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Obesity, Mediterranean Diet and Asthma

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LIST OF ORIGINAL PUBLICATIONS

The present thesis is based on the following studies:

STUDY I

Obesity and airway inflammation in asthma. Barros R., Moreira A., Fonseca J., Moreira P., Fernandes L., Ferraz de Oliveira J., Delgado L., Castel-Branco M.G. *J Allergy Clin Immunol 2006; 117(6):1501-2.*

STUDY II

Adherence to the Mediterranean diet and fresh fruit intake are associated with improved asthma control. Barros R., Moreira A., Fonseca J., Ferraz de Oliveira J., Delgado L., Castel-Branco M.G., Haahtela T., Lopes C., Moreira P. *Submitted publication*

LIST OF ORIGINAL PRESENTATIONS IN SCIENTIFIC MEETINGS RELATED TO THE DISSERTATION

Poster presentations

Body Mass Index Associated With Poor Asthma Control, Quality of Life but Decreased Exhaled Nitric Oxide. R. Barros, P. Moreira, A. Moreira, J.A. Fonseca, J. Ferraz de Oliveira, L. Delgado, M.G. Castel-Branco. World Allergy Congress - XXIV EAACI Annual Meeting, organized by European Academy of Allergy and Clinical Immunology (EAACI) and World Allergy Organization (WAO), July 2005, Munich, Germany;

[Overweigh and obesity in asthma – relationship with quality of life, asthma control and airway inflammation]. Barros R., Moreira P., Moreira A., Fonseca J., Ferraz de Oliveira J., Delgado L., Castel-Branco M.G. XXVI Annual Meeting of SPAIC [Portuguese Society of Allergology and Clinical Immunology], October 2005, Porto, Portugal;

Mediterranean diet and asthma severity. Barros R., Moreira A., Fonseca J., Ferraz de Oliveira J., Delgado L., Castel-Branco M.G., Lopes C., Moreira P. XXV EAACI Annual Meeting, June 2006, Vienna, Austria;

[Mediterranean diet and asthma severity]. Barros R., Moreira A., Fonseca J., Ferraz de Oliveira J., Delgado L., Castel-Branco M.G., Lopes C., Moreira P. XXVII Annual Meeting of SPAIC, October 2006, Porto, Portugal.

Oral presentation

Mediterranean diet may have a protective role in asthma. Barros R., Moreira A., Fonseca J., Ferraz de Oliveira J., Delgado L., Castel-Branco M.G., Lopes C., Moreira P. 1st World Congress of Public Health Nutrition, September 2006, Barcelona, Spain.

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ABBREVIATIONS

ACQ: Asthma control questionnaire
aMED: Alternate Mediterranean diet
ALQ: Asthma life quality test
ATS: American Thoracic Society
BMI: Body mass index
CI: Confidence interval
FEV1: Forced expiratory volume during the first second
FFQ: Food Frequency Questionnaire
ICS: Inhaled corticosteroid
IPAQ: International Physical Activity Questionnaire
MET: Standard metabolic equivalent
MLR: Multiple linear regression
MUFA: Monounsaturated fatty acids
LR: Linear regression
NO: Nitric oxide
PA: Physical activity
Ppb: Parts per billion
OR: Odds ratio
SD: Standard deviation
SFA: Saturated fatty acids
WHO: world health organization

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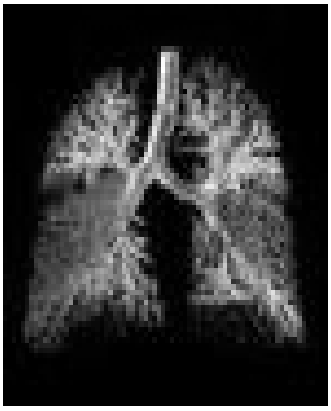
ABSTRACT



ABSTRACT

The increase of asthma prevalence in westernized societies has been suggested to be related to environment exposures and lifestyle changes in the last decades. The concurrent increase in the prevalence of obesity and asthma lead to the interest in potential mechanisms linking these two epidemics. Nevertheless, the evidence connecting obesity and asthma airways inflammation is still scarce. Dietary pattern changes, mainly in antioxidant micronutrients and fatty acids intake, have been furthermore associated with this trend. However the association between a whole healthy dietary pattern and asthma control is still lacking.

In this dissertation we aimed to investigate the associations between: obesity and asthma airway inflammation (study I); and adherence to the traditional Mediterranean dietary pattern and asthma control (study II).

A cross-sectional study of 297 non smoking patients, with medical diagnosis of asthma, recruited from an asthma and allergy outpatient clinic at a University Central Hospital, was performed. Exhaled nitric oxide (NO) (NIOX® system, Aerocrine, Sweden), forced expiratory volume in the 1st second (FEV_1) (PIKO-1®, Ferraris, UK), and height and weight (Mecanical balance with stadiometer, Seca model 700 ®, Germany) were measured. Body mass index (BMI) was calculated and defined according to the World Health Organization (WHO) BMI Classification. Atopy and inhaled corticosteroid (ICS) use were registered. General linear models (GLM) were fitted to estimate the association between BMI and exhaled NO, adjusted for confounders. One in five (20%) of the patients was obese, 38% overweight, 40% normal and 2% underweight. A negative association was found between BMI and exhaled NO (B= -0.032, 95%CI: -0.051 to -0.014; p= 0.001), independent of gender, atopy, FEV1 and ICS use. Considering overweight/obese patients, BMI was negatively associated with exhaled NO (B= -0.047, 95%IC: -0.077 to -0.017; p= 0.003); while in normal/underweight asthmatics no significant association was observed.

To investigate the association between the adherence to the mediterranean diet and asthma control, a cross sectional study was following developed in 174 adult patients. Study protocol

included exhaled NO, FEV1, and Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire scores assessment. Subjects were defined as “controlled”, in opposition to “non-controlled”, if simultaneously had FEV1 ≥80% of predicted, exhaled NO ≤ 35ppb, and ACQ score <1.0. Dietary intake was obtained by a semi-quantitative food frequency questionnaire and mediterranean dietary pattern was assessed by alternate Mediterranean Diet score (aMED score). BMI was calculated after anthropometric measurements and International Physical Activity Questionnaire score was assessed. Atopic status, rhinitis diagnosis, ICS use, education and smocking were registered. Multiple and logistic regression models were performed to estimate the association between adherence to Mediterranean diet and asthma outcomes, adjusting for confounders. Controlled asthmatics (23%) had significantly higher aMED score, dietary intake of fresh fruit, and lower intake of ethanol compared to non-controlled (77%).

In multiple regression models for asthma outcomes, higher aMED score was associated with decreased ACQ score; and higher intakes of nuts and of the ratio MUFA: SFA were respectively associated with increased lung function and exhaled NO. In logistic regression analysis, high adherence to the mediterranean diet reduced 78% the risk of non-controlled asthma, after adjusting for gender, age, education, ICS and energy intake. The higher consumption of fresh fruit decreased significantly the probability of having non-controlled asthma (OR=0.29; 95%CI=0.10 to 0.83; p-trend=0.015), while the higher intake of ethanol had the opposite effect (OR=3.16; 95%CI=1.10 to 9.11; p-trend=0.035). In conclusion, increased BMI was associated with decreased exhaled NO in overweight/ obese adult asthmatics, and high adherence to a healthy dietary pattern based on the traditional Mediterranean diet was associated with improved asthma control measured by symptoms, lung function and exhaled NO. Our findings provided additional support for the mechanical hypothesis linking obesity and asthma, and introduced a novel link between diet and asthma control, suggesting that adult patients might benefit from a nutritional approach based on mediterranean diet type.

Keywords: obesity, body mass index, airways inflammation, exhaled nitric oxide, asthma, control, nutrition, mediterranean diet.

RESUMO

O aumento da prevalência da asma nas sociedades ocidentais, observado nas últimas décadas, tem sido relacionado com alterações no ambiente e no estilo de vida. O aumento concomitante na prevalência da obesidade tem vindo a despertar um interesse crescente nos potenciais mecanismos que ligam as duas epidemias. No entanto, a evidência da ligação entre a obesidade e a inflamação das vias aéreas não está ainda esclarecida. A contribuição das alterações nos padrões alimentares nesta tendência, principalmente na ingestão nutricional de micro nutrimentos antioxidantes e de ácidos gordos, tem sido também questionada. No entanto, a associação entre um padrão alimentar saudável e o controlo da asma está ainda investigada.

A presente dissertação teve como objectivos investigar as associações entre: a obesidade e a inflamação das vias aéreas na asma (estudo I); e a adesão ao tradicional padrão alimentar Mediterrânico e o controlo da asma (estudo II).

Num estudo transversal, foram incluídos 297 utentes não fumadores, com diagnóstico médico de asma, seguidos na consulta de Imunoalergologia do Hospital Universitário de S. João. Foram realizadas as seguintes medições: óxido nítrico (NO) no ar exalado (NIOX® system, Aerocrine, Suécia); volume expiratório forçado no primeiro segundo (FEV_1) (PIKO-1®, Ferraris, Reino Unido); e peso e estatura corporais (balança mecânica com estadiómetro, modelo Seca 700 ®, Alemanha). O índice de massa corporal (IMC) foi calculado e categorizado de acordo com a classificação de IMC da Organização Mundial de Saúde. Foram recolhidas informações sobre a medicação com corticosteroide inalado (ICS) e atopia. A análise estatística incluiu modelos de regressão (GLM) para estimar a associação entre o IMC e o NO exalado, ajustados para variáveis confundidoras. Um quinto (20%) dos doentes tinha obesidade, 38% excesso de peso, 40% peso normal e 2% baixo peso. Observou-se uma associação negativa significativa entre o IMC e o NO exalado (B= -0.032, IC95%: -0.051 a -0.014; p= 0.001), independente do género, FEV1, atopia ou medicação com ICS.

Ao analisar os doentes com excesso de peso/ obesidade observou-se uma associação negativa entre o IMC e o NO exalado (B= -0.047, IC95%: -0.077 a -0.017; p= 0.003); enquanto para os asmáticos com peso normal ou baixo a associação não foi significativa.

