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Dietary Inflammatory Index and Cardiovascular Disease Risk in Australian Adults: A Secondary Analysis of the OLIVAUS Trial

Jocelynne Young [1], Elena S. George [2], Wolfgang Marx [3], Hannah L. Mayr [4,5], James R. Hebert [6,7], Sherry Price [6,7], Colleen J. Thomas [8], Catherine Itsiopoulos [9], George Moschonis [1,10], Yingting Cao [1,*] and Katerina Sarapis [1,*]

[1] Department of Food, Nutrition and Dietetics, School of Allied Health, Human Services and Sport, La Trobe University, Melbourne 3086, Australia
[2] Institute for Physical Activity and Nutrition (IPAN), School of Exercise and Nutrition Sciences, Deakin University, Geelong 3220, Australia
[3] Impact (the Institute for Mental and Physical Health and Clinical Translation), Food & Mood Centre, Deakin University, Geelong 3220, Australia
[4] Department of Nutrition and Dietetics, Princess Alexandra Hospital, Woolloongabba, QLD, 4102, Australia
[5] PA-Southside Clinical Unit, Faculty of Health, Medicine and Behavioural Sciences, the University of Queensland, St Lucia, QLD, 4072, Australia
[6] Department of Epidemiology and Biostatistics and Cancer Prevention and Control Program, Arnold School of Public Health, University of South Carolina, Columbia, SC 29206 USA
[7] Department of Nutrition, Connecting Health Innovations LLC (CHI), Columbia, SC 29201 USA
[8] Department of Microbiology, Anatomy, Physiology and Pharmacology, School of Agriculture, Biomedicine and Environment, La Trobe University, Bundoora, 3086, VIC. Australia
[9] College of Science Technology Engineering Mathematics (STEM), RMIT University, Melbourne 3000, Australia
[10] Department of Nutrition & Dietetics, Harokopio University, Athens 17671, Greece
* Correspondence: tina.cao@latrobe.edu.au (Y.C.); k.sarapis@latrobe.edu.au (K.S.)

Abstract

Background: The Dietary Inflammatory Index (DII®) is a commonly used tool to assess diet-related inflammation. Higher DII scores are associated with increased cardiovascular disease risk in large observational cohorts yet, controlled-trial evidence evaluating cardiovascular outcomes across DII levels is scarce. This secondary analysis examined cross-sectional differences and longitudinal associations between dietary inflammatory potential and cardiovascular outcomes in healthy Australian adults. **Methods:** In a double-blind randomised crossover trial, 50 participants consumed 60 mL/day of either high-phenolic (320 mg/kg) or low-phenolic (86 mg/kg) olive oil for two 3-week intervention periods, separated by a 2-week washout. Anthropometry (weight, height, waist circumference, BMI) and cardiovascular outcomes (i.e., blood pressure, lipids, oxidised LDL, and HDL-cholesterol efflux capacity) were measured at four timepoints. DII and energy-adjusted DII (E-DII™) scores were calculated from 3-day food diaries at baseline and follow-up of each 3-week intervention phase. Linear mixed-effects models compared cardiovascular outcomes across DII tertiles (low, medium, high) adjusting for intervention, period, sequence, age, sex, and waist circumference. **Results:** Forty-three participants completed the study. At baseline, BMI, waist circumference, systolic blood pressure, total cholesterol, and LDL differed significantly across DII tertiles ($p<0.05$). Across the study period, cardiovascular outcomes did not differ between medium or high versus low DII tertiles, and no significant time-by-tertile interactions were observed (all $p>0.05$). DII values remained stable across timepoints, while E-DII decreased modestly within individuals in both intervention periods. **Conclusions**: In this healthy cohort, DII was not associated with adverse short-term changes in cardiovascular outcomes. Longer-duration studies with greater

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contrast in dietary inflammatory potential are warranted to clarify the relationship between DII and cardiovascular health.

Keywords: cardiovascular risk factors; energy-adjusted dietary inflammatory index; inflammation; diet; polyphenol; olive oil

1. Introduction

Cardiovascular disease (CVD) remains one of the leading causes of morbidity and mortality worldwide and in Australia [1,2]. In 2022, over 4.5 million Australians self-reported living with CVD, and it accounted for approximately 24% of all deaths, with more than 1500 hospitalisations each day [2,3]. This burden underscores the need to identify modifiable determinants of early CVD risk and to implement effective prevention strategies across the life course.

Chronic, low-grade systemic inflammation is widely recognised as a key pathophysiological contributor to the initiation and progression of CVD. Persistent inflammatory signalling can disrupt vascular homeostasis by promoting endothelial dysfunction and reducing nitric oxide bioavailability, while accelerating oxidative modification of lipoproteins and facilitating atherogenesis and plaque instability [4]. Over time, these processes can impair lipid metabolism, blood pressure regulation, glucose homeostasis, and oxidative balance, collectively contributing to cardiovascular risk [5].

Multiple factors contribute to systemic inflammation, including genetic, environmental, and lifestyle factors. Among these, long-term adherence to specific dietary patterns has shown to either exacerbate or attenuate systemic inflammation, thereby influencing cardiovascular risk [6,7]. Diets high in saturated fats, refined grains, added sugars, and ultra-processed foods have been associated with metabolic dysfunction and higher concentrations of pro-inflammatory biomarkers, including C-reactive protein (CRP), interleukin-6 (IL-6), and tumour necrosis factor-α (TNF-α) [8–10]. In contrast, diets rich in vegetables, fruits, whole grains, legumes, nuts, and unsaturated fats are generally associated with lower inflammation and improved vascular health [9,11]. The Mediterranean dietary pattern is the most extensively studied example, with reported benefits for blood pressure (BP), lipid profile, oxidative stress and other cardiovascular outcomes across diverse populations. A meta-analysis of 18 randomised controlled trials found that anti-inflammatory dietary patterns, including the Mediterranean diet (MedDiet), significantly reduced systolic BP, low density lipoprotein (LDL) cholesterol, total cholesterol, and high-sensitivity CRP (hsCRP) compared with omnivorous diets [11]. An umbrella review further reported consistent associations between MedDiet adherence and lower circulating hs-CRP and IL-6, alongside higher adiponectin concentrations [12]. These favourable inflammatory profiles may, in part, reflect the diet's richness in bioactive compounds—particularly polyphenols—found in fruits, vegetables, nuts, wine, and olive oil, which exhibit well-established antioxidant and anti-inflammatory properties [13]. Overall, this growing body of evidence suggests that diet quality plays an important role in modulating inflammation and may influence CVD risk.

