Improvement in dietary inflammatory Index score after 6-month dietary intervention is associated with reduction in interleukin-6 in patients with coronary heart disease

Mayr, Hannah L.; Itsiopoulos, Catherine; Tierney, Audrey C.; Ruiz-Canela, Miguel; Hebert, James R.; Shivappa, Nitin; Thomas, Colleen J.

Published in:
Nutrition Research

DOI:
10.1016/j.nutres.2018.04.007

Published: 01/07/2018

Document Version:
Peer reviewed version

Link to publication in Bond University research repository.

Recommended citation(APA):
Improvement in dietary inflammatory index score after 6-month dietary intervention is associated with reduction in interleukin-6 in patients with coronary heart disease: The AUSMED heart trial

Hannah L Mayr, Catherine Itsiopoulos, Audrey C Tierney, Miguel Ruiz-Canela, James R. Hebert, Nitin Shivappa, Colleen J Thomas

PII: S0271-5317(17)31106-5
DOI: doi:10.1016/j.nutres.2018.04.007
Reference: NTR 7880

To appear in:

Received date: 30 November 2017
Revised date: 20 March 2018
Accepted date: 10 April 2018

Please cite this article as: Hannah L Mayr, Catherine Itsiopoulos, Audrey C Tierney, Miguel Ruiz-Canela, James R. Hebert, Nitin Shivappa, Colleen J Thomas, Improvement in dietary inflammatory index score after 6-month dietary intervention is associated with reduction in interleukin-6 in patients with coronary heart disease: The AUSMED heart trial. The address for the corresponding author was captured as affiliation for all authors. Please check if appropriate. Nutr(2018), doi:10.1016/j.nutres.2018.04.007

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
Improvement in Dietary Inflammatory Index score after 6-month dietary intervention is associated with reduction in interleukin-6 in patients with coronary heart disease: the AUSMED Heart Trial

Hannah L Mayr\textsuperscript{a,b}, Catherine Itsiopoulos\textsuperscript{a}, Audrey C Tierney\textsuperscript{a,c}, Miguel Ruiz-Canela\textsuperscript{d,e}, James R. Hebert\textsuperscript{f,g}, Nitin Shivappa\textsuperscript{f,g}, Colleen J Thomas\textsuperscript{h}.

\textsuperscript{a} Department of Rehabilitation, Nutrition and Sport, School of Allied Health, La Trobe University, Melbourne, Victoria, Australia, 3086. \textsuperscript{b} Department of Nutrition and Dietetics, Northern Health, Melbourne, Victoria, Australia, 3076. \textsuperscript{c} Department of Clinical Therapies, University of Limerick, Castletroy, Limerick, V94 T9PX, Ireland. \textsuperscript{d} Department of Preventive Medicine and Public Health, University of Navarra, Pamplona, Spain. \textsuperscript{e} CIBER Fisiopatología de la Obesidad y Nutrición (CIBERobn), Madrid, Spain. \textsuperscript{f} Cancer Prevention and Control Program and Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC 29208 USA. \textsuperscript{g} Connecting Health Innovations LLC, Columbia, SC 29201 USA. \textsuperscript{h} Department of Physiology, Anatomy and Microbiology, School of Life Sciences, La Trobe University, Melbourne, Victoria, Australia, 3086.

Email contacts: HLM: h.mayr@latrobe.edu.au, CI: C.Itsiopoulos@latrobe.edu.au, ACT: A.Tierney@latrobe.edu.au, MRC: mcanela@unav.es, JRH: jhebert@mailbox.sc.edu, NS: shivappa@mailbox.sc.edu, CJT: colleen.thomas@latrobe.edu.au.

Corresponding author: colleen.thomas@latrobe.edu.au

Department of Physiology, Anatomy and Microbiology, School of Life Sciences, La Trobe University, Melbourne, Victoria, Australia, 3086
Abbreviations

DII, Dietary inflammatory index
CHD; coronary heart disease
IL; interleukin
AMI; acute myocardial infarction
CRP; C-reactive protein
MedDiet; Mediterranean diet
MetS; Metabolic syndrome
BMI; body mass index
CONSORT; Consolidated Standards of Reporting Trials
MUFA; monounsaturated fatty acids
PUFA; polyunsaturated fatty acids
MEDAS; Mediterranean Diet Adherence Screener
MVPA, moderate-to-vigorous physical activity
DXA; Dual-energy X-ray Absorptiometry
VAT; Visceral adipose tissue
SAT; subcutaneous adipose tissue
SBP; Systolic blood pressure
DBP; diastolic blood pressure
LDL; low-density lipoprotein
HDL: high-density lipoprotein
Hs; high sensitivity
ELISA; enzyme-linked immunosorbent assay
T2DM; type 2 diabetes mellitus
SD; standard deviation
IQR; interquartile range
OR; odds ratio
CI; confidence interval
ANOVA; analysis of variance
ACE; angiotensin converting enzyme
Abstract

The Dietary Inflammatory Index (DII®) was designed to measure the inflammatory potential of one’s diet. Evidence from observational studies supports that a higher (i.e., more pro-inflammatory) DII score is associated with inflammation and cardiometabolic diseases. We hypothesized that reduction in DII score would improve inflammatory cytokines. To test this hypothesis, we assessed data from a dietary intervention trial in patients with diagnosed coronary heart disease (CHD) to determine whether reduction in DII scores through healthy diets is linked to improvement in inflammatory and related cardiometabolic risk markers. Participants (n=65, 83% male) were randomized to a Mediterranean diet or low-fat diet interventions for 6-months. Anthropometry, body composition and blood markers were measured and DII scores were calculated from 7-day food diaries. After 6-months, in participants who completed the intervention (n=56), reduction in DII score correlated significantly with high sensitivity interleukin-6 (hs-IL-6) (r=0.34, 95%CI 0.05, 0.56) and triglycerides (r=-0.30, 95%CI -0.51, -0.06) but not with C-reactive protein, adiponectin, glucose, body composition or anthropometry. The adjusted mean difference in hs-IL-6 and triglycerides between the highest and lowest tertiles of DII improvement was -0.47pg/mL (95%CI 0.41, 1.10 ) and +0.30mmol/L (95%CI 1.06, 1.59), respectively. The present study found that improvement in DII score through healthy diet intervention was linked with reduced levels of hs-IL-6, but also increased triglycerides, in adult Australian patients with CHD. Future research is warranted to investigate the impact of change in DII on cardiometabolic risk markers in larger cohorts, other disease populations or healthy subjects and with longer-term follow up.

Keywords: Diet; dietary inflammatory index; inflammation; cytokines; coronary disease; clinical trial.
1. Introduction

Chronic, low-grade, systemic inflammation is recognized as an underlying pathophysiological cause of coronary heart disease (CHD)[1]. Inflammatory markers are involved in both atherogenesis as well as vulnerability of plaque to rupture and consequent acute myocardial infarction (AMI)[2, 3]. Inflammatory markers have therefore emerged as targets for treatment of CHD in addition to classic risk factors such as cholesterol and blood pressure[4, 5].

Nutrition, especially adherence to dietary patterns, can have an impact on inflammation[6-8]. The Dietary Inflammatory Index (DII®) was designed specifically to measure the inflammatory potential of one’s diet[9]. Derived from review of the diet-inflammatory marker literature, this index is based on identifying 45 known nutrient/food intake parameters which have either a pro- or anti-inflammatory effect on a range of inflammatory biomarkers.

The DII was validated based on its ability to predict elevated C-reactive protein (CRP) levels (>3 mg/L)[10]. Other studies have investigated the association between higher DII scores (indicating more pro-inflammatory diets) and elevated CRP with mixed results[11, 12]. The DII has also been shown to be associated with the inflammatory markers interleukin (IL)-6 and tumor necrosis factor-α [13, 14]. Higher DII scores have been positively associated with blood pressure, triglycerides and incident metabolic syndrome (MetS)[15], obesity[16, 17] and CHD[18-21].

The DII also has been investigated against dietary pattern scores and other cardiovascular disease risk markers and outcomes[22]. A lower DII has been linked to healthy low-fat diet scores[23] and adherence to the Mediterranean diet (MedDiet) pattern [16, 24]. Only two
published studies have investigated the effect of diet intervention on DII, demonstrating a short-term improvement with vegetarian diets[25] and modest long-term improvement with a low-fat diet[26]. Recent analyses from the current study, demonstrated that 6-month MedDiet intervention in Australian CHD patients significantly improved DII scores (more anti-inflammatory values), whereas a low-fat diet did not [27].

