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Original article

Comparing dietary score associations with lipoprotein particle subclass profiles: A cross-sectional analysis of a middle-to older-aged population

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SUMMARY

Background and objectives: Lipoprotein particle concentrations and size are associated with increased risk for atherosclerosis and premature cardiovascular disease. Studies also suggest that certain dietary behaviours may be cardioprotective. Limited comparative data regarding any dietary score/index-lipoprotein particle subclass associations exist. Thus, our objective was to assess relationships between the Dietary Approaches to Stop Hypertension (DASH), Health Eating Index-2015 (HEI-2015), Mediterranean Diet (MD) and Energy-adjusted Dietary Inflammatory Index (E-DII™) scores and plasma lipids and lipoprotein profiles to test the hypothesis that healthier diet (better quality and more anti-inflammatory) would be associated with a more favourable lipoprotein profile.

Materials and methods: This was a cross-sectional study of 1862 men and women aged 46–73 years, randomly selected from a large primary care centre in Ireland. DASH, HEI-2015, MD and E-DII scores were derived from food frequency questionnaires. Lipoprotein subclass particle concentrations and size were determined using nuclear magnetic resonance spectroscopy. Correlation and multivariate-adjusted linear regression analyses with correction for multiple testing were performed to examine dietary score relationships with lipoprotein particle subclasses.

Results: In fully adjusted models, higher diet quality or a more anti-inflammatory diet was associated with less large and medium very low-density lipoprotein (VLDL) (DASH and HEI-2015), intermediate-density lipoprotein (IDL) (DASH, MD and E-DII) and small high-density lipoprotein (HDL) (DASH, HEI-2015 and E-DII) particles. After accounting for multiple testing, relationships with large VLDL (DASH: $\beta = -0.102$, $p = .037$), IDL (DASH: $\beta = -0.089$, $p = .037$) and small HDL (DASH: $\beta = -0.551$, $p = .014$ and E-DII: $\beta = 0.483$, $p = .019$) concentrations persisted.

Conclusions: These findings provide evidence that better diet quality, determined by the DASH score, may be more closely associated with a more favourable lipoprotein particle subclass profile in middle-to older-aged adults than the HEI-2015, MD and E-DII scores. A less pro-atherogenic lipoprotein status may be a potential mechanism underlying the cardioprotective effects of higher dietary quality.

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1. Introduction

Chronic non-communicable diseases are reaching epidemic proportions worldwide [1]. Accumulating evidence has identified diet as a substrate for mechanisms with the potential for contributing to chronic disease risk [2,3]. Examination of global dietary quality trends among adults across 187 nations from 1990 to 2010 by the Global Burden of Diseases Nutrition and

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Chronic Diseases Expert Group revealed increased consumption of healthy foods over those 20 years. However, during the same period they identified an even greater increase in consumption of unhealthy foods [4].

The relationship between diet and chronic conditions is thought to be due to complex interactions between foods and nutrients with bioactive properties [5]. Accordingly, studies have highlighted the importance of characterising the relationship between diet and cardiometabolic health through assessment of dietary patterns and numerous dietary scores have been developed. The Dietary Approaches to Stop Hypertension (DASH) diet emphasises consumption of fruits, vegetables, nuts, beans, wholegrains and low-fat dairy and restricting intake of red meat, sugar, sweetened beverages, total fat and saturated fat [6]. The Healthy Eating Index (HEI) is a measure for assessing dietary quality, specifically with regard to the degree which a set of foods align with the Dietary Guidelines for Americans (DGA); the HEI-2015 is the latest version of HEI score [7]. The Mediterranean Diet (MD) is characterised by high consumption of vegetables, fruits and nuts, pulses, cereals and fish, a high ratio of monounsaturated fat to saturated fat, low consumption of meat and dairy products and moderate consumption of alcohol [8]. The Energy-adjusted Dietary Inflammatory Index (E-DII™) was developed specifically to measure the inflammatory potential of diet based on the overall inflammatory properties of dietary components such as macronutrients, vitamins and minerals, flavonoids and other bioactive compounds [5,9–11].

The causal role of high cholesterol concentrations in the pathogenesis of chronic conditions, in particular cardiovascular disease (CVD), is well established [12], and higher plasma triglyceride and low-density lipoprotein (LDL) cholesterol concentrations and reduced high-density lipoprotein (HDL) cholesterol levels are considered the hallmark of pro-atherogenic dyslipidaemia [13]. Yet, there is a lack of data regarding the association between dietary quality measures and lipoprotein profiles determined by nuclear magnetic resonance (NMR) spectroscopy, which quantifies the number and size of lipoprotein particles. Evidence suggests that in addition to traditional lipoprotein risk factors, CVD risk is also influenced by lipoprotein particle concentration and subclass distribution [13]. In particular, smaller LDL particles and increased numbers of very low-density lipoprotein (VLDL) particles, intermediate-density lipoprotein (IDL) particles and smaller HDL particles are associated with increased incidence and/or progression of angiographically-determined atherosclerosis [14–17].

Insight into the relationship between diet and the lipoprotein subclass profile is therefore necessary to better understand the association between diet and chronic disease. This is of particular relevance in middle-to older-aged adults when both dietary quality and lipid parameters may deteriorate [18,19]. Also, it is important to test the applicability of dietary indices in different populations, as the validity of a diet score depends on the extent to which it characterises the underlying quality of the diet and is able to distinguish between individuals on relevant health-related intermediate markers [20].

