when predicted with HB (p-value 0.01) and 15 (31%) with AM (p-value 0.01), respectively. Using REE HB predicting formula, 1 patient with a balance between energy intake and REE was classified as negatively unbalanced and 8 negatively unbalanced patients were classified as balanced, with an accuracy of 82%, a sensitivity of 33% and a specificity of 97%. Using REE AM estimating formula, 6 balanced patient were classified as negatively unbalanced and 3 negatively unbalanced patients were classified as balanced, with an accuracy of 82%, a sensitivity of 75% and a specificity of 84%.

Figure 1 Boxplot comparing Resting Energy Expenditure measured with Indirect Calorimetry and estimated with Harris-Benedict and Angelillo-Moore formulas.

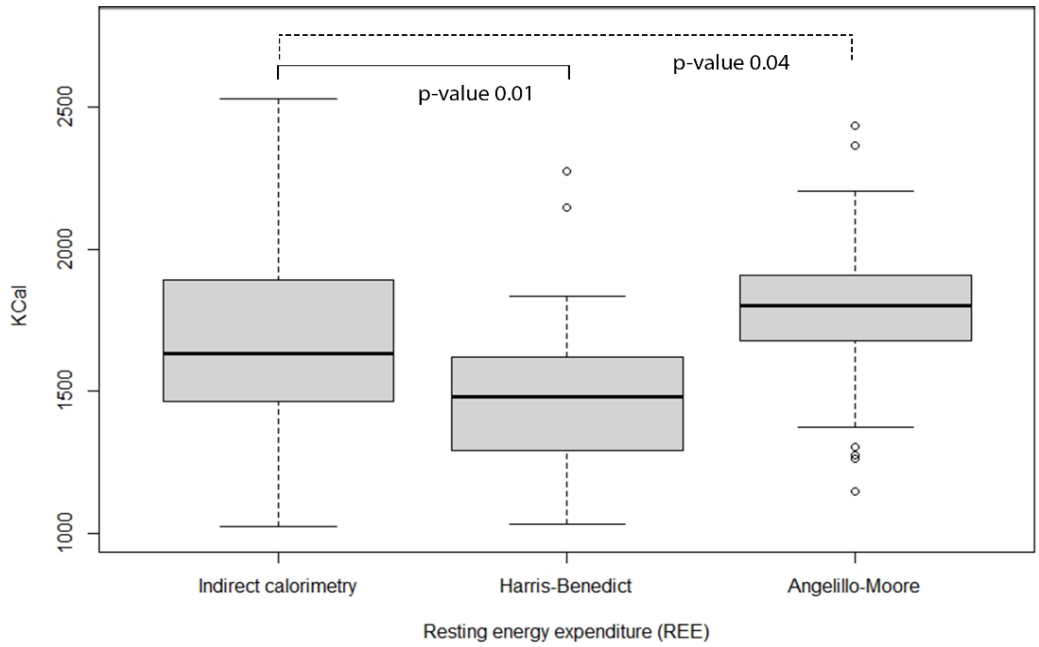
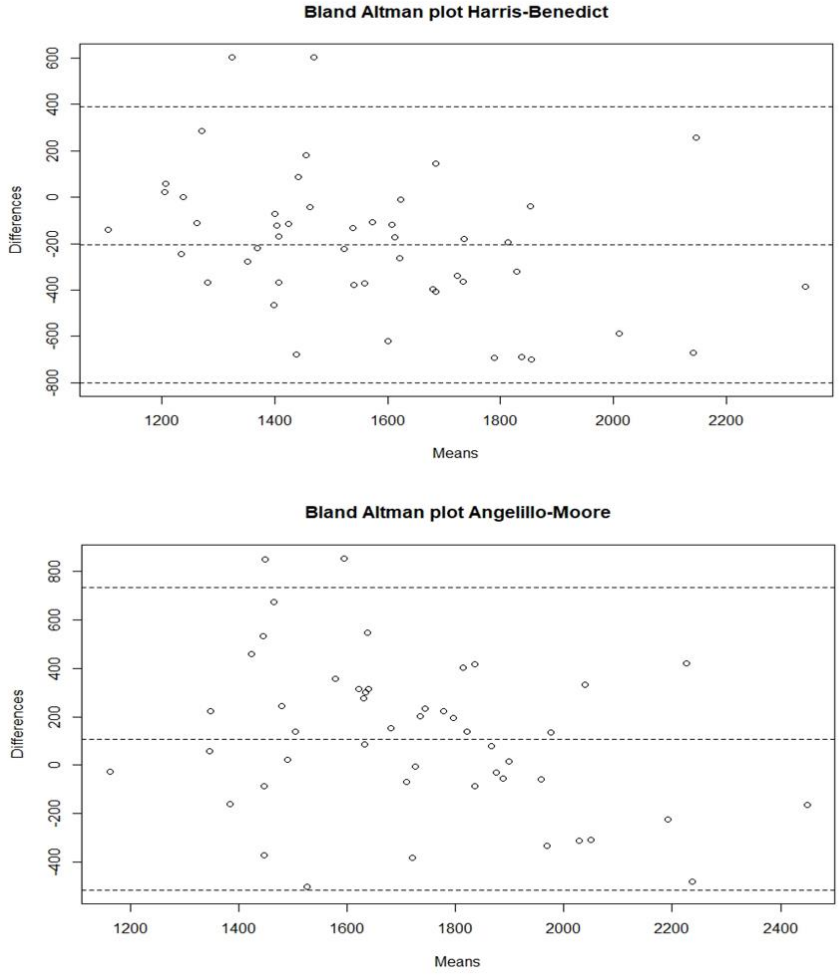


Figure 2 Bland Altman plot comparing Resting Energy Expenditure measured with Indirect Calorimetry and estimated with Harris-Benedict and Angelillo-Moore formulas.



2.5 DISCUSSION AND CONCLUSION

In conclusion, albeit the mean underestimation of HB was -200 Kcal and the mean overestimation of AM was 100 Kcal, in line with previous literature [7], the high variability makes the predicted REE unreliable, with HB unable to capture 66% and AM 25% of negatively unbalanced patients. These figures should be interpreted in the light of a study limitation: the lack of data about participant physical activity level prevented us from calculating total energy expenditure (TEE), forcing to define the negative balance limited to REE. However, considering that in persons with sedentary or light activity lifestyle TEE is at least 40% higher than REE [11], negatively unbalanced patients likely were more prevalent than estimated. Predicting formulas should be therefore discouraged in clinical practice in cases requiring a precise measurement, such as COPD patients with an overt malnutrition, but, if IC is unavailable, AM should be preferred to HB. A daily energy intake of at least 1900 Kcal should be recommended to COPD in stable condition, corresponding to about 30 Kcal/Kg, which covers REE in 75% of participants. If confirmed in larger samples and in studies measuring TEE, these findings might lead to reconsider both the caloric needs of COPD patients and the potential of formulas predicting REE.

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PREDICTORS OF UNDERNUTRITION IN COPD PATIENTS.

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Clinical Nutrition ESPEN 2022 July 13, 2022. doi:10.1016/j.clnesp.2022.06.109

3.1 ABSTRACT:

Background & Aims: Chronic obstructive pulmonary disease (COPD) is a chronic disease characterized by persistent respiratory symptoms and airflow limitation. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) report recommends smoking cessation, pharmacological therapy and pulmonary rehabilitation, but this clinical course can be negatively influenced by undernutrition, a condition documented in about 20% of COPD patients. An altered energy balance characterized by an insufficient intake of energy and nutrients is the primary cause of undernutrition, therefore the aim of this study is to investigate whether clinical and instrumental variables collected during a routine respiratory assessment associate with an altered energy balance in order to identify COPD patients at higher risk of undernutrition worth of further assessment.

Methods: A total of forty-nine participants with a diagnosis of stable COPD were included in this mono-center and longitudinal study. Subjects underwent a multidimensional assessment including evaluation of medical history, evaluation of pulmonary function, evaluation of nutritional status, evaluation of energy intake and resting energy expenditure (REE) using EPIC questionnaire and indirect-calorimetry (IC), respectively, evaluation of physical impairment and mood status.

Results: The 24% of participants was at risk of undernutrition with a mean energy intake, total protein intake and lipid intake significantly lower than not at risk subjects, while REE was significantly higher. Age, sex, multimorbidity, disability and depression, and pulmonary function tests were not associated with a negative energy balance, with the exception of the Cumulative Illness Rating Scale (CIRS) severity index, which showed a significant association.

Conclusion: Clinical evaluation and pulmonary function tests are unable to reliably predict undernutrition in COPD patients, so a nutritional screening should always be forecast in this population based on an accurate evaluation of energy intake and expenditure and body composition.

Keywords: Chronic obstructive pulmonary disease, undernutrition, clinical predictors

Abbreviations

ADL: Activities of daily living

BMI: Body mass index

CIRS: Cumulative illness rating scale

COPD: Chronic obstructive pulmonary disease

FFMI: Fat-free mass index

GDS: Geriatric depression scale

IADL: Instrumental activities daily living

IC: Indirect calorimetry

REE: Resting energy expenditure

TEE: Total energy expenditure

3.2 INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic disease characterized by persistent respiratory symptoms and airflow limitation [1]. COPD is a leading cause of morbidity and mortality worldwide and it is manageable by reducing the factors that influence disease development and progression. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) report recommends smoking cessation, pharmacological therapy and pulmonary rehabilitation, but this clinical course can be negatively influenced by undernutrition [2], a condition documented in about 20% of COPD patients [3]. Undernutrition is characterized by a lack of intake of nutrients that leads to altered body composition (decreased fat-free mass) and body cell mass ending in a diminished physical and mental function and impaired clinical outcome [4]. Studies have shown that 25% to 40% of all COPD patients have low body weight, with 25% of patients having moderate to severe weight loss and 35% of patients with extremely low fat-free mass index (FFMI), and that patients who are underweight and/or have low FFMI have a worse prognosis when compared with patients with a similar severity of disease but without undernutrition [5]. It has been demonstrated that effective screening and management of patients at risk of malnutrition can prevent undernutrition and consequently improve nutritional status, clinical outcomes and reduce healthcare cost [6].

Hence, a nutritional risk screening should be performed using validated nutritional screening tests in all subjects that come in contact with healthcare services, before they develop weight loss and/or alterations in body composition. Subjects identified as at risk need to undergo nutritional assessment [7].

Although National Institute for Health and Care Excellence (NICE) guidelines [8] provided a practical guide to support healthcare professionals in identifying people with COPD at risk of disease-related malnutrition, malnutrition still remains under-recognised and under-treated maybe due to the misconception that it is an integral part of the disease progression or because of the lack of time for an in-depth evaluation during a routine outpatient visit.

Indeed, even if a precise quantification of the energy balance is essential in COPD patients who have an increased resting energy expenditure (REE), clinicians usually replace Indirect Calorimetry (IC) by REE predicting formulas like the Harris-Benedict (HB) and the Angelillo-Moore (AM) that are not validated for the use in COPD population [9].

Moreover, the unintentional weight and muscle mass loss are often masked by a normal Body Mass Index (BMI) [10].

An altered energy balance characterized by an insufficient intake of energy and nutrients is the primary cause of undernutrition, therefore the aim of this study is to investigate whether clinical and instrumental variables collected during a routine respiratory assessment associate with an altered energy balance in order to identify COPD patients at higher risk of undernutrition worth of further assessment.

3.3 MATERIAL AND METHODS

Individuals with a diagnosis of stable COPD, according to the latest GOLD report [1], were included in this mono-center and longitudinal study. We excluded subjects with inability to perform a multidimensional assessment and an acceptable spirometry, a diagnosis of active cancer, chronic heart failure in stage NYHA III or IV and other chronic lung diseases and refusal to provide informed consent. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Campus Bio-Medico University of Rome. All participants provided written informed consent.

Participants underwent a multidimensional assessment including: evaluation of medical history, using Cumulative Illness Rating Scale (CIRS) to quantify the burden of chronic diseases [11], evaluation of pulmonary function, evaluation of nutritional status (anthropometric parameters and body composition analysis) evaluation of energy intake and resting energy expenditure (REE) using EPIC questionnaire and indirect-calorimetry (IC), respectively, evaluation of physical impairment (Activities of Daily Living and Instrumental Activities Daily Living) and evaluation of mood status (Geriatric Depression Scale). Bio-impedance analysis was performed using the BIA 101 (Akern, Firenze, Italy). EPIC questionnaire provides providing detailed information about energy intake, macro and micronutrients composition, foods portion size and frequencies of consumption. IC was performed using the Quark CPET device (COSMED, Albano Laziale, Italy), after calibrating the calorimeter, in the early morning, on fasting subjects completely at rest supine on a bed in a thermally stable environment, with the mask tightly fitting to the face. Only measurements of respiratory gas samples from steady states were considered for the analysis. We defined participants at risk of undernutrition if they had a energy intake (Kcal), measured using EPIC® questionnaire, lower than REE (Kcal), measured with IC. Indeed, considering that the REE is the largest portion (50–75%) of total energy expenditure (TEE) and that participants were outpatients with a light activity lifestyle, energy intakes lower than REE was certainly below TEE.

The descriptive analysis of participants' characteristics was performed using median and 25^{th}-75^{th} percentile or mean and standard deviation (SD) for continuous variables and frequency and percentage (%) for categorical variables. FFMI below the age, sex and BMI specific 10^{th} percentile was considered abnormally low.

The association between the anthropometric features, the lung function and the burden of diseases collected in a routine visit for COPD and reduced intake has been evaluated using logistic regression models, while the association between energy intake and REE with the previously reported variables was evaluated using linear models, reporting the regression coefficient (beta) and the 95% confidence interval. Models were adjusted for age, sex and height. Receiver Operating Characteristic curve was created for variables significantly associated with and the area under the curve (ROC-AUC) calculated. The optimal cut-off point was defined using the Youden index.

All the analyses were performed using R version 4.0.2 (The R Foundation for Statistical Computing, Wien, Austria, 2020).

3.4 RESULTS

A total of 49 participants were included in the analysis, of which 12 were at risk (24%) and 37 not at risk of undernutrition (76%). Clinical characteristics divided according to the energy balance are reported in table 1. In particular, the mean BMI of subjects with a negative energy balance was 31 (SD: 7) Kg/m^2, versus 27 Kg/m^2 (5.3), with a mean FFMI of 20.7 Kg/m^2 (SD: 2.9), versus 20.1 Kg/m2 (SD:2.4). FFMI was abnormally low in 25% versus 11% of cases.

CIRS severity index of subjects at risk of malnutrition was 0.8 (SD: 0.3) versus 0.5 (SD: 0.2) in not at risk subjects with a statistically significant difference (p-value 0.02).

The mean energy intake was significantly lower in individuals at risk of undernutrition (mean Kcal 1577 vs 2216), while REE was significantly higher (mean Kcal 1907 vs 1605). Likewise, patients at risk of undernutrition had a lower total protein intake [0.8 gr/Kg (SD:0.1) versus 1.2 gr/Kg (SD:0.3), p-value <0.001], total lipid intake [0.7 gr/Kg (SD:0.1) versus 1.2 gr/Kg (SD:0.4), p-value <0.001], without animal/vegetal protein and lipid ratio, calcium intake [635 mg (SD 247) versus 850 mg (SD 252), p-value 0.02] and phosphorus [1084 mg (SD 195) versus 1419 mg (SD 306), p-value 0.001].

The description of nutritional intake and energy expenditure is collected in table 2.

Age, sex, multimorbidity, disability and depression, and pulmonary function tests were not associated with a negative energy balance, with the exception of the Cumulative Illness Rating Scale (CIRS) severity index, which showed a significant association (OR 51, P-value <0.01). Higher the CIRS severity index, lower was the energy intake (beta: -96.2 Kcal per decimal point of increase, -171.2 – -21.2; p=0.01) and higher the REE (beta:57 Kcal per decimal point of increase, 5 – 109.1; p=0.03) (Table 3). The ROC-AUC of CIRS severity index was 0.76, with 0.45 as optimal cut-off point.

Table 1. Clinical characteristics of study population.

	At risk of undernutrition (n:12)	**No at risk of undernutrition (n:37)**	**P-value**
Age (year)	73.7 (8.5)	73.2 (7)	0.87
Gender (M)	8(67)	29(78)	0.66
BMI (Kg/m^2)	31.1 (7.1)	27.3 (5.3)	0.11
Hip circumference (cm)	108.2 (13.7)	102.2 (11.3)	0.19
Waist circumference (cm)	105.8 (11.8)	101 (13.5)	0.26
Smoking history (smoker+former smokers)	11(100)	35(97)	0.99
Smoked packs/year	49 (44.8)	38.5 (27.6)	0.14
Dyspnea (mMRC>1)	7(58)	26(70)	0.68
Exacerbators (>1/y)	1(8)	3(8)	0.99
Cardiac disease	7(64)	14(39)	0.27
Liver disease	1(9)	1(3)	0.96
Renal disease	1(9)	0(0)	0.53
Endocrin disease	4(36)	11(31)	0.99
Multimorbidity (2 or more comorbidities)	5(45)	14(39)	0.97
CIRS severity index	0.8 (0.3)	0.5 (0.2)	0.02
CIRS comorbility index	5(45)	8(22)	0.26
Katz ADL (<6)	2(17)	5(14)	0.99
Lawton IADL (<8)	6(50)	18(49)	0.99
15-item GDS (>5)	1(8)	7(19)	0.68
FEV1/FVC	64 (8)	64 (8)	0.99
FEV1 (L)	1.8 (0.5)	2 (0.7)	0.21
FEV1 (%)	72 (17)	78 (20)	0.29

FVC (L)	3 (0.9)	3.3 (1.2)	0.36
FVC (%)	89 (22.1)	94.3 (19)	0.47
TLC (L)	6.1 (1.7)	6.7 (2.2)	0.37
TLC (%)	85.6 (34.1)	108.5 (23.8)	0.09
RV/TLC (%)	120 (37)	122 (27)	0.84
FFM (Kg)	57 (9)	56 (10)	0.64
FFM (%)	67 (7)	74 (11)	0.04
FFMI (Kg/m^2)	20.7 (2.9)	20.1 (2.4)	0.49
FM (Kg)	29 (10)	19 (10)	0.01
FM (%)	33 (7)	26 (10)	0.02
Emphysema	2(25)	14(42)	0.62

Legend: Data are presented as mean (SD).