The Dietary Inflammatory Index (DII®) was developed to quantify the inflammatory potential of an individual's diet. It is as a literature-derived score that incorporates up to 45 food and nutrient parameters identified as having pro- or anti- inflammatory associations with circulating inflammatory biomarkers [9]. The DII was initially validated against hs-CRP, demonstrating its ability to predict elevated (>3 mg/L) concentrations [14]. It has since been associated with other inflammatory markers including IL-6 and TNF-α. Higher DII scores reflect more pro-inflammatory dietary patterns, typically characterised by higher saturated fat and refined carbohydrate intake and lower consumption of fruits, vegetables, and nutrient-dense foods [9]. In observational studies, diet patterns with more pro-inflammatory DII profiles have been associated with adverse cardiometabolic outcomes, including higher CVD incidence and mortality. For example, in the SUN cohort—a longitudinal study of Spanish university graduates- individuals in the highest DII quartile had approximately twice the risk of developing CVD compared with the lowest quartile, and higher DII

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categories have also been associated with increased all-cause mortality [15,16]. Conversely, lower (more anti-inflammatory) DII scores are commonly observed in those following healthier dietary patterns such as low-fat diets and Mediterranean style eating patterns [17,18].

Despite these associations, important gaps remain in the literature with regards to DII and CVD outcomes. Most evidence comes from observational studies, limiting causal inference and the ability to assess temporality, particularly cannot adequately capture within-individual changes in dietary inflammatory potential alongside corresponding changes in cardiovascular markers over time [18,19]. Furthermore, many studies examining dietary influences on inflammation and cardiovascular risk have been conducted in populations with established cardiovascular or metabolic disease, with fewer investigations in healthy adults. Collectively, these observations underscore the need for high-quality intervention studies that combine repeated dietary and biomarker assessments using comprehensive biomarker panels to better clarify how dietary inflammatory potential relates to early CVD risk [20]. Compared with observational studies, repeated measurements within an intervention allow clearer temporal ordering and enable assessment of changes in dietary inflammatory potential alongside corresponding changes in cardiometabolic markers across defined timepoints. Such designs may partially mitigate residual confounding and between-person variability inherent to purely observational research [20]. The present study addresses these gaps by examining DII scores in healthy Australian adults within a controlled dietary intervention. Using data from a randomised, cross-over trial (the OLIVAUS study), originally designed to investigate the effects of dietary olive oil polyphenols on CVD markers, this secondary analysis aims to examine longitudinal associations between dietary inflammatory potential and cardiovascular outcomes (including BP, systemic inflammation, oxidative stress, lipid metabolism) in healthy adults.

2. Materials and Methods

The present study is a secondary analysis of data collected in a 10-week double-blind, randomised, controlled crossover trial (OLIVAUS) designed to explore the effects of high-phenolic olive oil (HPOO) versus low-phenolic olive oil (LPOO) on cardiovascular risk markers in healthy Australian adults[21,22]. The study was conducted in accordance with Good Clinical Practice guidelines, the Declaration of Helsinki, and CONSORT reporting standards. All procedures were approved by the La Trobe University Human Research Ethics Committee (HEC17-067). The trial was prospectively registered with the Australia New Zealand Clinical Trials Registry (ACTRN12618000706279), and written informed consent was obtained from all participants.

2.1. Study Participants

Volunteers were recruited in Melbourne, Australia, via social media, La Trobe University email databases, word of mouth, and campus posters. Eligibility was determined using a standardised screening procedure. Participants were required to be aged 18–75 years with a body mass index (BMI) between 18.5 and 40 kg/m^2. Exclusion criteria included non-English-speaking individuals, pregnant or lactating women, smokers, those following medically prescribed special diets (e.g., gluten-free for coeliac disease), and individuals with high habitual olive oil intake (>1 tablespoon/day). Participants were also excluded if they regularly consumed vitamin or antioxidant supplements and were unable to cease them for the study duration (except iron, calcium, and vitamin D), or if they were taking prescribed medications such as antihypertensive agents, lipid-lowering drugs, or non-steroidal anti-inflammatory drugs. Additional exclusions included diagnosed chronic disease (e.g., diabetes, hyperlipidaemia, hypertension, inflammatory conditions), gastrointestinal disease, or any other condition likely to impair adherence to the protocol.

2.2. Study Design and Procedure

Participants were randomly assigned to one of two intervention sequences (HPOO vs. LPOO). The intervention comprised two 3-week periods (Period 1 and Period 2). During the first intervention

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period (Period 1, timepoints T1 to T3), participants were asked to consume 60 mL/day of either HPOO (320 mg/kg phenolics) or LPOO (86 mg/kg phenolics), incorporated raw into their usual diet. Following a 2-week washout period, participants crossed over to consume the alternate oil for further 3 weeks (Period 2; timepoints T4 and T6). The test oils were stored in identical sealed containers with concealed codes to maintain blinding of participants and investigators. Codes were revealed only after completion of statistical analyses.

Full protocol details, including randomisation procedures, sample size, dietary and physical activity procedures, anthropometry, compliance, blinding, and adverse event reporting are reported elsewhere [21–23].

2.3. Sample Characteristics

At screening and baseline, socio-demographic information was collected, including age, sex, languages spoken at home, education level, ethnicity, and parental country of birth. Anthropometric and lifestyle data (e.g., weight, height, waist circumference, smoking status), as well as medical history, medication use, and dietary supplement use, were also recorded. Waist circumference was included as a covariate as a marker of adiposity; however, as it may lie on the causal pathway between diet and cardiometabolic outcomes, results should be interpreted with consideration of potential over-adjustment.