To our knowledge, no study has compared associations between dietary quality defined by the DASH, HEI-2015, MD and E-DII scores and a wide range of lipoprotein particle subclasses in a middle-to older-aged population. Therefore, the aim of the present study was to assess relationships between these four dietary scores and plasma lipid and lipoprotein particle profiles, including lipoprotein particle concentrations and sizes, using a random sample of 1862 men and women aged 46–73 years, to test the hypothesis that a healthy diet (better quality and more anti-inflammatory) would be associated with a more favourable lipoprotein profile.

2. Materials and Methods

2.1. Study population and setting

The Cork and Kerry Diabetes and Heart Disease Study (Phase II – Mitchelstown Cohort) was a single-centre study conducted between 2010 and 2011. A random sample was recruited from a large primary care centre in Mitchelstown, County Cork, Ireland. The Living Health Clinic serves a population of approximately 20,000 white European subjects, with a mix of urban and rural residents. Stratified sampling was employed to recruit equal numbers of men and women from all registered attending patients in the 46–73-year age group. In total, 3807 potential participants were selected from the practice list. Following the exclusion of duplicates, deaths and subjects incapable of consenting or attending appointment, 3051 were invited to participate in the study and of these, about two-thirds (2,047, 49% male) completed the questionnaire and physical examination components of the baseline assessment. Dietary data were available for 1862 subjects. Details regarding the study design, sampling procedures and methods of data collection have been reported previously [21].

Ethics committee approval conforming to the Declaration of Helsinki was obtained from the Clinical Research Ethics Committee of University College Cork. A letter signed by the contact GP in the clinic was sent out to all selected participants with a reply slip indicating acceptance or refusal. All participants gave signed informed consent, including permission to use their data for research purposes.

2.2. Clinical procedures and lipoprotein profiling

Study participants attended the clinic in the morning after an overnight fast and blood samples were taken on arrival. Fasting glucose and glycated haemoglobin A_{1c} (HbA_{1c}) concentrations were measured in fresh samples by Cork University Hospital Biochemistry Laboratory using standardised procedures. Glucose concentrations were determined using a glucose hexokinase assay (Olympus Life and Material Science Europa Ltd., Lismeehan, Co. Clare, Ireland) and HbA_{1c} levels were measured in the haematology laboratory on an automated high-pressure liquid chromatography instrument Tosoh G7 [Tosoh HLC-723 (G7), Tosoh Europe N.V, Tessenderlo, Belgium]. Total cholesterol, triglyceride, LDL and HDL cholesterol levels were measured by Cork University Hospital Biochemistry Laboratory on Olympus 5400 biochemistry analysers with Olympus reagents using standardised procedures and fresh samples (Olympus Diagnostica GmbH, Hamburg, Germany).

Lipoprotein subclass particle concentrations and average VLDL, LDL and HDL particle diameters were measured on serum specimens by NMR spectroscopy at LipoScience, Inc (Raleigh, NC). VLDL, LDL and HDL subclasses were quantified based on the amplitudes of their spectroscopically-distinct lipid methyl group NMR signals [22]. Weighted-average VLDL, LDL and HDL particle sizes (in nanometre diameter units) were computed as the sum of the diameter of each subclass multiplied by its relative mass percentage as estimated from the amplitude of its NMR signal. The following subclass categories were investigated: large VLDL (including chylomicrons, if present) (>60 nm), medium VLDL (42–60 nm), small VLDL (29–42 nm), IDL (25–35 nm), large LDL (20.5–23 nm), small LDL (18–20.5 nm), large HDL (9.4–14 nm), medium HDL (8.2–9.4 nm) and small HDL (7.3–8.2 nm). Particle concentrations are expressed as nanomoles per litre (VLDL and LDL) and micromoles per litre (HDL). A Lipoprotein Insulin Resistance score (LP-IR), ranging from 0 (least) to 100 (most) insulin resistant, which is a weighted combination of the six lipoprotein

subclass and size parameters most closely associated with insulin resistance, was calculated [23].

Anthropometric measurements were performed by trained researchers with reference to a standard operating procedures manual. Height was measured with a portable Seca Leicester height/length stadiometer (Seca, Birmingham, UK) and weight was measured using a portable electronic Tanita WB-100MA weighing scale (Tanita Corp, IL, USA). The weighing scale was placed on a firm flat surface and was calibrated weekly. Body mass index (BMI = weight(kg)/height(m)^2) was calculated from measured weight and height.

2.3. Data collection

A general health and lifestyle questionnaire assessed demographic variables, lifestyle behaviours and morbidity. Information on sex, age, education, use of prescription cholesterol-lowering medications, smoking status and presence of type 2 diabetes was provided by participants. Physical activity levels were measured using the validated International Physical Activity Questionnaire (IPAQ) [24].

2.4. Dietary assessment

Diet was evaluated using a modified version of the self-completed European Prospective Investigation into Cancer and Nutrition (EPIC) Food Frequency Questionnaire (FFQ) [25], which has been validated extensively in several populations [26]. Adapted to reflect the Irish diet, the 150-item semi-quantitative FFQ used in the current study was originally validated for use in the Irish population using food diaries and a protein biomarker in a volunteer sample [27] and incorporated into the SLÁN Irish National Surveys of Lifestyle, Attitudes and Nutrition 1998, 2002 and 2007 [28–30]. The FFQ was also validated using a 7-day weighed food record completed in another Irish study (Lifeways Cross-generational Study), with reasonable agreement for fat, carbohydrate, and their components, and with lower agreement for protein [31].