Table 2. Description of nutritional intake and energy expenditure.

	At risk of undernutrition (n:12)	**No at risk of undernutrition (n:37)**	**P-value**
Energy intake (Kcal)	1577.4 (330.8)	2216.2 (509.4)	<0.001
Water intake (ml)	1002 (261)	1125 (279)	0.18
Alcohol (g)	5 (7)	15 (19)	0.008
Total proteins (g)	68 (11)	86 (19)	<0.001
Animal/Vegetal protein ratio	2.06 (0.73)	1.97 (0.91)	0.75
Total lipids (g)	57 (9)	85 (27)	<0.001
Lipid ratio	1.02 (0.56)	1.24 (0.6)	0.28
Calcium	635 (247)	850 (252)	0.02
Phosphorus	1084 (195)	1419 (306)	0.001
Vitamin D	3 (2)	3 (2)	0.47
REE (Kcal)	1907 (415)	1605 (309)	0.03
RQ	0.89 (0.11)	0.87 (0.08)	0.49
Carb (%)	58 (27)	53 (19)	0.56
Lipid (%)	42 (27)	47 (19)	0.57
Harris-Benedict (Kcal)	1555 (256)	1447 (250)	0.22
Angelillo-Moore (Kcal)	1857.2 (251.1)	1765.2 (270.8)	0.29

Legend: Data are presented as mean (SD).

Table 3. Linear regression models evaluating the association between routine clinical variables with energy intake (A) and REE (B).

A	**Beta (95%CI, p value)** **– univariable –**	**Beta (95%CI, p value)** **– univariable –**
Age (year)	-3.26 (-25 – 19, 0.77)	1.08 (-24 – 23, 0.92)
Gender (M)	373(22 – 794, 0.04)	-14 (-556 – 528, 0.95)
Height (cm)	19(4 – 35, 0.01)	16 (-8 – 39, 0.18)
FEV1 (% of GLI predicted)	3 (-5.4 – 11.4, 0.48)	0.40 (-7.6 – 8.4, 0.92)
CIRS severity index*	-66.4 (-123.3 – -9.3 ,0.02)	-96.2 (-171.2 – -21.2, 0.01)
Multimorbidity	-31 (-354 – 291, 0.85)	304 (-87 – 695, 0.12)
B	**Beta (95%CI, p value)** **– univariable –**	**Beta (95%CI, p value)** **– univariable –**
Age (year)	-1.14 (-15 – 13, 0.88)	-11 (-26 – 5, 0.19)
Gender (M)	182 (-53 – 419, 0.13)	124 (-253 – 500, 0.51)
Height (cm)	8 (-2.4 – 18, 0.13)	5 (-11 – 21, 0.51)
FEV1 (% of GLI predicted)	1.03 (-4.5 – 6.6, 0.71)	-0.37 (-6 – 5.3, 0.89)
CIRS severity index*	43.6 (4.9 – 82.3, 0.03)	57 (5 – 109.1, 0.03)
Multimorbidity	157 (-56 – 371, 0.14)	13 (-259 – 284, 0.93)

Legend: FEV1, forced expiratory volume in the first second; GLI, Global Lung Function Initiative.

** Beta refers to the decimal point variation of CIRS severity index.*

3.5 DISCUSSION AND CONCLUSION

The exact cause of undernutrition in COPD patients still remains unclear, as a number of factors could contribute to a progressive reduction in fat-free mass. However, it was already shown that the incidence of undernutrition increased as the disease severity of the patients increased [4].

Our results show that clinical evaluation and pulmonary function tests are unable to reliably predict undernutrition in COPD patients, so a nutritional screening should always be forecast in this population based on an accurate evaluation of energy intake and expenditure and body composition.

Nevertheless, the severity, rather than the number, of comorbidities increases the risk of undernutrition by reducing the energy intake and increasing the REE, thus the screening is highly recommended in COPD patients with a CIRS severity index ≥ 0.45.

These results should take into account study limitations: the sample size that needs to be improved and the lack of data about participants physical activity level that did not allow us to calculate the total energy expenditure (TEE), forcing to define the negative energy balance limited to REE.

Our findings confirm results of previously studies and suggest that**,** in order to immediately identify patients at risk of undernutrition that need to undergo nutritional evaluation, a screening procedure should be distinguished from a full nutritional assessment and should be performed during routine respiratory assessment.

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EFFECT OF MACRO OR MICRONUTRIENTS SUPPLEMENTATION ON NUTRITIONAL STATUS, PHYSICAL FUNCTIONAL CAPACITY AND QUALITY OF LIFE IN PATIENTS WITH COPD: A SYSTEMATIC REVIEW AND META-ANALYSIS.

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4.1 ABSTRACT

Background: Given the importance that a correct and balanced nutrition has on patients with chronic obstructive pulmonary disease, supplementation of macro and micronutrients has been proposed but the results of previous meta-analyses are contrasting.

We performed an update of the latest evidence through a systematic search of studies to assess the role of nutritional supplements in improving pulmonary function, physical performance, and quality of life of these patients.

Methods: Articles indexed in the Medline database between January 2010 and January 2020 were searched and RCTs in English, Spanish, or Italian language were included evaluating the effectiveness of nutritional support in patients affected by stable pulmonary disease (COPD) with an intervention of at least 2 weeks of duration. The primary outcomes were changes in body mass index (BMI) and fat free mass index (FFMI). Secondary outcomes were 6-minute walking test (6MWT), quality of life (QoL) and respiratory function (QoL). Two reviewers independently selected trials for inclusion, assessed quality and extracted the data. Data were analyzed after grouping the studies according to the supplements type (macronutrients or micronutrients) and the pooled adjusted mean difference (95% CI) of selected outcomes were calculated, using random-effects models in presence of heterogeneity or fixed-effects models otherwise. The risk of publication bias was also evaluated.

Results: From 967 references, 19 RCTs were eventually included. The results showed that macronutrients supplementation in COPD patients improves BMI, FFMI, exercise tolerance and quality of life, while it does not ameliorate respiratory function. Micronutrients supplementation alone did not improve any of the considered outcomes.

Conclusions: The current evidence confirm that macronutrients supplementation should be offered to COPD patients even if well-nourished, in order to improve anthropometric parameters, quality of life, and exercise tolerance.

4.2 INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic disease characterized by poor prognosis and in more severe cases by exacerbations leading to frequent hospitalizations. This clinical course can be negatively influenced by undernutrition (1,2), a condition documented in about 20% of COPD patients that is characterized by a mismatch of nutrition that leads to altered body composition (decreased fat free mass) and body cell mass (3). It has been demonstrated that COPD patients with low body weight, low body mass index (BMI) and/or low fat-free mass index (FFMI) have a worse prognosis and quality of life (QoL) when compared with patients with a similar severity of disease but without undernutrition (4-6). On the other hand, a BMI falling within the overweight range has shown a protective effect against mortality (obesity paradox) in these patients (7,8). The high prevalence of undernutrition with consequent weight loss and muscle wasting among COPD patients is related to several factors such as increased resting energy expenditure (REE) as a consequence of increased work of breathing and hypermetabolism due to systemic inflammation, and decreased dietary intake because of appetite loss, and reduction of physical activity (9,10). Despite these evidences, disease-related undernutrition still remains under-recognised and under-treated by healthcare professionals maybe due to the misconception that it is an integral part of the disease progression (11).

Hence, nutritional risk screening should be performed in all subjects that come in contact with medical services and subjects identified as being at risk of undernutrition should undergo detailed assessment of the nutritional status (3).

In consideration of the high prevalence of undernutrition and its association with negative outcomes, nutritional counselling and nutritional supplementation have been proposed in COPD patients who are undernourished to promote an overall better quality of life, to help weight gain, to improve physical activity, and to improve prognosis (12).

Despite current guidelines recommend nutritional supplementation alone or used in addition to exercise training in undernourished patients (13,14), the evidence on this topic is controversial, probably due to heterogeneity in the tested interventions. Indeed, previous reviews and meta

analyses have shown that nutritional supplementation is not useful in improving anthropometric or functional measures of COPD undernourished patients (2,5,16), while the latest available meta-analysis on this topic, published in 2012, concluded that among COPD patients nutritional support can lead to improvements in nutritional status, anthropometric measures, and grip strength, but there is a lack of evidence on efficacy in improving respiratory function. Furthermore, none of the RCTs included in the latest meta-analysis supplied micronutrients supplementation.

Given the contrasting results of the previous meta-analyses and the lack of studies supplying micronutrients, the aim of this systematic review and meta-analysis of randomized controlled trials (RCTs) is to investigate the role of nutritional supplements in improving pulmonary function, nutritional status, and quality of life in patients affected by stable COPD, stratifying studies according to type of supplementation (micro or macronutrients supplementation).

4.3 MATERIALS AND METHODS

Search Strategy, inclusion and exclusion criteria, outcomes

This systematic review was performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA statement) guidelines (17) and Cochrane Guidelines (18) A systematic search of articles indexed in the Medline database investigating the role of macro and micronutrients supplementation on nutritional status, physical function, respiratory capacity, or quality of life in COPD patients was independently performed by two researchers (GL, DL). In addition to an electronic database search, a manual search of previous reviews on nutritional supplementation in COPD patients as well as the bibliography of the included studies was also searched to retrieve further potential publications.

The search strategy was based on the following keywords that were also used in combination to identify trials: Chronic obstructive pulmonary disease, COPD, nutrition, nutritional supplement, nutritional intervention, nutritional support, with publication date between January 2010 and January 2022.

The time period was limited between 2010 and 2022 because studies published before 2010 and included in the latest available meta-analysis did not evaluate the role of micronutrients supplementation (only macronutrients were supplied). The titles and abstract of the resulting studies was screened and the full-text of the potential eligible studies was evaluated to check for inclusion criteria.

We included only randomized controlled trials (RCT) in English, Spanish, or Italian language evaluating the effectiveness of nutritional support in patients affected by stable COPD (no acute exacerbation in the previous month); with an intervention of at least 2 weeks of duration and with a control group receiving placebo or usual diet and based on oral nutritional supplement (ONS) or enteral tube feeding (ETF) of macro- and/or micro-nutrients. Studies using parenteral nutrition or not including evaluation of nutritional status were excluded.

The primary measures of outcome were changes from baseline to endline in BMI and changes in FFMI, that, when reduced, is an important risk factor of undernutrition (19).

Secondary outcomes were:

- exercise tolerance, evaluated by 6-minute walking test (6MWT), that has proven useful in assessing the functional status of patients with COPD because it is easy to perform, inexpensive, and well standardized (20)
- quality of life (QoL), evaluated by St. George's Respiratory Questionnaire (SGRQ), a reproducible questionnaire that consists of 50 items useful to measure the impact on overall health, daily life and well-being in patients with obstructive airways disease. Scores range from 0 to 100, with lower scores indicating better QoL (21)
- respiratory function, evaluated using the postbronchodilator forced expiratory volume in 1 s (FEV_1)

The information about first author's name, study population (gender, mean age, sample size, setting), intervention and control characteristics, mean follow-up time and outcomes were systematically extracted by two independent authors.

Risk of bias assessment

We used Cochrane's risk of bias tool for the quality assessment of RCTs. The tool consists of the following domains: adequacy of randomization process, deviations from the intended interventions, missing outcome data, selective outcome reporting, and measurement of outcome assessment. Author judgments fall into three categories: "low", "unclear" or "high" risk of bias for each domain (18).

Data synthesis and statistical analysis

Data were analyzed after grouping the studies according to the supplements type: macronutrients supplementation, defined as calorie-protein or aminoacids (AA) supplementation, or micronutrients supplementation, defined as vitamins or bioactive compounds supplementation.

Studies suppling both micronutrients and macronutrients, were included both in micronutrients supplementation and macronutrients supplementation group.

Regarding studies comparing the effect of different nutrients with respect to placebo, we considered which estimates come from the same study using a three-level meta-analysis model.

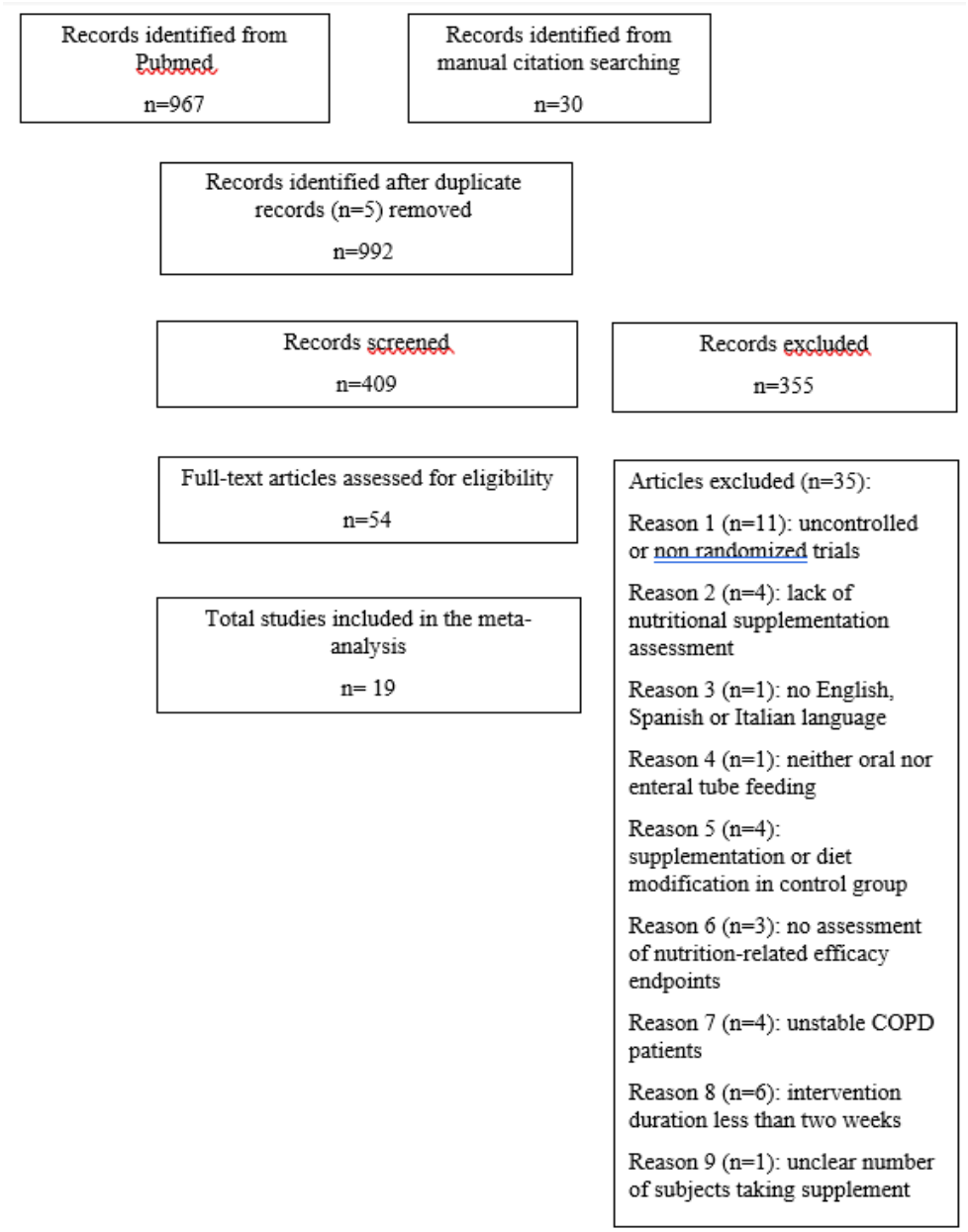
Finally, we performed a sensitivity analysis on macronutrients supplementation group excluding AA supplementation in order to evaluate whether the effect of nutritional support is due to the overall increase in calorie-protein intake or it is specifically due to the supplementation of AA (22).

The pooled adjusted mean difference (95% CI) of selected outcomes were calculated, using random-effects models in presence of heterogeneity of the effects ($I^2 > 50\%$) or fixed-effects models otherwise. The risk of publication bias was evaluated using funnel plots and the trim and fill method for meta-analyses with more than three studies. Statistical analysis was performed by using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

4.4 RESULTS

A total of 967 publication were retrieved from the Pubmed search and 30 from the manual citation search; 5 duplicate records were removed before screening; 409 records were screened and selected for abstract evaluation, 54 of those were obtained for full-text examination: 19 RCTs met the inclusion criteria and were therefore included in the meta-analysis, while 35 trials were excluded (Figure 1) for the following reasons: uncontrolled or non randomized trials in 11 studies (7,20–29) , lack of nutritional supplementation assessment and nutritional support in 4 studies (30–33) no English, Spanish or Italian language in one study (34), neither oral nor enteral tube feeding in one study (35), supplementation or diet modification in control group in four studies (36–39), no assessment of nutrition-related efficacy endpoints as changes in body weight and body composition and lung function outcomes in 3 studies (40–42), not only COPD patients or unstable COPD included in 4 studies (43–46), a intervention duration less than two weeks in 6 studies (47–52) and unclear number of subjects taking the supplements in one study (53).

Figure 1 Flow diagram.



The systematic review included a total of 986 participants affected by COPD which were randomly assigned into either a treatment group (n=506) or a control group (n=480); the weighted average age of the study population was 63 years. Considering the overall population from studies reporting male to female proportion, 29% of the participants were female. Patients' nutritional status varied among the analysed studies: for example, five studies (54–58) included undernourished individuals (BMI<23), while one study (59) recruited obese individuals (BMI>30). The setting of the studies was outpatient clinic in ten studies (54–57,59–64), inpatient in eight (58,65–71) and both in one study (72).