2.4. Measurements

2.4.1. Dietary Intake Assessment

Dietary intake was assessed using a 3-day food diary collected at baseline (T1 and T4) and at the end of each intervention period (T3 and T6), as described in the trial protocol [22]. Participants recorded all foods and beverages consumed over two weekdays and one weekend day (preferably non-consecutive), including portion sizes, brands, preparation methods, and cooking techniques. Guidance on diary completion and incorporation of the trial oils in raw, uncooked form was provided at the pre-baseline visit. Diaries were reviewed at assessment visits for completeness and accuracy.

Nutrient analyses (energy, macro- and micronutrients) were performed using FoodWorks® 9 (Xyris Software Pty Ltd., Queensland, Australia) and relevant databases: Australia—AusFoods 2017, Aus Brands 2017, AUSNUT 2011-2013). To characterise intake of phenolic-rich foods during the intervention, data for relevant phenolic classes (including flavonoids, lignans, total polyphenols, other polyphenols, and stilbenes) were extracted from dietary records. The Phenol-Explorer database was used to estimate polyphenol composition of foods [24]. Average phenolic concentrations from the database were applied to calculate phenolic content of specified food groups for inclusion in analyses.

2.4.2. Dietary Inflammatory Index (DII®) and Energy-Adjusted DII (E-DII™)

In the present study, the inflammatory potential of the diet was calculated based on the Dietary Inflammatory Index (DII®), which was developed to quantify the inflammatory potential of individuals' diets on a scale from maximally anti-inflammatory (most negative score) to maximally pro-inflammatory (most positive score). The development of the DII has been described in detail elsewhere [25]. Briefly, the DII scoring algorithm was based on a careful review of the literature through which 1943 articles identified 45 food parameters (i.e.,: macronutrients including specific categories of fatty acids, carbohydrate, and proteins; macronutrients including vitamins and minerals; flavonoids; and whole food items including herbs and spices) as having sufficiently robust literature in relation to six inflammatory biomarkers—i.e., interleukins (IL)-1b, -4, -6, -10, TNFα, and CRP [26,27].

In this study, self-report values for 29 of these food parameters were available from the 3-day food diaries. These were translated into z-scores using a global comparative database consisting of data from 11 countries by subtracting from the individual's self-report value the mean of the global

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database then dividing by the standard deviation. These scores were then converted to proportions (i.e., with values ranging from 0 to 1) and centered on zero by doubling each and subtracting 1 (xx-1). These centered proportions were then multiplied by their respective coefficients (overall food parameter-specific inflammatory effect scores) to obtain DII scores for each food parameter. These were summed to obtain the overall DII score at T1, T3, T4, and T6.

Energy-adjusted DII (E-DII™) scores were calculated using the density approach by calculating DII per 1000 kcal consumption. This employed the same procedure for scoring but relies on an energy-adjusted global comparison database [28–31]. These DII and E-DII scores have a potential range from approximately -9 to +8; i.e., from minimally to maximally pro-inflammatory, respectively. The DII and E-DII are scored similarly and scaled identically; so, the scores are comparable across studies [28]. The DII/E-DII has been construct-validated in many (>60) studies, including one meta-analysis on CRP [32].

For this study, the following 29 of the 45 food parameters were used to calculate an individual's overall DII score: energy, protein, total fat, saturated fat, trans fat, monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA), cholesterol, carbohydrate, alcohol, fibre, thiamine, riboflavin, niacin, vitamin C, vitamin E, vitamin B6, vitamin B12, vitamin A, folic acid, beta-carotene, magnesium, iron, zinc, selenium, omega-6, omega-3, caffeine, and mercury. For the E-DII, energy was in the denominator; so, xx-1 parameters were used for computation. The decision to use the DII or E-DII was based on model goodness of fit or overall model explanatory ability.

In the present analysis, the DII was selected as the primary exposure to reflect absolute dietary inflammatory potential. However, given that total energy intake may vary within individuals over time, E-DII was also examined in secondary analyses. Both metrics are presented to provide a comprehensive assessment of dietary inflammatory potential.

2.4.3. Biochemical Analyses

Fasting venous blood samples were collected in the early morning at baseline (T1, T4) and at the end of each intervention period (T3, T6) following a 10 h fast. Blood was centrifuged (Hettich Rotina 420R, Massachusetts, USA) at 2350 rpm for 10 min at 4 °C. Serum and/or plasma were aliquoted into 500 µL volumes and stored at −80 °C until analysis[23].

Total cholesterol and triglycerides were measured using Alinity c Cholesterol Assay and Alinity c Triglyceride Assay, respectively (Abbott GmbH & Co., Wiesbaden, Germany). LDL cholesterol was measured using a direct quantitative method (Alinity c Direct LDL Assay; Sekisui Diagnostics, Charlottetown, Canada) and HDL cholesterol using a homogeneous method (Ultra HDL Assay; Abbott GmbH & Co., Wiesbaden, Germany). Oxidised LDL was measured using a solid-phase, two-site enzyme-linked immunosorbent assay (ELISA; Mercodia, Uppsala, Sweden). HDL-C efflux was measured using Cholesterol Efflux Fluorometric Assay Kit (BioVision). Finally, the Alinity c CRP Vario assay (SENTINEL CH, Milano, Italy) was used for the quantitative immunoturbidimetric determination of hs-CRP in human serum.

The methodology and primary results for these biochemical markers have been reported previously [21,33]. In the present secondary analysis, these biomarker data were re-analysed after stratifying participants according to tertiles of DII score to examine whether cardiometabolic outcomes differed across levels of dietary inflammatory potential.

2.4.4. Blood Pressure Measurements

Blood pressure (BP) was measured using applanation tonometry with a SphygmoCor XCEL system (AtCor Medical, Australia) at baseline (T1, T4) and at the end of each intervention period (T3, T6) [22]. After a minimum 5 min rest in the supine position, peripheral/ brachial systolic and diastolic BP were measured using an appropriately sized cuff placed on the upper left arm. Three consecutive recordings were obtained, and the average of the final two measurements was used for analysis. Central (aortic) SBP, DBP, and pulse pressure (PP) were derived from the brachial BP cuff [22].