Despite strong evidence from observational studies, there is limited evidence from intervention trials to support that reduction in DII scores through dietary change leads to improvements in inflammation or related health risk factors[19, 28-31]. In the context of CHD, one could assume that a reduction in DII could improve disease risk associated with inflammation. However, the possible anti-inflammatory effect of an improvement in DII may be limited in patients diagnosed with CHD[8], as current CHD medication regimes have pleiotropic anti-inflammatory effects[32, 33]. Our previous analysis found that the theoretically anti-inflammatory MedDiet intervention did not lead to a significant reduction in CRP or IL-6 compared to a low-fat diet[27]. Our primary aim in this paper was to investigate specifically whether reduction in DII score following 6-month dietary intervention with these healthy diets (in the pooled study cohort) was associated with improvement in inflammatory and related cardiometabolic risk markers in adult patients with CHD. Our primary hypothesis was that participants with CHD who had the greatest reduction in DII score would experience the greatest reduction in inflammation. Our secondary aims were to elucidate which nutrient and food group changes were linked to improved DII following diet intervention, and to determine which sociodemographic and clinical characteristics may be associated with DII score in a CHD cohort.

2. Methods and Materials
2.1. Study Design

The AUStalian MEDiterranean Diet Heart Trial (AUSMED Heart Trial) is a parallel design, randomized controlled trial for the secondary prevention of CHD (Australia and New Zealand Clinical Trials Register: ACTRN1261600156482, http://www.anzctr.org.au/). In a multi-ethnic Australian population consisting of individuals who have experienced a cardiac event, the trial delivers a 6-month intervention with a MedDiet versus low-fat diet. The primary outcome is an aggregate of cardiovascular events at 12-month follow-up and secondary outcomes include intermediate markers of cardiometabolic risk and diet adherence at 6 months. In a pilot cohort of AUSMED participants, the present study explores whether improvement in DII through healthy diet intervention is associated with improved risk factors for CHD after 6-months. In the following analyses the diet study groups have been pooled so that the effect of change in DII score, rather than the individual dietary interventions, on risk markers could be elucidated.

Our protocol was approved by the Human Research Ethics Committees of La Trobe University, the Northern Hospital and St Vincent’s Hospital Melbourne. The nature and risks of the study procedure were explained to each participant, and all participants provided written informed consent prior to enrollment. The study is being conducted in accordance with the CONSORT guidelines[34] and the guidelines of the Declaration of Helsinki[35].

2.2. Participants and recruitment
Details regarding eligibility criteria and recruitment have been detailed elsewhere[27].

Briefly, patients were recruited from two teaching hospitals in Melbourne, Australia from 2014 to 2016. Eligible patients were adults with CHD who had experienced at least one of the following: AMI, coronary artery bypass grafting, percutaneous coronary intervention (with or without stenting) or angina pectoris with documented coronary artery disease on imaging. Exclusion criteria included: symptomatic chronic heart failure (New York Heart Association Functional Classification II, III & IV[36]), chronic inflammatory disease, chronic kidney disease stage 3 or above[37], decompensated liver disease, malignant tumor, pregnancy or breastfeeding, inability to read and write in English, or current participation in a lifestyle program (including cardiac rehabilitation), drug or supplement trial.

Eligible and interested patients attended a pre-baseline appointment where consent was obtained and randomization was conducted. Randomization to diet study groups was based on a computer generated stratified approach including gender, age and history of AMI.

2.3. Diet interventions

During the trial all participants continued to receive their standard medical care provided in primary care settings or at their respective treating hospital. Face-to-face appointments were conducted at baseline, 3-months (mid-intervention) and 6-months (end-intervention) for dietetic counselling and to conduct study measures. Five phone reviews with the dietitian also occurred across the 6-months at weeks 3, 6, and 9 and months 4 and 5. Consultation frequency and data collection time points were consistent across the two diet study groups. Meal plans were provided as a guide only as participants were provided with individualized advice on incorporating the MedDiet or low-fat diet principles in their diets. Both diets were
prescribed *ad libitum*, without energy restriction, and exercise was not a target of either intervention. This paper was not designed to distinguish the effect of intervention on DII between the diet study groups as this has been reported elsewhere[27]. A brief description of the two diet interventions is given here to provide an overview of the healthy diet recommendations given to participants.

2.3.1. Mediterranean diet

The diet was designed based on the principles of a traditional Cretan MedDiet[38] with reference to MedDiet trials[39-42] and dietary guidelines of Greece[43]. A model diet was created as a 2-week meal plan incorporating key dietary components of a MedDiet and a mix of traditional and modified recipes[44]. Macronutrient intake targets were 42% total fat, of which at least 50% was from monounsaturated fatty acids (MUFA) and 25% from polyunsaturated fatty acids (PUFA), 35% carbohydrate, 15% protein, <10% saturated fatty acids, and ≤5% alcohol as contributions to total energy consumption. In addition to the 2-week meal plan participants were provided with a recipe book (Itsiopoulos, 2013, ISBN 9781742610825) and shopping list, food group pyramid and food-label reading resources which were designed for this intervention.

The MedDiet specifically included promotion of extra virgin olive oil, nuts, leafy greens, tomatoes, onion, garlic, legumes, oily fish and fermented dairy foods, and significantly reduced intake of red meat, which were not key components of the low-fat diet[45]. At baseline and mid-intervention appointments, a food hamper was provided to participants which included nuts (almonds, walnuts and hazelnuts to achieve 30g/day), extra virgin olive
oil (to achieve 60-80mL/day) and samples of canned legumes, tinned tuna and salmon, and
Greek yoghurt.

2.3.2. Low-fat diet

Participants in the low-fat diet group were instructed to follow the standard diet recommendations provided to cardiac patients. Australian recommendations from the National Heart Foundation as well as Dietary Guidelines and Nutrient Reference Values were consulted for design of the diet[46-48]. Macronutrient intake targets were <30% total fat, <7% saturated fat, 45-65% carbohydrate, 15-25% protein and ≤5% alcohol as contributions to total energy consumption. Food group recommendations included daily intake of grains and cereals (mostly whole grains, 5-7 serves/day), vegetables (5-6 serves/day), fruit (2 serves/day), protein foods (2-3 serves/day) and low-fat dairy foods (2 serves/day)[47]. A 1-week meal plan was created to model this diet for participants. Additional resources were provided for recommended daily food group serves, label reading and low-fat cooking. To aid participant dietary compliance and continuation in the trial, individuals were provided with a supermarket voucher at each face-to-face appointment.

2.4. Study Measurements

This study reports on baseline and end-intervention data measurements only. Data on medical conditions was collected from medical records and in consultation with hospital staff during the screening process, and via a questionnaire at the pre-baseline appointment. Participants completed a self-report survey prior to their baseline appointment which recorded sociodemographic, lifestyle and clinical (including medication and supplement use)
characteristics. A modified version of the survey was completed at the end-intervention appointment, which re-assessed lifestyle and clinical characteristics.

2.4.1. Dietary assessment

Our methods for assessing dietary intake and calculation of the DII score also have been detailed previously[27]. Briefly, the week prior to the baseline and end-intervention appointments, participants completed a 7-day food diary in household measures. The diary included quantity, type, brand and cooking methods for consumed foods with unclear details clarified by the dietitian. All food diaries were entered into FoodWorks8® (Xyris software Australia Pty Ltd) for nutrient and food group intake analyses. Food group serve sizes were based on FoodWorks8 data[49]. The 14-point Mediterranean Diet Adherence Screener (MEDAS), generated and validated for the PREDIMED study[50], was measured at baseline and end-intervention for each participant.

2.4.2. Dietary Inflammatory Index (DII®)

The development[9] and validation[10] of the DII has previously been reported. Peer-reviewed literature published between 1950 to 2010 was evaluated and 1943 articles identified 45 individual nutrient, food or flavonoid intake that were associated with six established inflammatory biomarkers; IL-1β, IL-6, tumor necrosis factor-α, CRP, IL-4 and IL-10. Points were assigned to each of these parameters according to whether they increased, decreased or had no effect on each of the six inflammatory biomarkers. The score for each of the food parameters was weighted based on the study designs and total number of research articles. An overall inflammatory effect score was then calculated for each parameter based
on the ratio of the total weighted number of articles to the weighted pro- and anti-inflammatory articles for that parameter, followed by subtracting the anti-inflammatory fraction from the pro-inflammatory fraction. The inflammatory effect score of each parameter was then mediated against its number of weighted articles.