All of the trials included in the systematic review provided nutritional supplement by ONS with the intervention period ranging from 6 (63,66,67) to 24 (64,70) weeks. Six trials (56,58,59,61,62,71) provided a macronutrients supplementation plus a pulmonary rehabilitation program and two trials provided only a macronutrients supplementation (57,68), three studies supplied only essential amino acids (EAAs) (54,55,72), five more studies issued only a micronutrients supplementation (63,64,66,69,70), one study provided a micronutrients supplementation plus a pulmonary rehabilitation program (67), in one study the nutritional support provided both amino acid and micronutrient supplementation (65) and one more study supplied both macro and micronutrients (60). Most of the macronutrients supplementation (n=7) was liquid supplement and just in one study it was a bar, while the micronutrients supplementation included primarily vitamins and antioxidant compounds. The bromatological analysis of the macronutrients supplementation showed a high proportion of calories from carbohydrates (>50 %) except for two studies (60, 68) in which the nutritional support was protein based (Table1).

Table 1. Summary of the randomized control trials included in the meta-analysis.

First author, ref. number, year, nation	Sample size (Treatment/Control)	FU time (weeks)	Mean age ± SD (Treatment/Control)	Sex (female, %)	Inclusion/Exclusion criteria	Nutritional intervention (type, amount)	Control group (Type, amount)	Setting	Outcome measures
Ahmadi Afsane, 60, 2020, Iran	23/23	8	62.08 ± 7 / 63.47 ± 7.2	0	BMI < 25 kg/m2, fixed dose and type of medications, not being hospitalized in the last 3 months, living in Shiraz/ malignancy, severe renal, hepatic, or rheumatic disorders, active inflammation or infection, regular use of antioxidants, mineral or protein supplements	ONS: 250 ml/d of whey beverage fortified with magnesium + vitamin C (113.6 Kcal, 275 mg elemental magnesium, 685 mg vitamin C, 15.9 g whey protein) + dietary advice	Dietary advice	Outpatient clinic	BMI, FFMI, FEV_1, FVC, SGRQ
Ahnfeldt-Mollerup, 59, 2015, Denmark	28/25	9	67 ± 9.7 / 70 ± 7.3	57	BMI>30 kg/m^2, no exacerbation of COPD within last 4 weeks / diabetes, heart failure, malignancy	ONS one bar (35 g) twice a day (134.8 Kcal) + exercise pulmonary rehabilitation	Usual diet + exercise training	Rehabilitation centre	SGRQ
Baldi, 72, 2010, Italy	14/14	12	73.1 ± 6 /70.1 ±5.8	29	Weight loss (>5% of body weight) over the previous 6 months / malignancy or recent surgery, respiratory tract infection, edema	ONS: 4 g/twice a day of EAAS	Usual diet	Inpatient and outpatient clinic	BW, FFM
Bjerk, 63, 2013, USA	18/18	6	67.7 ± 7 / 68 ± 8	0	Ex- smokers / use of >500 IU/day of vitamin D, asthma, heart failure, acute myocardial infarction, malignancy, psychiatric disease	ONS 2000 IU vitamin D3/day	Placebo	Outpatient pulmonary clinic	SGRQ

Bool, 61, 2017, Netherlands	42/39	16	62.8 ± 1.3 / 62.2 ± 1.3	49	Low muscle mass: FFMI<25th percentile / allergy or intolerance to nutritional components , Pregnancy, Life expectancy <6months	ONS two to three portion (125 ml) of nutritional supplements / d (187,5 Kcal, C: 60%, P: 20%, L: 20%) + high-intensity exercise pulmonary rehabilitation	Placebo (blinded) + high-intensity exercise training	Outpatient clinic	BW, FM, 6MWT
Dal Negro, 55, 2010, Italy	16/16	12	75 ± 7 / 75 ± 7	22	Sarcopenic (BMI ≤23 Kg/m^2) / pulmonary diseases, malignancy, lack of minimal autonomy, acute exacerbation of COPD in the last month	ONS: 4 g /twice a day of EAAS	Placebo (blinded)	Outpatient clinic	BW, BMI, FFM, SGRQ, FEV_1
Dal Negro, 54, 2012, Italy	44/44	12	75 ± 5 73 ± 8	31	BMI <23 Kg/m^2, daily energy ≥28 Kcal/Kg and protein intake≥1 g/Kg / malignancy, lack of minimal autonomy, acute exacerbation of COPD in the last month, assumption of respiratory drugs since long time	ONS: 4 g /twice a day of EAAS	Placebo (blinded)	Outpatient clinic	BW, BMI, FFM, SGRQ, FEV_1, FEV_1/FVC
De Benedetto, 65, 2018, Italy	45/45	8	73 ± 7 / 73 ± 7	24	No acute exacerbation of COPD or hospitalizations in the last month /mechanical ventilation, malignancy, lack of minimal autonomy, chronic oral steroid or immunosuppressive therapy, use of statins or amino acid supplements	ONS: 160 mg QTer + 170 mg Creatine/ twice a day	Placebo (blinded)	Nine Italian hospitals	BMI, FEV_1, FVC, 6MWT
Ghobadi, 66, 2016, Iran	45/45	6	63.6±10.9 / 61.6 ±10.6	-	No chronic diseases or malignancy	ONS: 3.2 g/d of CLA soft gel	Placebo (blinded)	Pulmonary ward	BW, BMI
Gurgun, 56, 2012, Turkey	*15/16*	8	64 ± 10.8 /67.8 ± 6.6	7	Nutritional depletion (a. BMI≤ 21 kg/m^2 ,FFMI ≤15 kg/m^2 for women or 16 kg/m^2 for men; b. BMI ≤25 kg/m^2 plus weight loss of 5% in 1 month or 10% in 6 months before admission) / malignancy, lack of minimal autonomy, acute exacerbation of COPD in the last month	ONS: 250 mL/d of nutritional drink (C:83.3 %, P: 16.7 %, F: 30%) and encouragement to eat their own meal portions + pulmonary rehabilitation	Usual diet	Outpatient clinic	BW, BMI, FFMI, SGRQ, 6MWT

						program			
Hamada, 67, 2018, Japan	18/15	12	75.3 ± 6.1 / 74.7 ± 7.1	9	% IBW<100%, smoking history of more than 10 pack-year/pulmonary diseases, acute exacerbation of COPD in the last month, pulmonary transplantation, assumption of bronchodilators or systemic corticosteroids within 2 weeks before the study, pregnant women, malignancy, lack of minimal autonomy	ONS: (TJ-41) 2.5 g/three times a day of Hochuekkito powder + pulmonary rehabilitation program	Usual diet	Six clinical hospitals	BW, BMI, FFM, 6MWT, FEV_1, FVC, FEV_1/FVC
Khan, 68, 2016, India	30/30	12	55.03 ± 10.41 / 53.33 ± 10.76	10	-/ No acute exacerbation of COPD in the past three months, ex-smokers/ chronic diseases or malignancy	ONS 30 g/d of nutritional powder (90 Kcal, C:55%, P: 45%, L: 0%)	Usual diet	Chest clinic of hospit52,18al	BW, BMI, 6MWT, FEV_1, FVC, FEV_1/FVC,
Lu, 69, 2018, Taiwan	13/14	8	71 ± 2 / 72 ± 2	-	Absence of kidney disease, liver disease, no assumption of antioxidant supplements, antibiotics / -	ONS 150 mg/day of oligomeric proanthocyanidins (OPC)	Placebo	Hospital	FEV_1, FVC, FEV_1/FVC
Martinez, 57, 2016, Spain	38/49	12	52.18 ± 20.3 / 35 ± 15.7	71	Nutritional depletion : BMI≤ 21 kg/m^2 ,FFMI ≤15 kg/m^2 for women or 16 kg/m^2 for men, weight loss > 10% % in 6 months before admission or > 5% in the past month/ assumption of other nutritional supplement, parenteral nutrition, tuberculosis, respiratory insufficiency	ONS 57g / d of nutritional powder (258 Kcal)	Usual diet	Outpatients clinic	BMI, FFMI, 6MWT, FEV_1
Pirabbasi, 64, 2015, Malaysia	15/18	24	64.2 ± 7.8 / 64.17 ± 8.3	-	- / COPD stage IV, antioxidant supplementation, tuberculosis, inflammatory diseases, malignancy	ONS (NAC) 600 mg/ d of N-acetylcysteine	Usual diet	Outpatients clinic	BMI, FFMI, FM
Pirabbasi, 64, 2015, Malaysia	13/18	24	64.5 ± 10.2 / 64.17 ± 8.3	-	- / COPD stage IV, antioxidant supplementation, tuberculosis, inflammatory diseases, malignancy	ONS (Vitamin C) 500 mg/ d of Vitamin C	Usual diet	Outpatients clinic	BMI, FFMI, FM

Pirabbasi, 64, 2015, Malaysia	15/18	24	63.7 ± 8.5 / 64.17 ± 8.3	-	- / COPD stage IV, antioxidant supplementation, tuberculosis, inflammatory diseases, malignancy	ONS (NAC+ Vitamin C) 600 + 500 mg/ d of N-acetylcysteine + Vitamin C	Usual diet	Outpatients clinic	BMI, FFMI, FM
Rafiq, 70, 2017, Netherlands	24/26	24	64 [61-66] / 61 [58-66]	48	Vitamin D deficiency / Severe vitamin D deficiency, suspicion of osteoporosis, malignancy, pregnant or lactating women, mental impairment	ONS 1,200 IU vitamin D3/d	Placebo (blinded)	Pulmonary ward	BMI, 6MWT, FEV_1, FVC, FEV_1/FVC
Sugawara, 58, 2010, Japan	17/15	12	77.3 ± 7 / 78.2 ± 6.6	-	No recent acute exacerbation of COPD, BMI< 19 kg/ m^2 / Gastrointestinal abnormalities, recent surgery, severe endocrine disorders, malignancy	ONS two 200 ml packages of nutritional drink/d (200 Kcal, C: 60%, P: 15%, L: 25 %) + low-intensity exercise pulmonary rehabilitation + 45-min education program monthly	Usual diet + 45-min education program monthly	Pulmonary ward	BW, FFMI, FMI, 6MWT
Sugawara, 71, 2012, Japan	17/14	12	77.4 ± 5.2 / 77.1 ± 5.8	6	-/ smokers, mental diseases, difficulty in oral ingestion	ONS 200 ml of nutritional drink/ twice a day (200 Kcal, C: 53.2 %, P: 20%, L: 25 %) in addition to dietary instruction + low- intensity exercise pulmonary rehabilitation	Usual diet + dietary instruction	Pulmonary ward	BW, FFMI, FMI, 6MWT

van Wetering, 62, 2010, Netherlands	16/14	12	64 ± 8.7 /64 ± 8.7	38	Low muscle mass: FFMI<15 kg/m^{2}female and FFMI<16 kg/m^{2}male, weight loss > 10% % in 6 months before admission or > 5% in the past month / prior rehabilitation, serious comorbidity that precluded exercise	ONS three portion (125 ml) of nutritional supplement (564 kcal) /d in addition to nutritional counselling + low- intensity exercise pulmonary rehabilitation	Usual diet + exercise training	Community acquired	BMI, FFMI, 6MWD, SGRQ

Abbreviations: BW: body weight; BMI: body mass index; IBW: Ideal Body Weight; FM: fat mass; FFMI: free fat mass index; 6MWT: 6-min walk test; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; SGRQ: St. George's Respiratory Questionnaire; ONS: oral nutritional supplement; CLA: conjugated linoleic acid; EAAS: essential amino acids; COPD: Chronic obstructive pulmonary disease.

Quality assessment

The risk of bias assessment revealed that overall studies' quality is fair, although for the most part there are uncertainties with randomization (that was unknown in 14 studies) (Figure 2).

Figure 2 Risk of bias assessment.

	RANDOMIZATION PROCESS	DEVIATION FROM THE INTENDED INTERVENTIONS	MISSING OUTCOME DATA	SELECTION OF THE REPORTED RESULTS	MEASUREMENT OF THE OUTCOME
Ahmadi, 2020	-	-	-	?	-
Ahnfeldt-Mollerup, 2015	?	-	-	?	+
Baldi, 2010	?	-	-	?	?
Bjerk, 2013	?	-	-	-	-
Bool, 2017	-	-	-	-	-
Dal Negro, 2010	?	-	-	-	-
Dal Negro,2012	?	-	-	-	-
De Benedetto, 2018	?	-	-	-	-
Ghobadi, 2016	?	-	-	-	-
Gurgun, 2012	?	-	-	+	-
Hamada,2018	?	?	-	+	+
Khan, 2016	?	-	-	?	+
Lu, 2018	?	-	-	-	-
Martinez, 2016	+	-	-	+	+
Pirabbasi, 2015	-	-	-	-	-
Rafiq, 2017	?	-	-	+	+
Sugawara, 2010	?	-	-	-	-
Sugawara, 2012	?	-	-	-	-
van Wetering, 2010	+	?	+	+	+

Legend:

+ High risk of bias

- Low risk of bias

? Some concerns

Nutritional supplementation and BMI

BMI was considered as an outcome in 12 (54-57, 60, 62, 64-68, 70) studies.

Two studies performed multiple comparisons (60,64), therefore it ended up in a total of 16 comparisons, 8 using macronutrients supplementation and 8 using micronutrients supplementation.

When the macronutrients supplementation including AA was given, BMI increased significantly compared to the control group (Mean difference 1.25 kg/m^2, 95% CI: 0.47, 2.02) (Figure 3), with high heterogeneity across the studies (I2=57.1 %). The risk of publication bias was low (see supplementary information, figure 1). The mean difference adjusted for publication bias was 1.40 kg/m^2 (95% CI 0.65, 1.17). The BMI increase was confirmed also in a sensitivity analysis excluding three studies supplying only AA (Mean difference 0.59 kg/m^2, 95% CI: 0.04,1.13) (Figure 4), with no heterogeneity across studies, as documented by a I2 of 0%. The trim and fill correction of the funnel plot identified two potentially missing studies (see supplementary information, figure 2). The mean difference adjusted for publication bias was 0.45 kg/m^2 (95% CI -0.05, -0.95).

Micronutrients supplementation alone, compared to the usual diet, did not increase BMI (Mean difference 0.02 kg/m ^{2}, 95% CI: -0.38, 0.41) (see supplementary information, figure 3), with no heterogeneity across studies as documented by a I^2 of 0%. There was no risk of publication bias (see supplementary information, figure 4). The mean difference does not change after adjustment for publication bias. A sensitivity analysis excluding one study supplying only AA was carried out, with no changes in the results (Mean difference 0.02 kg/m ^{2}, 95% CI: -0.38, 0.41) (see supplementary information, figure 5). There was no risk of publication bias (see supplementary information, figure 6). There were no changes in the mean difference after adjustment for publication bias.

Figure 3 Forest plot of mean difference for BMI in macrosupplementation (including aminoacids) group.

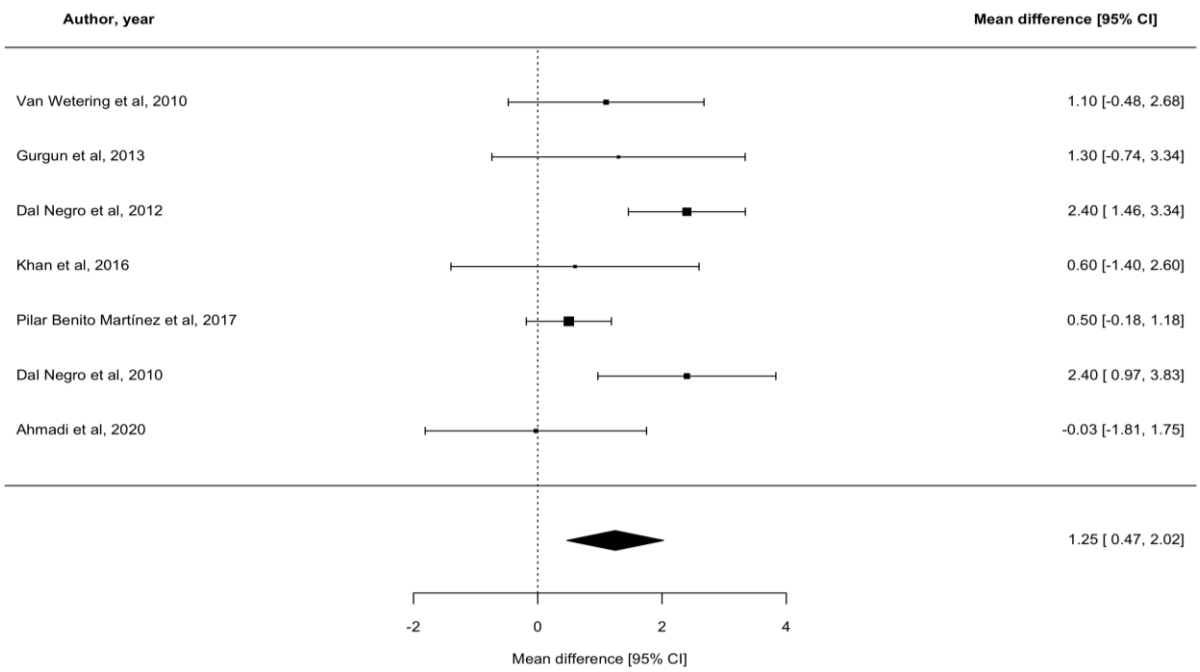
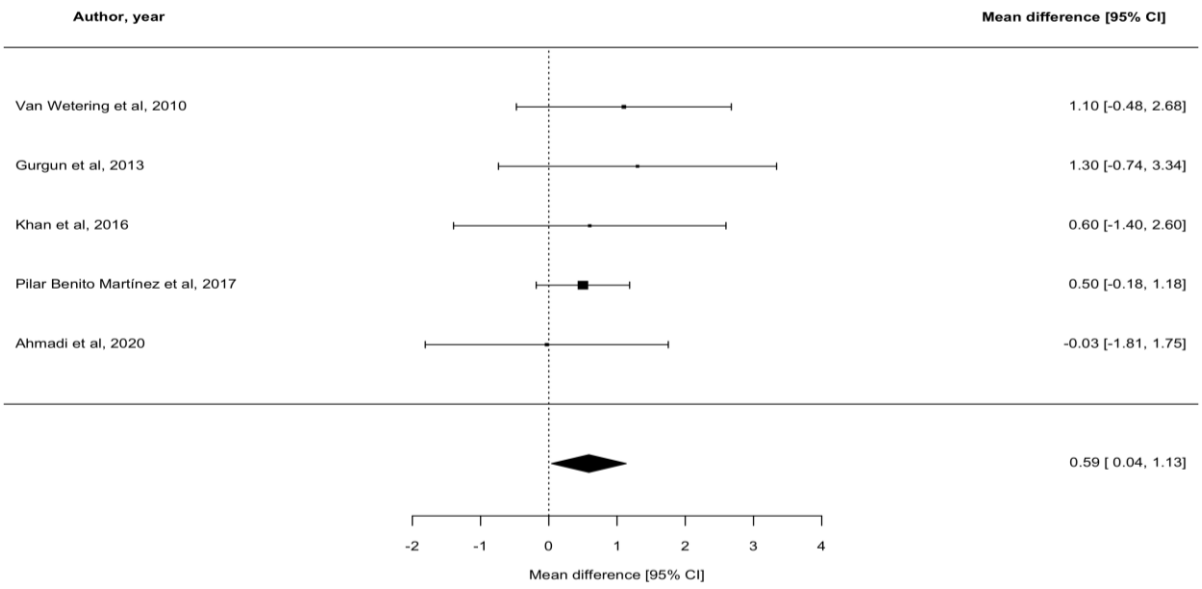


Figure 4 Forest plot of mean difference for BMI in macrosupplementation (excluding aminoacids) group



Nutritional supplementation and body composition

FFMI was an outcome taken into account in 13 (54–58,60,62,64,67,71,72) RCTs, 9 using macronutrients supplementation and 5 using micronutrients supplementation.