The average medium serving of each food item consumed by participants over the last 12 months was converted into quantities using standard portion sizes. Food item quantity was expressed as (g/d) and beverages as (ml/d). The daily intake of energy and nutrients was computed from FFQ data using a tailored computer programme (FFQ Software Version 1.0; developed by the National Nutrition Surveillance Centre, School of Public Health, Physiotherapy and Sports Science, University College Dublin, Belfield, Dublin 4, Ireland), which linked frequency selections with the food equivalents in McCance and Widdowson Food Tables [32].

2.5. DASH score

Based on the FFQ, the DASH diet score was constructed. DASH is a dietary pattern rich in fruits, vegetables, whole grains and low-fat dairy foods and is limited in sugar-sweetened foods and beverages, red meat and added fats. This diet has been promoted by the National Heart, Lung and Blood Institute (part of the National Institutes of Health, a United States government organisation) to prevent and control hypertension. DASH diet scores ranged from 11 to 42. Lower scores represent poorer and higher scores represent better quality diet [33].

2.6. HEI-2015 score

The HEI-2015 is a measure of overall diet quality that determines alignment with the 2015–2020 DGA [34]. The HEI-2015 contains 13 components which are scored on a density basis out of 1000 calories, with the exception of fatty acids, which is a ratio of unsaturated to saturated fatty acids [7]. Total fruits, whole fruits, total vegetables, greens and beans, total protein containing foods and seafood and plant proteins scored 5 in the highest consumption and 0 in the lowest consumption. The highest consumption of three components including whole grains, dairy and fatty acids (ratio of poly- and monounsaturated fatty acids to saturated fatty acids) are scored as 10 and the lowest consumption scored as 0. Four components (refined grains, sodium, added sugars and saturated fats) scored 10 in the lowest consumption and 0 in the highest consumption [7]. Component scores are summed to yield a total score ranging from 0 to 100, with a higher score indicating greater adherence to the DGA.

2.7. MD score

A scale indicating the degree of adherence to the traditional Mediterranean diet was developed by Trichopoulou et al. [35] and revised to include fish intake [8]. This score is proposed for implementation and uptake in non-Mediterranean countries such as Ireland in order to incorporate Irish dietary guidelines [36]. Scoring is based on intake of nine items: vegetables, legumes, fruit and nuts, dairy products, cereals, meat and meat products, fish, alcohol and the ratio of monounsaturated to saturated fat. A value of 0 or 1 was assigned to each of nine items with the use of the sex-specific median as the cut-off. For beneficial components (vegetables, legumes, fruits and nuts, cereals and fish), consumption above the study median received 1 point; all other intakes received 0 points. For components presumed to be detrimental (dairy products, meat and meat products), consumption below the median received 1 point. For fat intake, we used the ratio of monounsaturated lipids to saturated lipids. For ethanol, men who consumed 10–50 g/day and women who consumed 5–25 g/day received 1 point; otherwise, the score was 0. Thus, the total MD score ranged from 0 (minimal adherence to the traditional Mediterranean diet) to 9 (maximal adherence).

2.8. E-DII score

DII scores were calculated using a method previously reported by Shivappa et al. [11]. Briefly, the scoring algorithm based on an extensive review of the literature focused on the effect of diet on six inflammatory biomarkers (IL-1β, IL-4, IL-6, IL-10, TNF-α, and CRP) from 1950 to 2010. A total of 27 of the 45 possible food parameters were used for DII calculation based on the FFQ in this study and these were as follows: total energy, carbohydrate, protein, fat, alcohol, fibre, cholesterol, saturated fat, mono-unsaturated fat, poly-unsaturated fat, niacin, thiamin, riboflavin, vitamin B12, vitamin B6, iron, magnesium, zinc, selenium, vitamin A, vitamin C, vitamin D, vitamin E, folic acid, onion, garlic and tea.

Dietary information for each study participant was linked to a regionally representative database that provides a global estimate of mean intake for each of the foods, nutrients and other food components along with its standard deviation considered in the DII definition [37]. These parameters were then used to derive the participant's exposure relative to the standard global mean as a z-score, derived by subtracting the mean of the regionally representative database from the amount reported and dividing this value by the parameter's standard deviation. These z-scores were then converted to proportions (i.e., with values ranging from 0 to 1) and then centred by doubling and subtracting 1. The resulting value was then multiplied by the corresponding food parameter effect score (derived from a literature review on the basis of 1943 peer-reviewed articles) [37]. All of the food parameter-specific DII

scores were then summed to create the overall DII score for every participant in the study. E-DII scores were calculated by converting raw dietary components from study and global database to amount per 1000 kcal, and then repeating a process analogous to that used for the DII but employing an energy-adjusted global comparison database [38]. For the E-DII, higher scores are more pro-inflammatory and lower scores are anti-inflammatory.

2.9. Classification and scoring of variables

Categories of education included 'some primary (not complete)', 'primary or equivalent', 'intermediate/group certificate or equivalent', 'leaving certificate or equivalent', 'diploma/certificate', 'primary university degree' and 'postgraduate/higher degree'. These were collapsed and recoded into a dichotomous variable: 'primary education only' (finished full-time education at age 13 years or younger) and 'intermediate or higher'. Type 2 diabetes was determined as a fasting glucose level ≥7.0 mmol/l or a HbA_{1c} level ≥6.5% (≥48 mmol/mol) [39] or by self-reported diagnosis.