Our assessment of the DII included all of its 45 parameters. Dietary intake data were adjusted against a reference global daily mean and standard deviation (SD) intake for each parameter to obtain a Z-score. The global intake data was based on consumption data from 11 countries. To reduce the effect of right-skewing of the dietary data, the z-score was then expressed as a proportion (i.e., with value from 0 to 1). Centering these scores on zero (0) was achieved by doubling the proportion and subtracting one (1). The resulting centered proportion score for each intake parameter was multiplied by its respective parameter-specific inflammatory effect score and then each of these 45 scores were summed to obtain an overall DII score for each participant. Finally, the DII scores were re-calculated with the inclusion of nutrient supplement intake (DII_diet+supplements).

In this study, the DII was measured at baseline and end-intervention. The intake values for most of the DII parameters (energy, protein, carbohydrate, total fat, MUFA, PUFA, omega-3, omega-6, saturated fatty acids, trans fat, cholesterol, fiber, alcohol, caffeine, folate, beta carotene, vitamin A, vitamin B6, vitamin B12, vitamin C, vitamin E, iron, magnesium, niacin, riboflavin, selenium, thiamin and zinc) were obtained from FoodWorks8 nutrient analyses of the food diaries. Isolated food components in the DII (green/black tea, garlic, ginger, onion, pepper, rosemary, saffron, turmeric and thyme/oregano) were extracted from the food diaries and the total daily intake in grams calculated. Vitamin D was calculated using an electronic Australian nutrient table database[51]. Intake of eugenol was calculated
Based on the recognized content in cloves in *Phenol Explorer*[52]. For calculation of flavonoids (flavan-3-ol, flavones, flavonols, flavonones, anthocyanidins and isoflavones) the USDA Databases for the Flavonoid Content of Selected Foods (Release 3.2, November 2015) and Isoflavone Content of Selected Foods (Release 2.0, September 2008) were used.

2.4.3. Cardiometabolic risk markers

Activity levels, anthropometry, body composition and blood pressure were measured and a blood sample collected at baseline and end-intervention appointments. Participants wore a triaxial Actigraph accelerometer (WGT3X-BT; Actigraph Corp, Florida, United States) for one week prior to their appointments. Established criteria[53] were used to determine time spent as moderate-to-vigorous physical activity (MVPA) minutes per week and as sedentary hours per week. Anthropometry measures were performed according to the International Society for the Advancement of Kinanthropometry standards by trained research personnel [54]. Body weight was measured to the nearest 0.1kg using calibrated digital scales after an 8-h fast, without shoes and after removal of heavy jewelry, outer layers of clothing and pocket contents. Height was measured to the nearest 0.1cm, while barefoot, using a wall-mounted stadiometer. Two measures of waist circumference directly over the skin at the level of the narrowest point between the lower costal (10th rib) and top of the iliac crest were taken to the nearest 0.1cm, and the average calculated. If the two measures differed by 2% or more a third measure was taken and the average of all three measures calculated.

Whole body composition was measured using a fan beam densitometer Dual-energy X-ray Absorptiometry (DXA) machine (Hologic, Discovery W), with analysis performed using QDR™ (Quantitative Digital Radiography) for Windows. All of the scans were conducted by
a trained licensed technician who had undergone DXA and radiation training. Procedures and positioning of participants on the scanning bed were standardized according to recommendations of the Australian and New Zealand Bone and Mineral Society and manufacturer guidelines. Participants were required to be fasted for at least 8 hours, void their bladder, wear light clothing free from metal and remove shoes, jewelry, watches, glasses and hearing aids. Participants were instructed to lie supine on the scanning bed with slight internal rotation of legs from the hip, with arms straightened by the sides and palms flat on the bed or placed against thighs. All scans were conducted in the normal length and standard thickness mode with regions of interest and analyses automatically generated by the software. Three measurements were obtained from each scan: total body fat percentage, subcutaneous adipose tissue (SAT) area and visceral adipose tissue (VAT) area. Hologic scientists developed their method for measuring VAT from DXA[55], which is highly correlated (r=0.93) and linearly related to VAT measurements by computed tomography[56].

Anthropometry measures were performed according to the International Society for the Advancement of Kinanthropometry standards by trained research personnel [54]. Measurements were taken at least at 1 min intervals after the participant had been seated for 5 min. At least two measures were performed and then a third measure if either the SBP or DBP differed by 10%.

A fasting blood sample was taken from the antecubital vein using standard venous puncture techniques. All blood samples were processed immediately and aliquots were stored at -80°C until assay. Serum low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides and high sensitivity (hs)-CRP levels were measured at a commercial laboratory (Dorevitch Pathology Pty Ltd, Heidelberg, Australia). Lipids were measured using
an automated blood analyzer (ADVIA 2400 Chemistry System, Siemens) and hs-CRP by chemical analyzer (Cobas Integra 400, Roche). All other biomarkers were measured by trained personnel at La Trobe University. Briefly, serum high-sensitivity (hs-)IL-6 levels were measured by enzyme-linked immunosorbent assay (ELISA) (Abcam, #ab46042, detection sensitivity <0.81 pg/mL) in duplicate. Serum adiponectin levels were measured by ELISA (Invitrogen, Thermofisher Scientific, #KHP0041, detection sensitivity <100 pg/mL) in duplicate. Fasting serum glucose levels were measured using enzymatic hexokinase method by a chemical analyzer (Indiko, Thermofisher Scientific) in duplicate following blood collection in sodium fluoride and oxalate vacutainers. The presence of MetS was calculated using the National Cholesterol Education Program ATP III definition[57]. Diagnosis of Type 2 diabetes mellitus (T2DM) was determined by consulting participant medical history records.

2.5. Statistical Analyses

This study was designed to be an exploratory analysis in a pilot cohort of AUSMED participants, hence no formal power calculation was performed[58]. Baseline analyses were based on the full cohort of participants who started the intervention in order to demonstrate the full strength of associations between sociodemographic and clinical characteristics with DII scores. The 6-month and change analyses (i.e., baseline to 6-months) were based on participants who completed the intervention only. Intention-to-treat analyses was not deemed appropriate for the follow-up outcomes assessed, as we aimed to determine whether actual change in DII score was related to change in risk markers. An imputation of no change for drop-outs would have increased the likelihood of obtaining a significant result and would not have given a true reflection of actual results.
Data are presented as n (%), means ± SD or medians (interquartile range [IQR]) as appropriate. All statistical analyses were conducted using SPSS® statistical package version 23 (IBM Corp, Released 2015). Normality of continuous variables was assessed by the Kolmogorov–Smirnov test. According to this, the Independent Student’s T-test or Mann-Whitney U test was applied to compare continuous variables. The Chi-square test was performed to compare categorical variables. For all analyses regarding hs-CRP, participants with serum levels >10mg/L were excluded as these higher concentrations reflect acute rather than chronic inflammation[59]. Pathology marker variables were log transformed (base 10) to normalize the distributions and the geometric means were calculated from results. A paired Samples T-test was conducted to determine the difference in 6-month change in DII score calculated with and without nutrient supplements. McNemar’s test assessed whether the proportion of participants with an anti-inflammatory (-) DII score changed. Logistic regression models assessed the odds of elevated hs-CRP levels (>3mg/L)[59] based on DII score at baseline and 6-months, presented as odds ratios (OR), 95% confidence intervals (CI); this analysis was conducted to allow for comparison of this CHD cohort to results of previously reported studies which validated the DII against CRP in other subjects.

Tertiles of change in participant DII scores from baseline to 6-months were created in SPSS (participant numbers were deemed insufficient to create quartiles). The tertiles were based on having an equal number of participants across three groups rather than pre-defined cut-offs of DII change. Least-squared means (95%CI) of cardiometabolic risk markers at 6-months were estimated across the tertiles of DII change. Multi-variable general linear models were used to estimate the differences (and 95%CI) in the indices of 6-month cardiometabolic risk markers according to the tertiles of DII change. Partial correlations (R-values, 95%CI) were used to
assess the linear relationship between these 6-month cardiometabolic risk maker measures and change in DII score, while controlling for baseline values. One-way ANOVA (analysis of variance), Kruskal-Wallis test or Chi-square test also assessed change in dietary intake and activity levels, and differences in sociodemographic characteristics between these tertiles, with post hoc Independent Student’s T-test or Mann-Whitney U test to assess differences between specific tertiles.

Covariates included in the logistic regression and general linear models were sex, age, time since coronary event, T2DM status and MVPA levels, as well as baseline risk marker values. Models were not adjusted for total energy intake because it is one of the DII components. Statistical significance was set at p<0.05, except for when multiple post-hoc comparisons were performed within or between study groups a Bonferroni correction was applied.