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Participants were classified using the American College of Cardiology (ACC) and American Heart Association (AHA) BP categories (normal, elevated, stage I hypertension, stage II hypertension).

2.4.5. Statistical Analysis

DII and E-DII were analysed as continuous variables across four timepoints (T1, T3, T4, T6) and were also categorised into tertiles for baseline comparisons and linear mixed-effects models. Descriptive statistics are presented as mean ± standard deviation (SD) for continuous variables and as counts and percentages for categorical variables. Baseline differences (T1) across DII tertiles were explored using one-way ANOVA for continuous variables and χ^2 tests for categorical variables.

Within-person changes during each intervention period were initially explored using paired t-tests comparing pre- and post-period values (Period 1: T1 to T3; Period 2: T4 to T6). Period-specific change scores were calculated as Δ = end − baseline for each period. Between-sequence differences in period-specific and overall change scores were assessed using independent t-tests. These t-tests and change-from-baseline analyses were exploratory. Assumptions of normality and homogeneity of variance were assessed, and non-parametric tests were used in sensitivity analyses where appropriate. Analyses were repeated for E-DII.

The primary analyses used linear mixed-effects models fitted to long-format data to examine longitudinal associations while accounting for the crossover design and repeated measurements. Separate models were constructed for each cardiometabolic outcome (average systolic and diastolic BP, total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, oxidised LDL, and HDL-cholesterol efflux capacity). DII scores were categorised into tertiles (low, medium, high) using data-driven cut-points that divided participants into approximately equal-sized groups. In mixed-effects models, DII tertile, timepoint, period, intervention and sequence were specified as fixed effects and participant as a random effect to account for within-person correlation. Timepoint was treated as categorical. Models estimated differences in outcomes between DII tertiles averaged across the study period, with β coefficients and 95% confidence intervals reported. Timepoint × tertile interactions were examined to assess whether associations differed across measurement occasions. Models were estimated using restricted maximum likelihood (REML). Unadjusted models were fitted initially, followed by adjustment for age, sex, and waist circumference. All analyses were conducted using Jamovi version 2.7.9 [34]. As a supplementary analysis, linear mixed-effects models were used to examine the association between DII tertiles and CRP across repeated measures, using the same model structure as the primary analyses to account for within-subject correlation and the crossover design.

3. Results

Of the 105 volunteers who expressed interest, 50 eligible individuals (aged 38.5±13.9 years, 66% females) were recruited and randomly allocated to either the LPOO (n = 25) or HPOO (n = 25) sequence. At the end of the 10-week intervention, 43 participants completed the study (LPOO sequence, n = 23; HPOO sequence, n = 20). Participant flow diagram (Figure 1) and the primary trial outcomes have been reported previously [22].

Baseline characteristics by DII tertile are presented in Table 1. Across tertiles, age, height, and weight did not differ significantly (all $p > 0.05$). BMI and waist circumference values were significantly higher in the medium DII tertile compared with the low DII tertile (BMI 26.4 (3.31) vs 22.9 (2.67) kg/m^2, $p = 0.008$; waist circumference 91.2 (9.60) vs 80.6 (6.85) cm, $p = 0.003$). Peripheral SBP differed significantly across tertiles ($p = 0.043$), with the medium tertile highest (127 (14.7) mmHg) compared with the low tertile (115 (11.1) mmHg). Total cholesterol and LDL-cholesterol were significantly higher in the medium and high DII tertiles compared with the low tertile (total cholesterol $p = 0.043$; LDL-cholesterol $p = 0.035$) (Table 1). Central DBP, peripheral DBP, HDL-cholesterol, oxidised LDL, and HDL-cholesterol efflux capacity were similar across tertiles, while triglycerides and central SBP showed non-significant trends toward higher values in the medium tertile ($p = 0.060$ and $p = 0.080$, respectively).

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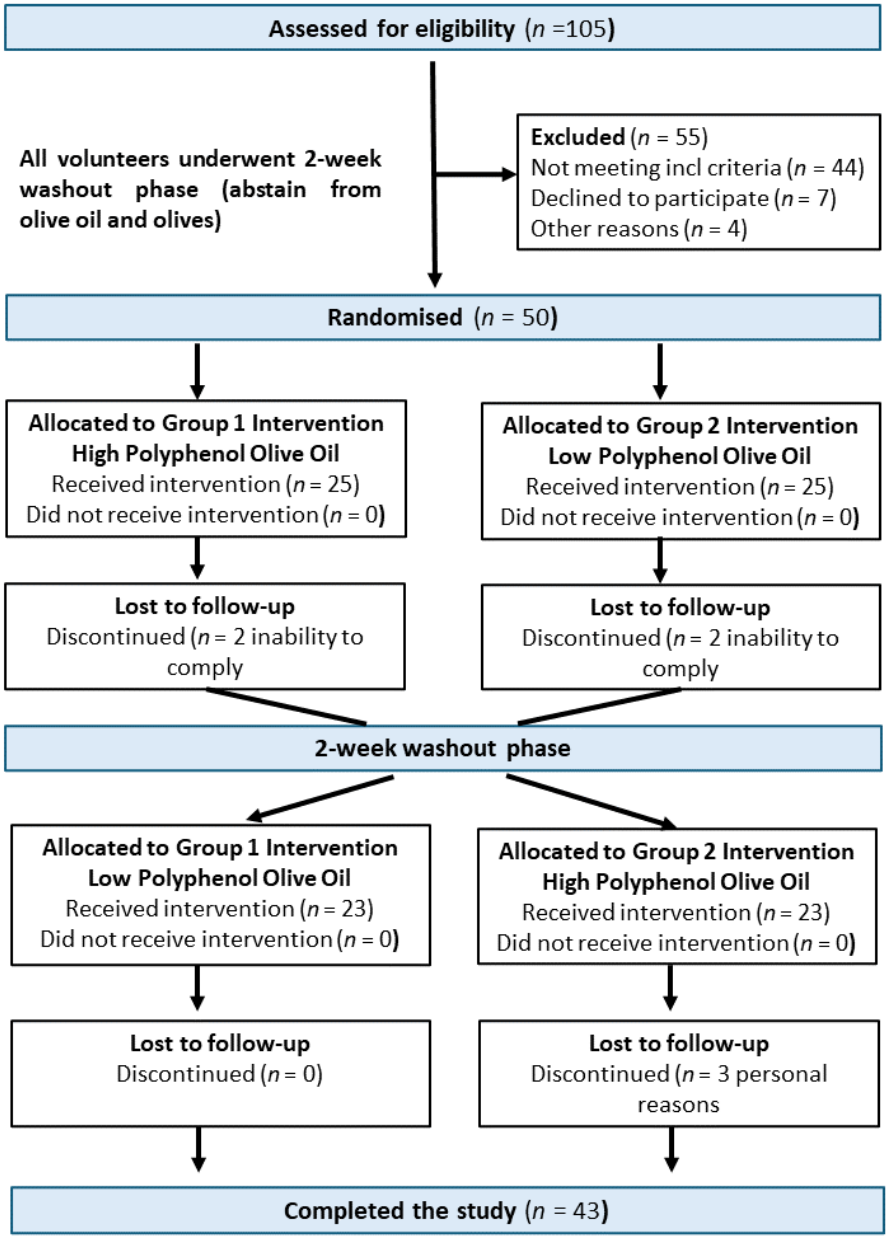