Para investigar a associação entre a adesão à dieta Mediterrânica e o controlo da asma, foi desenvolvido um outro estudo transversal em 174 doentes. O protocolo do estudo incluiu as determinações do NO exalado, do FEV1, e das pontuações finais nos Questionários de Controlo da Asma (ACQ) e de Qualidade de Vida relacionada com a asma (ALQ). Os participantes foram classificados como "controlados", por oposição a "não-controlados", se simultaneamente tivessem FEV1 ≥ 80% do previsto, NO exalado ≤ 35ppb, e pontuação no ACQ <1.0. A ingestão alimentar foi avaliada através de um questionário semi-quantitativio de frquência de consumo alimentar e o padrão alimentar Mediterrânico através do índice *Alternate Mediterranean Diet score (aMED score)*. O IMC foi calculado após medições antropométricas, e determinou-se a pontuação final no questionário *International Physical Activity Questionnaire*. Foram ainda recolhidas informações sobre diagnóstico de rinite, atopia, medicação com ICS, educação e hábitos tabágicos. Para estimar a associação entre a adesão à dieta Mediterrânica e os outcomes da asma foram analisados modelos de regressão múltipla e logística, ajustados para variáveis confundidoras. Comparativamente aos doentes não-controlados (77%), os asmáticos controlados (23%) apresentavam uma ingestão de etanol significativamente inferior, e ingestão de fruta fresca e pontuação no índice aMED significativamente superiores.

Nos modelos de regressão linear múltipla para os *outcomes* da asma, uma maior pontuação no índice aMED estava associada a menor pontuação no ACQ; uma maior ingestão de frutos secos e um maior rácio MUFA: SFA estavam significativamente associadas a um aumento no FEV1 e no NO exalado, respectivamente. Na análise de regressão logística, uma maior adesão à dieta Mediterrânica reduziu 78% do risco de asma não controlada, após ajuste para o género, idade, educação, ICS e ingestão energética total. Uma maior ingestão de fruta fresca diminuiu significativamente a probabilidade de ter asma não controlada (OR=0.29; IC95% =0.10 a 0.83;

p-trend=0.015), enquanto uma maior ingestão de etanol teve o efeito contrário (OR=3.16; IC95%=1.10 a 9.11; p-trend=0.035).

Em conclusão, em adultos asmáticos com excesso de peso ou obesidade verificou-se que o aumento do IMC estava associado a menores níveis de NO no ar exalado; enquanto uma maior adesão a um padrão alimentar saudável, baseado na dieta mediterrânica tradicional, estava associada a um melhor controlo da asma, quando avaliado pelo NO exalado, função respiratória e sintomas. Os resultados encontrados nestes estudos suportam uma ligação entre a obesidade e a asma, com base na hipótese mecânica; e introduzem uma nova ligação entre a alimentação e o controlo da asma, sugerindo que uma abordagem nutricional baseada nos princípios da dieta Mediterrânica poderá beneficiar os asmáticos em idade adulta.

Palavras-chave: obesidade, índice de massa corporal, inflamação das vias aéreas, NO exalado, asma, controlo, nutrição, dieta mediterrânica.

GENERAL INTRODUCTION

GENERAL INTRODUCTION

Asthma overview

Asthma is a complex and chronic inflammatory disorder of the airways[1;2]. Despite there is no standard asthma definition, an operational description has been proposed by the Global Initiative for Asthma (GINA), based on the functional consequences of airway inflammation: *Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment[3].*

Asthma is one of the most common chronic pathological conditions throughout the world, with an estimated 300 million affected individuals and 250 thousand annual deaths [3]. The most up-to-date prevalence rates of asthma across Europe can be obtained from the International Study of Asthma and Allergies in Childhood (ISAAC)[4] and the European Community Respiratory Health Survey (ECRHS)[5]. Higher prevalence was observed in Western Europe countries. In Portugal these studies indicate a prevalence of asthma of 11.0% in children (6-7 years)[4], 11.8% in adolescents (13-14 years)[4] and 5.2% in adults (20-44 years)[5]. There is widespread concern that the prevalence of asthma is still rising in developed world. However, more recently a similar increase has been noted in developing countries, where asthma now represents an important problem. [1] In fact, some recent reviews [1;6] suggests that the prevalence of asthma in some areas of the Western world may have plateaued after increasing for decades, mainly due to a earlier detection and improved treatment of asthmatic patients.

Asthma represents a serious economic and social impact in health care systems and patient's quality of life. Despite advances in knowledge, management and treatment of this disease, asthma control still remains difficult to attain.[7] The temporal evolution and the remarkable variation in asthma prevalence between regions, countries or near geographically areas

suggest that environmental factors play a determinant role, even though gene-environment interactions could not be neglected.[8] Over the past 50th years lifestyle and environmental exposures have changed in westernized societies as a consequence of progress and modernization, and the capacity to provide protection against allergic diseases has started lacking. The increase in prevalence of asthma has stimulated research into which factors concerning to westernized lifestyle might be responsible and several hypothesis have been proposed [9-12]: changes in indoor environment and exposure to the house dust mite; hygiene and cleanliness, associated with reduced exposure to microorganisms and widespread antibiotic therapy, as highlighted by the "hygiene hypothesis"; increase in prevalence of obesity, associated with successive positive imbalances between total energy intake (dietary intake) and energy expenditure (physical activity); and changes in western dietary patterns and nutritional intake.

Obesity and asthma

The concomitant increase in the prevalence of obesity and asthma lead to the interest in potential mechanisms linking these two epidemics.[13] Obesity has also been proposed to be a risk factor for asthma [3]. Several cross-sectional and case-control studies have found obesity to be associated with asthma diagnosis, respiratory symptoms, poor lung function and increased airway hyperreactivity (AHR). [14] In addition, weight reduction in obese patients with asthma has been demonstrated to improve lung function, symptoms, morbidity, and health status [15].

Increases in body mass index (BMI) have been associated with increased prevalence of asthma, however the mechanisms behind this association are unclear[16]. Obesity has been recently suggested as a pro-inflammatory state [17] but the links with airway inflammation are still scarce. Plausible links between asthma and obesity include mechanical factors, inflammatory conditions and stress models. The increased abdominal and chest wall mass causes decreased functional residual capacity and reduced lung and tidal volumes. [18;19] Obesity is also a state of chronic and low-grade systemic inflammation with increased levels of the pro-inflammatory leptin and plasminogen activator inhibitor and decreased serum levels of the protective anti-

inflammatory adiponectin.[17] The relation between BMI and exhaled NO has provided conflicting evidence. In children, BMI had no association with exhaled NO [20-22], while in non-asthmatic and non-obese adults a positive association has been reported [23]. Recently, a case-control study described a positive association in normal weight and obese healthy adults, but no significant association was observed in asthma group. Although BMI was correlated with serum leptin levels in both groups, exhaled NO was not related also with serum leptin levels in asthmatic patients [24].

Nutritional factors, dietary patterns and asthma

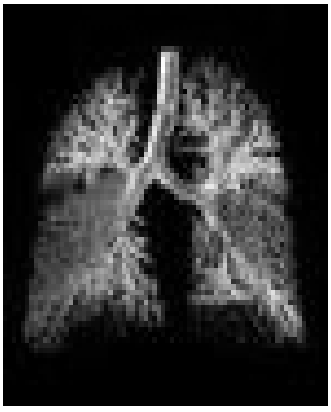
The prevalence of asthma and allergy has markedly increased in westernised countries since about 1960. Over these decades marked changes in dietary patterns were also observed, including a decreased intake of fresh fruit and vegetables, whole cereals, milk and fish [25-27], and an increased consumption of vegetable oils and margarines [28]. Evidence exists supporting that some of the observed increase in asthma could be at least partially explained by marked changes in dietary intake and nutritional factors [10;25;26;29], mainly in antioxidant micronutrients and fatty acids intake. Antioxidant[27] and lipid[30] hypotheses have been supported by several epidemiological studies that have been reported beneficial associations for nutritional factors including vitamin C [31-33], vitamin E [34;35], carotenoids [36;37], selenium [38], magnesium [39], manganese [33], and n-3 PUFA [32]. In addition, low serum levels of vitamin C were associated with adult asthma [33;40], while serum vitamin C, carotene, and selenium were associated with lower risk of prevalent asthma among youth [41]. However these findings are not conclusive [42-44], and intervention studies with single nutrients supplementation, such as vitamins E [45;46] and C [45;47;48], carotene[45], selenium[45], magnesium[47] and n-3 PUFA[49;50] have been disappointed. Beyond the difference in study designs and methods, the inconsistence in results might therefore reflect the complexity of dietary intake and the interactions between nutrients, foods and meals.

Inverse associations with asthma were observed also for dietary intake of whole foods, including citrus fruits[33], apples and pears[43;51;52]; tomato, carrots and leafy vegetables[51];

butter, whole milk[43] and non-pasteurized farm milk[53], suggesting that looking at the whole diet is an important shift in approaching the synergistic effects between nutrients and non-nutritive components of foods. In addition, a converse fast food dietary pattern was also currently associated with asthma in childhood[54]. However, studies addressing the associations between healthy dietary patterns and asthma are still lacking.