Smoking status was defined as follows: (i) never smoked, i.e. having never smoked at least 100 cigarettes (5 packs) in their entire life; (ii) former smoker, i.e. having smoked 100 cigarettes in their entire life and do not smoke at present; and (iii) current smoker, i.e. smoking at present. These definitions were the same as those used in the SLÁN National Health and Lifestyle Survey [40]. A binary variable was then created: 'never/former smoker' or 'current smoker'. Physical activity was categorised as low, moderate and high levels of activity using the IPAQ. This was then recoded as a dichotomous variable: 'moderate/high' or 'low' physical activity.

2.10. Statistical analysis

Descriptive characteristics were examined according to sex. Categorical features are presented as percentages and continuous variables are shown as a mean (plus or minus one standard deviation) or a median and interquartile range for skewed data. Differences were analysed using a Pearson's chi-square test, Student's t-test, or a Mann Whitney U. The relationships between dietary scores and lipoprotein subclasses were examined using Spearman's rank-order correlation.

Dietary scores were standardised and skewed biomarker data were log-transformed. Linear regression analysis was performed to determine DASH, HEI-2015, MD and E-DII score associations with lipoprotein subclasses. Two models were run: the first model was adjusted for sex and age; a second model was adjusted for sex, age, education, use of cholesterol-lowering medications, type 2 diabetes, smoking, physical activity, BMI and total energy intake. Models which examined the E-DII were not adjusted for total energy intake as this was accounted for in the formulation of the E-DII score. To correct for the multiple testing performed, we calculated false discovery rate (FDR) adjusted p values via the Romano-Wolf multiple hypothesis correction method using the **rwolf** command in Stata [41].

Data analysis was conducted using Stata SE Version 13 (Stata Corporation, College Station, TX, USA) for Windows. For all analyses, a p value (two-tailed) of less than .05 was considered to indicate statistical significance.

3. Results

3.1. Descriptive characteristics

Characteristics of the study population for the full sample and according to sex are presented in Table 1. Significant differences between the sexes were noted for education, type 2 diabetes, physical activity, BMI and each dietary score. Notable sex differences were also observed for all lipoprotein subclasses except for IDL concentrations.

3.2. Correlation analysis

In correlation analysis (Table 2), a better quality diet (higher DASH, HEI-2015 or MD score) was significantly inversely correlated with triglycerides (DASH and HEI-2015), total TRL (DASH only), large VLDL (DASH, HEI-2015 and MD), medium VLDL (DASH and HEI-2015), total LDL (DASH only), IDL (DASH, HEI-2015 and MD), small LDL (DASH and HEI-2015), total HDL (MD only), small HDL, VLDL size and the LP-IR score (DASH and HEI-2015), and was positively correlated with HDL cholesterol (DASH only), small VLDL (MD only), large LDL (DASH and HEI-2015), total HDL (DASH only), large HDL (DASH and HEI-2015), medium HDL (DASH only) and both LDL and HDL size (DASH and HEI-2015).

A more pro-inflammatory diet indicated by a higher E-DII score was positively correlated with triglycerides, total TRL, large VLDL, medium VLDL, total LDL, IDL, small LDL, small HDL, the LP-IR score, and was inversely correlated with HDL cholesterol, large LDL, total, large and medium HDL and both LDL and HDL particle size. In general, lipoprotein subclasses were more strongly correlated with the DASH diet than with the HEI-2015, MD or E-DII scores.

3.3. Linear regression

Linear regression analyses describing associations between dietary scores and plasma lipids, lipoprotein particle concentrations and lipoprotein particle sizes are shown in Tables 3–5. In fully adjusted models, higher diet quality or a less pro-inflammatory diet was associated with lower total cholesterol (DASH and HEI-2015) triglycerides (DASH only) and LDL cholesterol (DASH and E-DII), and less large and medium VLDL (DASH and HEI-2015), IDL (DASH, MD and E-DII), small HDL (DASH, HEI-2015 and E-DII) and greater small VLDL (MD) particle concentrations. Significant associations with lipoprotein particle sizes were observed for LDL size (DASH: $\beta = .027$, $p = .043$) and HDL size (E-DII: $\beta = -.026$, $p = .021$). The LP-IR score was inversely associated with the DASH score. After accounting for multiple testing, relationships with large VLDL (DASH: $\beta = -0.102$, $p = .037$), IDL (DASH: $\beta = -0.089$, $p = .037$) and small HDL (DASH: $\beta = -0.551$, $p = .014$ and E-DII: $\beta = 0.483$, $p = .019$) concentrations persisted.

Discussion

In this study of 1862 middle-to older-aged men and women we compared relationships between four dietary scores and plasma lipid and lipoprotein particle profiles, including lipoprotein particle concentrations and sizes, to test the hypothesis that healthier diet (better quality and more anti-inflammatory) would be associated with a more favourable lipoprotein profile. In fully adjusted analyses which accounted for multiple testing, higher diet quality or a more anti-inflammatory diet was significantly associated with less large VLDL (DASH only), IDL (DASH only) and small HDL (DASH and E-DII) particle concentrations. In contrast, no significant relationships with any of the examined biomarkers were observed with the HEI-2015 or MD scores. In general, lipoprotein subclasses were more strongly correlated with the DASH score than with the HEI-2015, MD or E-DII scores Collectively, these findings provide evidence that compared to other dietary indices, the DASH score may be a better marker for more favourable cardiometabolic health characterised by a less pro-atherogenic cardiometabolic profile. Furthermore, although observed associations between dietary intake and lipoprotein subclass markers were modest, perhaps

Table 1
Characteristics of the study population – full sample and stratified by sex.