Figure 1. OLIVAUS study participant flow diagram.

Table 1. Baseline (T1) characteristics and cardiovascular parameters of OLIVAUS participants by DII tertiles.

	Tertile 1: Low DII DII≤-1.68 (n=17)	**Tertile 2: Medium DII −1.68 < DII ≤ −0.315 (n=16)**	**Tertile 3: High DII DII>-0.315 (n=17)**	**p-Value**
Age (years)	33.1 (12.2)	41.4 (14.2)	41.2 (14.4)	0.127
Height (m)	1.72 (0.0968)	1.70 (0.108)	1.65 (0.0715)	0.057
Weight (kg)	67.9 (11.1)	76.5 (13.9)	67.9 (12.1)	0.125
BMI (kg/m²)	22.9 (2.67)	26.4 (3.31)	24.9 (3.56)	0.008*
Waist circumference (cm)	80.6 (6.85)	91.2 (9.60)	88.6 (13.9)	0.003*
Gender (%)				
Females	58.8%	56.3%	82.4%	
Males	41.2%	43.8%	17.6%	
Education (years)	16.1 (1.96)	17.6 (3.18)	18.1 (4.71)	0.144

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Educational level (%)				
Secondary	0.0%	6.3%	5.9%	
Tertiary	88.2%	81.3%	88.2%	
Trade	5.9%	6.3%	0.0%	
Other	5.9%	6.3%	5.9%	
English first language (%)				
Yes	76.5%	75.0%	76.5%	
No	23.5%	25.0%	23.5%	
Country of Birth (%)				
Australia, NZ, Pacific Islanders	82.4%	75.0%	52.9%	
Europe	0.0%	0.0%	29.4%	
South America	0.0%	25.0%	0.0%	
Middle East and Asia	17.6%	0.0%	17.6%	
Ethnicity (%)				
Asian	23.5%	6.3%	23.5%	
Caucasian Australian	70.6%	68.8%	41.2%	
Caucasian European	0.0%	6.3%	35.3%	
Islander	5.9%	0.0%	0.0%	
Latin American	0.0%	18.8%	0.0%	
Lifestyles and medical conditions				
Medications (%)				
Yes	0.0%	0.0%	0.0%	
No	100.0%	100.0%	100.0%	
Medical condition (%)				
Yes	0.0%	0.0%	0.0%	
No	100.0%	100.0%	100.0%	
Haemodynamic Indices				
Peripheral SBP (mmHg)	115.0 (11.1)	127.2 (14.7)	118.3 (11.9)	0.043*
Peripheral DBP (mmHg)	68.5 (7.17)	72.3 (9.79)	70.2 (8.04)	0.457
Central SBP (mmHg)	102.0 (9.92)	112.8 (15.6)	106.4 (12.6)	0.080
Central DBP (mmHg)	67.8 (7.58)	73.6 (10.2)	70.8 (7.85)	0.189
Pathology				
Triglycerides (mmol/L)	0.81 (0.32)	1.30 (0.84)	1.01 (0.33)	0.060
Total cholesterol (mmol/L)	4.59 (1.12)	5.21 (0.96)	5.45 (0.74)	0.043*
HDL-cholesterol (mmol/L)	1.55 (0.31)	1.49 (0.31)	1.64 (0.38)	0.471
LDL-cholesterol (mmol/L)	2.63 (0.86)	3.19 (0.87)	3.37 (0.71)	0.035*
Oxidised LDL (mU/mL)	73.0 (25.4)	76.7 (19.4)	81.8 (23.1)	0.575
HDL- Cholesterol efflux capacity (%)	51.7 (5.0)	53.6 (4.5)	53.8 (4.8)	0.407
hsCRP (mg/L)	1.00 (1.85)	1.86 (2.77)	2.59 (3.56)	0.239

[1] Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; DII, dietary inflammatory index; hsCRP, high-sensitivity C-reactive protein; [2] Values are presented as mean ± SD for continuous variables and n (%) for categorical variables; [3] Difference across DII tertiles at baseline, Independent Student t test, Mann–Whitney U test or Chi-square test of independence; [4] Negative numbers reflect anti-inflammatory scores, while positive numbers reflect pro-inflammatory scores; [5] *Indicates statistically significant inter-tertile differences, $p < 0.05$.

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3.1. Association Between DII Tertiles and Cardiovascular Profiles

The mixed-effects analyses included 183 repeated-measures observations across four timepoints (T1, T3, T4, and T6). Participant contributions at each timepoint were: T1, n = 50; T3, n = 47; T4, n = 43; T6, n = 43, reflecting discontinuation by seven participants.