Mediterranean dietary pattern, traditional found in Mediterranean basin countries and some parts of Portugal, is recognised as a health–promoting dietary pattern[55;56], and is claimed to have antioxidant[57;58] and immunomodulator[59;60] properties in several chronic diseases, including CHD [59;61;62], HTA [63], cancer [64], diabetes [65], metabolic syndrome [66], arthritis rheumatoid [58] or Alzheimer's disease [67]. Mediterranean diet (MD) has been defined has as the dietary patterns found in olive-growing areas of Mediterranean region in the early 1960s and it was first described by Keys A. [68], after observing the longevity and the low incidence of mortality and morbidity by coronary heat disease and cancer in Mediterranean populations, comparing with Northern European Countries or United States [69]. Actually, a similar geographic north–south gradient has been observed also for asthma [1], with some Southern Europe Mediterranean countries, such as Greece or Albania, presenting the lowest prevalence of this disease. Despite their several variants, MD is characterized by: high intake of fruits, vegetables, pulses, whole grain cereals and nuts; high intake of unsaturated fatty acids (primarily as olive oil); low intake of meat and meat products; high intake of fish (depending on the proximity of the sea); moderate intake of dairy products (mostly cheese or yogurt); and a regular but moderate intake of ethanol (in the form of wine and generally during meals). Mediterranean diet appears to be a natural "cocktail" of many components reported as potentially protective for asthma. [10] Information on the relationship between adherence to a Mediterranean dietary pattern and the occurrence of asthma and atopy is scarce. In children, the intake of fruits, vegetables and nuts was recently associated with a beneficial effect on symptoms of asthma and rhinitis.[70;71] However, the effect of an adherence to a Mediterranean diet on asthma outcomes is unknown.

AIMS OF THE THESIS



AIMS OF THE THESIS

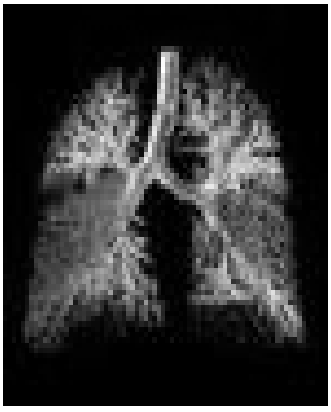
The general aim of this thesis was to study the association between obesity, Mediterranean diet and asthma outcomes, in adult asthmatic patients.

The specific aims were:

a. To investigate the association between obesity and airway inflammation *(Study I)*;

b. To investigate the association between adherence to the Mediterranean dietary pattern and asthma control *(Study II)*.

METHODS



METHODS

Data obtained during the research project has led to the studies I and II.

In this section a global approach of the methods developed in the research project will be described.

Participants and studies design

Consecutive patients, older than 15 years old, attending an outpatient Asthma and Allergy clinic at a University Central Hospital, with medical diagnosis of asthma, were invited to participate in a cross-sectional study. The research protocol was applied between July 2004 and June 2005, and included asthma (airway inflammation, lung function, asthma control and related quality of life), anthropometric, dietary intake and physical activity assessments. The research project was approved by the institutional ethics committee and written informed consent was obtained by patients previous to inclusion.

In the study I, 297 patients were analysed (114 subjects firstly included in our research project, plus 183 subjects from a parallel study that has been developed at the same setting, and who presented similar demographic and clinical characteristics). Exclusion criteria were: smoking; acute illness in the last four weeks; or inability to comply with the measurement instruments.

In the study II, a total of 219 patients were invited to participate and 174 were included in the final analysis (21 were excluded due to not fill inclusion criteria, 9 due to dietary changes in the last 12 months, 8 due to incomplete data record, 4 were considered energy intake outliers, and 3 refused to participate). Exclusion criteria were: medical diagnosis of food allergy, changing of dietary patterns in the last 12 months; pregnancy; presence of diseases which involved specific nutritional therapy and dietary planning; acute illness in the last four weeks; or inability to comply with the measurement instruments.

Asthma assessment

Lung function was measured by determination of forced expiratory volume 1 second (FEV1) using the PIKO-1® (Ferraris Respiratory Europe Ltd, Hertford, UK), a low-cost and easy-to-use pocket-size electronic monitoring device. The PIKO-1® can be an adequate and helpful tool for objective screening and monitoring airway obstruction, showing good compliance, very good reproducibility and an excellent agreement with the conventional office Fleisch-type Pneumotachograph [72-74]. Patients were asked to perform a set of three technically acceptable manoeuvres and the highest FEV1 measurement (ranging from 0.15 to 9.99 litres) was registered and expressed as predicted percent. [75]

Exhaled nitric oxide (NO) was measured with the NIOX® system (Aerocrine, Stockholm, Sweden), using the online technique recommended by the American Thoracic Society (ATS)[76], at a flow rate of 50 ml per second. Repeated exhalations were performed up to a maximum of eight, until obtaining three reproducible measurements that agree within 10%. The mean exhaled NO of the 3 acceptable exhalations was calculated and expressed in parts per billion (ppb).

Asthma control score was measured by the self-administered Asthma Control Questionnaire (ACQ), developed by Juniper and Col [77]. The 7-item ACQ was designed to assess the adequacy of clinical asthma control in adults during the previous week, based on symptoms (night-time waking, symptoms on waking, limitation of daily activities, shortness of breath and wheeze), short–acting beta2-agonist use and FEV1% predicted. A 7-point scale (0=no impairment, 6= maximum impairment) was used and score was calculated as the mean of the 7 items, ranging from 0 (totally controlled) to 6 (severely uncontrolled).[77] The ACQ is recognised as a valid tool for measuring asthma control both in clinical practice and research, and also for identify ”well-controlled” and “not well-controlled” asthma patients. ACQ score was following transformed into a dichotomous categorical variable divided by median score (1.00), the same

crossover point recently proposed to classify patients as ”well-controlled asthma” (ACQ score < 1.00) and “not well-controlled asthma” (ACQ score ≥ 1.00).[78]

For the study II a composite asthma control score was defined by the combination of the measurements from FEV1, exhaled NO, and the Asthma Control Questionnaire (ACQ) score. Subjects were classified as having his asthma “controlled” if simultaneously had FEV1 equal or greater than 80% predicted[3], exhaled NO equal or below than 35ppb[79], and ACQ score below 1.00[78]. If any of these features was not present, subject were classified as “non-controlled” asthmatics.

Asthma quality of life was measured by the Asthma Life Quality Test (ALQ), developed by the American College of Allergy, Asthma and Immunology (ACAAI) and validated for the Portuguese population.[74] The self-administered ALQ, which has been shown to be a valid and helpful psychometric tool, includes 20 questions of dichotomous answer (yes/no) designed to assess 6 domains of asthma’s impact on patient’s life: activity and sleep; symptoms; triggers; unscheduled health care use; medication; and psychological. Total score was calculated as the sum of all affirmative responses, ranging from 0 to 20 (lower values indicate better asthma quality of life).

Anthropometry assessment

Body mass index (BMI) was calculated after body weight and height measurements with the subject lightly clothed and bare-footed, using a mechanical balance with stadiometer, Seca model 700® (Seca Headquarter, Hamburg, Germany). Weight and height were determined to the nearest 0.1 kilogram and 0.5 centimetres, respectively. BMI was calculated as weight (kilograms) divided by the square of height (metres). For the study I the WHO BMI Classification was used to define underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2) and obesity (≥30.0 kg/m^2) patients. [80]

Dietary intake and Mediterranean diet assessment

Dietary intake was obtained by a self-administered, semi-quantitative food frequency questionnaire (FFQ), validated for Portuguese adults by Lopes and col.[81;82] The FFQ is an 86-item questionnaire that assess usual dietary intake over the previous 12 months, including food groups and beverages. Food intake was calculated by weighting 1 of the 9 possibilities of frequency of consumption (from "never or less than 1 time per month", to "6 or more times a day"), by the weight of the standard portion size of the food-item. Energy and nutritional intake were estimated using an adapted Portuguese version of the nutritional analysis software Food Processor Plus® (ESHA Research Inc, Salem, Oregon, USA).

Mediterranean dietary pattern was assessed by alternate Mediterranean Diet Score [62], an adapted version of the original Mediterranean-Diet Scale[83], recently developed to use with FFQ. Alternate Mediterranean Diet Score (aMED) was based on dietary intake of 9 selected-items, including nutritional variables and food groups: pulses; vegetables; fresh fruits; nuts; whole grains; fish; red and processed meats; ethanol; and ratio of monounsaturated to saturated fat (MUFA:SFA). A value of 1 or 0 points was assigned to each of the 9 components, using the gender–specific median of study subjects as cut-off value; 1 point was given for intakes at or above the median and 0 points for intakes below, for almost all items; only red and processed meats intake less than median was criteria for 1 point. One point was also assigned for men with ethanol intake between 5 - 25 g/ day, and for women between 5 – 15 g/ day. Intakes bellows or above those cut-off values were criteria for 0 points. Adherence to the traditional Mediterranean diet was measured by total aMED score, ranging from 0 to 9 points; scores were categorised into tertiles corresponding to low, medium and high adherence.

Physical activity assessment

Physical activity (PA) was measured using the International Physical Activity Questionnaire (IPAQ), developed by an International Consensus Group from 12 Countries, including Portugal, for monitoring population physical activity and inactivity.[84] The short 7 days self-administered

version is a 7-item questionnaire that provides information about frequency and duration of four domains (sedentary activity, time spent walking and moderate- and vigorous-intensity physical activity). Physical activity within different domains was estimated by weighting the reported frequency (events per week) by duration (minutes per event) and by a standard metabolic equivalent (MET) level assigned to each type of activity (Walking = 3.3; Moderate-intensity PA = 4.0; and Vigorous-intensity PA = 8.0), defined as multiples of the resting metabolic rate. A combined total physical activity was computed as the sum of the activity domains scores (Total PA = Walking + Moderate-intensity PA + Vigorous-intensity PA) and reported as a continuous measure (Total PA score = total MET-min/ week).[84]

Additional data

Atopic status (defined by positive skin prick test to common aeroallergens); medical diagnosis of allergic rhinitis, current use of inhaled corticosteroid (ICS), education (≤ 4, 5 to 9, and ≥ 10 years) and smoking status (non-smoker, past smoker and current smoker) were also recorded.

Statistical analyses

The data analysis was performed using the statistical package SPSS ®, 12.0 version (SPSS Inc; Chicago, IL) and a 0.05 level of significance (p-value) and 95% confidence intervals (95%CI) were considered.

In the study I, descriptive analysis has included mean (SD) and proportions (%). Exhaled NO was logarithmical transformed to attain normal distribution and expressed as geometric mean and 95% confidence intervals. Spearman correlation and linear regression were fitted to estimate the association between BMI and exhaled NO, and general linear model (GLM) was performed to investigate this effect after controlling for confounders (gender, age, FEV_1, atopy and ICS use).