Variable	Full Sample (n = 1862)	Males (n = 911)	Females (n = 951)	*p*
General				
Age, years (median)	59.0 (54.0–63.0)	59.0 (54.0–64.0)	59.0 (54.0–63.0)	.927
Primary education only (%)	461 (26.2)	264 (30.2)	197 (22.2)	<.001
On cholesterol-lowering medications (%)	644 (34.6)	308 (33.8)	336 (35.3)	.490
Type 2 diabetes (%)	159 (8.5)	100 (11.0)	59 (6.2)	<.001
Current smoker (%)	265 (14.4)	131 (14.5)	134 (14.2)	.878
Low-level physical activity (%)	841 (47.2)	352 (41.2)	489 (52.9)	<.001
BMI, kg/m^2 (mean)	28.4 ± 4.6	29.0 ± 4.0	27.9 ± 5.0	<.001
Energy intake, kcal (mean)	2059.1 ± 797.6	2082.5 ± 789.4	2036.8 ± 805.2	.217
Dietary scores				
DASH score (mean)	26.77 ± 5.4	24.96 ± 5.0	28.50 ± 5.1	<.001
HEI-2015 score (mean)	39.60 ± 7.0	38.72 ± 6.9	40.43 ± 6.9	<.001
MD score (mean)	4.23 ± 1.9	4.40 ± 1.9	4.06 ± 1.8	<.001
E-DII score (mean)	−.78 ± 1.4	−0.43 ± 1.4	−1.11 ± 1.3	<.001
Plasma lipids				
Total cholesterol, mmol/l (mean)	5.3 ± 1.0	5.1 ± 1.0	5.4 ± 1.0	<.001
Triglycerides, mmol/l (median)	1.2 (0.9–1.7)	1.3 (0.9–1.9)	1.1 (0.8–1.5)	<.001
LDL cholesterol, mmol/l (mean)	3.2 ± 0.9	3.1 ± 0.9	3.3 ± 0.9	.003
HDL cholesterol, mmol/l (mean)	1.46 ± 0.4	1.29 ± 0.3	1.63 ± 0.4	<.001
Lipoprotein particle concentration				
Total TRL, nmol/l (median)	66.6 (33.9–89.6)	66.8 (39.7–103.3)	49.3 (30.5–78.0)	<.001
Large VLDL, nmol/l (median)	0.9 (0.4–2.9)	1.4 (0.5–4.1)	0.7 (0.4–2.0)	<.001
Medium VLDL, nmol/l (median)	21.0 (10.2–37.4)	25.0 (12.1–45.1)	17.9 (8.3–32.3)	<.001
Small VLDL, nmol/l (median)	30.6 (16.9–49.9)	33.7 (18.8–52.5)	27.5 (15.0–46.1)	<.001
Total LDL, nmol/l (mean)	1262.4 ± 408.0	1305.0 ± 404.7	1221.8 ± 407.3	<.001
IDL, nmol/l (median)	92.0 (50.0–158.0)	90.0 (48.0–165.0)	93.5 (52.0–153.8)	.991
Large LDL, nmol/l (mean)	600.3 ± 299.8	485.0 ± 265.3	710.2 ± 289.5	<.001
Small LDL, nmol/l (mean)	548.8 ± 414.6	704.2 ± 392.1	400.5 ± 379.8	<.001
Total HDL, μmol/l (mean)	38.4 ± 6.1	36.6 ± 5.8	40.1 ± 6.0	<.001
Large HDL, μmol/l (median)	6.1 (3.8–9.5)	4.5 (2.8–6.7)	8.3 (5.7–11.7)	<.001
Medium HDL, μmol/l (mean)	13.6 ± 6.2	12.4 ± 5.7	14.7 ± 6.4	<.001
Small HDL, μmol/l (mean)	17.8 ± 5.9	19.1 ± 5.4	16.5 ± 6.1	<.001
Lipoprotein particle size				
VLDL size, nm (mean)	45.0 ± 5.9	45.8 ± 6.5	44.1 ± 5.2	<.001
LDL size, nm (mean)	20.9 ± 0.6	20.6 ± 0.5	21.1 ± 0.5	<.001
HDL size, nm (mean)	9.3 ± 0.5	9.1 ± 0.4	9.5 ± 0.5	<.001
LP-IR score (median)	31.0 (14.0–15.0)	44.0 (27.0–58.0)	21.0 (8.0–38.0)	<.001

Abbreviations: DASH: Dietary Approaches to Stop Hypertension; E-DII: Energy-adjusted Dietary Inflammatory Index; HDL: high-density lipoprotein; HEI: Healthy Eating Index; IDL: intermediate-density lipoprotein; LDL: low-density lipoprotein; LP-IR: lipoprotein insulin resistance; MD: Mediterranean Diet; TRL: triglyceride-rich lipoprotein; VLDL: very low-density lipoprotein.
For the DASH, HEI-2015 and MD, lower scores represent poorer and higher scores represent better quality diet. For the E-DII, higher scores are more pro-inflammatory and lower scores are anti-inflammatory.

limiting the usefulness of a dietary score as a risk prediction tool, these results suggest that adopting a healthy diet may be an effective approach to improve lipoprotein profiles, and thereby attenuate atherogenesis, prevent CVD and chronic disease risk and promote healthy ageing.