3. Results

3.1. Participants

Figure 1 illustrates the pilot study flow of participant appointments. Of the 73 participants randomized, 65 started the intervention. There were 9 drop-outs during the intervention period due to medical or family related issues or loss to follow up. Thus, a total of 56 participants completed the study. There were no significant differences in sociodemographic or clinical characteristics between participants who dropped out compared with those who completed the 6-month intervention. However, participants who dropped out had a significantly more pro-inflammatory mean baseline DII (1.8 ± 2.3 vs. -0.3 ± 2.7, p=0.047).
Characteristics of the total cohort of participants and according to anti-inflammatory (-) or pro-inflammatory (+) DII score at baseline are reported in Table 1. One participant who dropped out did not have dietary intake data at baseline and was excluded from all analyses. Overall, the cohort were middle to older-aged adults (61.9 ± 9.3 years), mostly male (83%), and from multi-ethnic backgrounds. Most participants had experienced an AMI (70%), 28% had diagnosed T2DM and the majority were overweight (84%). Few participants were current smokers (14%) and the majority had completed a cardiac rehabilitation program (80%). All participants were taking medications, of which the most common were anti-platelets (90%), statins (88%) or a range of anti-hypertensives. Close to half the participants were taking supplements (44%). At baseline, mean DII score was almost neutral in terms of its inflammatory potential (-0.02 ± 2.72), whereas mean DII_diet+supplements score was more anti-inflammatory (-0.22 ± 2.76).

3.1.1. Pro- versus anti-inflammatory DII

There were a similar number of participants who had anti- (n=31) or pro-inflammatory (n=33) DII scores at baseline. The pro-inflammatory DII group had a higher proportion of females, a trend toward higher waist circumference and VAT area, and a significantly higher total body fat % and SAT area compared to the participants with an anti-inflammatory DII score. The pro-inflammatory DII group also tended to have higher prevalence of MetS and T2DM and higher plasma glucose levels. There was no significant difference between the pro- and anti-inflammatory DII groups for serum lipid levels; in both groups the mean levels for LDL, HDL and triglycerides met the reference target for secondary CHD prevention (<1.8 mmol/L, >1.0 mmol/L and <2.0 mmol/L, respectively)[46]. Mean hs-CRP levels were 1.6 times greater in the pro-inflammatory DII group; however, this difference was not
statistically significant and both groups had a mean hs-CRP level within the normal reference range (≤3 mg/L). Serum levels of hs-IL-6 and adiponectin were similar in the pro- compared to anti-inflammatory DII groups.

Participants with a pro-inflammatory DII score tended to have a higher proportion of current smokers and a lower proportion who had completed cardiac rehabilitation, compared to participants with an anti-inflammatory DII score. The anti-inflammatory DII group had significantly higher use of omega-3 and multivitamin supplements, and levels of MVPA per week.

### 3.2. Change in DII score

In the participants who completed the diet interventions, there was a significant increase in the proportion with an anti-inflammatory (-) DII score, from 28 out of 56 (50%) at baseline to 37 out of 56 (66%) at 6-months, \( p=0.049 \). Mean change in DII score in the pooled study cohort following 6-month diet intervention was \(-0.53 \pm 2.65\), and this change was not significantly different to the mean change in DII\(_{\text{diet+supplements}}\) \((-0.60 \pm 2.63, p=0.12\).

### 3.3. DII and high sensitivity CRP as dichotomous

Logistic regression analyses for elevated serum hs-CRP levels were performed at baseline and 6-months. At both time points, 20% of the assessed participants (13 out of 63 at baseline and 11 out of 55 at 6-months) had an elevated hs-CRP i.e., >3 mg/L. Unadjusted analyses with DII score as the independent variable demonstrated that higher DII score had a nonsignificant association with an increased odds of elevated hs-CRP at baseline (OR=1.10,
95%CI 0.87, 1.38) and at 6-months (OR=1.06, 95%CI 0.81, 1.39). At baseline, the association between DII score and increased odds of elevated hs-CRP was greater in the model adjusted for sex, age, time since coronary event, T2DM and MVPA levels, although it remained nonsignificant (OR=1.16, 95%CI 0.89, 1.51). Conversely, at 6-months, the association in the adjusted model was lower (OR=1.04, 95%CI 0.77, 1.39) than the unadjusted result. Odds ratios were also calculated for DII<sub>diet+supplements</sub> and the results were very similar (see Supplemental Materials, Table S1).

### 3.4. Tertiles of change in DII

Participants who completed the intervention were categorized into tertiles of change in DII score from baseline to 6-months. This resulted in the following tertiles (with range of DII change indicated): tertile 1 (T1, n=18) of -7.44 to -1.39, tertile 2 (T2, n=20) of -1.36 to 1.13, and tertile 3 (T3, n=18) of 1.18 to 4.00. Table 2 shows the adjusted means for 6-month measures of cardiometabolic risk markers, with lower and upper limits of each measure, according to tertiles of change in DII score. The corresponding adjusted differences between these mean values across the tertiles of change in DII, with T3 as the reference tertile, are presented in Table S2 in the Supplemental Materials. Adjusted mean values for weight, waist circumference, total body fat %, VAT area, SBP, DBP, LDL, HDL and adiponectin at 6-months were similar across tertiles. The adjusted mean value for SAT area was higher in T1 compared to both T2 and T3, however, this did not represent a significant difference across tertiles. Adjusted mean values for triglycerides and glucose each decreased linearly across the successive tertiles (from reduced to increased DII scores). For triglycerides, this represented a significant difference across tertiles (p=0.03), with a significant adjusted difference between T1 and T3 (0.31, 95%CI 1.06, 1.59 p=0.04) as well as T2 and T3 (0.25, 95%CI 1.02, 1.52
For both hs-CRP and hs-IL-6 the adjusted mean values were highest in T2, however, for hs-CRP T3 had the lowest value, whereas for hsIL-6 T1 had the lowest value. This represented a significant difference across tertiles for hs-CRP (p=0.004), with a significant adjusted difference between T2 and T3 (0.86, 95%CI 1.66, 6.43 p=0.001) but not T1 and T3 (0.30, 95%CI 0.89, 3.63 p=0.10). This also represented a significant difference across tertiles for hs-IL-6 (p=0.006), but no significant adjusted differences specifically between T1 and T3 (-0.47, 95%CI 0.41, 1.10 p=0.11) or T2 and T3 (0.64, 95%CI 0.90, 2.34, p=0.13).

Partial correlation coefficients between these cardiometabolic risk markers at 6-months and change in DII score, while controlling for baseline levels of the risk marker, are also presented in Table 2. A significant positive correlation was observed between change in DII score and 6-month hs-IL-6 levels (r=0.34, 95%CI 0.05, 0.56). A significant negative correlation was observed between change in DII score and 6-month triglyceride levels (r=-0.30, 95%CI -0.51, -0.06). There were no other statistically significant correlations.

The differences between these tertiles for change in DII scores and change in nutrient and food group intake and activity levels are presented in Table 3. Participants with greater reduction in DII (becoming more anti-inflammatory) across 6-months intervention increased their intake of total energy, total fat, MUFA, PUFA, omega-3 and -6, fiber, vitamins C and E, folate, potassium, flavones, flavonols, flavonones, isoflavones, vegetables, seafood and olive oil, and reduced intake of dairy products. Six-month changes in MVPA levels and sedentary time were not significantly different between tertiles. Finally, there were no significant differences in measured sociodemographic or clinical characteristics between the tertiles (Supplemental Materials, Table S3).
4. Discussion

The present study investigated the relationship between DII and cardiometabolic risk markers, including the impact of prospective change in DII, in Australian patients with CHD. Previous studies have not examined whether dietary-induced improvement in DII improves inflammatory markers. Our primary hypothesis that improvement in DII score after 6-months intervention with healthy diets (MedDiet or low-fat diet) would lead to reduced levels of inflammatory markers was partially supported by this study. A significant positive correlation between change in DII and end-intervention values for hs-IL-6, but not hs-CRP or adiponectin, was found in linear regression models. Our findings also showed a significant difference for change in hs-CRP and hs-IL-6 between tertiles of change in DII; tertile 1 (most reduced DII) had the lowest mean value for hs-IL-6 at 6-months; however, tertile 3 (most increased DII) had the lowest mean value for hs-CRP at 6-months. There was no significant difference between tertiles of DII change for adiponectin at 6-months.