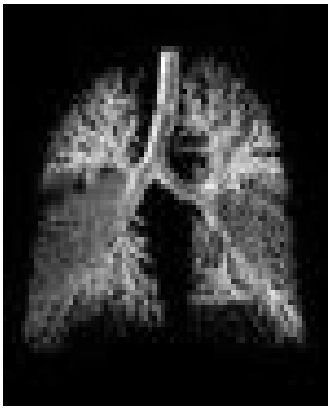
In the study II, mean (SD), proportions (%) and median (range) were used as descriptive statistics. Given de non-normal distribution of energy expenditure in many populations, physical activity data were presented as median (range), as proposed by the IPAQ Research Committee. Mediterranean dietary items were also presented as median range, as proposed by the original mediterranean diet score. Exhaled NO was logarithmical transformed to attain normal distribution and expressed as geometric mean and 95% confidence intervals. Energy intake outliers were previously excluded from the study and were defined as energy intake values above arithmetic mean + 2 standard deviations (SD) and implausible low intakes below than 500 kilocalories (kcal) for women and 800 kcal for men. Exhaled NO, FEV1 % predicted, ALQ and ACQ scores were analysed as dependent numeric variables. Ratio MUFA: SFA and ethanol were adjusted for total energy intake by nutrient residual model, as proposed by Willet WC. [27]

The associations between Mediterranean diet and asthma outcomes were performed using linear regression, multiple linear regression and logistic regression models. Linear regression was initially fitted to analyse the associations between absolute Mediterranean dietary items and score (independent variables) and the asthma outcomes (dependent variables). Multiple regression models were performed separately for exhaled NO, FEV1, ALQ and ACQ scores to analyse the effect of Mediterranean diet after adjusting for confounders (categorical confounder variables were transformed into dummy variables). Logistic regression models were also performed to analyse the associations between Mediterranean dietary items and score and asthma control level (controlled asthma and non-controlled). Mediterranean dietary items and score were categorised into tertiles, corresponding to the dietary intake and score values of 33- and 66 percentiles. Odds ratios (OR) were calculated by reference with the lowest tertile. Considering that Mediterranean score was obtained through all the dietary items, all the regression models were fitted separately for aMED score and each aMED dietary item.

Gender, education, age, total energy intake, body mass index, total physical activity score, smoking status, atopy, rhinitis medical diagnosis and current use of inhaled corticosteroid were

all first analysed as potential confounders of asthma outcomes. Only the variables significantly associated with each of the asthma outcome, in univariated analysis, were considered confounders in the respective final models. Considering that in this sample smoking status and physical activity were not significant associated with exhaled NO, FEV1, ALQ or ACQ scores, and that their inclusion in the models did not influenced the effects, these variables were therefore not included in presented models. Gender, age and total energy intake were considered in all models, considering the biological plausibility related also with dietary intake.

STUDIES



STUDY I

Obesity and airway inflammation in asthma

Barros R., Moreira A., Fonseca J., Moreira P., Fernandes L., Ferraz de Oliveira J., Delgado L., Castel-Branco M.G.

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sensitized subjects. Allergists thus need to be aware of such potential allergens to which patients may be exposed in routine medical procedures.

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Obesity and airway inflammation in asthma

To the Editor:

The concurrent increase in the prevalence of obesity and asthma leads to the interest in potential mechanisms linking these 2 epidemics.[1] Obesity has been recently suggested as a proinflammatory state,[2] but the links with airway inflammation are still scarce. Our study aimed to investigate the association between overweight or obesity assessed by the body mass index (BMI) and asthma airway inflammation assessed by exhaled nitric oxide (F_{ENO}), a simple, quick, noninvasive, and highly reproducible surrogate marker of airway inflammation that could enhance diagnosis and management of asthma.

After informed consent, 297 nonsmoking patients, age 15 to 73 years, with a medical diagnosis of asthma were recruited from an asthma and allergy outpatient clinic at University Central Hospital in Porto. The study protocol included F_{ENO} measurement using the online technique with the NIOX system (Aerocrine, Stockholm, Sweden)[3]; FEV_1 determination using PIKO-1 (Ferraris Respiratory, Hertford, United Kingdom)[4]; and body weight and height anthropometric measurements using a mechanical balance with stadiometer (Seca model 700; Seca, Hamburg, Germany) followed by BMI determination (weight/height^2). The World Health Organization BMI Classification was used to define underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obesity (≥30.0 kg/m^2).[5] Atopy, defined by skin prick test to common aeroallergens, and inhaled corticosteroid use were registered. The data analysis was performed by using the statistical package SPSS, 12.0 version (SPSS Inc, Chicago, Ill). F_{ENO} was logarithmically transformed to attain normal distribution. Spearman correlation, linear regression, and general linear model were fitted to estimate the association between BMI and F_{ENO} and the effect after adjusting for age, FEV_1, sex, atopy, and inhaled corticosteroid use. A .05 level of significance and 95% CIs were considered.

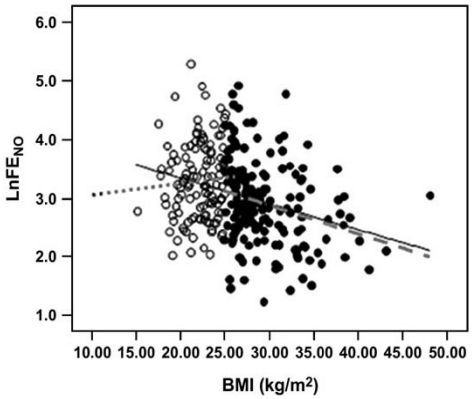

FIG 1. Association between BMI (kg/m^2) and F_{ENO} (ppb) in patients with asthma. (...) Normal/underweight regression line (R^2 – 0.004); (_ _) overweight/obese regression line (R^2 – 0.074); (__) all patients regression line (R^2 – 0.094). (○) Normal/underweight patients with asthma; (●) overweight/obese patients with asthma. *LnF_{ENO}*, F_{ENO} logarithmically transformed.

Subjects' mean (SD) age was 39 (15.1) years, 76% (n = 226) were female, 55% were atopic, and the mean (SD) percent predicted FEV_1 was 85.7 (20.5). Geometric mean (95% CI) of F_{ENO} was 30.6 (27.9-33.6) and of BMI was 26.0 (25.4-26.5). One in 5 (20%) of the patients was obese, 38% were overweight, 40% were normal, and 2% underweight. Spearman correlation and linear regression analysis showed a negative association between mean BMI and mean F_{ENO} ($r_s = -0.329$, $P < .001$; B = −0.044; 95% CI, −0.060 to −0.028; P < .001). A different relationship was noted between overweight or obese patients with asthma with the others. In normal weight/underweight patients with asthma, no association between BMI and F_{ENO} ($r_s = -0.061$, $P = .499$; B = 0.019; 95% CI, −0.039 to 0.077; $P = .511$) was found. In overweight or obese patients with asthma, a significant negative association with F_{ENO} ($r_s = -0.307$, $P < .001$; B = −0.049; 95% CI, −0.075 to −0.023; $P < .001$) was observed (Fig 1). By general linear model analysis, BMI maintained the negative association with F_{ENO} (B = −0.032, 95% CI, −0.051 to −0.014; $F = 11.75$, $P = .001$) after adjustment for age, FEV_1, sex, atopy, and inhaled corticosteroid use. Age was also negatively associated with F_{ENO} (B = −0.014; 95% CI, −0.020 to −0.008; $F = 18.10$, P < .001). In overweight or obese patients with asthma, BMI (B = −0.047, 95% CI, −0.077 to −0.017; $F = 9.38$, $P = .003$) and age (B = −0.013, 95% CI, −0.022 to −0.003; $F = 6.23$, $P = .014$) maintained a significant

negative association with FE_{NO}. In normal weight/underweight patients with asthma, only age affected FE_{NO} (B = −0.017, 95% CI, −0.026 to −0.008; $F = 13.89$, $P < .001$).

We observed a negative association between BMI and FE_{NO} in overweight or obese patients with asthma, independent from sex, atopy, lung function, or corticosteroid use. Despite the adjusting to these main confounders, we cannot exclude the hypotheses that FE_{NO} measurement could be affected by others factors that cannot have been controlled.

Several cross-sectional and case-control studies have found obesity to be associated with asthma diagnosis, respiratory symptoms, poor lung function, and increased airway hyperreactivity. Plausible links between asthma and obesity include mechanical factors, inflammatory conditions, and stress models. The increased abdominal and chest wall mass causes decreased functional residual capacity and reduced lung and tidal volumes.[6,7] Obesity is also a state of chronic and low-grade systemic inflammation with increased levels of the proinflammatory leptin and plasminogen activator inhibitor and decreased serum levels of the protective anti-inflammatory adiponectin.[3] The relation between BMI and FE_{NO} has provided conflicting evidence. In children, BMI had no association with FE_{NO},[8-10] whereas in 24 nonobese adults without asthma, a positive association has been reported.[11] Recently, a case-control study described a positive association in normal weight and obese healthy adults, but no significant association was observed in the asthma group. Although BMI was correlated with serum leptin levels in both groups, FE_{NO} was not related to serum leptin levels in patients with asthma.[12]

Our findings are based on cross-sectional data, and a causal relationship cannot be inferred. Although BMI is not the gold standard to assess body composition, it correlates with total body fat content and has been the most widely used measure to assess overweight or obesity and to monitor changes in body weight. In the future, research should include more complex anthropometric measures (eg, waist-circumference, skinfold thickness, or bioelectrical impedance analysis) that assess total body mass distribution, including body fat mass measure.

In conclusion, the observed negative association between BMI and FE_{NO} in overweight or obese patients with asthma provides additional support to the hypothesized mechanical link between obesity and asthma.