Dietary indices consider the fact that foods are eaten in combination, thus removing the limitation that single nutrients may not reflect the overall quality of diet as a whole and are restricted in their ability to take into account interactions among nutrients [42]. Nevertheless, no widely accepted single measure of overall dietary quality to assure the relationship between diet and non-communicable diseases is currently available [43], although numerous studies have examined dietary score relationships with chronic conditions. A systematic review and meta-analysis of 260,011 men and women showed that higher compliance to the DASH diet was associated with a 20% reduction in the risk of CVD [44]. A prospective analysis of 12,413 participants aged 45–64 years from the Atherosclerosis Risk in Communities Study found that compared with participants in the lowest HEI-2015 score quintile (i.e. poorest diet quality), subjects in the highest quintile had a 16% lower risk of incident CVD, 32% lower risk of CVD mortality and an 18% lower risk of all-cause mortality [45]. In a meta-analysis which examined whether higher adherence to the MD may decrease CVD incidence and mortality, Gross et al. found that individuals in the highest quantile of adherence to the diet had 24% lower incidence and mortality from CVD compared to those least adherent [46]. Another meta-analysis also found that individuals with the highest DII scores, and thus the most pro-inflammatory diet, displayed a 36% increased risk of CVD incidence and mortality relative to those with the lowest DII scores [47].

There are multiple biological processes that may serve as the etiological pathway for observed associations between dietary indices and chronic disease [48]. Nevertheless, although numerous studies have examined relationships between dietary scores and traditional lipid parameters, uncertainty still exists regarding the mechanisms that explain the association between diet and chronic disease. With regard to the effects of dietary patterns on conventional lipid profiles, a systematic review and meta-analysis of randomised controlled trials found the DASH diet to result in significant decreases in concentrations of total and LDL cholesterol [49]. A randomised crossover trial of 36 participants who consumed, in random order, a control diet, a standard DASH diet and a higher-fat, lower carbohydrate modified DASH (HF-DASH) diet for 3 weeks each, examined lipoprotein levels. They reported that the DASH diet, but not the HF-DASH diet, significantly reduced LDL and HDL cholesterol concentrations compared with the control diet [50]. In a cross-sectional analysis of 775 healthy women from the Nurses' Health Study, subjects with better diet quality defined

Table 2
Spearman correlation coefficients between dietary scores and lipoprotein particles.

Variable	DASH score		HEI-2015 score		MD score		E-DII score	
	ρ coefficient	*p*	ρ coefficient	*p*	ρ coefficient	*p*	ρ coefficient	*p*
Plasma lipids								
Total cholesterol, mmol/l	0.009	.708	−0.045	.058	−0.044	.062	0.009	.719
Triglycerides, mmol/l	−0.124	<.001	−0.056	.017	−0.020	.398	0.061	.009
LDL cholesterol, mmol/l	−0.011	.637	−0.036	.129	−0.028	.245	0.043	.07
HDL cholesterol, mmol/l	0.175	<.001	0.027	.248	−0.040	.091	−0.132	<.001
Lipoprotein particle concentration								
Total TRL, nmol/l	−0.099	<.001	−0.035	.141	0.023	.327	0.052	.029
Large VLDL, nmol/l	−0.150	<.001	−0.115	<.001	−0.068	.004	0.112	<.001
Medium VLDL, nmol/l	−0.135	<.001	−0.099	<.001	−0.038	.104	0.073	.002
Small VLDL, nmol/l	−0.027	.259	0.020	.387	0.055	.019	0.016	.49
Total LDL, nmol/l	−0.083	<.001	−0.035	.135	−0.029	.221	0.075	.001
IDL, nmol/l	−0.083	<.001	−0.069	.003	−0.087	<.001	0.083	<.001
Large LDL, nmol/l	0.150	<.001	0.049	.039	−0.019	.426	−0.106	<.001
Small LDL, nmol/l	−0.171	<.001	−0.049	.039	0.006	.802	0.129	<.001
Total HDL, μmol/l	0.052	.028	0.012	.6	−0.050	.033	−0.078	.001
Large HDL, μmol/l	0.185	<.001	0.054	.023	−0.026	.272	−0.142	<.001
Medium HDL, μmol/l	0.065	.006	0.034	.15	−0.020	.408	−0.102	<.001
Small HDL, μmol/l	−0.143	<.001	−0.066	.006	−0.008	.737	0.124	<.001
Lipoprotein particle size								
VLDL size, nm	−0.087	.001	−0.062	.014	−0.033	.2	0.042	.097
LDL size, nm	0.200	<.001	0.052	.027	−0.017	.465	−0.142	<.001
HDL size, nm	0.162	<.001	0.065	.006	0.007	.768	−0.143	<.001
LP-IR score	−0.205	<.001	−0.090	<.001	−0.024	.311	0.157	<.001

Abbreviations: DASH: Dietary Approaches to Stop Hypertension; E-DII: Energy-adjusted Dietary Inflammatory Index; HDL: high-density lipoprotein; HEI: Healthy Eating Index; IDL: intermediate-density lipoprotein; LDL: low-density lipoprotein; LP-IR: lipoprotein insulin resistance; MD: Mediterranean Diet; TRL: triglyceride-rich lipoprotein; VLDL: very low-density lipoprotein.
Values are presented as Spearman correlation coefficients between continuous dietary scores and lipoprotein subclasses among the Mitchelstown Cohort (n = 1862).
For the DASH, HEI-2015 and MD, lower scores represent poorer and higher scores represent better quality diet. For the E-DII, higher scores are more pro-inflammatory and lower scores are anti-inflammatory.

Table 3
Linear regression analysis of the associations between dietary scores and plasma lipids (n = 1862).