Previous studies investigating DII and inflammation have investigated whether higher DII scores were associated with elevated CRP (>3 mg/L). Significant associations have been demonstrated in some healthy adult subjects[10, 11, 14] and in those with MetS[60]. In contrast, no association has been demonstrated in other studies of healthy subjects, cross-sectionally[61] or in a prospective cohort with follow-up of 12 years[12]. In the present study of CHD patients, a higher DII score was associated with increased odds of mean CRP >3 mg/L before and after the diet intervention; however, these findings did not reach statistical significance. Furthermore, mean hs-CRP values at 6-months did not significantly differ
between the tertiles of greatest reduction versus greatest increase in DII score, which was unexpected.

Previous research has demonstrated a significant relationship between higher DII score and higher levels of IL-6 in large populations of healthy subjects[61, 62] and post-menopausal women[14]. In the present cohort of patients with CHD, there was no difference in mean hs-IL-6 values between participants with a pro- versus anti-inflammatory DII score at baseline. However, a reduction in DII score was correlated with a lower hs-IL-6 score at 6-months, which has not previously been demonstrated. The significant association we found between improvement in DII and hs-IL-6, but not hs-CRP, may be related to the location of mechanism of these markers. IL-6 is a pleiotropic cytokine released from activated cells at the vascular endothelium, whereas CRP is released from the liver[63].

Adiponectin is an anti-inflammatory, insulin-sensitizing adipokine[64] and low circulating levels are associated with CHD[65]. To our knowledge, only one other study has investigated the association between DII and adiponectin, with no difference observed in adiponectin levels between quartiles of DII in subjects with MetS[60]. Similarly, in the present study, there was no difference in mean adiponectin values between participants with a pro- versus anti-inflammatory DII score at baseline. We also demonstrated that a reduction in DII had no effect on adiponectin at 6-months. In a previous trial conducted in subjects with MetS, a MedDiet with 10% reduction in body weight significantly improved adiponectin, whereas a MedDiet in the absence of weight loss had no effect[66]. Our intervention had no energy restriction and minimal changes to body weight or composition were observed, which may explain the lack of association between DII change and adiponectin.
Our *ad libitum* approach for the diet interventions might also explain the lack of association between improvements in DII and changes in anthropometric and body composition measurements. We found that participants with a more pro-inflammatory diet had greater total body fat %, but no significant differences were seen with BMI or waist circumference at baseline. One previous study, which also measured total body fat % by DXA scan, found no significant difference in total body fat % between quartiles of participants’ DII scores in a cohort of young adults[23]. Two previous studies conducted in Spanish cohorts have shown a relationship between DII and anthropometry; after long-term follow-up, incident cases of overweight and obesity were related to higher baseline DII scores[17] and DII was associated with higher average BMI and waist circumference in the elderly[16]. We also demonstrated a stronger association between pro-inflammatory DII score and SAT area compared to VAT area at baseline, which was unexpected. Whilst there is a known link between central adiposity and increased risk of cardiometabolic diseases[67], there is evidence to support a significant overlap between visceral fat distribution and adipose tissue inflammation[68]. No previous research has investigated the relationship between DII and compartmental adiposity.

In the present study, participants with an anti- versus pro-inflammatory DII score had significantly higher MVPA levels. This would suggest that participants with healthier diets also engaged in more physical activity. Other studies have considered whether physical activity levels were associated with DII, with one demonstrating that participants with lower DII had greater levels[15], whereas others demonstrated no relationship[10, 23]. There is evidence to support that exercise intervention significantly reduces levels of CRP and IL-6 in patients with CHD[69]. Our trial had no exercise intervention and we found no association between change in DII and change in MVPA levels, which demonstrates that changes observed in hs-CRP or hs-IL-6 were unlikely confounded by changes in physical activity.
Lipids and/or glucose levels have been related to DII in other studies [10, 15, 60, 70]. We showed no association between DII and LDL or HDL cholesterol, but this was not unexpected in our subjects who mostly had well-controlled lipid levels at the start of the study. There was a trend for higher glucose levels and higher rates of T2DM in participants with a pro-inflammatory DII score. There is evidence to support that poor adherence to healthy dietary patterns is linked with higher rates of T2DM[71, 72]. We also found that participants with greatest increase in DII score had lower 6-month triglyceride levels. This unexpected result does not agree with a previous study, which found increased odds of elevated triglycerides with higher DII score after 13-years of follow-up[15].

In the present study participants with greatest reduction in DII had increased their intake of the nutrients MUFA, omega-3 and -6, fiber, vitamin C and E, folate, potassium and flavonoids; and the food groups of vegetables, fruit, nuts, seafood and olive oil, and reduced their intake of dairy products. Similarly, a previous intervention trial of a 2-month vegan diet significantly reduced DII and led to significantly increased intake of fiber, folate and potassium, and decreased intake of calcium (likely reflective of the removal of dairy products), and total and saturated fat[25]. In previous cross-sectional analyses, lower DII scores were associated with greater consumption of fruits and vegetables[16, 24, 30] and cereals, nuts, legumes and fish[16, 24].

This study is strengthened by its prospective nature and detailed assessment of dietary intake. We were able to assess how the effect of dietary intervention on DII scores impacts on a range of cardiometabolic risk markers, including two of the six inflammatory biomarkers on which the DII development was based. We also included the novel outcomes of visceral
adiposity and the anti-inflammatory biomarker adiponectin. We collected nutrient and food intake data via 7-day food diaries that were clarified by the dietitian and calculated the DII based on all 45 intake parameters. This method would allow for the anti-inflammatory potential of a healthy diet to be more correctly estimated compared to 24-h dietary records or food frequency questionnaires, which are the most common methods used to calculate DII in other studies[22]. We also assessed whether DII score was impacted by supplement intake.

Our study was limited by being conducted in a small cohort of patients with CHD, of which the majority were male. Our results were affected by inadequate statistical power and are not necessarily applicable to healthy subjects, other disease populations or women. Only 20% of the participants had an elevated CRP value at baseline, which is likely related to the high rate of statin and aspirin prescription, as they both have pleiotropic effects on inflammatory markers[33, 73]. We were, however, able to demonstrate that participants with the greatest reduction in DII had the most improved levels of hs-IL-6 despite adjunct medical therapy. The majority of participants were also taking anti-hypertensive medication, which may in part explain the lack of association between DII and blood pressure. There were a number of participants who dropped out during the intervention and they had significantly more pro-inflammatory diets at baseline. It is unclear whether they would have achieved dietary improvement or changes in risk markers similar to those who completed the intervention. The results reported for the effect of change in DII on risk markers included statistical adjustment for key potential confounding factors (baseline values, sex, T2DM status, time since coronary event and physical activity levels). However, the ancillary results regarding the relationship between DII and baseline characteristics and food/nutrient intake changes were not adjusted statistically due to their exploratory nature in a small cohort and, therefore, should be interpreted with caution.
In conclusion, the present study demonstrated that improvement in DII score towards more anti-inflammatory values through healthy diet interventions was linked with reduced levels of hs-IL-6 but not hs-CRP, in adult Australian patients with CHD. This study also found that an improvement in DII score was associated with higher levels of triglycerides. Changes in DII were not associated with changes to other cardiometabolic risk markers, including adiponectin, visceral fat, HDL or LDL cholesterol, glucose, blood pressure or measures of anthropometry. Significant improvement in DII score was associated with increased intake of a variety of healthy foods and nutrients, and total energy. Future research is warranted to investigate the impact of change in DII on these risk markers in larger cohorts, other disease populations or healthy subjects and with longer-term follow up.