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Eosinophil β_1 integrin activation state correlates with asthma activity in a blind study of inhaled corticosteroid withdrawal

To the Editor:

Eosinophilic inflammation is a characteristic feature of asthma regulated by many factors, including treatment with corticosteroids.[1] On gradual inhaled corticosteroid (ICS) reduction, there is an increase in sputum eosinophils that often precedes changes in airway caliber and loss of asthma control.[2,3] Conversely, ICS treatment directed toward a reduction in sputum eosinophils improves asthma control and prevents exacerbations.[4] These and other reports suggest that eosinophils in the airway are associated with diminished asthma control and increased risk for exacerbation and that eosinophil recruitment to the airway likely is a key step in the development of bronchial inflammation and exacerbation.

Eosinophil recruitment to the airway involves integrins and their ligands.[5] $\alpha_4\beta_1$ Integrin mediates blood eosinophil adhesion to vascular cell adhesion molecule 1, preferentially induced on endothelium in response to T_H2

STUDY II

Adherence to the Mediterranean diet and fresh fruit intake are associated with improved asthma control.

Barros R., Moreira A., Fonseca J., Ferraz de Oliveira J., Delgado L., Castel-Branco M.G., Haahtela T., Lopes C., Moreira P.

Submitted publication

Adherence to the Mediterranean diet and fresh fruit intake are associated with improved asthma control

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Abstract

Background: Traditional Mediterranean diet is considered to promote health, and it is claimed to possess antioxidant and immune-regulatory properties.

Objective: To investigate the association between adherence to Mediterranean diet and asthma control.

Methods: Cross sectional study of 174 adult asthmatics, mean (SD) age of 40 (15) years. The patients were defined as “controlled”, in contrast to “non-controlled”, if they showed FEV1 ≥80% of predicted, exhaled nitric oxide ≤ 35ppb, and Asthma Control Questionnaire score <1. Dietary intake was obtained by a semi-quantitative food frequency questionnaire, and Mediterranean dietary pattern was assessed by alternate Mediterranean Diet Score. By logistic regression

models (adjusting for confounders) the association of adherence to Mediterranean diet and asthma control was estimated.

Results: Controlled asthmatics (23%) had significantly higher Mediterranean Diet Score (p=0.043), dietary intake of fresh fruit (p=0.024), and lower intake of ethanol (p=0.015) compared to non-controlled asthmatics (77%). In logistic regression analysis, high adherence to the Mediterranean diet reduced 78% the risk of non-controlled asthma after adjusting for gender, age, education, inhaled corticosteroids and energy intake (OR=0.22; 95%CI=0.05 to 0.85; p-trend = 0.028). The higher consumption of fresh fruit decreased significantly the probability of having non-controlled asthma (OR=0.29; 95%CI=0.10 to 0.83; p-trend=0.015), while the higher ingestion of ethanol had the opposite effect (OR=3.16; 95%CI=1.10 to 9.11; p-trend=0.035).

Conclusion: High adherence to traditional Mediterranean diet increased the likelihood of asthma to be under control.

Clinical implication: Adult asthmatics might benefit from a nutritional approach based on mediterranean type of diet.

Capsule summary:

The study introduces a novel link between diet and asthma control. High adherence to Mediterranean diet reduced by 78% the risk of uncontrolled asthma as measured by symptoms, lung function and exhaled nitric oxide.

Keywords: airway inflammation; exhaled nitric oxide; asthma; asthma control; cross-sectional; Mediterranean diet; quality of life; lung function; nutrition; physical activity

Abbreviations

ACQ: Asthma control questionnaire

aMED: Alternate Mediterranean diet

ALQ: Asthma life quality test

ATS: American Thoracic Society

BMI: Body mass index

CI: Confidence interval

FEV1: Forced expiratory volume during the first second

FFQ: Food Frequency Questionnaire

ICS: Inhaled corticosteroid

IPAQ: International Physical Activity Questionnaire

MET: Standard metabolic equivalent

MLR: Multiple linear regression

MUFA: Monounsaturated fatty acids

LR: Linear regression

NO: Nitric oxide

PA: Physical activity

Ppb: Parts per billion

PUFA: Polyunsaturated fatty acids

OR: Odds ratio

SD: Standard deviation

SFA: Saturated fatty acids

Introduction

Asthma is a chronic inflammatory disease that represents a serious economic and social impact in health care systems and patient's quality of life. Despite advances in knowledge, management and treatment of this disease, asthma control still remains difficult to attain. [1] The temporal evolution and the remarkable variation in asthma prevalence between regions, countries or near geographically areas suggest that environmental factors play a determinant role, even though gene-environment interactions should be, also, important. Published studies suggest that some of the observed increase could be, at least, partially explained by marked changes in dietary patterns over this time period, mainly in antioxidant micronutrients and fatty acids intake [2]. Nevertheless, intervention studies with supplementation of a single nutrient have been disappointing [3-5]. Looking at the whole diet is an important shift in approaching the synergistic effects between nutrients and non-nutritive components of foods, and their possible association with asthma control. Several studies reported that asthma outcomes were negatively associated with dietary intake of citrus fruits [6], apples, pears [7-9], tomato, carrots, leafy vegetables [7], butter, whole milk [9] and non-pasteurized farm milk [10], and positively associated with fast foods [11]. However, studies addressing the associations between healthy dietary patterns and asthma are still lacking.

In epidemiologic studies [12;13], the Mediterranean diet, a cultural model for healthy eating, has been associated with greater quality of life which was illustrated after examining the low incidence of mortality and morbidity by chronic diseases in Mediterranean populations, compared to USA or Northern European countries. Actually, a similar geographic north–south gradient has been observed also for asthma [14], with some Southern Europe Mediterranean countries, such as Greece or Albania, presenting the lowest prevalence of this disease. Despite their several variants, Mediterranean diet is characterized by: high intake of fruits, vegetables, pulses, whole grain cereals and nuts; high intake of unsaturated fatty acids, mainly from olive oil; low intake of meat and meat products; high intake of fish; moderate intake of dairy products, mostly cheese or yogurt; and a regular but moderate intake of ethanol [13]. Mediterranean diet appears to be a "cocktail" of many components reported as potentially protective for asthma.[2]

Information on the relationship between adherence to a Mediterranean dietary pattern and the occurrence of asthma and atopy is scarce. In children, the intake of fruits, vegetables and nuts was associated with a beneficial effect on symptoms of asthma and rhinitis [15;16]. However, the effect of an adherence to a Mediterranean diet on asthma outcomes is unknown.

Our study aimed to test the hypothesis that increased adherence to the Mediterranean diet might be associated with better asthma control in asthmatics adults.

Methods

Participants and study design

Consecutive 219 patients, older than 16 years old, attending an outpatient Asthma and Allergy clinic at a University Central Hospital, with medical diagnosis of asthma, were invited to participate in a cross-sectional study. The research protocol was applied between July 2004 and June 2005, and included anthropometric, physical activity, dietary intake and asthma assessments (airway inflammation, lung function, asthma control and related quality of life). Exclusion criteria were: food allergy, changing of dietary patterns in the last 12 months; pregnancy; presence of diseases which involved specific nutritional therapy and dietary planning; acute illness in the last four weeks; or inability to comply with the measurement instruments. From the total patients invited, 21 were excluded because did not fill inclusion criteria, 9 due to dietary changes in the last 12 months, 8 due to incomplete data record, 4 were considered energy intake outliers, and 3 refused to participate. The characteristics of excluded patients were similar to others, regarding to age, education, smoking status and asthma severity. Finally, 174 (81%) were included in the analysis. Atopic status (defined by positive skin prick test to common aeroallergens); medical diagnosis of allergic rhinitis, current use of inhaled corticosteroid (ICS), education (≤ 4, 5 to 9, and ≥ 10 years) and smoking status (non-smoker, past smoker and current smoker) were also recorded. The study was approved by the

institutional ethics committee and written informed consent was obtained by patients previous to inclusion.

Anthropometry, physical activity, dietary intake and Mediterranean diet assessment

Body mass index (BMI) was calculated after body weight and height measurements with the subject lightly clothed and bare-footed, using a mechanical balance with stadiometer, Seca model 700® (Seca Headquarter, Hamburg, Germany). Weight and height were determined to the nearest 0.1 kilogram and 0.5 centimetres, respectively. BMI was calculated as weight (kilograms) divided by the square of height (metres).

Physical activity (PA) was measured using the International Physical Activity Questionnaire (IPAQ), developed by an International Consensus Group from 12 Countries, including Portugal, for monitoring population physical activity and inactivity.[17] The short 7 days self-administered version is a 7-item questionnaire that provides information about frequency and duration of four domains (sedentary activity, time spent walking and moderate- and vigorous-intensity physical activity). Physical activity within different domains was estimated by weighting the reported frequency (events per week) by duration (minutes per event) and by a standard metabolic equivalent (MET) level assigned to each type of activity (Walking = 3.3; Moderate-intensity PA = 4.0; and Vigorous-intensity PA = 8.0), defined as multiples of the resting metabolic rate. A combined total physical activity was computed as the sum of the activity domains scores (Total PA = Walking + Moderate-intensity PA + Vigorous-intensity PA) and reported as a continuous measure (Total PA score = total MET-min/ week).[17]

Dietary intake was obtained by a self-administered, semi-quantitative food frequency questionnaire (FFQ), validated for Portuguese adults by Lopes and col.[18] The FFQ is an 86-item questionnaire that assess usual dietary intake over the previous 12 months, including food groups and beverages. Food intake was calculated by weighting 1 of the 9 possibilities of

frequency of consumption (from “never or less than 1 time per month”, to “6 or more times a day”), by the weight of the standard portion size of the food-item. Energy and nutritional intake were estimated using an adapted Portuguese version of the nutritional analysis software Food Processor Plus® (ESHA Research Inc, Salem, Oregon, USA).