Patients in the macronutrients supplementation group had an increase of the FFMI with respect to the control group of 0.77 Kg/m^2 (95% CI: 0.48,1.06) (Figure 5). There was no heterogeneity across trials (I2=0 %). The trim and fill correction of the funnel plot showed a low risk of publication bias (see supplementary information, figure 7). The mean difference adjusted for publication bias does not change. These results were confirmed also excluding three studies with AA supplementation only (Mean difference 0.63 kg/m^2, 95% CI: 0.31,0.95) (see supplementary information, figure 8). However, we found a potential publication bias, with one potentially missing studies identified with the trim and fill method (see supplementary information, figure 9). The mean difference adjusted for publication bias was 0.62 kg/m 2, 95% CI: 0.28-0.95.

Conversely, micronutrients supplementation had no effect in increasing FFMI (Mean difference (kg/m^2) :0.34, 95% CI: -0.33,1.02) (Figure 6). There was no heterogeneity across trials (I^2=0 %) and the risk of publication bias was low (see supplementary information, figure 10).

The mean difference adjusted for publication bias was 0.58 kg/m^2, 95% CI: 0.006, 1.16).

Figure 5 Forest plot of mean difference for FFMI in macrosupplementation (including aminoacids) group.

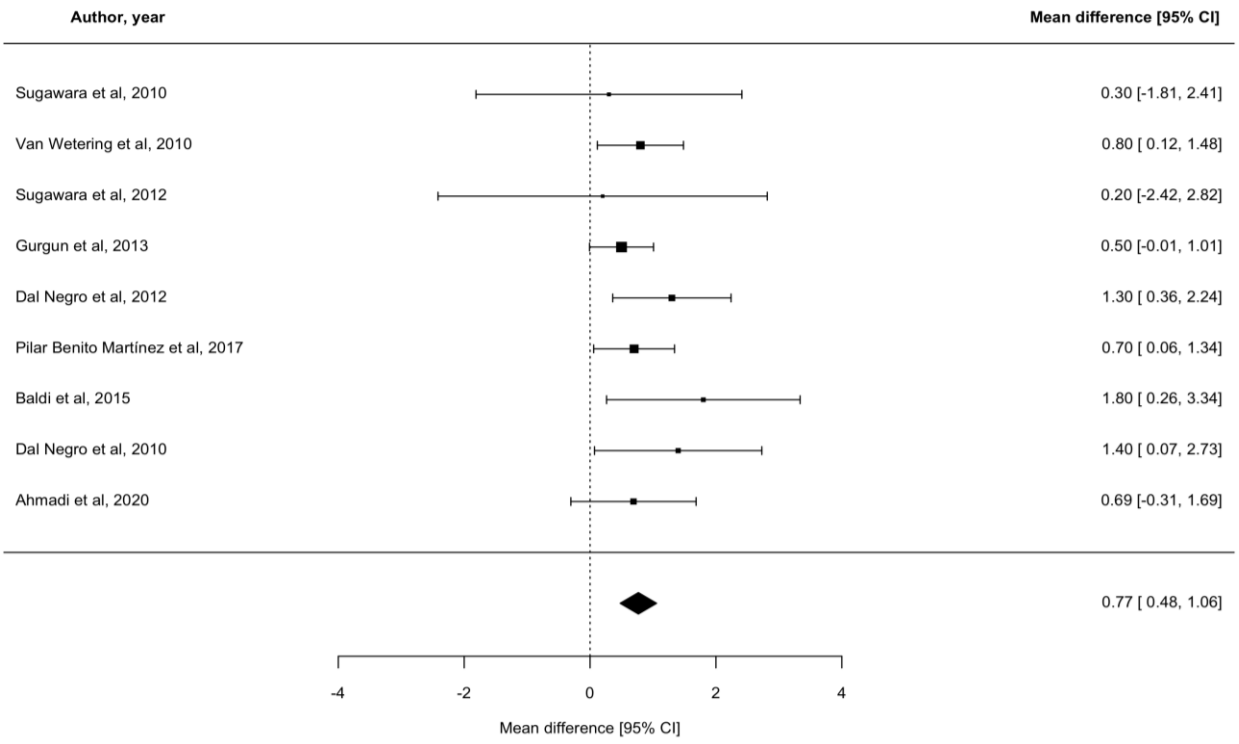
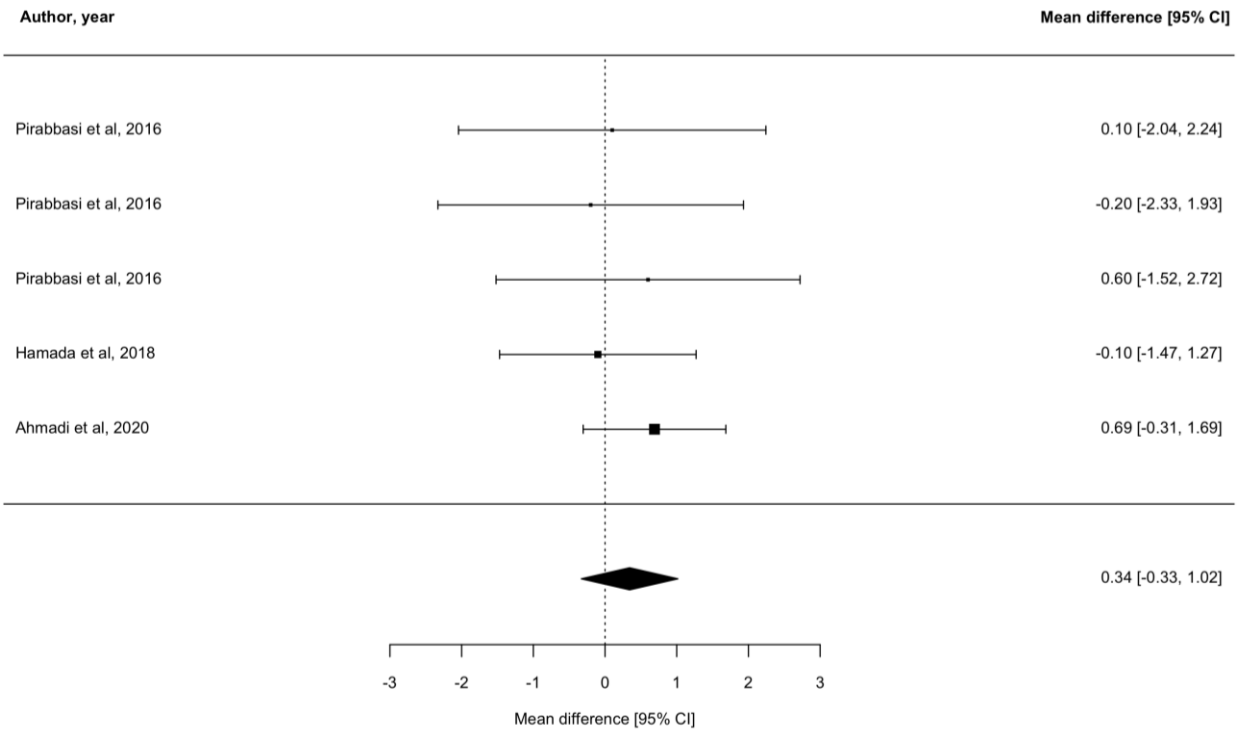


Figure 6 Forest plot of mean difference for FFMI in microsupplementation group.



Nutritional supplementation and respiratory function

The FEV1 (%) was an outcome taken into account in 8 (55,57,60, 65,67–70) studies.

Two studies performed multiple comparisons (60,65), therefore it ended up in a total of 10 comparisons, 5 using macronutrients supplementation and 5 using micronutrients supplementation.

One study (54) only reported absolute values of FEV 1 and was therefore excluded in this analysis.

The macronutrients supplementation did not improve the pulmonary function compared to the usual care (Mean difference (%) :1.03, 95% CI: -1.47,3.53) (see supplementary information, figure 11). There was no heterogeneity across trials (I2=0 %). The trim and fill method documented a risk of publication bias, with three potentially missing studies (see supplementary information, figure 12). The mean difference adjusted for publication bias was 0.26 (95% CI -1.87,2.40). Only two (55,65) studies supplied essential amino acids, therefore the sensitivity analysis of trials excluding supplementation with AA only was not carried out.

The micronutrients supplementation had no effect on respiratory function as documented by fixed-effect model (Mean difference (%): -1.63, 95% CI: -3.79, 0.53) (see supplementary information, figure 13). There was no heterogeneity across studies (I^2=0 %) and a risk of publication bias was documented (see supplementary information, figure 14).

The mean difference adjusted for publication bias was -1.63 (95% CI -3.79, 0.52).

Nutritional supplementation and exercise tolerance

Ten (56–58,61,62,65,67,68,70,71) studies reported mean changes in 6-min walk test.

One study performed multiple comparisons (65), therefore it ended up in a total of 11 comparisons, 8 using macronutrients supplementation and 3 using micronutrients supplementation.

Considering the macronutrients supplementation, the distance walked at the 6-min walking test increased significantly with respect to control group (Mean difference (m): 42.65, 95% CI: 16.39, 68.90) (Figure 7). There was a high heterogeneity between studies (I^2=92.44%). Only one missing study was identified using the trim and fill method (see supplementary information, figure 15).

The mean difference adjusted for publication bias was 64.22, 95% CI: 35.13, 93.32). A sensitivity analysis excluding the study supplementing AA confirmed the improvement in exercise tolerance (Mean difference (m): 43.24, 95% CI: 13.02, 73.46) (Figure 8), and the high heterogeneity across studies (I^2= 94.10 %). The funnel plot documented a low risk of bias (see supplementary information, figure 16). The mean difference adjusted for publication bias was 58.57, 95% CI: 27.04, 90.10).

The micronutrients supplementation had no effect on 6-min walking test performance (Mean difference (m): 18.41, 95% CI: -7.62, 44.43) (see supplementary information, figure 17). There was low heterogeneity across trials (I^2= 40.89 %). The trim and fill correction documented two potentially missing study (see supplementary information, figure 18).

The mean difference adjusted for publication bias was 36, 95% CI: -2.10, 74.10).

Figure 7 Forest plot of mean difference for 6MWT in macrosupplementation (including aminoacids) group.

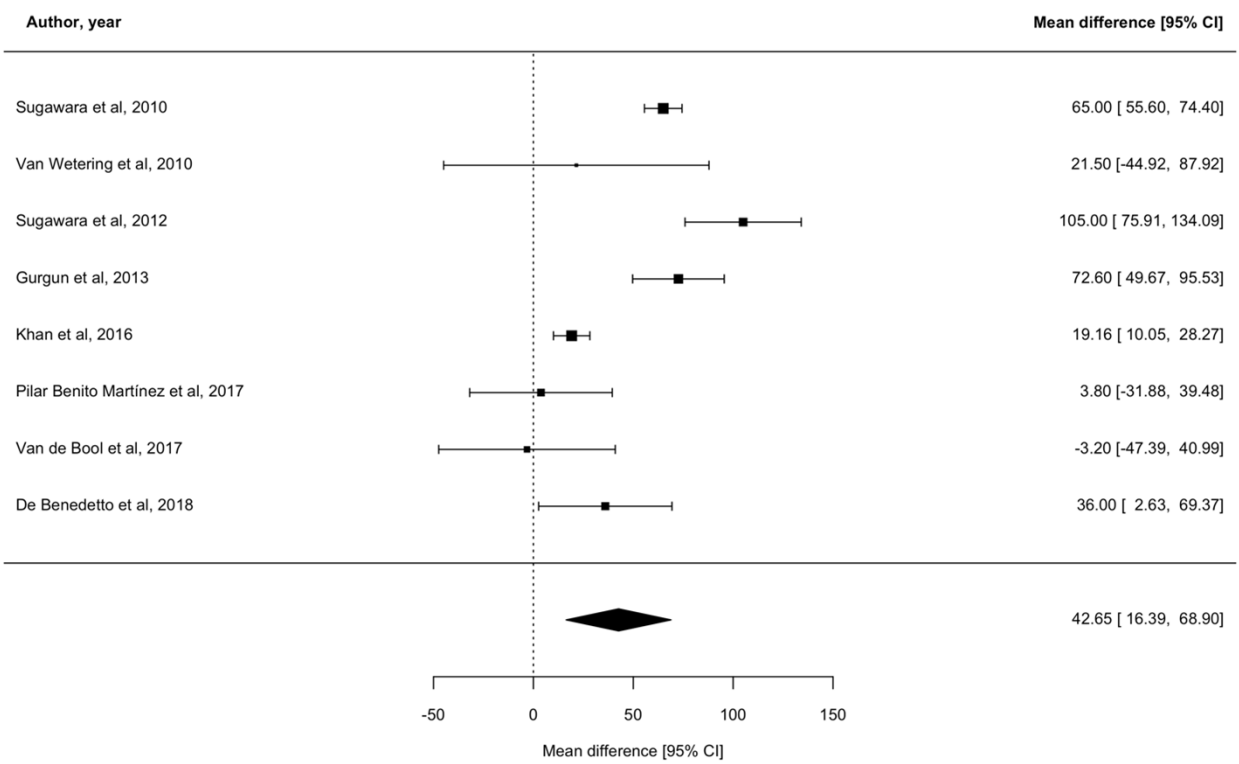
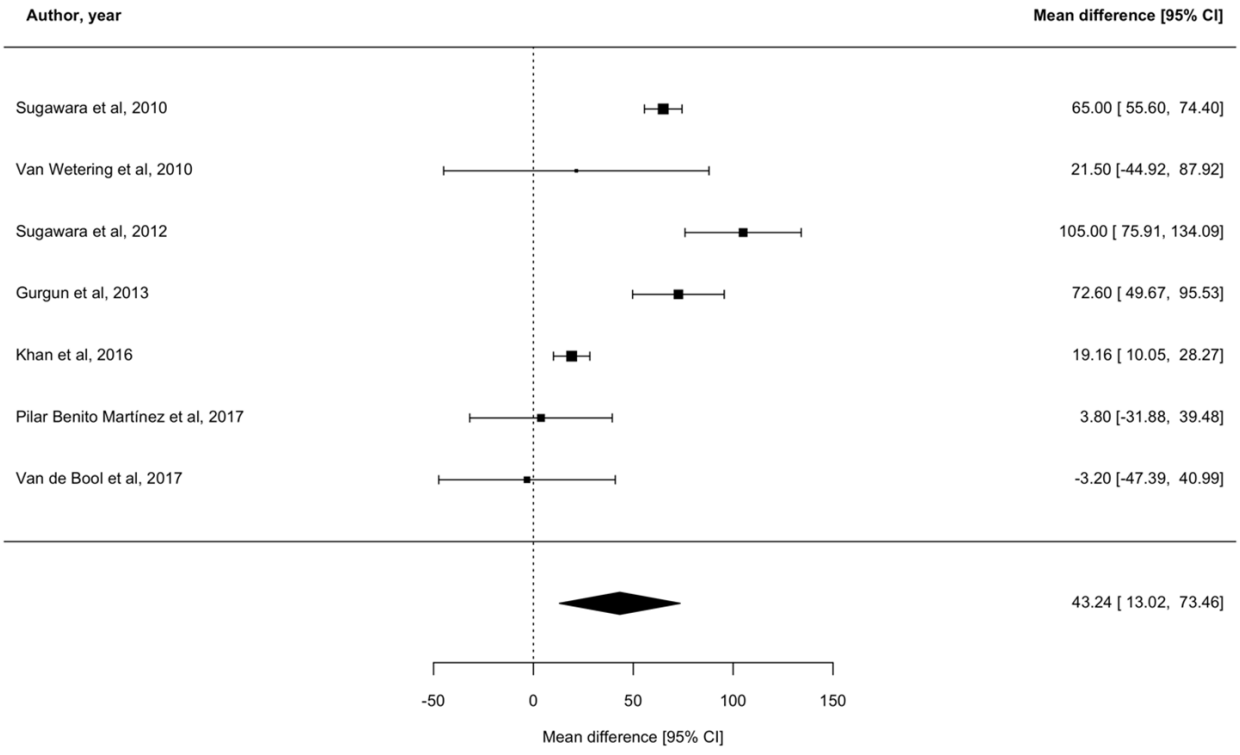


Figure 8 Forest plot of mean difference for 6MWT in macrosupplementation (excluding aminoacids) group.



Nutritional supplementation and quality of life

Seven (54–56,59,60,62,63) studies examined the effect of nutritional support on QoL.

One study performed multiple comparisons (60), therefore it ended up in a total of 8 comparisons, 6 using macronutrients supplementation and 2 using micronutrients supplementation.

The macronutrients supplementation, with respect to controls, improved the SGRQ's total score (Mean difference: -5.14, 95% CI: -7.31,-2.97) (Figure 9), with no heterogeneity across trials (I2=0 %). A risk of publication bias was documented (see supplementary information, figure 19).