Repeated measures DII values were grouped into low (more anti-inflammatory), medium, high (more anti-inflammatory) tertiles to reflect the relative dietary inflammatory potential of each observation across all timepoints. Tertiles were defined by dividing observations into three equal-sized groups (n = 61 per tertile). DII cut-offs were: tertile 1, DII ≤ −1.62; tertile 2, −1.62 < DII ≤ −0.180; and tertile 3, DII > −0.180.

Across the four timepoints of the study period, there were no significant differences in mean cardiovascular outcomes between medium versus low DII or high versus low DII (all $p > 0.05$) (Table 2). Relative to the low DII tertile, neither the medium nor high DII tertile was associated with statistically significant differences in peripheral or central BP, triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol, oxidised LDL, or HDL-cholesterol efflux capacity (Table 2). In linear mixed-effects models, DII tertiles were not significantly associated with CRP across repeated measures. There was no consistent evidence of a DII-by-time interaction, although a significant difference was observed at one time point for the high versus low DII group ($p = 0.047$), which was not consistent across other time points.

Table 2. Differences in cardiovascular outcomes comparing DII tertiles across the study period .

Cardiovascular outcomes	Medium DII vs Low DII β (95% CI)	p-Value	High DII vs Low DII β (95% CI)	p-Value
Peripheral SBP (mmHg)	0.36 (−2.19, 2.91)	0.778	1.14 (−1.78, 4.06)	0.442
Peripheral DBP (mmHg)	0.00 (−1.97, 1.96)	0.996	1.49 (−0.74, 3.72)	0.190
Central SBP (mmHg)	0.60 (-1.76, 2.95)	0.619	1.19 (-1.43, 3.81)	0.372
Central DBP (mmHg)	0.07 (-1.86, 2.00)	0.943	1.04(-1.10, 3.185)	0.338
Triglycerides (mmol/L)	0.02 (−0.13, 0.18)	0.758	-0.02 (−0.20, 0.16)	0.826
Total cholesterol (mmol/L)	0.08 (−0.10, 0.26)	0.372	−0.08 (−0.29, 0.16)	0.440
HDL-cholesterol (mmol/L)	0.05 (−0.01, 0.12)	0.101	0.03 (−0.05, 0.10)	0.460
LDL-cholesterol (mmol/L)	0.05 (−0.09, 0.19)	0.518	−0.07 (−0.24, 0.09)	0.368
Oxidised LDL (mU/mL)	−4.03 (−12.01, 3.95)	0.320	3.58 (−4.96, 12.12)	0.408
HDL-Cholesterol efflux (%)	−0.20 (−1.15, 0.75)	0.679	−0.33 (−1.43, 0.77)	0.559
hsCRP (mg/L)	0.08 (-0.56, 0.72)	0.805	0.42 (-0.27, 1.11)	0.235

[1] Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; DII, dietary inflammatory index; hsCRP, high-sensitivity C-reactive protein; [2] β = adjusted mean difference for medium vs low DII [34] and high vs low DII; [3] Models adjusted for age, gender, and waist circumference; [4] *Indicates statistically significant inter-tertile differences, $p < 0.05$.

Overall, average cardiovascular levels were similar across DII tertiles (Table 3). Estimated peripheral SBP remained unchanged across tertiles (119 mmHg in the low and medium tertiles and 121 mmHg in the high tertile). Peripheral DBP was also comparable, with only a small difference in the high tertile (70.3 mmHg) compared with the low and medium tertiles (68.8mmHg). Central SBP was unchanged across tertiles (106 mmHg in the low tertile and 107 mmHg in the medium and high tertiles). Central DBP was also stable, with a small increase in the high tertile (70.7 mmHg) compared with the low and medium tertiles (both 69.7 mmHg). Triglyceride levels also remained stable across all tertiles (low DII, 0.93 mmol/L; medium DII, 0.96 mmol/L; high DII, 0.91mmol/L). Total cholesterol and LDL-cholesterol showed small variation between groups. HDL-cholesterol was likewise similar (low DII, 1.55 mmol/L; medium DII, 1.60 mmol/L; high DII, 1.57mmol/L). Oxidised LDL and HDL-cholesterol efflux capacity did not differ meaningfully by DII tertile, Confidence intervals were overlapping, suggesting no clear changes in these outcomes across DII tertiles (Table 3). Additionally,

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time and DII tertile interactions showed no evidence of different cardiometabolic trajectories across low, medium, and high DII tertiles (all $p > 0.05$). Model-estimated marginal means of cardiovascular outcomes across tertiles of E-DII are presented in Supplementary Table S1.

Table 3. Model-estimated marginal means of cardiovascular outcomes by DII tertile.

Cardiovascular outcomes	Tertile 1 (low DII)	Tertile 2 (medium DII)	Tertile 3 (high DII)
Peripheral SBP (mmHg)	119 (116-123)	120 (117-123)	121 (117-124)
Peripheral D BP (mmHg)	68.8 (66.5-71.2)	68.8 (66.5-71.2)	70.3 (68.0-72.7)
Central SBP (mmHg)	106 (103-109)	107 (104-109)	107 (104-110)
Central DBP (mmHg)	69.7 (67.4-72.0)	69.7(67.5-72.0)	70.7 (68.4-73.0)
Triglycerides (mmol/L)	0.93 (0.753-1.11)	0.96 (0.781-1.13)	0.91 (0.731-1.09)
Total cholesterol (mmol/L)	4.97 (4.67-5.26)	5.05 (4.75-5.34)	4.88 (4.75-5.34)
HDL-cholesterol (mmol/L)	1.55 (1.44-1.64)	1.60 (1.50-1.69)	1.57 (1.47-1.67)
LDL-cholesterol (mmol/L)	3.01 (2.77-3.26)	3.06 (2.81-3.31)	2.94 (2.69-3.19)
Oxidised LDL (mU/mL)	72.1 (65.4-78.9)	68.1 (61.5-74.7)	75.7 (69.0-82.4)
HDL-cholesterol efflux (%)	52.9 (51.5–54.4)	52.7 (51.3–54.2)	52.6 (51.1–54.1)
hsCRP (mg/L)	0.97 (0.38-1.56)	1.05 (0.48-1.62)	1.39 (0.80-1.98)

[1] Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; DII, dietary inflammatory index; hsCRP, high-sensitivity C-reactive protein; [2] Values are estimated marginal means (95% confidence intervals) from linear mixed-effects models adjusted for intervention, period, sequence, age, sex, and waist circumference, averaged across the study period.