Acknowledgment

The authors are very grateful to all the participants of the study for their enthusiastic involvement and to the personnel of the affiliated hospital sites. We thank Teagan Kucianski for her work in developing the trial protocol, Elena George for her work in designing the Mediterranean diet and low-fat diet interventions of this study, Cassandra Bendall for her assistance with data collection and entry, Jessica Radcliffe for her support during the data collection process and Jessica Radcliffe, Diana Navarro-Perez and Antony Vinh for their assistance with laboratory analyses of pathology markers. This work was supported by La Trobe University (Understanding Disease RFA Start-Up Grant, 2013). HLM was supported by an Australian Government Research Training Program Scholarship and a Northern Health PhD Scholarship. NS and JRH were supported by the United States National Institute for Diabetes, Digestive and Kidney Diseases (grant no. R44DK103377). HLM collected the
presented data and analyzed the dietary intake, dietary inflammatory index and
cardiometabolic risk marker data (with support from CJT, CI and ACT) and wrote the
manuscript. All co-authors critically reviewed and edited the manuscript. MRC assisted with
design of the data and statistical analyses reported in the manuscript. NS and JRH performed
calculation of the DII from dietary intake data and provided important input in reviewing and
editing drafts of the manuscript. However, they were not involved in performing statistical
analyses on which the actual results are based.
The roles of the sponsors are as follows: the supplemental foods used in the study were
generously donated by Cobram Estate of Boundary Bend Limited (extra virgin olive oil); the
Almond Board of Australia (almonds); Jalna Dairy Foods Pty Ltd (Greek yoghurt); Simplot
Australia Pty Ltd (canned fish and legumes); HJ Heinz Company Australia (canned fish and
legumes); and Carman’s (muesli bars). However, the sponsors had no role in the design,
collection, analysis or writing of this article. The authors have no relevant interests to
declare. However, in the spirit of full disclosure, JRH and NS make the following statement
regarding their other work on DII-derived products. JRH owns controlling interest in
Connecting Health Innovations LLC (CHI), a company planning to license the right to his
invention of the dietary inflammatory index (DII) from the University of South Carolina in
order to develop computer and smart phone applications for patient counselling and dietary
intervention in clinical settings. NS is an employee of CHI. The subject matter of this paper
will not have any direct bearing on that work, nor has that activity exerted any influence on
this project.
Figure captions

Figure 1. Study flow diagram of AUSMED participant appointments and inclusion in analyses, 2014-2016. a No comparison of diet study groups, total cohort reported together. b One participant who dropped out had no dietary data.

References


in Dietary Inflammatory Index scores and macronutrient intake compared with diets that contain meat. Nutr Res 2015;35:97-106.


[71] Schwingshackl L, Hoffmann G. Diet quality as assessed by the Healthy Eating Index, the Alternate Healthy Eating Index, the Dietary Approaches to Stop Hypertension score, and health outcomes: a systematic review and meta-analysis of cohort studies. J Acad Nutr Diet 2015;115:780-800. e5.
Table 1. Characteristics of AUSMED participants between anti(-) or pro(+) inflammatory DII score at baseline², 2014-2016

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total cohort n=64</th>
<th>DII Score (-)Anti-inflammatory n=31</th>
<th>DII Score (+)Pro-inflammatory n=33</th>
<th>P³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>61.9 ± 9.3</td>
<td>63.2 ± 8.2</td>
<td>60.6 ± 10.3</td>
<td>0.26</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>11 (17.2)</td>
<td>2 (6.5)</td>
<td>9 (27.3)</td>
<td>0.06</td>
</tr>
<tr>
<td>Male</td>
<td>53 (82.8)</td>
<td>29 (93.5)</td>
<td>24 (72.7)</td>
<td></td>
</tr>
<tr>
<td>Region of birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>37 (57.8)</td>
<td>19 (61.3)</td>
<td>18 (54.5)</td>
<td>0.77</td>
</tr>
<tr>
<td>Other</td>
<td>27 (42.2)</td>
<td>12 (38.7)</td>
<td>15 (45.5)</td>
<td></td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary School</td>
<td>4 (6.3)</td>
<td>2 (6.5)</td>
<td>2 (6.1)</td>
<td>0.56</td>
</tr>
<tr>
<td>Secondary School</td>
<td>14 (21.9)</td>
<td>5 (16.1)</td>
<td>9 (27.3)</td>
<td></td>
</tr>
<tr>
<td>Trade/ University</td>
<td>46 (71.9)</td>
<td>24 (77.4)</td>
<td>22 (66.7)</td>
<td></td>
</tr>
<tr>
<td>Acute coronary syndrome history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>45 (70.3)</td>
<td>21 (67.7)</td>
<td>24 (72.7)</td>
<td>0.87</td>
</tr>
<tr>
<td>Coronary artery bypass grafting</td>
<td>15 (23.4)</td>
<td>9 (29.0)</td>
<td>6 (18.2)</td>
<td>0.47</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>49 (76.6)</td>
<td>23 (74.2)</td>
<td>26 (78.8)</td>
<td>0.89</td>
</tr>
<tr>
<td>Time since cardiac event (months)†</td>
<td></td>
<td>5.4 (18.2)</td>
<td>4.7 (5.0)</td>
<td>0.34</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>18 (28.1)</td>
<td>6 (19.4)</td>
<td>12 (36.4)</td>
<td>0.21</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>26 (41.3)</td>
<td>10 (33.3)</td>
<td>16 (48.5)</td>
<td>0.33</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>87.2 ± 18.8</td>
<td>85.6 ± 16.7</td>
<td>88.7 ± 20.7</td>
<td>0.52</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.9 ± 5.2</td>
<td>29.1 ± 4.9</td>
<td>30.7 ± 5.4</td>
<td>0.23</td>
</tr>
<tr>
<td>Overweight (&gt;25 kg/m²)</td>
<td>54 (84.3)</td>
<td>26 (83.9)</td>
<td>28 (84.8)</td>
<td>1.00</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>100.7 ± 13.4</td>
<td>105.8 ± 15.3</td>
<td>105.8 ± 15.3</td>
<td>0.16</td>
</tr>
<tr>
<td>Total body fat (%)</td>
<td>34.0 ± 6.7</td>
<td>31.4 ± 6.4</td>
<td>36.5 ± 6.1</td>
<td>0.002*</td>
</tr>
<tr>
<td>Visceral adipose tissue (cm²)</td>
<td>196.0 ± 79.6</td>
<td>180.1 ± 78.8</td>
<td>210.4 ± 78.8</td>
<td>0.13</td>
</tr>
<tr>
<td>Subcutaneous adipose tissue (cm²)</td>
<td>324.5 ± 120.0</td>
<td>287.8 ± 115.7</td>
<td>358.0 ± 115.7</td>
<td>0.02*</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>136.5 ± 17.9</td>
<td>140.0 ± 19.8</td>
<td>133.1 ± 15.4</td>
<td>0.13</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>81.9 ± 8.5</td>
<td>81.8 ± 8.7</td>
<td>82.0 ± 8.4</td>
<td>0.92</td>
</tr>
<tr>
<td>Pathology‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>1.17 ± 1.3</td>
<td>1.76 ± 1.4</td>
<td>1.69 ± 1.6</td>
<td>0.67</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.72 ± 1.3</td>
<td>1.19 ± 1.3</td>
<td>1.15 ± 1.3</td>
<td>0.61</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.29 ± 1.6</td>
<td>1.19 ± 1.6</td>
<td>1.39 ± 1.7</td>
<td>0.23</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.4 ± 1.3</td>
<td>5.06 ± 1.28</td>
<td>5.73 ± 1.29</td>
<td>0.05</td>
</tr>
<tr>
<td>High sensitivity CRP (mg/L)</td>
<td>0.86 ± 3.6</td>
<td>0.68 ± 3.8</td>
<td>1.08 ± 3.2</td>
<td>0.15</td>
</tr>
<tr>
<td>High sensitivity IL-6 (pg/mL)</td>
<td>1.44 ± 3.2</td>
<td>1.39 ± 2.8</td>
<td>1.49 ± 3.6</td>
<td>0.82</td>
</tr>
<tr>
<td>Adiponectin (ng/mL)</td>
<td>7.63 ± 1.56</td>
<td>7.31 ± 1.54</td>
<td>7.92 ± 1.57</td>
<td>0.48</td>
</tr>
<tr>
<td>Lifestyle</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVPA (min/wk)†</td>
<td>118.0 (194.5)</td>
<td>187 (201.0)</td>
<td>94.0 (174.5)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Sedentary time (h/wk)</td>
<td>58.1 ± 11.6</td>
<td>57.0 ± 12.3</td>
<td>59.0 ± 11.0</td>
<td>0.51</td>
</tr>
<tr>
<td>Current smoker</td>
<td>9 (14.1)</td>
<td>2 (6.5)</td>
<td>7 (21.2)</td>
<td>0.15</td>
</tr>
<tr>
<td>Cardiac rehabilitation</td>
<td>51 (79.7)</td>
<td>26 (83.9)</td>
<td>25 (75.8)</td>
<td>0.62</td>
</tr>
<tr>
<td>Dietitian</td>
<td>21 (32.8)</td>
<td>10 (32.3)</td>
<td>11 (33.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Medication use</td>
<td>64 (100.0)</td>
<td>31 (100.0)</td>
<td>33 (100.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Anti-platelet</td>
<td>58 (90.6)</td>
<td>28 (90.3)</td>
<td>30 (90.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Statin</td>
<td>56 (87.5)</td>
<td>28 (90.3)</td>
<td>28 (84.8)</td>
<td>0.71</td>
</tr>
<tr>
<td>β-blocker</td>
<td>44 (68.8)</td>
<td>22 (71.0)</td>
<td>22 (66.7)</td>
<td>0.92</td>
</tr>
<tr>
<td>ACE-inhibitor</td>
<td>31 (48.4)</td>
<td>14 (45.2)</td>
<td>17 (51.5)</td>
<td>0.80</td>
</tr>
<tr>
<td>Supplement use</td>
<td>Omega-3</td>
<td>Vitamin D</td>
<td>Multivitamin</td>
<td>Magnesium</td>
</tr>
<tr>
<td>------------------------</td>
<td>---------</td>
<td>-----------</td>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td></td>
<td>14 (21.9)</td>
<td>9 (14.1)</td>
<td>16 (25.0)</td>
<td>28 (43.8)</td>
</tr>
<tr>
<td></td>
<td>8 (25.8)</td>
<td>4 (12.9)</td>
<td>6 (19.4)</td>
<td>15 (48.4)</td>
</tr>
<tr>
<td></td>
<td>6 (18.2)</td>
<td>5 (14.2)</td>
<td>10 (30.3)</td>
<td>13 (39.4)</td>
</tr>
<tr>
<td></td>
<td>0.66</td>
<td>1.00</td>
<td>0.47</td>
<td>0.64</td>
</tr>
</tbody>
</table>