Mediterranean dietary pattern was assessed by alternate Mediterranean Diet Score [19], an adapted version of the original Mediterranean-Diet Scale [20], recently developed to use with FFQ. Alternate Mediterranean Diet Score (aMED) was based on dietary intake of 9 selected-items, including nutritional variables and food groups: pulses; vegetables; fresh fruits; nuts; whole grains; fish; red and processed meats; ethanol; and ratio of monounsaturated to saturated fat (MUFA:SFA). A value of 1 or 0 points was assigned to each of the 9 components, using the gender–specific median of study subjects as cut-off value; 1 point was given for intakes at or above the median and 0 points for intakes below, for almost all items; only red and processed meats intake less than median was criteria for 1 point. One point was also assigned for men with ethanol intake between 5 - 25 g/ day, and for women between 5 – 15 g/ day. Intakes bellows or above those cut-off values were criteria for 0 points. Adherence to the traditional Mediterranean diet was measured by total aMED score, ranging from 0 to 9 points; scores were categorised into tertiles corresponding to low, medium and high adherence.

Asthma control and quality of life: definitions and assessment

Asthma Control was defined by the combination of the results from FEV1, exhaled NO, and the Asthma Control Questionnaire (ACQ) score. Subjects were classified as having his asthma “controlled” if simultaneously had FEV1 equal or greater than 80% predicted (21), exhaled NO equal or below than 35ppb [22], and ACQ score below 1.00 [23]. If any of these features was not present, subject were classified as “non-controlled” asthmatics.

Lung function was measured by determination of forced expiratory volume 1 second (FEV1) using the PIKO-1® (Ferraris Respiratory Europe Ltd, Hertford, UK). Patients were asked to perform a set of three technically acceptable manoeuvres and the highest FEV1 measurement (ranging from 0.15 to 9.99 litres) was registered and expressed as predicted percent.

Exhaled nitric oxide (NO) was measured with the NIOX® system (Aerocrine, Stockholm, Sweden), using the online technique recommended by the American Thoracic Society (ATS) [24], at a flow rate of 50 ml per second. Repeated exhalations were performed up to a maximum of eight, until obtaining three reproducible measurements that agree within 10%. The mean exhaled NO of the 3 acceptable exhalations was calculated and expressed in parts per billion (ppb).

The 7-item ACQ was designed to assess the adequacy of clinical asthma control in adults during the previous week, based on symptoms (night-time waking, symptoms on waking, limitation of daily activities, shortness of breath and wheeze), short–acting beta2-agonist use and FEV1% predicted. A 7-point scale (0=no impairment, 6= maximum impairment) was used and score was calculated as the mean of the 7 items, ranging from 0 (totally controlled) to 6 (severely uncontrolled).[25] The ACQ is recognised as a valid tool for measuring asthma control both in clinical practice and research, and also for identify ”well-controlled” and “not well-controlled” asthma patients. ACQ score was following transformed into a dichotomous categorical variable divided by median score (1.00), the same crossover point recently proposed to classify patients as”well-controlled asthma” (ACQ score < 1.00) and “not well-controlled asthma” (ACQ score ≥ 1.00). [23]

Asthma quality of life was measured by the Asthma Life Quality Test (ALQ), developed by the American College of Allergy, Asthma and Immunology (ACAAI) and validated for the Portuguese population.[26] The self-administered ALQ, which has been shown to be a valid and

helpful psychometric tool, includes 20 questions of dichotomous answer (yes/no) designed to assess 6 domains of asthma's impact on patient's life: activity and sleep; symptoms; triggers; unscheduled health care use; medication; and psychological. Total score was calculated as the sum of all affirmative responses, ranging from 0 to 20 (lower values indicate better asthma quality of life).

Statistical analyses

Mean (SD), proportions (%) and median (range) were used as descriptive statistics. Given de non-normal distribution of energy expenditure in many populations, physical activity data were presented as median (range), as proposed by the IPAQ Research Committee. Energy intake outliers were previously excluded from the study and were defined as energy intake values above arithmetic mean + 2 standard deviations (SD) and implausible low intakes below than 500 kilocalories (kcal) for women and 800 kcal for men. Exhaled NO, FEV1 % predicted, ALQ and ACQ scores were analysed as dependent numeric variables. Exhaled NO was logarithmical transformed to attain normal distribution and presented as geometric mean and 95% confidence intervals. Ratio MUFA: SFA and ethanol were adjusted for total energy intake by nutrient residual model, as proposed by Willet WC.[27]

The associations between Mediterranean diet and asthma outcomes were performed using linear regression, multiple linear regression and logistic regression models. Linear regression was initially fitted to analyse the associations between absolute Mediterranean dietary items and score (independent variables) and the asthma outcomes (dependent variables). Multiple regression models were performed separately for exhaled NO, FEV1, ALQ and ACQ scores to analyse the effect of Mediterranean diet after adjusting for confounders (categorical confounder variables were transformed into dummy variables).

Logistic regression models were also performed to analyse the associations between Mediterranean dietary items and score and asthma control level (controlled asthma and non-

controlled). Mediterranean dietary items and score were categorised into tertiles, corresponding to the dietary intake and score values of 33-and 66 percentiles. Odds ratios (OR) were calculated by reference with the lowest tertile. Considering that Mediterranean score was obtained through all the dietary items, all the regression models were fitted separately for aMED score and each aMED dietary item.

Gender, education, age, total energy intake, body mass index, total physical activity score, smoking status, atopy, rhinitis medical diagnosis and current use of inhaled corticosteroid were all first analysed as potential confounders of asthma outcomes. Only the variables significantly associated with each of the asthma outcome, in univariated analysis, were considered confounders in the respective final models. Considering that in this sample smoking status and physical activity were not significant associated with exhaled NO, FEV1, ALQ or ACQ scores, and that their inclusion in the models did not influenced the effects, these variables were therefore not included in presented models. Gender, age and total energy intake were considered in all models, considering the biological plausibility related also with dietary intake. A 0.05 level of significance (p-value) and 95% confidence intervals (95%CI) were considered. The data analysis was performed using the statistical package SPSS ®, 12.0 version (SPSS Inc; Chicago, IL).

Results

Based on the asthma control definition, 23% and 77% of the subjects were classified, respectively, as having controlled and non-controlled asthma. Demographic, clinical, and lifestyle data, namely physical activity and dietary intake, according to asthma control are presented in table1. Controlled asthmatics had significantly higher mean aMED score (p=0.043), dietary intake of fresh fruit (p=0.024), and lower intake of ethanol (p=0.015) compared to non-controlled. No further significant differences were observed for the other aMED nutritional and dietary items, including energy intake, between controlled and non-controlled subjects.

Table 2 summarizes the results of linear regression models between aMED and asthma outcomes, adjusting for confounders. In the multiple regression analysis, after adjusting for gender, age, education, inhaled steroids use and energy intake, Mediterranean diet score was significantly and negatively associated with ACQ score. Considering the aMED dietary items, significant positive associations were observed between monounsaturated to saturated fatty acids ratio (MUFA: SFA) and exhaled NO, and nuts and FEV1, even after adjustment for confounders. Dietary intake of ethanol was associated with increased ACQ score; however, after adjusting for confounders this association was no longer significant.

Table 3, figure 1 show logistic regression models, between tertiles of aMED score and dietary items, and asthma control, considering the adjustment for confounders. Asthmatics with high adherence to Mediterranean diet had a 78% reduction risk of having non-controlled asthma compared to those with low adherence, after controlling for gender, age, education, ICS and energy intake (OR=0.22; 95%CI=0.05 to 0.85; p-trend = 0.028). The higher consumption of fresh fruit decreased significantly the probability of having non-controlled asthma (OR=0.29; 95%CI=0.10 to 0.83; p-trend=0.015) while the higher ingestion of ethanol had the opposite effect increasing three fold the chance for having non-controlled asthma (OR=3.16; 95%CI=1.10 to 9.11; p-trend=0.035). No other Mediterranean diet items were associated with asthma control.

Discussion

In our study, the probability of a classification of controlled asthma was associated with higher adherence to Mediterranean diet and fresh fruit intake, while higher intake of ethanol increasing three fold the risk of having non-controlled asthma. Higher intakes of nuts and of the ratio MUFA: SFA were respectively associated with increased lung function and exhaled NO. These findings remained significant in the models after adjusting for confounders.

The dietary index used in this study [19], categorize subjects according the adherence to Mediterranean diet. Traditional Mediterranean diet is widely claimed as a health–promoting dietary pattern [28;29], with strong evidence of antioxidant [30;31] and immunomodulator [32;33]

properties in several chronic diseases. Two recent ecological studies addressed the relationship between Mediterranean diet and asthma.[15;16] Chatzi et al. observed in rural areas of Crete a protective effect of Mediterranean diet on allergic rhinitis and of fruits, vegetables and nuts intake on self reported wheezing in 690 children and adolescents. In the Spanish multicentre study, including 20160 school aged children, a protective effect of Mediterranean diet on the risk of current severe asthma in girls was observed.[16] Additionally, nuts, seafood and cereals were also protective for asthma, while fast-food was a risk factor. However these studies presented several limitations including the fact that the potential confounding effects of education and energy intake were not considered in the analysis.[27;34;35]

In our study, daily ingestion of fresh fruit above 300g decreased by 71% the chance of having non-controlled asthma. Similar findings have been previously reported in schoolchildren, where consumption of fruit more than once a day, was associated with a reduced risk of wheezing. [36] Furthermore, in adults [8] and young adults [9], apples and pears consumption was associated with a lower prevalence of asthma and bronchial hyperresponsiveness. A dietary pattern rich in fruit may provide higher intakes of fibre and antioxidants, including vitamin C, beta-carotene, selenium and flavonoids. Antioxidants intake may reduce oxidative stress and, therefore, oxidative stress-related inflammatory diseases, as recognised by Seaton et al [37] in the Antioxidant Hypothesis in asthma. However, studies with antioxidants supplementation [3;38] have been disappointed reinforcing the need to assess the interactions that may occur in natural foods, between nutrients and bioactive compounds. By the contrary, ethanol intake was associated with increased risk of having non-controlled asthma. In other studies [39-41], alcohol consumption has been associated with asthma and hay fever symptoms, allergic sensitization, and serum IgE levels. Regular and moderate intake of wine is a characteristic of Mediterranean diet, but the aMED score consider ethanol intake, irrespective to the type of the different alcoholic beverages contribution. The association between these specific beverages, such as wine, beer, distilled and spirituous drinks and asthma was not studied, needing further investigation.