Paired analyses were used to describe within-person changes in DII across each intervention period. Unadjusted DII scores did not change within individuals in either period (Period 1, $p=0.484$; Period 2, $p=0.576$). In contrast, E- DII decreased within individuals in both periods (mean reduction of 0.886 units in Period 1, $p<0.001$) and 0.596 units in Period 2, $p=0.021$), indicating a modest shift toward a less inflammatory dietary profile when adjusted for energy intake (Supplementary Table S2). This change may reflect alterations in total energy intake and/or broader dietary behaviours during the intervention rather than substantial changes in the inflammatory composition of the diet. Corresponding changes in energy intake should be considered when interpreting these findings.

There was no evidence that treatment order influenced DII. Participants allocated to receive HPOO first versus LPOO first did not differ in DII scores at baseline or at any subsequent time point (all $p>0.05$). In addition, the magnitude of within-person DII change during Period 1 and Period 2 did not differ between sequences ($p=0.646$ and $p=0.730$, respectively). The average DII score change across both periods was also similar between intervention sequences (receiving HPOO vs. LPOO or receiving LPOO vs. HPOO) ($p=0.438$) (Supplementary Table S3).

4. Discussion

This secondary analysis investigated the relationship between the Dietary Inflammatory Index (DII) and CVD markers in healthy Australian adults participating in the OLIVAUS study [22]. We examined both cross-sectional differences in CVD markers by DII tertile and the change of cardiovascular outcomes across four time points by DII tertiles. Our primary hypothesis, that higher DII scores would be associated with less favourable CVD markers and changes in CVD risk over time, was not supported by this secondary analysis. Because E-DII is standardised per unit of energy intake, reductions in E-DII may partly reflect changes in total energy consumption rather than true shifts in dietary inflammatory composition.

In this study, baseline anthropometric and cardiovascular measures varied across tertiles of the DII. For instance, participants in the middle DII tertile exhibited markedly higher BMI and waist circumference compared with those in the low DII tertile. Although our baseline comparisons are descriptive and unadjusted as the focus of this study was designed to evaluate longitudinal changes

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over time using mixed-effects models rather than to test cross-sectional differences between tertiles at baseline. Therefore, the directional pattern is consistent with findings from the PREDIMED study, where higher (more pro-inflammatory) DII scores were independently associated with greater BMI and waist circumference after adjustment for confounders, including MedDiet adherence [35]. While the analytical approaches differ, the similar trend provides a meaningful point of comparison and suggests that more pro-inflammatory dietary patterns may cluster with higher adiposity, which is an established contributor to chronic inflammation and metabolic risk.

Similarly, SBP also differed peaking in the middle tertile in our baseline descriptive comparisons. A previous meta-analysis reported that being in the highest DII category was associated with a 1.2 mmHg significant increase in SBP and having higher odds of hypertension (OR 1.13) [36]. Cross-sectional and case-control studies also support this relationship; one analysis found a 1.6-fold higher risk of hypertension in individuals with elevated DII, particularly in men [37]. These findings may provide context for the observed SBP differences, highlighting diet-induced inflammation as a potential contributor to elevated SBP.

Lipid profiles differed across tertiles with total cholesterol and LDL-cholesterol been higher in the middle and high DII groups compared with the low group. In this context, a meta-analysis investigating the relationship between DII scores and serum lipid profiles in adult populations found that individuals with the highest DII scores had elevated total cholesterol (+5.16 mg/dL) and LDL-cholesterol (+3.99 mg/dL) compared to those in the lowest DII category. This supports the role of dietary inflammation in promoting an atherogenic lipid profile, aligning with our results in a distinct cohort [38]. However, it is important to acknowledge that our observations are based on baseline cross-sectional, unadjusted comparisons and are therefore hypothesis-generating only.

Although we observed some baseline differences across tertiles, the longitudinal mixed-effects models did not show consistent differences in changes over time. Consequently, our findings do not provide evidence for a clear longitudinal association between DII score and the assessed CVD risk outcomes [39]. Additional longitudinal and interventional studies are required to assess the temporal relationship between changes in DII and cardiovascular outcomes, and to identify the inflammatory biomarkers and mechanistic pathways that mediate these associations.

In this study, no significant differences in cardiovascular profiles were observed across DII tertiles over the study period (all $p > 0.05$). These findings are broadly consistent with the main OLIVAUS paper, which also reported no significant differences between HPOO and LPOO treatments in the total sample [22]. However, whereas the main OLIVAUS analysis demonstrated favourable within-arm changes following HPOO consumption, particularly among participants with higher cardiometabolic risk, the present secondary analysis indicates that stratification by DII tertiles did not identify differential cardiovascular responses over the study period. Neither medium nor high DII tertiles were associated with changes in BP, lipid parameters, oxidised LDL, or HDL-cholesterol efflux. These findings suggest that, despite baseline differences, dietary inflammatory potential did not translate into measurable cardiovascular effects during the intervention. Although the DII is designed to reflect the inflammatory potential of the diet, we did not observe a significant association with CRP in this cohort. This may reflect the limited exposure contrast and short-term nature of the intervention, suggesting that any effects of dietary inflammatory potential on cardiometabolic outcomes may not be mediated through detectable changes in circulating CRP within this timeframe in the current study sample. A plausible explanation for the observed non-significant findings of cardiovascular outcomes across DII tertiles lies in the study design. Participants consumed olive oil throughout the study, with one group receiving olive oil rich in polyphenols (320 mg/kg) and the other consuming olive oil with a lower polyphenol concentration (86 mg/kg). Both oils contained polyphenols, which are known for their anti-inflammatory and antioxidant properties [33]. These compounds can improve endothelial function, reduce oxidative stress, and modulate lipid metabolism [33,40] Their presence may have contributed to attenuating potential differences across DII tertiles, although this cannot be directly inferred from the present analysis. Previous research has demonstrated that polyphenol-rich olive oil can lower markers of

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oxidative stress and inflammation, even in individuals with less favourable dietary patterns, supporting this interpretation [33,41].