**Abbreviations:** BMI, body mass index; LDL, low density lipoprotein; HDL, high density lipoprotein; CRP, C-reactive protein; IL-6, interleukin-6; MVPA, moderate-to-vigorous physical activity; wk, week; β, beta; ACE, angiotensin converting enzyme; DII, dietary inflammatory index; DII_{diet+supplements}, intake of nutrients from supplements included.

*a* Values are n (%), means ± SD or medians (IQR).

*b* Difference between participants with anti- versus pro-inflammatory DII score at baseline, Independent Student’s T-test, Mann-Whitney U test or Chi-square test of independence.

*c* Two participants excluded for value >10mg/L.

*d* Negative numbers reflect anti-inflammatory scores, while positive numbers reflect pro-inflammatory scores.

*Significant difference between participants of pro- versus anti-inflammatory DII (without supplements) at baseline, p<0.05.

†Non-parametric variables presented as medians (IQR).

‡Non-parametric variable presented as geometric means.
Table 2. Adjusted means of cardiometabolic risk markers at 6-months by tertiles of 6-month change in DII score, AUSMED Study, 2014-2016

<table>
<thead>
<tr>
<th>Risk variable</th>
<th>T1 (-7.4 to -1.4) n=18</th>
<th>T2 (-1.4 to 1.1) n=20</th>
<th>T3 (1.2 to 4.0) n=18</th>
<th>Correlation with 6-month change DII score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthropometry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>86.8</td>
<td>85.3, 88.4</td>
<td>85.5, 88.3</td>
<td>85.5, 83.9, 87.1</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>101.9</td>
<td>100.0, 103.8</td>
<td>102.4, 104.1</td>
<td>101.4, 99.5, 103.2</td>
</tr>
<tr>
<td><strong>Body composition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total body fat (%)</td>
<td>32.9</td>
<td>31.9, 33.9</td>
<td>33.6, 34.6</td>
<td>33.0, 32.0, 34.0</td>
</tr>
<tr>
<td>Visceral adipose tissue (cm²)</td>
<td>196.1</td>
<td>185.1, 208.1</td>
<td>199.7, 210.8</td>
<td>194.0, 181.5, 206.5</td>
</tr>
<tr>
<td>Subcutaneous adipose tissue (cm²)</td>
<td>325.1</td>
<td>305.2, 345.1</td>
<td>300.9, 319.8</td>
<td>301.8, 280.8, 322.9</td>
</tr>
<tr>
<td><strong>Haemodynamic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>135.9</td>
<td>131.3, 140.6</td>
<td>137.2, 141.8</td>
<td>133.9, 128.8, 139.0</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>83.7</td>
<td>80.9, 86.4</td>
<td>82.1, 83.7</td>
<td>80.7, 77.8, 83.7</td>
</tr>
<tr>
<td><strong>Pathology†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>1.20</td>
<td>1.13, 1.28</td>
<td>1.24, 1.31</td>
<td>1.19, 1.12, 1.27</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>1.76</td>
<td>1.55, 2.00</td>
<td>1.93, 2.17</td>
<td>1.64, 1.43, 1.87</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.35</td>
<td>1.18, 1.55</td>
<td>1.30, 1.48</td>
<td>1.04, 0.90, 1.21</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.36</td>
<td>4.90, 5.86</td>
<td>5.24, 5.69</td>
<td>4.92, 4.48, 5.41</td>
</tr>
<tr>
<td>hs-CRP (mg/L)</td>
<td>0.69</td>
<td>0.42, 1.11</td>
<td>1.24, 0.80, 1.94</td>
<td>0.38, 0.23, 0.62</td>
</tr>
<tr>
<td>hs-IL-6 (pg/mL)</td>
<td>0.96</td>
<td>0.70, 1.33</td>
<td>2.08, 1.52, 2.83</td>
<td>1.42, 1.01, 2.00</td>
</tr>
<tr>
<td>Adiponectin (ng/mL)</td>
<td>7.24</td>
<td>5.96, 8.79</td>
<td>7.23, 6.03, 8.69</td>
<td>8.05, 6.50, 9.84</td>
</tr>
</tbody>
</table>

Participants were distributed into tertiles of 6-month change in DII score based on having an equal number of participants across three groups using SPSS statistical software. Negative numbers reflects anti-inflammatory scores, while positive numbers reflect a pro-inflammatory scores.

Abbreviations: DII, Dietary Inflammatory Index; T, tertile; CI, confidence interval; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hs-CRP, High sensitivity C-reactive protein; Hs-IL-6, High sensitivity interleukin-6.

a Adjusted average indices as least-square means with 95%CI from multi-variable linear models adjusted for baseline value, sex, age, type 2 diabetes mellitus, time since cardiac event and change in moderate-to-vigorous activity levels.

b Pearson correlations between risk marker at 6-months and change in DII score, controlling for baseline marker value. Presented as Pearson (r) coefficient and 95%CI.

c Excluded one participant value for >10 mg/L.

† All pathology markers were log-transformed and data are presented as difference in adjusted geometric means and confidence intervals have been backwards logged.

* Significant correlation, p<0.05 and 95%CI does not include 0.
### Table 3. Baseline to 6-months change in nutrient and food group intake and activity levels between tertiles of 6-month change in DII score<sup>a</sup>, AUSMED Study, 2014-2016.