In the present study, intake of nuts, including almonds, hazelnuts, walnuts, peanuts, pine nuts, pistachios and cashews, was positively associated with improved lung function. This has been

reported also in epidemiological studies in children where inverse associations of nuts with wheezing [15;42] and asthma [16] occurred.

Nuts have been consumed in moderate quantities since ancient times in Mediterranean countries. [43] These foods contain a high proportion of MUFA and alfa-linolenic acid, fibre, vitamins (folate, vitamins E and B6), minerals (cooper, magnesium, zinc and selenium) and many bioactive compounds, including a variety of polyphenols (43) that may modulate redox status [44], inflammatory and immune response [45]. A recent cross-sectional study found lower levels of the circulating inflammatory markers C-reactive protein, interleukin-6, and fibrinogen with a higher nut consumption [46], supporting the hypothesis that nuts antioxidants may reduce oxidative stress and inflammation.[47] However the association between nuts and asthma were poorly addressed until now, probably because nuts, namely peanuts and walnuts, are also involved in food allergy.[48] Although inflammatory effects of n-6 and n-3 PUFA in asthma have been subject of growing interest [4;5], poor attention has been paid to other fatty acids, such as MUFA and SFA. In our study, we observed a positive association between exhaled NO and the ratio MUFA:SFA; that is either an increased dietary intake of MUFA, or a decreased intake of SFA, were associated with increased exhaled NO. Although different effects are to be expected for each fatty acid, total intake of MUFA has been positively associated with allergic sensitization [49;50] and hay fever [49;51], while dairy products (dietary sources of SFA), have been associated with reduced asthma risk(9). However, recent studies in farming environments reported that dietary intake of unpasteurized farm milk also may offer protection against asthma in childhood, independent of other determinants [10] and farm-related co-exposures [50].

Fatty fish (sardine, salmon, tuna, trout, mackerel or herring) are a high source of marine n-3 PUFA with potential anti-inflammatory properties, inhibiting arachidonic acid metabolism.[52] The aMED consider the overall fish intake, either fatty or lean, which could have accounted for the lack of association between dietary intake of fish and asthma outcomes that we observed. Furthermore, no significant associations were observed between dietary intake of vegetables, pulses, whole grains or red and processed meat, and asthma outcomes, suggesting the beneficial effects of Mediterranean diet when considered as a whole dietary pattern.

The Mediterranean diet index that we used, summarize the diet as an integral entity, by means of a single score that results from a combination of food groups and nutrients. Although it is difficult to quantify the adherence to a diet and despite the fact that indexes require operational definitions, grouping foods to obtain complex scores are useful tools to measure food consumption trends and to evaluate epidemiological associations.[53] To the best of our knowledge this is the first study reporting the association between a healthy dietary pattern and asthma control. While a Mediterranean diet is claimed in the present study to improve asthma control, a westernized dietary pattern has been reported to be related to asthma symptoms and airway bronchial hyperreactivity.[11;16]

Our results are limited by the cross sectional nature of the study which does not allow us to establish a cause-effect relationship. Mediterranean dietary factors adherence might just reflect known or unknown healthy lifestyle factors associated with better asthma control. However, our analyses were extensively adjusted for confounders. We assessed established lifestyle factors that could have an important role in asthma, and that we know that certainly influence dietary intake, such as physical activity, body mass index and total energy intake. One of the strengths of this study was the ability to examine a whole approach of a healthy dietary pattern in relation to several asthma outcomes and to asthma control. The aMED score was calculated based on a validated food frequency questionnaire, allowing a separate examination of the specific effects of the various dietary items of the Mediterranean diet. The composite score we used to classify patients under controlled and non-controlled uses established and a validated tool such as the ACQ score [23], and incorporates, as it is being currently suggested, other dimensions of disease control, namely inflammation [24] and lung function [21].

In summary, the present study introduces a novel beneficial link between the adherence to a global healthy Mediterranean dietary pattern and adult asthma, independent of other lifestyle confounders. Our results suggest that high adherence to Mediterranean diet and to so some of their typical plant foods, such as fresh fruits and nuts, may have a protective role in asthma control and lung function in adult patients. Our study reinforces furthermore the damaging effect of a high intake of ethanol per se in asthma control, irrespective to the alcoholic beverage provenience. Prospective studies, both in children and adults, will be necessary to examine

whether changes in dietary pattern towards a Mediterranean diet leads to improved asthma control and disease outcomes.

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Table 1. Characteristics of participants according to asthma control

	Controlled asthma n = 40	Non-controlled asthma n = 134	p-value
Demographic			
Age (years)	42.9 (13.4)	39.7 (15.6)	0.206*
Gender (Female/Male)	31/9	111/23	0.445^{+}
Education, n (%)			0.723^{+}
≤ 4	14 (35)	55 (41)	
5 – 9	10 (25)	34 (25)	
≥ 10	16 (40)	45 (34)	
BMI (kg/ m^2)	26.8 (4.5)	27.3 (5.3)	0.620*
Smoking status, n (%)			0.119^{+}
Non-smoker	28 (70)	105 (79)	
Past smoker	6 (15)	22 (16)	
Current smoker	6 (15)	7 (5)	
Clinical			
Atopic, n (%)	24 (65)	97 (77)	0.138^{+}
Allergic rhinitis, n (%)	26 (65)	90 (68)	0.753^{+}
Current ICS, n (%)	22 (55)	103 (77)	**0.007^{+}**
Exhaled NO (ppb)	19.5 (16.8-22.6)	33.0 (28.8-37.9)	**<0.001^**
FEV1 (% predicted)	103.8 (22.3)	82.7 (22.3)	**<0.001***
ALQ score	10.1 (3.8)	11.7 (4.2)	**0.027***
ACQ score	0.4 (0.3)	1.5 (1.0)	**<0.001***
Lifestyle			
Physical Activity (MET-min/week)			
Total	1405 (8739)	1844 (9492)	0.328^
Walking	247 (2772)	396 (2772)	0.077^
Moderate PA	960 (3360)	480 (3360)	0.863^
Vigorous PA	0 (5760)	0 (6720)	0.649^
Sitting, h/ day	5.0 (11)	4.0 (13)	0.412^
Energy intake (kcal/ day)	3375 (978)	3217 (1227)	0.457*
aMED Dietary-items			
Vegetables, g/ day	295.5 (1292.9)	321.4 (1397.4)	0.634^
Pulses, g/ day	25.7 (112.5)	25.7 (185.5)	0.700^
Fruit, g/ day	302.9 (818.2)	234.8 (3226.6)	**0.024^**
Nuts, g/ day	0.0 (71.0)	0.0 (178.0)	0.856^
Whole grains, g/ day	33.5 (198.8)	19.3 (332.7)	0.118^
Fish, g/ day	58.7 (290.2)	52.7 (527.1)	0.282^
Red and processed meats, g/ day	59.1 (236.0)	63.8 (271.4)	0.219^
Ethanol, g/ day	5.2 (141.4)	16.8 (301.6)	**0.015^**
Ratio MUFA/ SFA	0.86 (1.0)	0.90 (1.0)	0.325^
aMED Score	5.0 (7.0)	4.0 (9.0)	**0.043^**

Data presented as mean (SD), except for aMED score, dietary-items and score and physical activity expressed as median (range) and exhaled NO expressed as geometric mean (IC95%). Mediterranean dietary items and total score presented as unadjusted variables, except for ratio MUFA: SFA and ethanol (energy adjusted). **t* test; ^ Mann-Whitney *U* test; $^{+}$Qui-square test; ACQ: asthma control questionnaire; AQL: asthma quality of life; aMED: alternate mediterranean diet; exhaled NO: fraction of exhaled nitric oxide; FEV1: forced expiratory volume in the first second; SFA: saturated fatty acids; MUFA: monounsaturated fatty acids.

Table 2. Associations between mediterranean diet and airway inflammation, lung function, asthma quality of life and asthma control questionnaire score in asthmatics adults

	Exhaled NO, ppb		FEV1, % predicted		ALQ score		ACQ score	
	Unadjusted Models[#]	Confounders-adjusted Models [$]	Unadjusted Models[#]	Confounders-adjusted Models [%]	Unadjusted Models[#]	Confounders-adjusted Models [&]	Unadjusted Models[#]	Confounders-adjusted Models [+]
	β (95%CI)	β (95%CI)	β (95%CI)	β (95%CI)	β (95%CI)	β (95%CI)	β (95%CI)	β (95%CI)
aMED Dietary items								
Vegetables, g/ day	0.000 (0.000; 0.001)	0.000 (0.000; 0.001)	-0.006 (-0.020; 0.008)	-0.006 (-0.023; 0.011)	0.001 (-0.001; 0.003)	-0.001 (-0.003; 0.002)	0.000 (0.000; 0.001)	0.000 (0.000; 0.001)
Pulses, g/ day	-0.001 (-0.004; 0.003)	-0.001 (-0.004; 0.003)	0.036 (-0.071; 0.143)	0.023 (-0.085; 0.131)	0.003 (-0.015; 0.021)	0.000 (-0.016; 0.016)	-0.002 (-0.006; 0.002)	-0.002 (-0.006; 0.002)
Fruit, g/ day	0.000 (-0.001; 0.000)	0.000 (0.000; 0.000)	0.009 (-0.004; 0.021)	0.011 (-0.003; 0.024)	0.002 (0.000; 0.004)	0.000 (-0.002; 0.002)	0.000 (0.000; 0.001)	0.000 (-0.001; 0.000)
Nuts, g/ day	0.006 (0.000; 0.011)	0.004 (-0.001; 0.010)	**0.239 (0.059; 0.419)***	**0.239 (0.056; 0.421)***	-0.019 (-0.050; 0.011)	-0.019 (-0.046; 0.004)	-0.005 (-0.012; 0.003)	-0.004 (-0.011; 0.003)
Whole grains, g/ day	-0.001 (-0.003;0.002)	0.000 (-0.002; 0.002)	0.025 (-0.043; 0.094)	0.023 (-0.051; 0.097)	-0.001 (-0.012; 0.011)	-0.007 (-0.018; 0.008)	-0.001 (-0.004; 0.001)	-0.003 (-0.005; 0.000)
Fish, g/ day	-0.001 (-0.003; 0.000)	-0.001 (-0.003; 0.001)	0.026 (-0.035; 0.086)	0.031 (-0.031; 0.092)	0.007 (-0.003; 0.017)	0.001 (-0.008; 0.010)	0.001 (-0.002; 0.003)	0.000 (-0.000; 0.000)
Red meats, g/ day	-0.002 (-0.005; 0.001)	-0.002 (-0.005; 0.001)	-0.006 (-0.094; 0.082)	-0.021 (-0.113; 0.071)	0.012 (-0.003; 0.026)	0.008 (-0.005; 0.021)	0.002 (-0.002; 0.005)	0.000 (-0.003; 0.004)
Ethanol, g/ day »	0.002 (0.000; 0.005)	0.000 (-0.002; 0.003)	-0.013 (-0.090; 0.064)	-0.038 (-0.113; 0.037)	0.007 (-0.005; 0.020)	0.007 (-0.004; 0.018)	**0.004 (0.001; 0.007)***	0.001 (-0.002; 0.004)
Ratio MUFA/ SFA »	**0.640 (0.104; 1.176)***	**0.637 (0.075; 1.199)***	2.417 (-15.139; 19.972)	3.417 (-14.765; 21.600)	1.104 (-1.836; 4.044)	1.902 (-0.724; 4.529)	0.323 (-0.376; 1.022)	0.355 (-0.321; 1.030)
aMED Score	0.011 (-0.054; 0.075)	0.029 (-0.041; 0.099)	1.670 (-0.389; 3.728)	2.056 (-0.174; 4.286)	0.163 (-0.184; 0.510)	-0.008 (-0.337; 0.321)	-0.052 (-0.134; 0.031)	**-0.085 (-0.169; -0.002)***