Plasma lipids	DASH score			HEI-2015 score			MD score			E-DII score		
	β	*p*	*p* (FDR)	B	*p*	*p* (FDR)	β	*p*	*p* (FDR)	β	*p*	*p* (FDR)
Total cholesterol												
Model 1	−0.042	.093	.397	−0.059	**.015**	.13	−0.046	.055	.386	0.041	.099	.549
Model 2	−0.072	**.006**	.068	−0.052	**.037**	.305	−0.047	.056	.424	0.030	.229	.853
Log triglycerides												
Model 1	−0.040	**<.001**	**.01**	−0.015	.178	.747	−0.015	.162	.592	0.006	.599	.943
Model 2	−0.025	**.036**	.272	−0.002	.835	.997	0.001	.977	.997	−0.005	.638	.983
LDL cholesterol												
Model 1	−0.024	.278	.603	−0.037	.081	.535	−0.030	.149	.592	0.051	**.018**	.164
Model 2	−0.052	**.022**	.191	−0.039	.07	.472	−0.034	.104	.594	0.046	**.033**	.302
HDL cholesterol												
Model 1	0.010	.218	.594	−0.012	.12	.607	−0.001	.854	.967	−0.010	.232	.817
Model 2	−0.001	.907	.903	−0.012	.128	.675	−0.009	.27	.851	−0.004	.624	.983

Abbreviations: DASH: Dietary Approaches to Stop Hypertension; E-DII: Energy-adjusted Dietary Inflammatory Index; HDL: high-density lipoprotein; HEI: Healthy Eating Index; LDL: low-density lipoprotein; MD: Mediterranean Diet.
Model 1: adjusted for sex and age.
Model 2: adjusted for sex, age, education, use of cholesterol-lowering medications, type 2 diabetes, smoking, physical activity, BMI and total energy intake. Models which examine the E-DII score do not adjust for total energy intake.
Unstandardised β coefficients are shown. Significant *p* **highlighted**.
For the DASH, HEI-2015 and MD, lower scores represent poorer and higher scores represent better quality diet. For the E-DII, higher scores are more pro-inflammatory and lower scores are anti-inflammatory.

by the DASH or MD were found to have lower levels of triglyceride concentrations compared to subjects with poorer diet quality [48]. However, in a longitudinal study of 136 youth with type 1 diabetes, Sanjeevi et al. found no association between the HEI-2015 score and total cholesterol, triglycerides, LDL or HDL cholesterol concentrations [51]. Similarly, a 2019 intervention review by the Cochrane Collaboration, which examined the MD in relation to CVD risk factors, found little or no effect on triglyceride or LDL and HDL cholesterol concentrations [52]. Using data from US National Health and Nutrition Examination Survey (n = 17,689), Mazidi et al. [53] found that the triglycerides/HDL-C ratio increased across quartiles of the E-DII, while HDL cholesterol levels decreased ($p < .001$ for both).

No study to date has compared the DASH, HEI-2015, MD and E-DII scores in the context of lipoprotein particle subclasses determined by NMR. We report associations between the DASH score and large VLDL, IDL and small HDL particles. Lipoprotein particle size, in particular large VLDL and small HDL particles have been found to be associated with increased risk for atherosclerosis and premature CVD [15,17]. Large VLDL particles are important in terms

Table 4
Linear regression analysis of the associations between dietary scores and lipoprotein particle concentrations (n = 1862).

Lipoprotein particle concentration	DASH score			HEI-2015 score			MD score			E-DII score		
	β	*P*	*p* (FDR)	β	*p*	*p* (FDR)	β	*p*	*p* (FDR)	β	*p*	*p* (FDR)
Log total TRL												
Model 1	−0.031	.065	.347	−0.008	.623	.993	0.008	.606	.967	0.003	.852	.97
Model 2	−0.010	.601	.874	0.012	.502	.968	0.027	.107	.594	−0.018	.3	.914
Log large VLDL												
Model 1	−0.125	**<.001**	**.002**	−0.095	**.002**	**.027**	−0.082	**.007**	.09	0.058	.06	.408
Model 2	−0.102	**.002**	**.037**	−0.076	**.016**	.157	−0.051	.094	.571	0.042	.177	.793
Log medium VLDL												
Model 1	−0.091	**<.001**	**.01**	−0.078	**.002**	**.027**	−0.059	**.016**	.164	0.040	.107	.556
Model 2	−0.067	**.015**	.136	−0.052	**.046**	.358	−0.031	.219	.812	0.015	.558	.983
Log small VLDL												
Model 1	0.020	.402	.645	0.026	.247	.831	0.057	**.011**	.12	−0.006	.799	.97
Model 2	0.036	.165	.651	0.043	.081	.502	0.071	**.003**	.05	−0.030	.22	.853
Total LDL												
Model 1	−15.115	.138	.463	−8.218	.395	.948	−18.079	.061	.41	20.591	**.037**	.303
Model 2	−19.463	.078	.443	−4.863	.643	.988	−13.526	.182	.762	16.156	.121	.688
Log IDL												
Model 1	−0.088	**.001**	**.013**	−0.052	**.039**	.322	−0.082	**.001**	**.02**	0.074	**.004**	.051
Model 2	−0.089	**.002**	**.037**	−0.054	.052	.38	−0.068	**.011**	.149	0.068	**.013**	.148
Large LDL												
Model 1	12.332	.078	.377	−0.199	.976	.993	3.641	.583	.967	−4.647	.493	.942
Model 2	4.504	.530	.874	−0.534	.937	.997	1.330	.84	.997	−4.463	.509	.983
Small LDL												
Model 1	−20.430	**.035**	.22	−2.366	.797	.993	−14.665	.111	.542	17.827	.058	.408
Model 2	−19.974	.103	.51	1.701	.863	.997	−8.946	.349	.911	13.929	.156	.771
Total HDL												
Model 1	−0.320	**.031**	.215	−0.189	.178	.747	−0.211	.133	.579	−0.101	.481	.942
Model 2	−0.298	.064	.406	−0.168	.27	.881	−0.238	.108	.594	−0.060	.694	.983
Log large HDL												
Model 1	0.024	.114	.462	−0.005	.703	.993	0.011	.428	.913	−0.015	.308	.854
Model 2	0.015	.359	.821	−0.004	.778	.997	0.005	.712	.99	−0.011	.480	.983
Medium HDL												
Model 1	0.006	.970	.97	0.062	.668	.993	−0.071	.624	.967	−0.391	**.008**	.087
Model 2	0.168	.317	.821	0.231	.147	.721	0.016	.92	.997	−0.431	**.007**	.076
Small HDL												
Model 1	−0.508	**<.001**	**.01**	−0.220	.109	.596	−0.220	.107	.542	0.450	**.001**	**.017**
Model 2	−0.551	**<.001**	**.014**	−0.353	**.018**	.172	−0.268	.063	.462	0.483	**.001**	**.019**