<table>
<thead>
<tr>
<th>Intake change variable</th>
<th>T1 (-7.4 to -1.4)</th>
<th>T2 (-1.4 to 1.1)</th>
<th>T3 (1.2 to 4.0)</th>
<th>P&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DII Score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DII</td>
<td>-3.68 ± 1.65</td>
<td>-0.15 ± 0.83†</td>
<td>2.18 ± 0.84‡</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>DII+diet+supplements</td>
<td>-3.70 ± 1.70</td>
<td>-0.28 ± 0.76†</td>
<td>2.14 ± 0.81‡</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td><strong>Macronutrients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Energy (kcal)</td>
<td>176.6 ± 521.9</td>
<td>-61.5 ± 427.9</td>
<td>-220.4 ± 289.6‡</td>
<td>0.02*</td>
</tr>
<tr>
<td>Carbohydrate (g)</td>
<td>-9.5 ± 59.2</td>
<td>-9.9 ± 55.4</td>
<td>-25.0 ± 46.4</td>
<td>0.61</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>0.8 ± 18.3</td>
<td>-3.4 ± 26.0</td>
<td>-13.0 ± 26.1</td>
<td>0.21</td>
</tr>
<tr>
<td>Fat (g)</td>
<td>20.5 ± 37.8</td>
<td>-1.9 ± 21.9</td>
<td>-5.5 ± 22.6‡</td>
<td>0.02*</td>
</tr>
<tr>
<td>Saturated fats (g)</td>
<td>-4.4 ± 9.4</td>
<td>-1.3 ± 9.7</td>
<td>-3.4 ± 8.2</td>
<td>0.56</td>
</tr>
<tr>
<td>MUFA (g)</td>
<td>15.2 (34.6)</td>
<td>2.4 (11.6)†</td>
<td>1.9 (16.1)‡</td>
<td>0.01*</td>
</tr>
<tr>
<td>PUFA (g)</td>
<td>6.51 ± 8.9</td>
<td>0.25 ± 6.8</td>
<td>-1.03 ± 5.7‡</td>
<td>0.006*</td>
</tr>
<tr>
<td>Omega-3 (g)</td>
<td>1.07 ± 1.3</td>
<td>-0.13 ± 0.9†</td>
<td>0.07 ± 0.9†</td>
<td>0.002*</td>
</tr>
<tr>
<td>Omega-6 (g)</td>
<td>5.45 ± 8.0</td>
<td>0.55 ± 6.0</td>
<td>-1.04 ± 5.3†</td>
<td>0.01*</td>
</tr>
<tr>
<td>Fiber (g)</td>
<td>9.7 ± 6.2</td>
<td>0.2 ± 5.5†</td>
<td>-3.8 ± 11.3‡</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Alcohol (g)</td>
<td>0.0 (8.0)</td>
<td>0.0 (1.9)</td>
<td>0.0 (1.8)</td>
<td>0.89</td>
</tr>
<tr>
<td><strong>Micronutrients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin C (mg)</td>
<td>32.6 ± 45.2</td>
<td>17.7 ± 89.3</td>
<td>-55.9 ± 133.6‡</td>
<td>0.02*</td>
</tr>
<tr>
<td>Vitamin E (mg)</td>
<td>8.7 (12.0)</td>
<td>-0.6 (5.5)†</td>
<td>1.02 (10.0)‡</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Folate (μg)</td>
<td>68.2 ± 123.8</td>
<td>-13.6 ± 120.6</td>
<td>-70.2 ± 206.0‡</td>
<td>0.03*</td>
</tr>
<tr>
<td>Beta-carotene (μg)</td>
<td>4379 (3865)</td>
<td>2693 (2403)</td>
<td>1853 (1854)</td>
<td>0.07</td>
</tr>
<tr>
<td>Magnesium (mg)</td>
<td>-132.8 ± 169.3</td>
<td>-160.8 ± 137.6</td>
<td>-232.2 ± 163.7</td>
<td>0.15</td>
</tr>
<tr>
<td>Potassium (mg)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>545.0 ± 597.0</td>
<td>164.0 ± 545.6</td>
<td>-519.8 ± 525.7‡</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Sodium (mg)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-384.4 (574.8)</td>
<td>-209.9 (898.5)</td>
<td>-50.3 (979.1)</td>
<td>0.54</td>
</tr>
<tr>
<td><strong>Flavonoids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flavan-3-ol (mg)</td>
<td>0.94 (96.1)</td>
<td>-8.4 (328.1)</td>
<td>-44.8 (142.0)</td>
<td>0.22</td>
</tr>
<tr>
<td>Flavones (mg)</td>
<td>0.90 (1.55)</td>
<td>0.50 (3.33)</td>
<td>-0.59 (1.18)‡</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Flavanols (mg)</td>
<td>9.84 (20.9)</td>
<td>-5.10 (16.7)†</td>
<td>-4.34 (12.7)‡</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Flavanones (mg)</td>
<td>0.27 (18.3)</td>
<td>0.80 (16.5)</td>
<td>-1.77 (37.6)‡</td>
<td>0.001*</td>
</tr>
<tr>
<td>Anthocyanidins (mg)</td>
<td>11.2 (13.8)</td>
<td>10.2 (22.1)</td>
<td>7.6 (17.1)</td>
<td>0.41</td>
</tr>
<tr>
<td>Isoflavones (mg)</td>
<td>0.03 (1.7)</td>
<td>-0.03 (0.2)</td>
<td>-0.14 (0.6)‡</td>
<td>0.02*</td>
</tr>
<tr>
<td><strong>Food group (serves)&lt;sup&gt;d&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruit /d</td>
<td>0.43 (1.2)</td>
<td>0.24 (1.7)</td>
<td>-0.27 (1.7)</td>
<td>0.08</td>
</tr>
<tr>
<td>Vegetables /d</td>
<td>1.14 (2.9)</td>
<td>-0.02 (2.0)†</td>
<td>-0.46 (1.7)‡</td>
<td>0.002*</td>
</tr>
<tr>
<td>Wholegrain cereals /d</td>
<td>0.21 (2.4)</td>
<td>-0.14 (2.1)</td>
<td>-0.20 (1.4)</td>
<td>0.22</td>
</tr>
<tr>
<td>Refined cereals /d</td>
<td>-0.95 (2.9)</td>
<td>-0.05 (2.0)</td>
<td>-0.43 (1.6)</td>
<td>0.43</td>
</tr>
<tr>
<td>Dairy products /d</td>
<td>-0.24 (0.7)</td>
<td>0.24 (0.7)†</td>
<td>-0.09 (0.5)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Red meat /wk</td>
<td>-1.25 (10.5)</td>
<td>-0.15 (5.5)</td>
<td>-2.6 (6.0)</td>
<td>0.27</td>
</tr>
<tr>
<td>Seafood /wk</td>
<td>2.44 ± 4.0</td>
<td>-0.47 ± 3.4</td>
<td>0.61 ± 2.8</td>
<td>0.04*</td>
</tr>
<tr>
<td>Legumes /wk</td>
<td>1.70 (3.1)</td>
<td>0.0 (2.4)</td>
<td>0.01 (2.1)</td>
<td>0.14</td>
</tr>
<tr>
<td>Nuts /wk</td>
<td>2.1 (5.7)</td>
<td>0.0 (4.9)</td>
<td>0.46 (3.3)</td>
<td>0.06</td>
</tr>
<tr>
<td>Olive oil /d (g)</td>
<td>26.6 (52.5)</td>
<td>0.87 (12.2)†</td>
<td>0.66 (19.2)‡</td>
<td>0.03*</td>
</tr>
<tr>
<td>Wine /wk (standard drinks)</td>
<td>0.0 (15.8)</td>
<td>0.0 (9.9)</td>
<td>0.0 (3.1)</td>
<td>0.66</td>
</tr>
<tr>
<td>MEDAS score&lt;sup&gt;e&lt;/sup&gt;</td>
<td>5.0 (4.5)</td>
<td>2.0 (4.0)</td>
<td>2.5 (4.3)</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Activity Levels</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVPA (min/wk)</td>
<td>-7.0 (177)</td>
<td>-19.3 (126)</td>
<td>-27.3 (126)</td>
<td>0.98</td>
</tr>
<tr>
<td>Sedentary time (h/wk)</td>
<td>-5.40 (12.2)</td>
<td>0.63 (10.8)</td>
<td>-1.41 (10.1)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Participants were distributed into tertiles of 6-month change in DII score based on having an equal number of participants across three groups using SPSS statistical software. Negative
numbers reflects anti-inflammatory scores, while positive numbers reflect a pro-inflammatory scores.

Abbreviations: DII, Dietary inflammatory index; T, tertile; DII\text{diet+supplements}, intake of nutrients from supplements included; PUFA, polyunsaturated fatty acids; MUFA, monounsaturated fatty acids; d, day; wk, week; MEDAS, Mediterranean diet adherence screener; MVPA, moderate-to-vigorous physical activity.

\textsuperscript{a}Values are means ± SD or medians (IQR).
\textsuperscript{b}Difference across tertiles, one-way ANOVA or Kruskal-Wallis test with post-hoc Tukey tests.
\textsuperscript{c}Not parameters of the DII.
\textsuperscript{d}Food group serve sizes were based on Foodworks8 analyses

\*Significant difference across tertiles, p<0.05.
†Significant difference between tertile 1 and 2, p<0.025 (Bonferroni correction).
‡Significant difference between tertile 1 and 3, p<0.025 (Bonferroni correction).
Pre-baseline and randomly assigned\(^a\) (n = 73)

- Withdrew (n = 7)
- Unhappy with study group, n = 1
- Mental health problems, n = 1
- Poor English, n = 1
- Peripheral vascular surgery, n = 1
- Nil transport, n = 1
- Lost to follow up, n = 2

Baseline, start intervention (n = 65), 64\(^b\) included in baseline analyses

- Dropout (n = 5)
  - Relocated, n = 2
  - Family crisis, n = 1
  - Lost to follow up, n = 2

3-Month, mid-intervention (n = 60)

- Dropout (n = 4)
  - Mother ill, n = 1
  - Ureteric calculi, n = 1
  - Renal issues, n = 1
  - Hip replacement, n = 1

6-month, end-intervention (n = 56), include in 6-month and change analyses

Figure 1