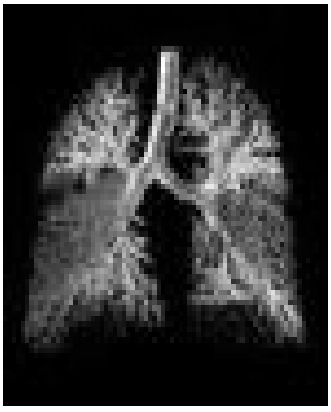
[#]LR between aMED dietary items and score (independent variable) and each one of the asthma outcomes (dependent variable); [$] MLR models adjusted for gender, age, energy intake, BMI, education, rhinitis and atopy; [%] MLR models adjusted for gender, age, energy intake, rhinitis and education; [&]MLR models adjusted for gender, age, energy intake, BMI, education and ICS; [+]MLR models adjusted for gender, age, energy intake, education and ICS; Regression models were performed for each one of asthma outcomes with mediterranean diet score and dietary-items as independent variables entered separately; »In MLR models adjusted for confounders, ratio MUFA: SFA and ethanol dietary intake were adjusted for energy intake by nutrient residual model; *p-value < 0.05; ACQ: asthma control questionnaire; AQL: asthma quality of life; aMED: alternate mediterranean diet; LR: linear regression; MLR: multiple linear regression; NO: nitric oxide; FEV1: forced expiratory flow in the first second; SFA: saturated fatty acids; MUFA: monounsaturated fatty acids.

Table 3. Association between mediterranean diet and asthma control in asthmatics adults

	Unadjusted Models[&]		Adjusted Models[$]	
	OR (95%CI)	p-trend	aOR (95%CI)	p-trend
aMED Dietary items				
Vegetables (g/day)				
< 211.54	1.00 [reference]		1.00 [reference]	
211.54-426.63	0.61 (0.26; 1.47)		0.60 (0.23; 1.53)	
> 426.63	0.81 (0.33; 1.99)	0.802	0.93 (0.32; 2.70)	0.918
Pulses (g/day)				
< 17.51	1.00 [reference]		1.00 [reference]	
17.51- 37.48	0.84 (0.32; 2.23)		0.81 (0.29; 2.24)	
> 37.48	0.69 (0.31; 1.53)	0.368	0.76 (0.32; 1.78)	0.560
Fruit (g/day)				
< 178.40	**1.00 [reference]**		**1.00 [reference]**	
178.40-304.97	**0.61 (0.23; 1.64)**		**0.61 (0.21; 1.76)**	
> 304.97	**0.30 (0.12; 0.76)***	**0.008***	**0.29 (0.10; 0.83)***	**0.015***
Nuts (g/day)				
< 0.00	1.00 [reference]		1.00 [reference]	
0.00 – 2.54	1.57 (0.42; 5.87)		1.57 (0.40; 6.18)	
> 2.54	0.84 (0.39; 1.81)	0.601	0.81 (0.36; 1.84)	0.563
Whole grains (g/day)				
< 13.05	1.00 [reference]		1.00 [reference]	
13.05- 41.52	0.40 (0.16; 1.03)		0.37 (0.13; 1.02)	
> 41.52	0.47 (0.18; 1.21)	0.334	0.42 (0.14; 1.21)	0.347
Fish (g/day)				
< 38.15	1.00 [reference]		1.00 [reference]	
38.15- 74.21	1.22 (0.51; 2.93)		1.22 (0.49; 3.07)	
> 74.21	1.00 (0.43; 2.34)	0.923	1.10 (0.43; 2.83)	0.905
Red and processed meats (g/day)				
< 51.88	1.00 [reference]		1.00 [reference]	
51.88-73.15	1.77 (0.75; 4.21)		1.64 (0.64; 4.17)	
> 73.15	1.59 (0.68; 3.72)	0.251	1.29 (0.51; 3.28)	0.530
Ethanol (g/day) **»**				
< 3.14	**1.00 [reference]**		**1.00 [reference]**	
3.14-29.92	**1.18 (0.53; 2.63)**		**1.41 (0.58; 3.39)**	
> 29.92	**3.90 (1.42; 10.73)***	**0.041***	**3.16 (1.10;9.11)***	**0.035***
Ratio MUFA/ SFA »				
< 0.81	1.00 [reference]		1.00 [reference]	
0.81-1.0	1.45 (0.62; 2.39)		1.44 (0.59; 3.52)	
> 1.0	1.69 (0.71; 4.01)	0.203	1.89 (0.75; 4.78)	0.072
aMED adherence				
Low	**1.00 [reference]**		**1.00 [reference]**	
Moderate	**0.28 (0.08; 1.05)**		**0.32 (0.08; 1.26)**	
High	**0.21 (0.06; 0.75)***	**0.016***	**0.22 (0.05; 0.85)***	**0.028***

Logistic regression models were performed with aMED score and dietary items entered separately; First tertile of aMED score and dietary items was considered as reference group; [&]Unadjusted logistic regression between mediterranean diet and asthma control (controlled versus non-controlled asthma); [$] Logistic regression models between mediterranean diet and asthma control, adjusted for gender, age, education, energy intake and ICS; * p< 0.05; aMED: alternate mediterranean diet; SFA: saturated fatty acids; MUFA: monounsaturated fatty acids.

GENERAL CONCLUSION



GENERAL CONCLUSION

The presented studies suggest the following conclusions:

A negative association was found between BMI and exhaled NO in adult asthmatics. Moreover, BMI was negatively associated with exhaled NO in overweight and obese patients, independent of gender, atopy, lung function and corticosteroid use. The negative association between overweight/ obesity and airway inflammation measured by exhaled NO provides additional support for the mechanical hypothesis linking obesity and asthma.

In addition, the probability of a classification of controlled asthma was associated with higher adherence to Mediterranean diet and fresh fruit intake, while higher intake of ethanol increasing three fold the risk of having non-controlled asthma, after adjusting for gender, age, education, ICS and energy intake. Higher intakes of nuts and of the ratio MUFA: SFA were respectively associated with increased lung function and exhaled NO. These findings introduce a novel beneficial link between adherence to the Mediterranean diet and adult asthma control assessed by symptoms, lung function and exhaled nitric oxide. Adult asthmatic patients might benefit from a nutritional approach based on Mediterranean type of diet.

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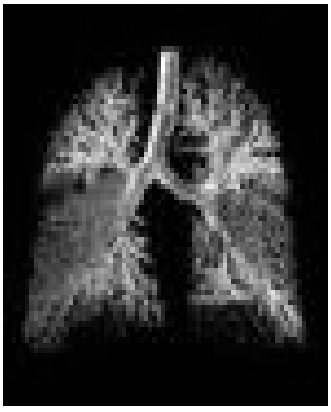

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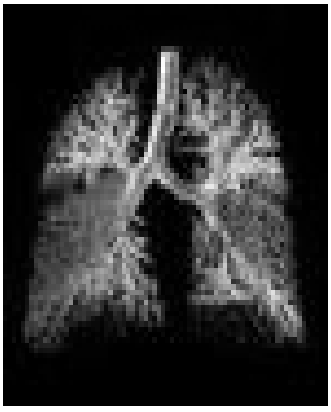

De uma dissertação…
fica a eterna gratidão para com todos os que permitiram a concretização
de um projecto de vida, fica cada gesto singular
fica tanto, fica tão pouco
fica o que se ganha, fica o que se perde
fica a presença, fica a ausência
fica a curiosidade, fica a decepção
fica a determinação, fica a impotência
fica o regozijo, fica o sacrifício
fica a energia, fica a exaustão
fica o êxtase, fica o vazio
fica o riso, fica a lágrima
fica a emoção, fica o silêncio
fica a incerteza de missão cumprida,
fica a certeza de querer continuar…

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FACULDADE DE CIÊNCIAS DA NUTRIÇÃO E ALIMENTAÇÃO
UNIVERSIDADE DO PORTO

MESTRADO EM NUTRIÇÃO CLÍNICA

Obesity, Mediterranean Diet and Asthma

RENATA SOFIA DA CUNHA OLIVEIRA BARROS

PORTO, 2007