There were no changes in the mean difference after adjustment for publication bias.

These results were confirmed also excluding two studies with AA supplementation only (Mean difference -6.35, 95% CI: -9.59, -3.12 (Figure 10), with no heterogeneity across studies, as documented by 0% of I2. The trim and fill analysis was not reliable due to the esigual number of studies included.

Only two (60, 63) studies supplied micronutrients supplementation with no effect on SGRQ's total score (Mean difference: -4.63, 95% CI: -18.11, 8.86) (see supplementary information, figure 20).

There was high heterogeneity across trials (I^2= 76,3 %).

The trim and fill analysis was not reliable due to the esigual number of studies included.

Figure 9 Forest plot of mean difference for QoL in macrosupplementation (including aminoacids) group.

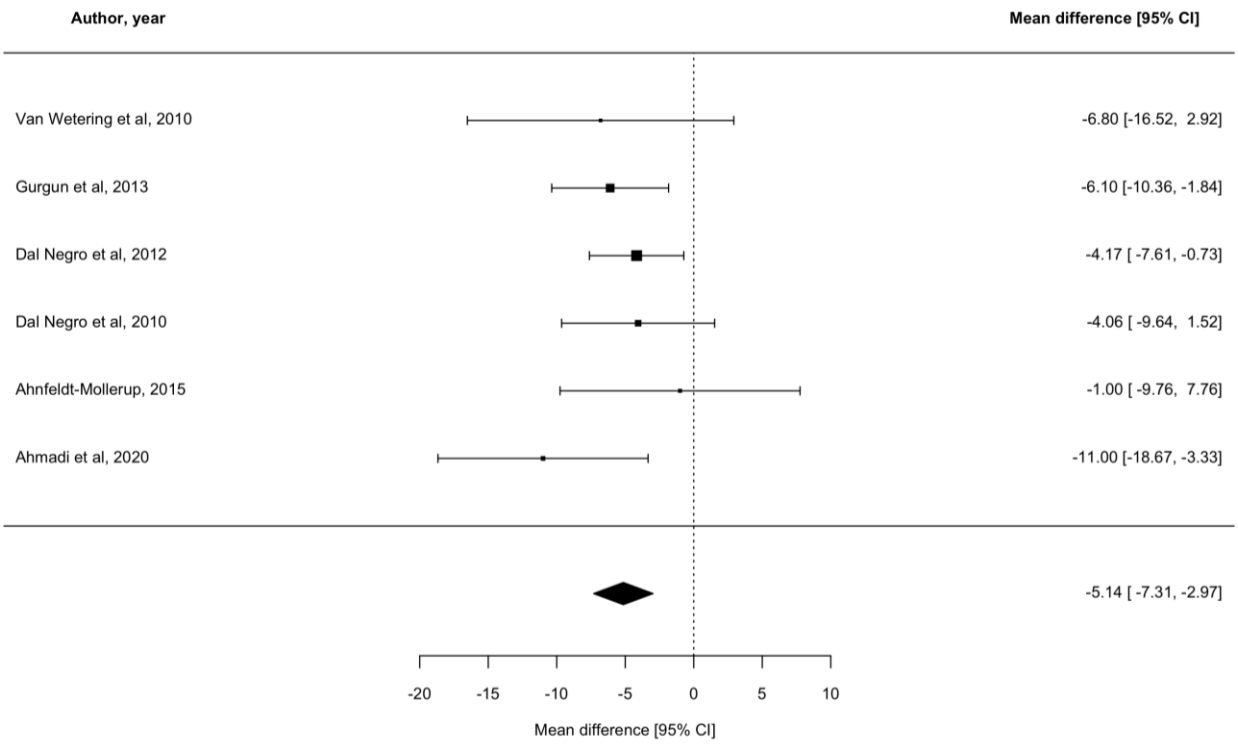
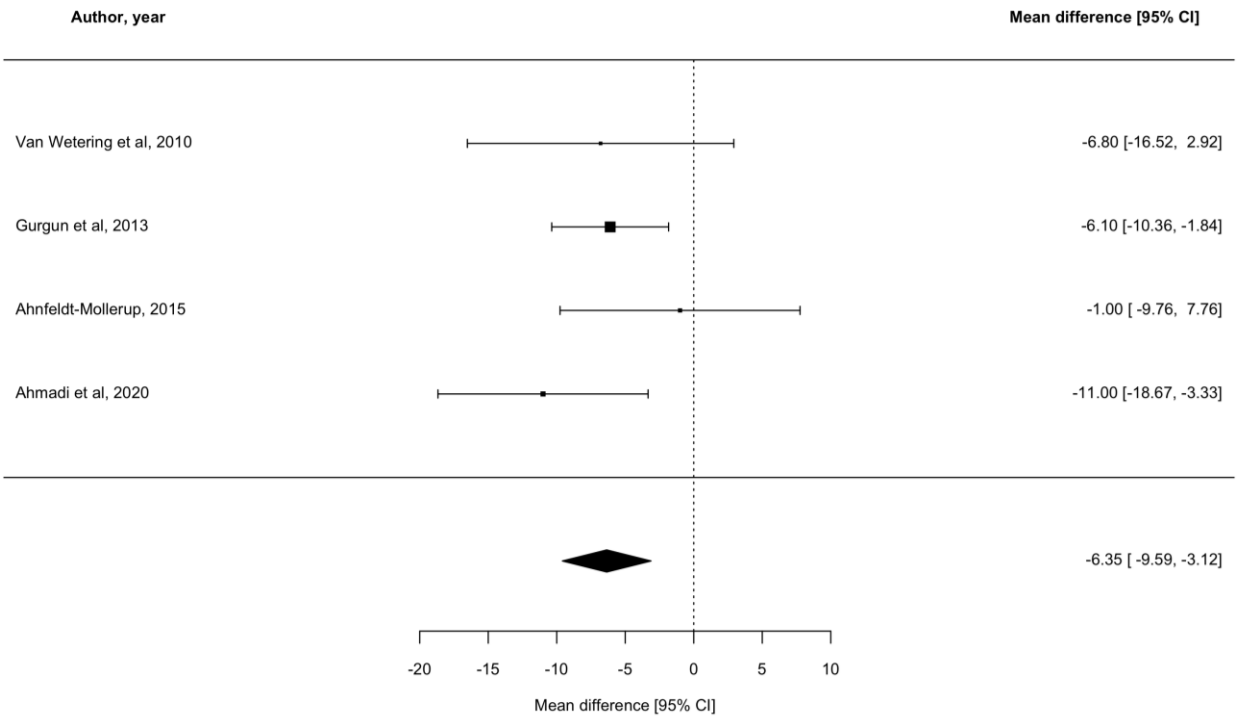


Figure 10 Forest plot of mean difference for QoL in macrosupplementation (excluding aminoacids) group.



4.5 DISCUSSION AND CONCLUSION

Our meta-analysis showed that the use of macronutrients supplementation in COPD patients improves BMI, FFMI, exercise tolerance and quality of life, while it does not ameliorate respiratory function. Micronutrients supplementation alone did not improve any of the considered outcomes.

Our findings on the positive effect of macronutrients supplementation on BMI and FFMI confirm the results reported by the latest meta-analysis available in literature (73).

Similar results were also observed in the meta-analysis of Ferreira et al. (2012) (1), although compared to the present study a different pool of RCTs was included due to different time range taken into account. On the other hand, a previous meta-analysis, conducted in 2000 by the same group (14) showed no positive effect of nutritional supplementation on anthropometric measures. There are several differences between this latter meta-analysis and our meta-analysis that may explain this discrepancy. First, we included a different set of studies with a pooled sample size that is about three times larger. Second, the meta-analysis by Ferreira et al. focused on undernourished patients: in this subgroup the nutritional requirements needed to bring forth a clinical improvement may be larger than the one provided by the intervention (14).

The reason for a poor response was an increased energy expenditure not correctly evaluated, therefore not properly balanced by an adequate overall dietary intake. Thus, the nutritional intervention itself was not of sufficient magnitude to produce a positive effect (14).

Our results on respiratory function are in line with those reported by previous systematic reviews and meta-analyses (1,13): nutritional support administered for more than two weeks failed to show a consistent improvement in lung function. Many authors advanced the hypothesis that the total energy expenditure is underestimated in COPD patients, mainly because of chronic inflammatory status and medications such as corticosteroids, therefore, despite nutritional supplementation, the dietary intake will result anyway insufficient to compensate for the increased metabolism.

We can speculate that although nutritional support was effective in improving anthropometrics parameters (e.g. BMI and FFMI), the multifactorial and complex mechanism of respiratory disease

in COPD prevented the supplementation from achieving the same effect on respiratory function outcomes. Indeed, it has to be taken into account that the obstructive alterations occurred overtime can not be modified by nutrition (74).

Concerning exercise tolerance, our results showing that macronutrients supplementation improves walking distance, are in contrast with those reported by Ferreira et al, 2012 (1) , that showed no clinically important difference between groups. This difference may be imputed to the larger number of studies reporting on that outcome included in our meta-analysis.

Regarding QoL, measured by the SGRQ, our results confirmed and extended on a larger population those reported by a previous meta-analysis (1), that analysed only two trials for this outcome: in the current meta-analysis were included 6 studies, all of them using macronutrients supplementation and/or AA.

A strength of the present study is that it is the first meta-analysis that stratify studies according to type of supplementation (micro or macronutrients supplementation). The results on BMI and exercise tolerance, however, are highly heterogeneous: this may be in part due to the different supplementation used, but other factors such as different nutritional status of the patient included or because of the exercise training or pulmonary rehabilitation performed mostly by patients from the macronutrients supplementation group.

In conclusion, our result confirm that macronutrients supplementation should be offered to COPD patients even if well-nourished, in order to improve anthropometric parameters, quality of life, and exercise tolerance.

4.6 SUPPLEMENTARY INFORMATION

This supplementary information file contains supplementary figures related to the results.

Figure 1 Risk of publication bias for BMI in macrosupplementation (including aminoacids) group. Open circles represent the potential missing studies identified using the Trim and Fill method.

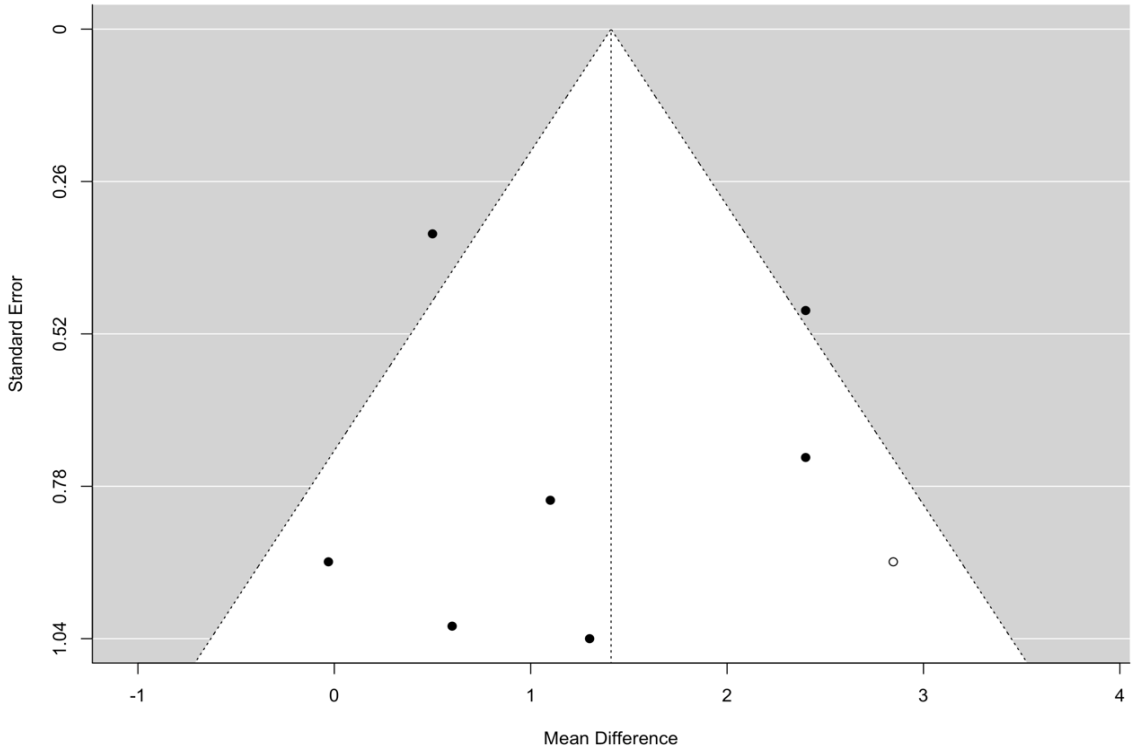


Figure 2 Risk of publication bias for BMI in macrosupplementation (excluding aminoacids) group. Open circles represent the potential missing studies identified using the Trim and Fill method.

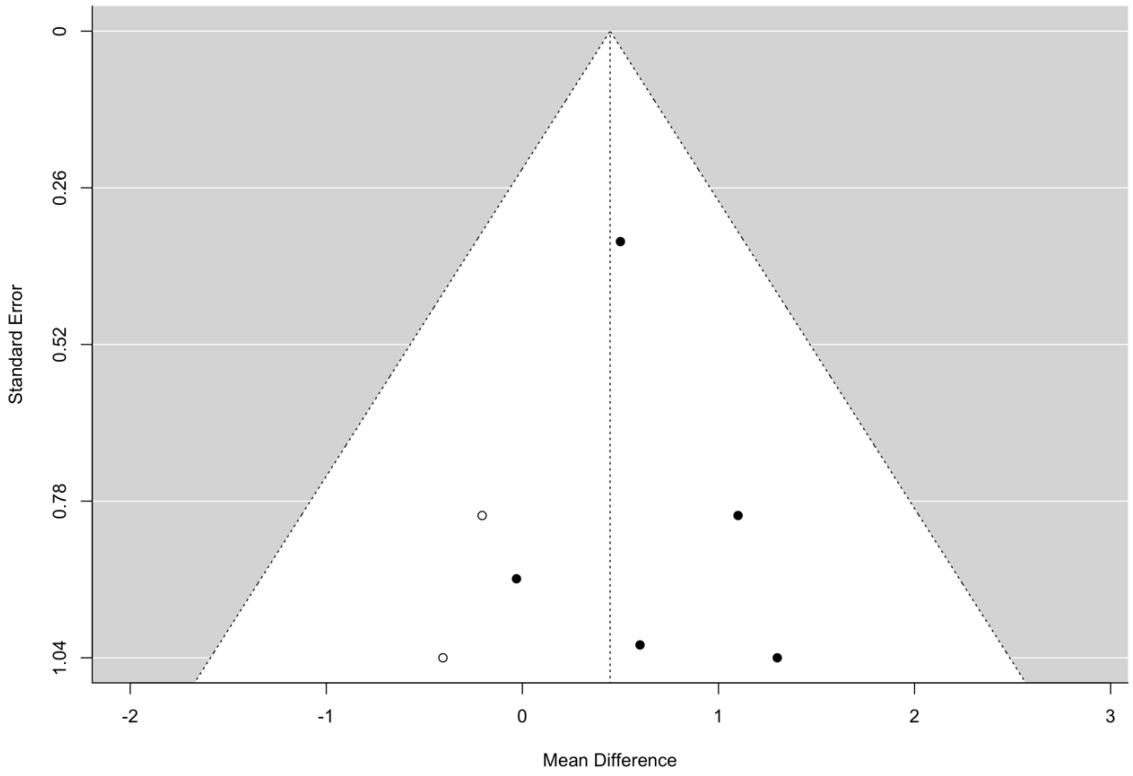


Figure 3 Forest plot of mean difference for BMI in microsupplementation (including aminoacids) group.

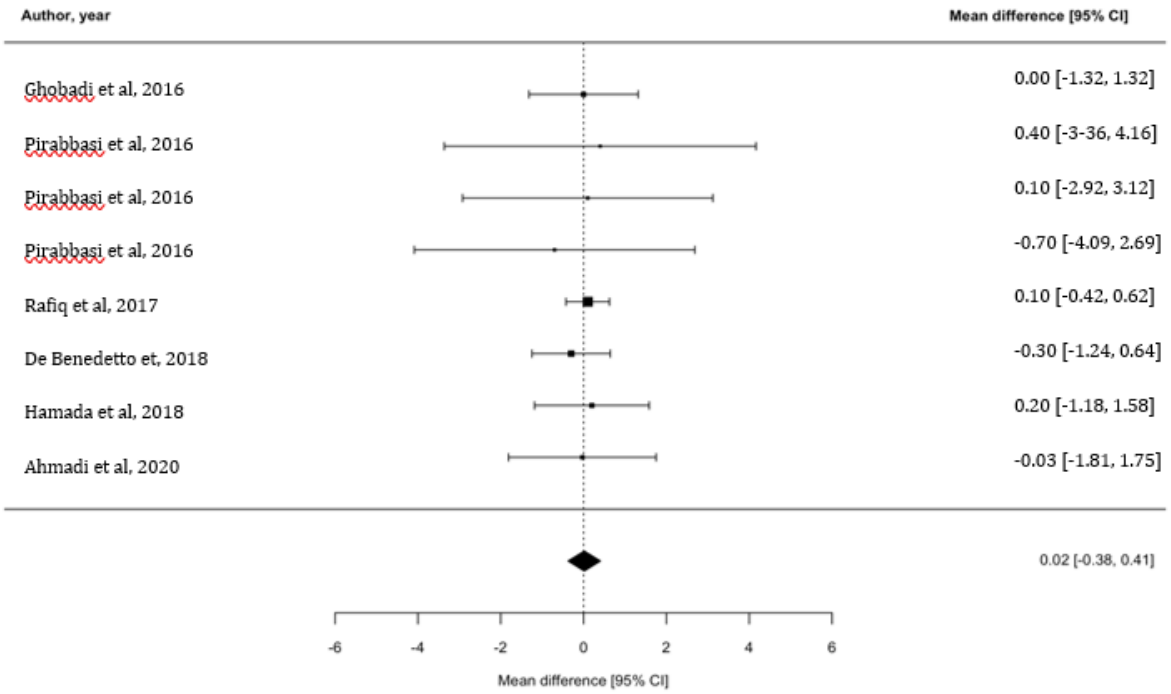


Figure 4 Risk of publication bias for BMI in microsupplementation (including aminoacids) group. Open circles represent the potential missing studies identified using the Trim and Fill method.