These findings highlight the complexity of diet–inflammation interactions and the potential for specific bioactive components to override the effects of overall dietary inflammatory potential. While DII captures the inflammatory potential of the diet as a whole, the inclusion of potent anti-inflammatory foods such as polyphenol-rich olive oil may diminish its predictive value in intervention settings. Future studies should examine whether similar attenuation occurs with other anti-inflammatory dietary components and assess the long-term impact of polyphenol-rich interventions on cardiometabolic health.[9,14,42]. Additionally, to our knowledge, intervention evidence directly linking DII to cardiovascular outcomes remains limited, with most intervention studies focusing on short-term changes in inflammatory biomarkers rather than downstream cardiometabolic endpoints. For instance, the AUSMED Heart study examined dietary-induced changes in DII scores in Australians with coronary heart disease and assessed inflammatory markers including hs-CRP and IL-6 but no clinical endpoints [20]. The study reported associations between improvements in DII scores and IL-6 concentrations, but limited effects on other cardiometabolic biomarkers, including hs-CRP, adiponectin, body composition). While IL-6 responds relatively rapidly to metabolic and oxidative stimuli, hs-CRP—a downstream acute-phase protein synthesised by the liver in response to IL-6 signaling—may be less sensitive to modest, short-term dietary changes [20]. An Umbrella review of systematic reviews and meta-analyses of dietary patterns and inflammation also show strong effects on inflammatory biomarkers (i.e., CRP, IL-6), but note insufficient evidence for downstream cardiometabolic outcomes due to the paucity of intervention studies [12].

In contrast, evidence linking DII to CVD outcomes largely comes from prospective observational studies with longer follow-up, where cumulative dietary inflammatory exposure can be captured. Several cohort studies have reported associations between higher DII scores and increased risk of CVD or mortality over multi-year follow-up periods [15,16,43,44]. These findings support the notion that dietary inflammatory potential may influence cardiovascular risk through longer-term, cumulative processes rather than short-term changes. In the OLIVAUS trial, each intervention period lasted only three weeks, which may not have been sufficient for differences in dietary inflammatory potential to translate into detectable changes in downstream cardiovascular outcomes such as lipid metabolism, vascular function, or HDL functionality. These outcomes are regulated by multiple physiological systems, including vascular tone and stiffness, renal sodium handling, autonomic regulation, and hepatic lipid metabolism, and are, therefore, less likely to respond to short-term dietary modulation [45–47].

The interpretation of these findings should consider both the strengths and limitations of the study. A key strength is a rigorously conducted randomised, double-blind crossover design with repeated assessments. This design reduces confounding by controlling individual-level variability and improves efficiency in small samples [22]. Dietary intake was assessed at four timepoints (pre- and post-intervention) using detailed 3-day food diaries, which were reviewed for completeness, hence providing a stronger estimate of dietary exposure than single time-point assessments. The study also included a range of cardiometabolic outcomes which assessed overall impact on cardiovascular markers beyond inflammation alone.

However, several limitations should be acknowledged. The small sample size (n=50) limits statistical power to detect subtle between-tertile differences after adjustments for key covariates. Larger sample sizes have shown to provide greater ability to detect associations [14,15,19,20,48]. Additionally, the relatively short intervention periods may have been insufficient for changes in dietary inflammatory potential to translate into detectable changes in cardiovascular markers. Furthermore, while 3-day food diaries are commonly used and repeated measures may strengthen exposure assessment, three days may be insufficient to capture full week-to-week variation and self-reported intake is subject to reporting bias. Importantly, OLIVAUS was an olive oil intervention rather than a whole-diet intervention. In contrast to AUSMED and PREDIMED, which examined

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broader Mediterranean dietary patterns, and with PREDIMED also supplementing extra virgin olive oil, all participants in the present study consumed olive oils containing polyphenols. Given the anti-inflammatory properties of polyphenols, which are also widely distributed across many foods, this may have reduced the contrast in dietary inflammatory exposure between groups. Therefore, changing olive oil alone may not have been sufficient to elicit detectable differences in cardiovascular markers across DII tertiles. Finally, as the study population consisted of healthy adults, the relatively low baseline CVD risk may have limited the ability to detect meaningful changes in these outcomes. Most participants fell within the anti-inflammatory end of the spectrum, leading to relatively low tertile cut-offs and minimal contrast between exposure groups. This narrow distribution of DII values reduces the ability to detect meaningful differences in dietary inflammatory potential and may partly account for the lack of observed associations. Future research including populations with a broader range of dietary inflammatory profiles would help clarify whether stronger contrasts in DII are associated with the outcomes of interest.

5. Conclusions

Overall, cardiovascular outcomes were similar across DII tertiles during the intervention. These findings suggest that short-term variation in dietary inflammatory potential may not translate into measurable changes in these markers within a healthy cohort. However, the limited sample size, short duration, and restricted range of DII values should be considered. Larger and longer-term studies with greater dietary contrast are needed to better characterise the relationship between dietary inflammatory potential and cardiovascular health.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Human Research Ethics Committee of La Trobe University (HEC25265, approval date 22/08/2025).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the OLIVAUS study.

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Conflicts of Interest: The authors declare no conflict of interest. However, Dr. James R. Hébert wishes to disclose that he owns controlling interest in Connecting Health Innovations LLC (CHI), a company that has licensed 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 counseling and dietary intervention in clinical settings. CHI owns exclusive right to the E-DII™. Sherry Price 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.

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