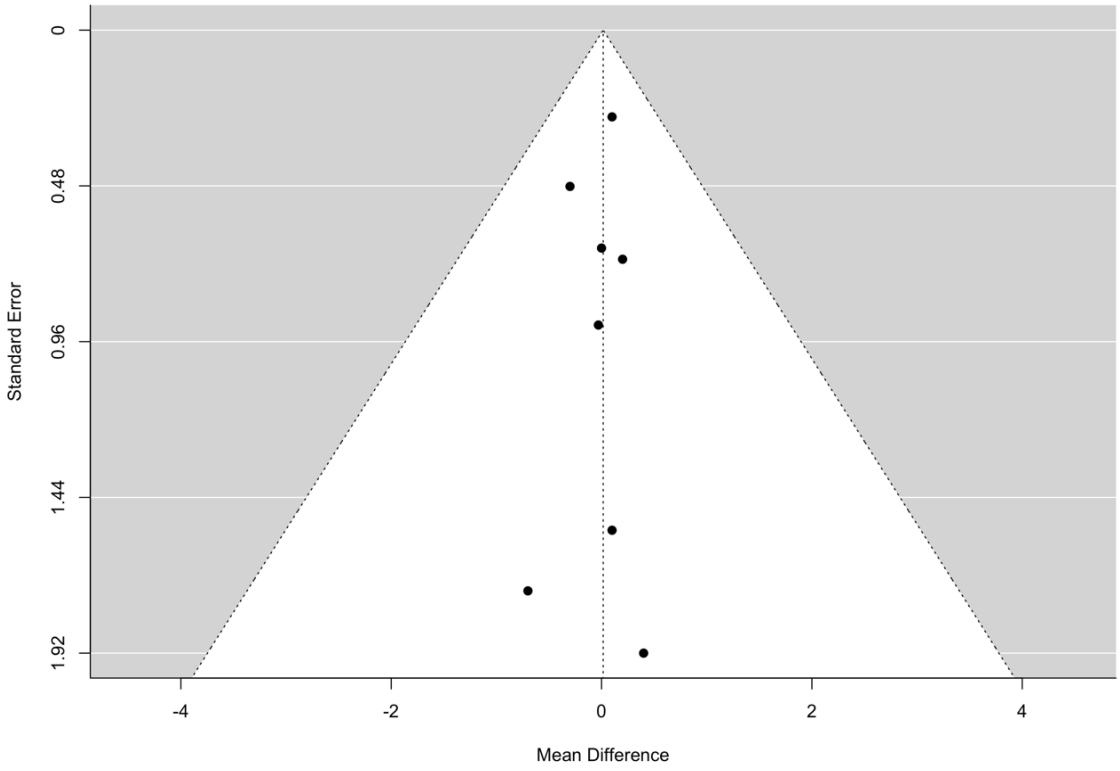


Figure 5 Forest plot of mean difference for BMI in microsupplementation (excluding aminoacids) group.

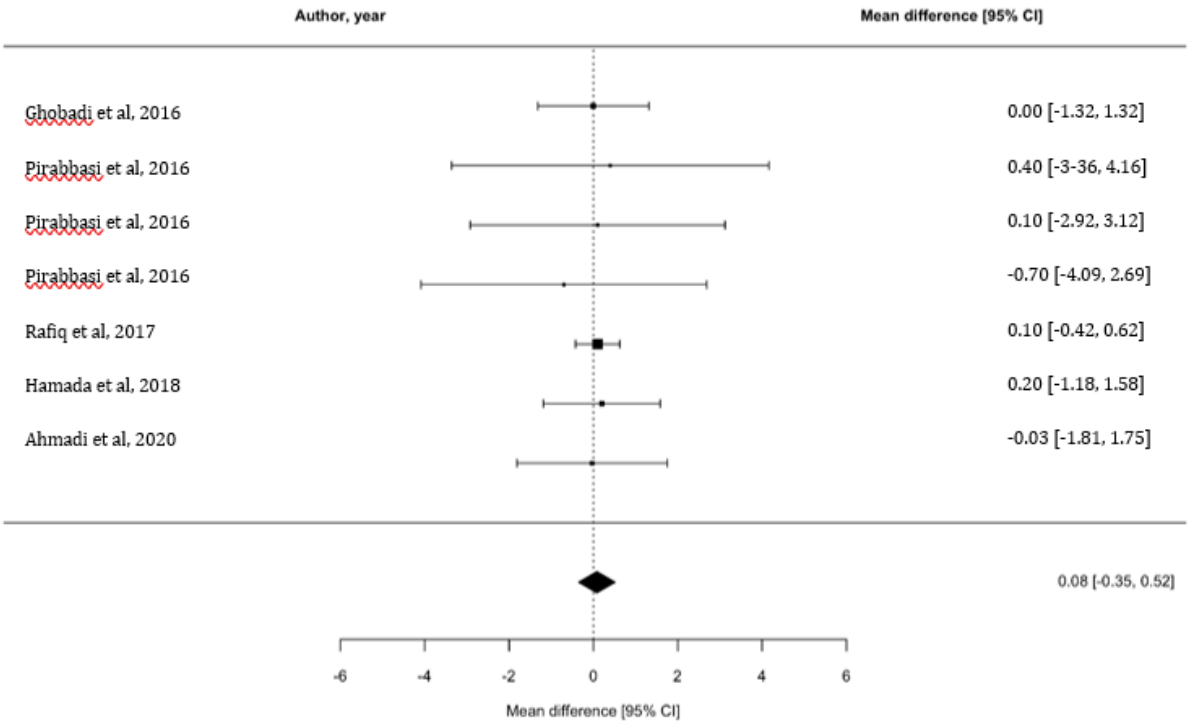


Figure 6 Risk of publication bias for BMI in microsupplementation (excluding aminoacids) group. Open circles represent the potential missing studies identified using the Trim and Fill method.

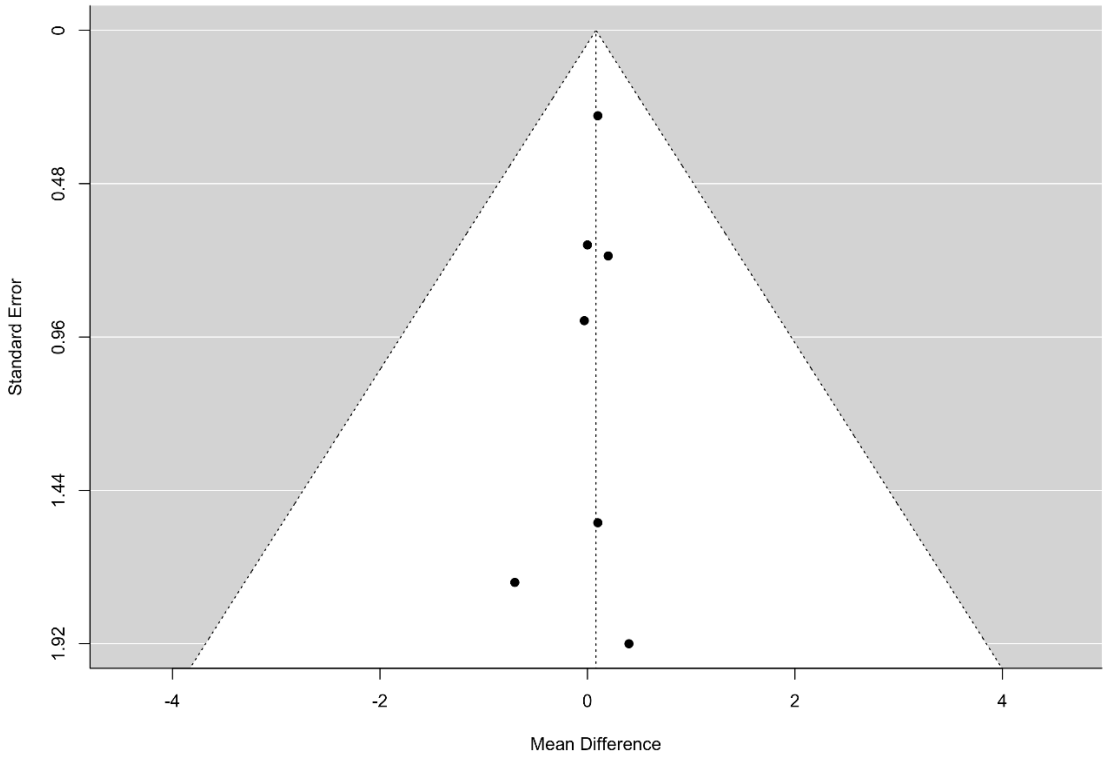


Figure 7 Risk of publication bias for FFMI in macrosupplementation (including aminoacids) group. Open circles represent the potential missing studies identified using the Trim and Fill method.

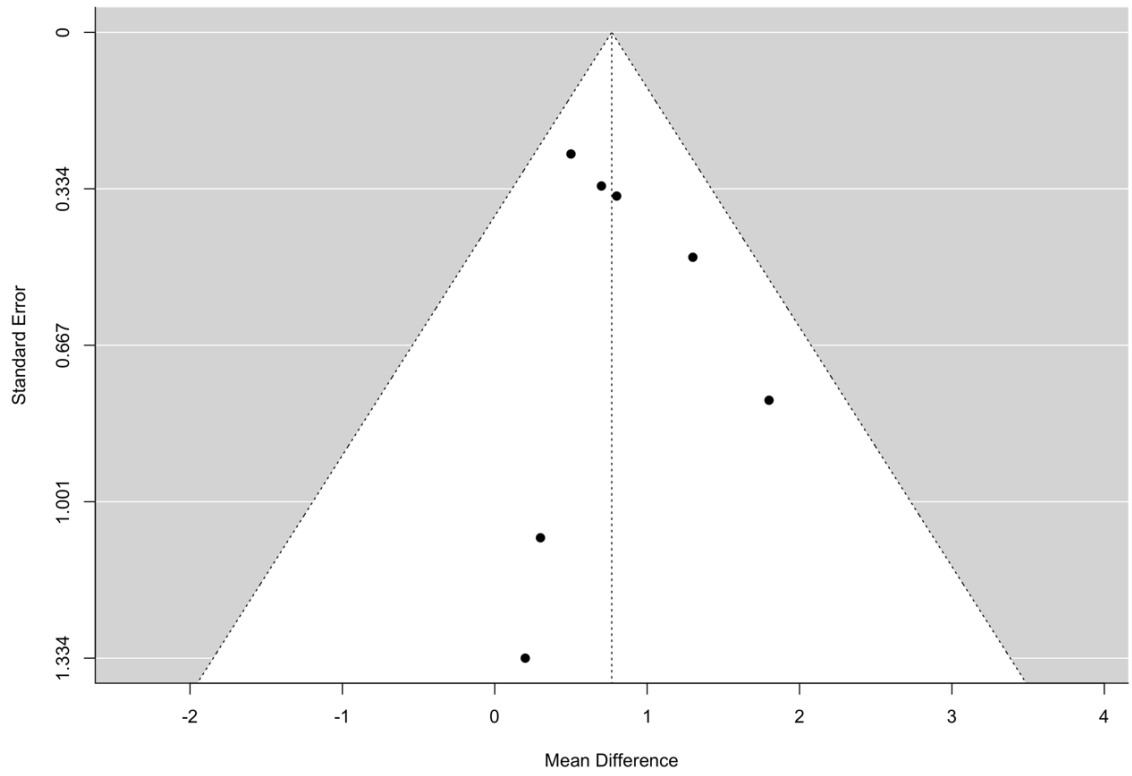


Figure 8 Forest plot of mean difference for FFMI in macrosupplementation (excluding aminoacids) group.

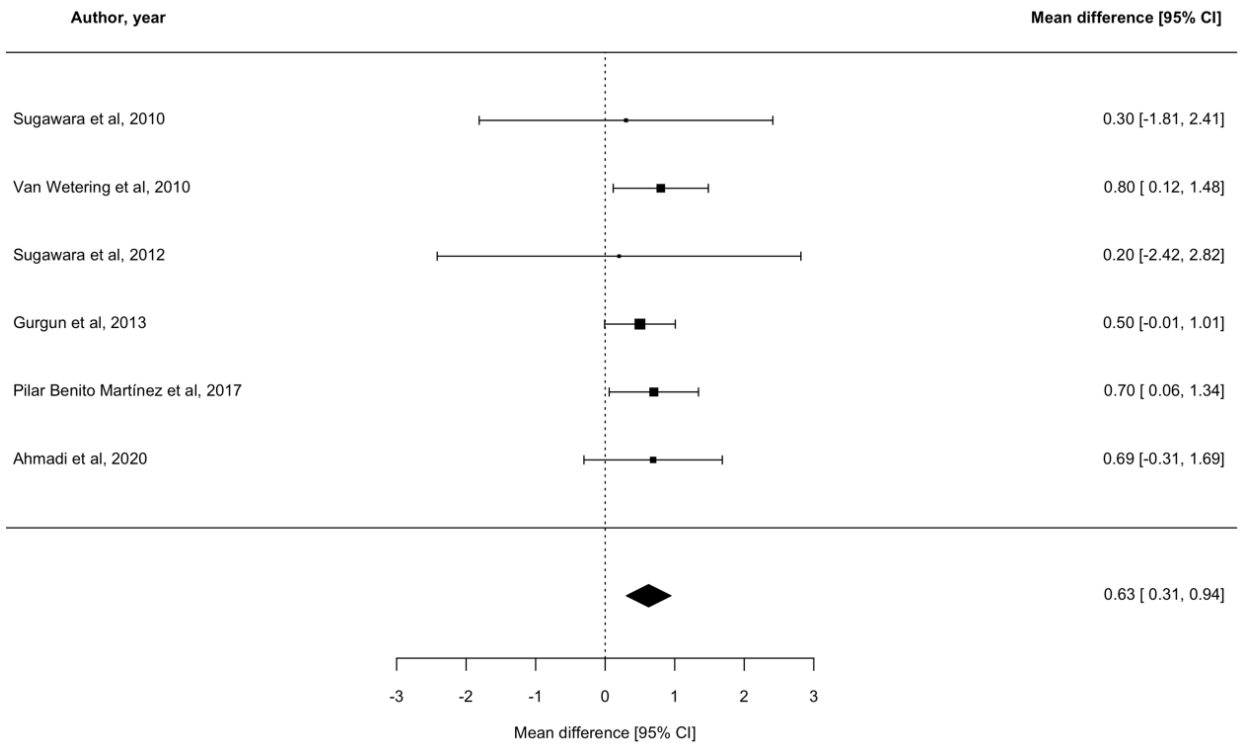


Figure 9 Risk of publication bias for FFMI in macrosupplementation (excluding aminoacids) group. Open circles represent the potential missing studies identified using the Trim and Fill method.

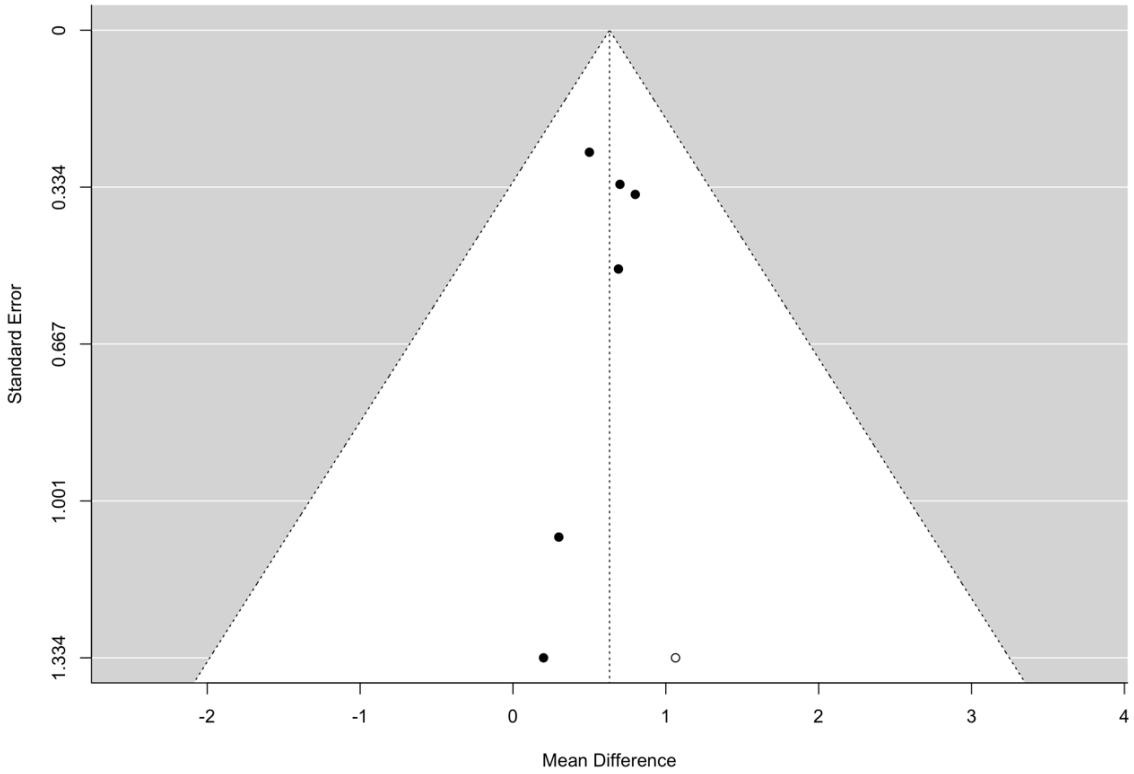


Figure 10 Risk of publication bias for FFMI in microsupplementation group. Open circles represent the potential missing studies identified using the Trim and Fill method.

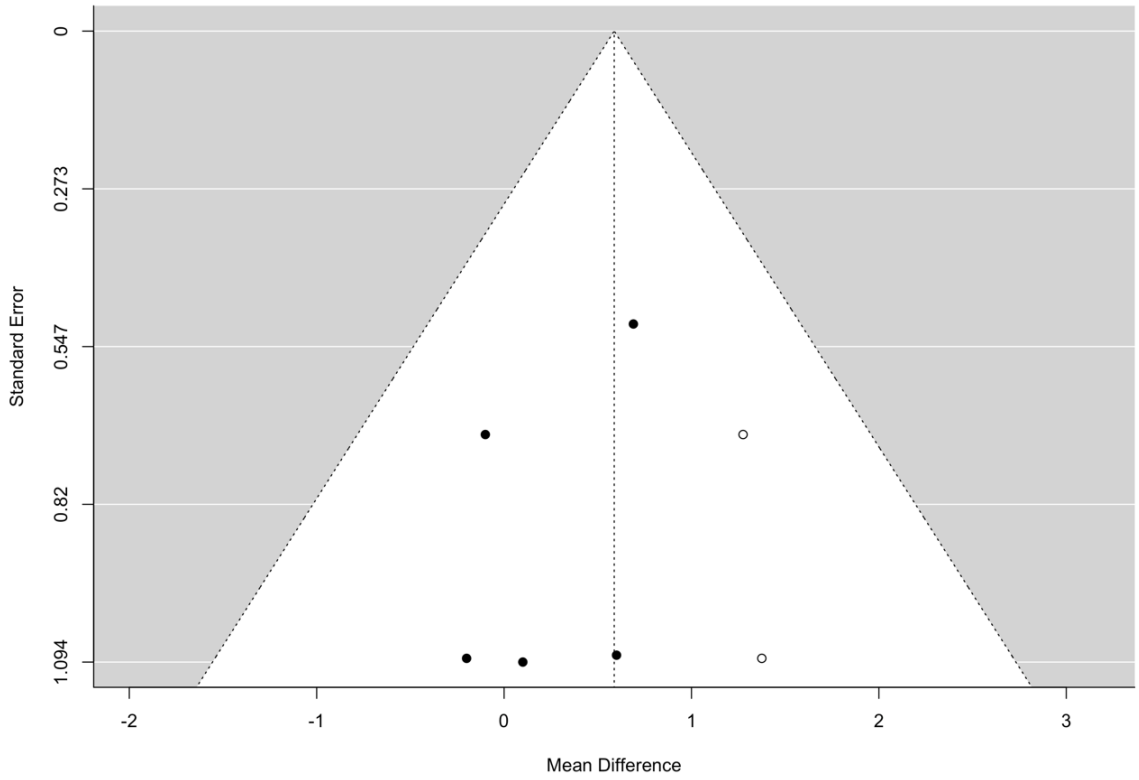


Figure 11 Forest plot of mean difference for FEV_1 in macrosupplementation (including aminoacids) group.

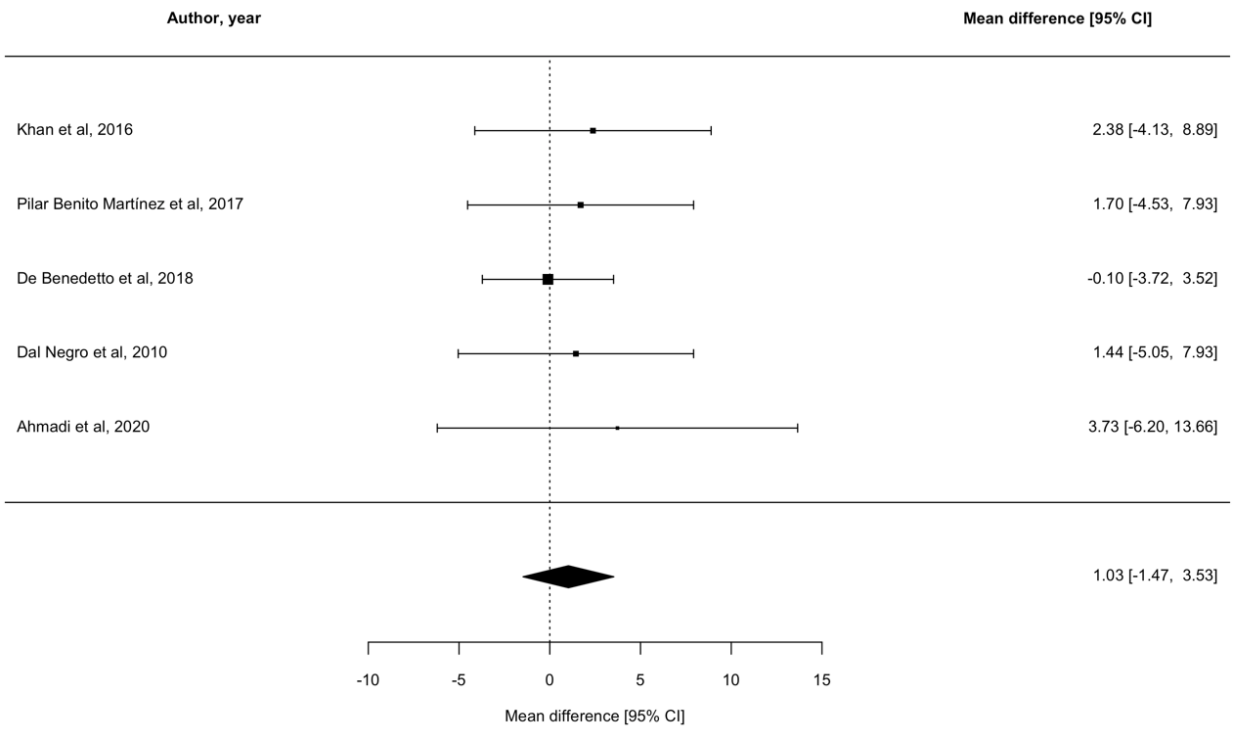


Figure 12 Risk of publication bias for FEV_1 in macrosupplementation (including aa) group. Open circles represent the potential missing studies identified using the Trim and Fill method.

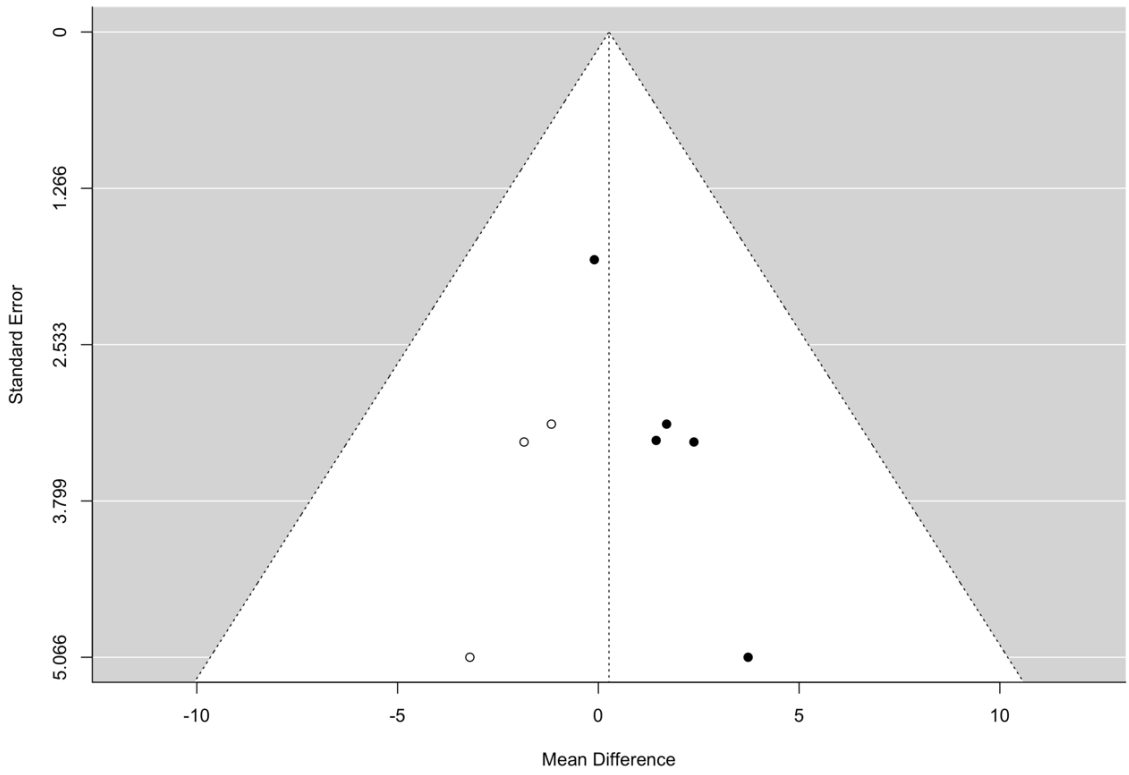


Figure 13 Forest plot of mean difference for FEV_1 in microsupplementation group.

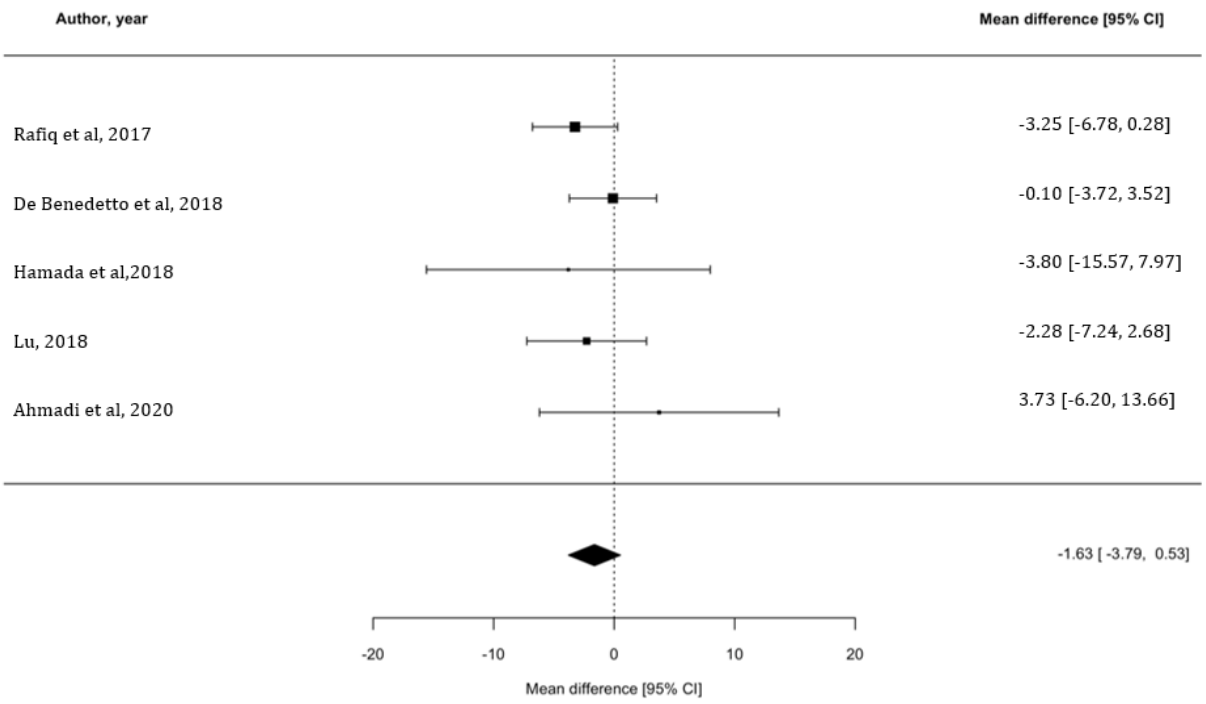


Figure 14 Risk of publication bias for FEV_1 in microsupplementation group. Open circles represent the potential missing studies identified using the Trim and Fill method.

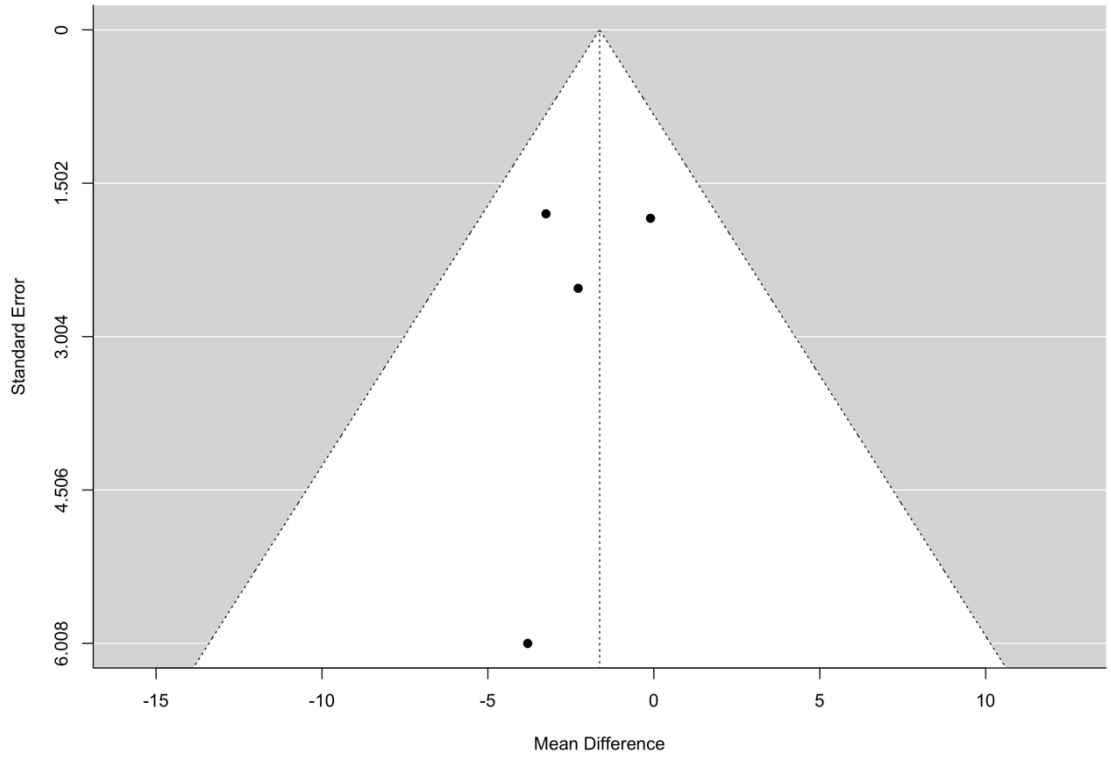


Figure 15 Risk of publication bias for 6MWT in macrosupplementation (including aminoacids) group. Open circles represent the potential missing studies identified using the Trim and Fill method.

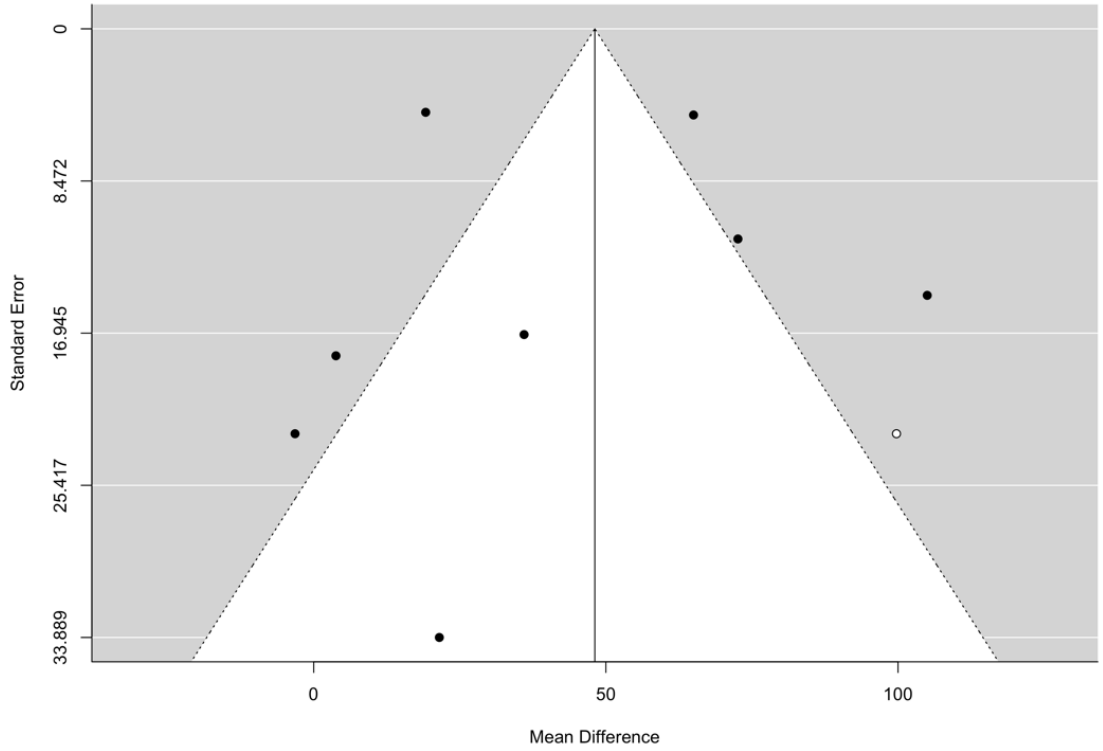


Figure 16 Risk of publication bias for 6MWT in macrosupplementation (excluding aminoacids) group. Open circles represent the potential missing studies identified using the Trim and Fill method.

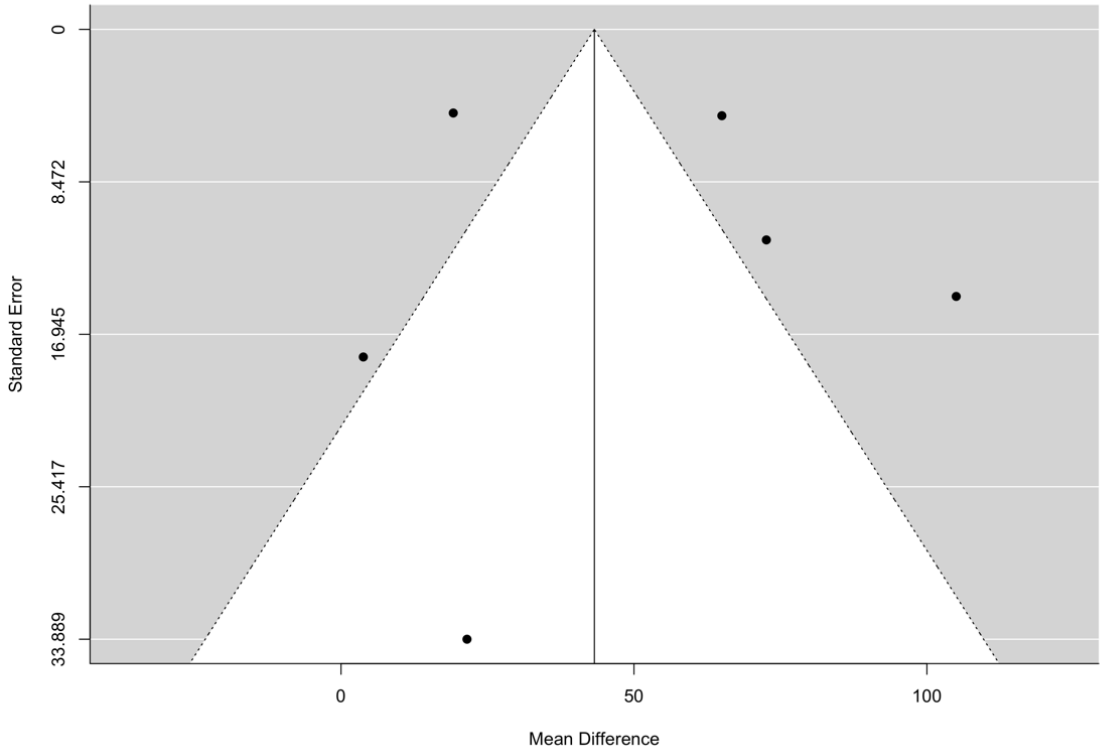


Figure 17 Forest plot of mean difference for 6MWT in microsupplementation group.

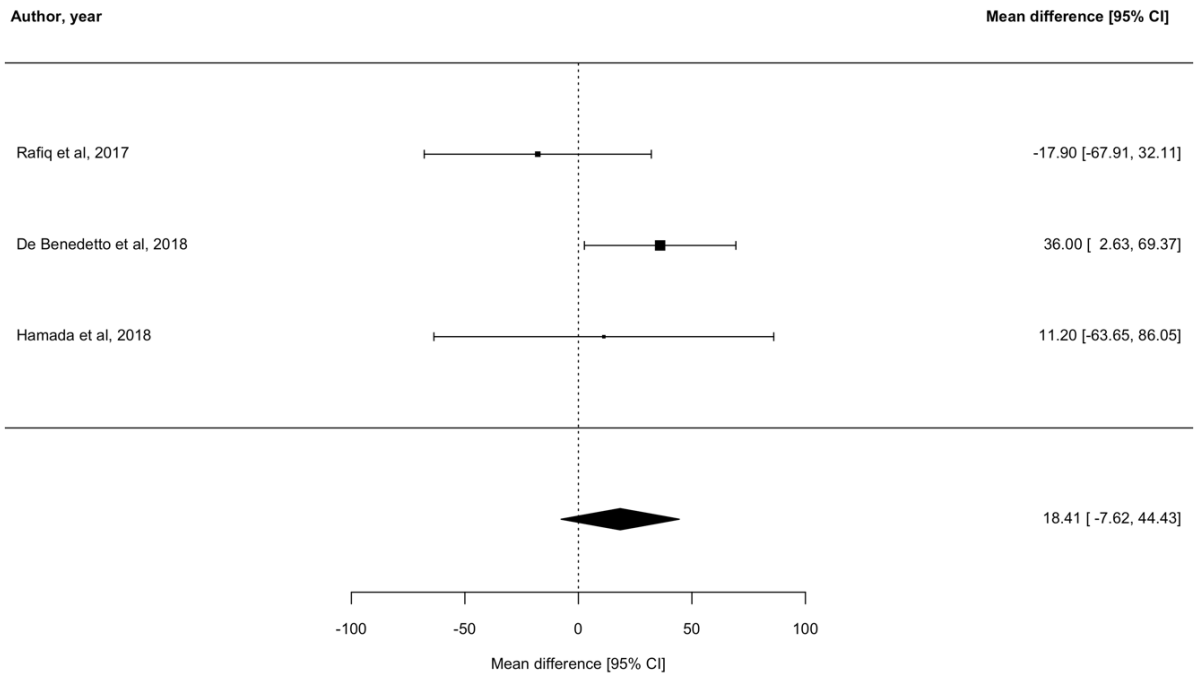


Figure 18 Risk of publication bias for 6MWT in microsupplementation group. Open circles represent the potential missing studies identified using the Trim and Fill method.

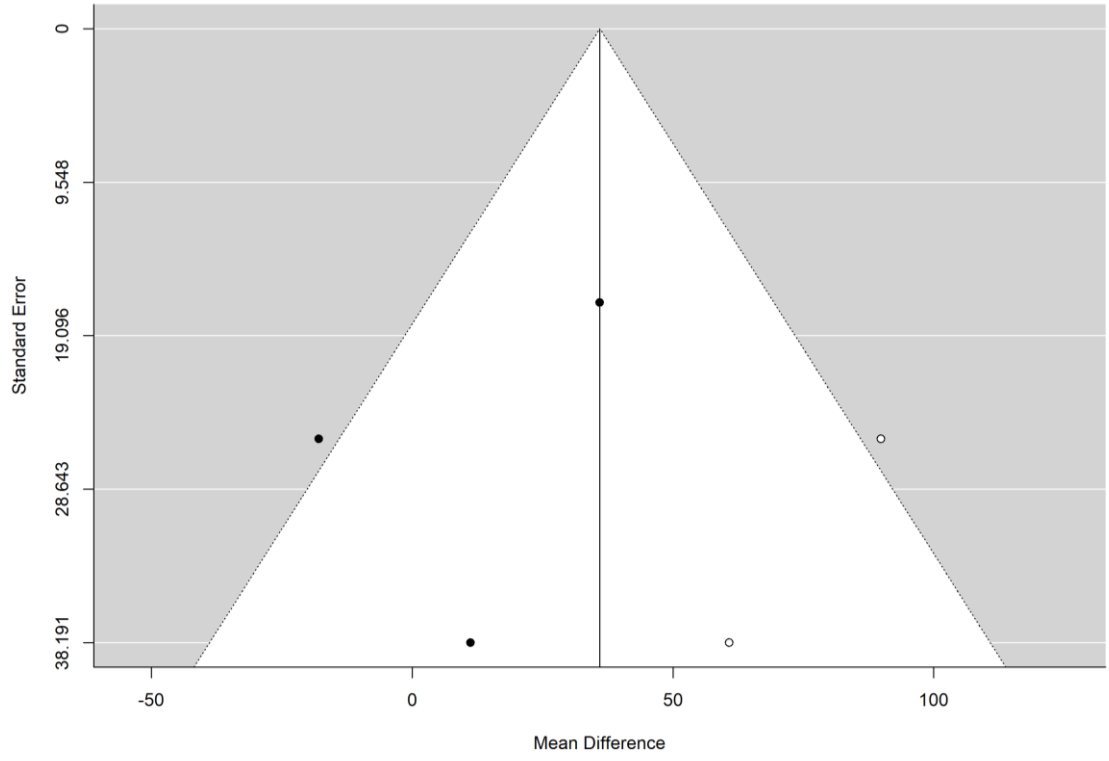


Figure 19 Risk of publication bias for QoL in macrosupplementation (including aminoacids) group. Open circles represent the potential missing studies identified using the Trim and Fill method.

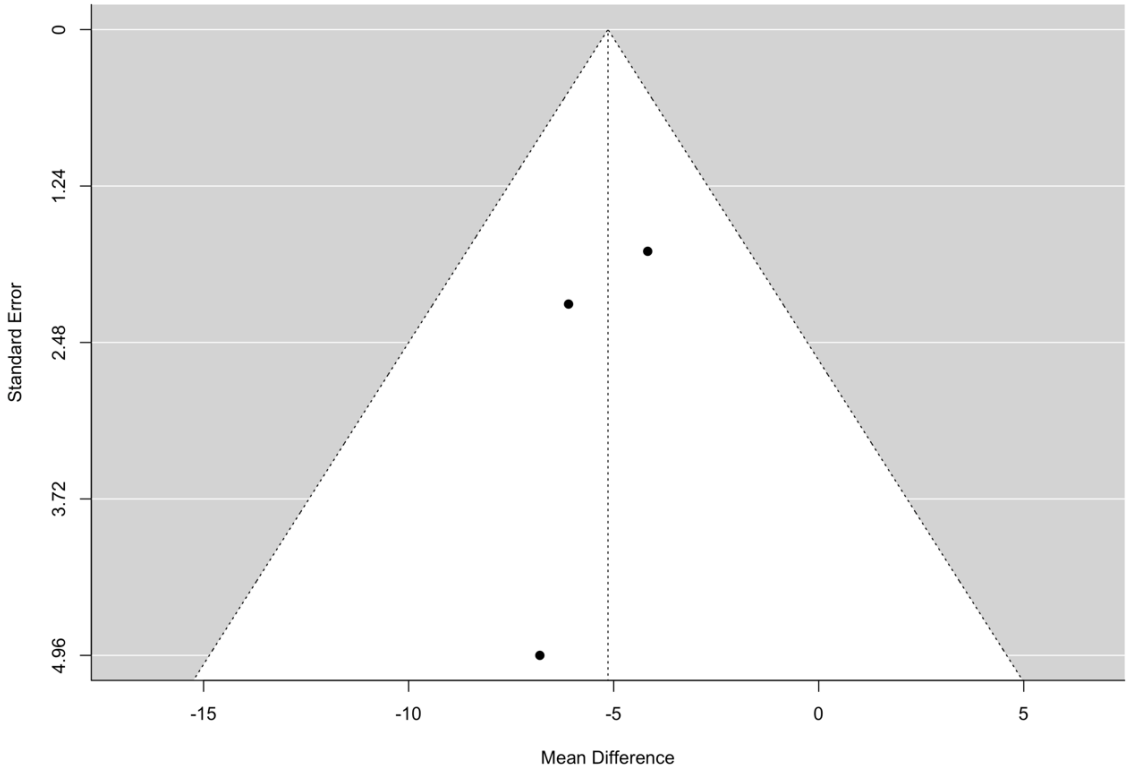
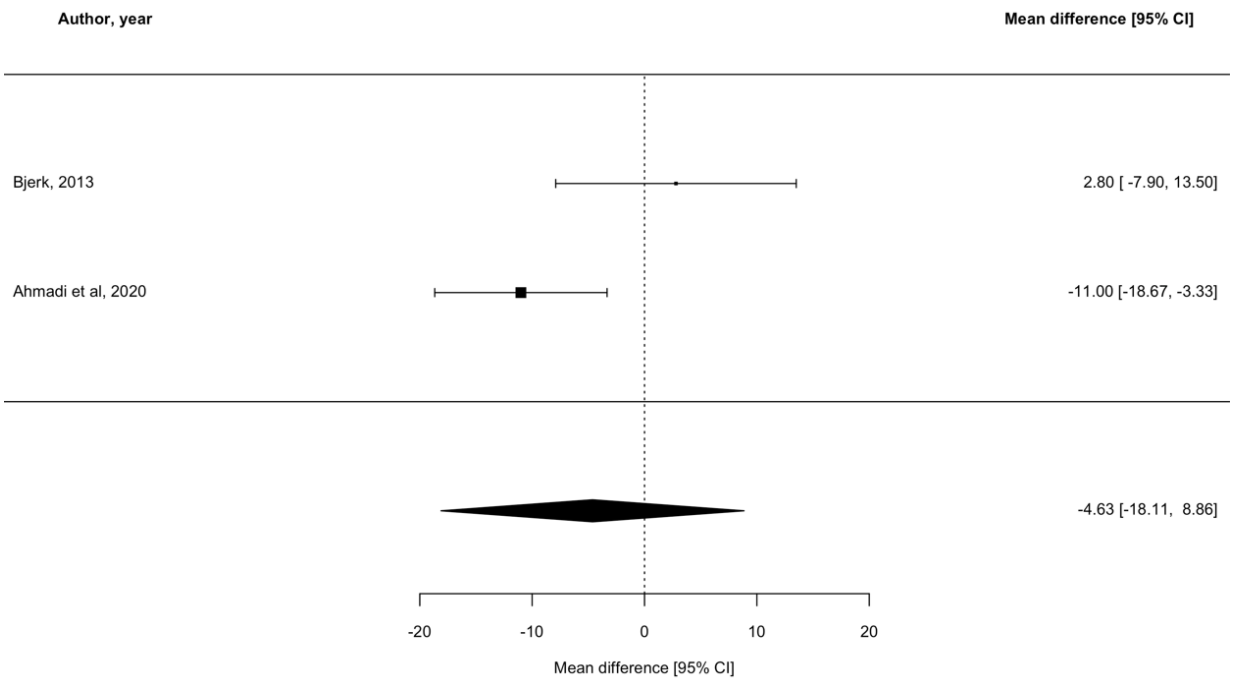


Figure 20 Forest plot of mean difference for QoL in microsupplementation group.



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GENERAL DISCUSSION AND PERSONAL CONSIDERATIONS

Undernutrition in COPD patients is an underestimated problem although it can lead to severe consequences both for the development and prognosis of the disease and for the healthcare system. Whilst the negative impact of lung function impairment on patients' survival and symptom burden has been widely clarified [1], body weight and body composition abnormalities in COPD have attracted few attention, considered for years a consequence rather than an independent determinant of patients' survival and quality of life. Nowadays, evidence about the importance of nutritional assessment and support is increasing and the effectiveness of nutritional support, at least in malnourished COPD patients, is clear with a demonstrated positive effects on body weight, fat and fat-free mass [2]

Despite that, it is not easy to identify patients at risk of undernutrition due to the bidirectional link with the disease.

In this context, the best management of COPD patients still remains unclear and leaves unresolved some questions: are predictive formulas suitable to establish the resting energy expenditure (REE) in COPD population? Is it possible to identify some clinical predictors able to recognize undernutrition prematurely? Are nutritional supplementations effective in the prevention or improvement of nutritional status and respiratory functions?

This thesis investigated these fields with the aim of highlight weaknesses and pitfalls in the screening and treatment of undernutrition in COPD patients.

The primary end-point was to evaluate the reliability of predicting formulas used for REE and to investigate to which extent the errors of REE predicting formulas affect the identification of an energy unbalance in COPD patients.

Although indirect calorimetry (IC) represents the gold standard for its measurement, its cost and the need of qualified technicians limit its use in the daily clinical practice, compelling clinicians to use

predictive equations not validated in COPD, like the Harris-Benedict (HB) or Moore-Angelillo (MA) [3,4].

In line with the previous literature [4], in *Chapter 2* it has been demonstrated that predictive formulas are unable to capture more than 50% of negatively unbalanced patients, therefore they should be discouraged in clinical practice especially in patients with an overt malnutrition.

In case of need or if IC is unavailable, the use of MA formula should be preferred to HB because of its tendency of overestimating rather than underestimating.

Given that the formulas lack for sensitivity in diagnosing undernutrition and being this latter highly prevalent in COPD patients, it would be of auspicial to identify predictive factors in the clinical setting of patients at risk of undernutrition.

Therefore, in *Chapter 3* the potential role of clinical predictors and instrumental variables collected during a routine respiratory assessment associate with undernutrition were investigated.

Previous studies have shown that the incidence of undernutrition increased as the disease severity of the patients increased [5], hence in our study patients underwent a multidimensional assessment including the use of Cumulative Illness Rating Scale (CIRS) to quantify the burden of chronic diseases [6] in addition to the evaluation of pulmonary function and nutritional status.

Our results show that clinical evaluation and pulmonary function tests are unable to reliably predict undernutrition in COPD patients, nevertheless they confirm that the severity, rather than the number of comorbidities, increases the risk of undernutrition by reducing the energy intake and increasing the REE.

Thus, as suggested by NICE guidelines [7], validated nutritional screening (e.g. Malnutrition Universal Screening Tool) should always be forecast in this population based on an accurate evaluation of energy intake and expenditure and body composition, but it is highly recommended in COPD patients with a CIRS severity index ≥ 0.45.

The previous steps of this thesis work aimed at identifying those COPD patients affected by undernutrion. Successively, it was investigated how undernutrition should be managed. The current available guidelines indicate to supplement patients with a low BMI (<20 kg/m^2) or in case of unintentional weight loss (>10% of body weight over 3-6 months), however the evidence on this topic is controversial, probably due to heterogeneity in the tested interventions.

Therefore, we performed a systematic review and meta-analysis of randomized controlled trials (RCTs) to investigate the effect of macro or micronutrients supplementation on nutritional status, physical functional capacity and quality of life in patients with COPD.

The results, that confirm the results reported by the latest meta-analysis available in literature [8], suggest that the use of macronutrients supplementation in COPD patients improves BMI, FFMI, exercise tolerance and quality of life, while it does not ameliorate respiratory function. Micronutrients supplementation alone did not improve any of the considered outcomes.

We can speculate that the reason for a poor response on respiratory function is due to an increased energy expenditure not correctly evaluated, as shown in *Chapter 2*, therefore not properly balanced by an adequate overall dietary intake. Thus, the nutritional intervention itself was not of sufficient magnitude to produce a positive effect. In fact, the multifactorial mechanism of respiratory disease in COPD prevented the supplementation from achieving positive effect on respiratory function since the obstructive alterations occurred overtime can not be modified by nutrition.

In general, macronutrients supplementation should be offered to COPD patients even if well-nourished, in order to avoid further weight loss, improve anthropometric parameters, quality of life, and exercise tolerance and prevent undernutrition.

In conclusion, undernutrition affects a high proportion of COPD patients and its association with increased exacerbation rates, hospital admission and costs and mortality requires that healthcare professionals include nutritional screening into the daily clinical practice.

Dietary advices and nutritional education can be of beneficial in the short term, providing for improved energy intake and correct balance of micro and macronutrients, however a more robust and patient's tailored nutritional assessment is desirable to constantly monitor the nutritional status and promptly adapt it to the variable COPD patient's phases.

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