Abbreviations: DASH: Dietary Approaches to Stop Hypertension; E-DII: Energy-adjusted Dietary Inflammatory Index; HDL: high-density lipoprotein; HEI: Healthy Eating Index; IDL: intermediate-density lipoprotein; LDL: low-density lipoprotein; MD: Mediterranean Diet; TRL: triglyceride-rich lipoprotein; VLDL: very low-density lipoprotein.
Model 1: adjusted for sex and age.
Model 2: adjusted for sex, age, education, use of cholesterol-lowering medications, type 2 diabetes, smoking, physical activity, BMI and total energy intake. Models which examine the E-DII score do not adjust for total energy intake.
Unstandardised β coefficients are shown. Significant *p* **highlighted**.
For the DASH, HEI-2015 and MD, lower scores represent poorer and higher scores represent better quality diet. For the E-DII, higher scores are more pro-inflammatory and lower scores are anti-inflammatory.

Table 5
Linear regression analysis of the associations between dietary scores and lipoprotein particle size and the lipoprotein insulin resistance score (n = 1862).

Lipoprotein particle size	DASH score			HEI-2015 score			MD score			E-DII score		
	β	*p*	*p* (FDR)	β	*p*	*p* (FDR)	β	*p*	*p* (FDR)	β	*p*	*p* (FDR)
VLDL size												
Model 1	−0.375	**.02**	.173	−0.260	.087	.537	−0.271	.072	.451	0.053	.731	.97
Model 2	−0.186	.277	.821	−0.153	.337	.903	−0.132	.395	.927	−0.002	.991	.994
LDL size												
Model 1	0.031	**.012**	.117	−0.003	.815	.993	0.011	.361	.884	−0.014	.232	.817
Model 2	0.027	**.043**	.292	−0.004	.764	.997	0.008	.486	.928	−0.012	.338	.939
HDL size												
Model 1	0.025	**.03**	.215	0.008	.467	.97	0.023	**.033**	.278	−0.031	**.006**	.065
Model 2	0.018	.139	.605	0.009	.417	.937	0.019	.086	.56	−0.026	**.021**	.212
Log LP-IR score												
Model 1	−0.079	**<.001**	**.01**	−0.031	.141	.662	−0.059	**.005**	.069	0.055	**.011**	.112
Model 2	−0.058	**.011**	.107	−0.022	.306	.892	−0.040	.053	.421	0.041	.055	.439

Abbreviations: DASH: Dietary Approaches to Stop Hypertension; E-DII: Energy-adjusted Dietary Inflammatory Index; HDL: high-density lipoprotein; HEI: Healthy Eating Index; LDL: low-density lipoprotein; LP-IR: lipoprotein insulin resistance; MD: Mediterranean Diet; VLDL: very low-density lipoprotein.
Model 1: adjusted for sex and age.
Model 2: adjusted for sex, age, education, use of cholesterol-lowering medications, type 2 diabetes, smoking, physical activity, BMI and total energy intake. Models which examine the E-DII score do not adjust for total energy intake.
Unstandardised β coefficients are shown. Significant *p* **highlighted**.
For the DASH, HEI-2015 and MD, lower scores represent poorer and higher scores represent better quality diet. For the E-DII, higher scores are more pro-inflammatory and lower scores are anti-inflammatory.

of CVD risk as they are associated with the pro-atherogenic small dense LDL phenotype [15]. Large VLDL particles have also been linked to metabolically unhealthy individuals, regardless of BMI and metabolic health definition [54]. Relative to LDL particles, large lipid-enriched VLDL particles are more efficiently hydrolysed by lipoprotein lipase, have greater capacity to penetrate the endothelial wall and be preferentially retained in the arterial intima [55]. Hepatic overproduction of large triglyceride-rich VLDL is a hallmark of dyslipidaemia in obesity and insulin resistance [56], and this may initiate diabetic dyslipidaemia [57]. Diminished mean HDL size represents another biomarker of HDL metabolism associated with CVD in large-scale clinical studies, although findings indicate that this relationship may be secondary to those established for plasma levels of HDL and large HDL, as HDL cholesterol is primarily carried in the circulation by large, buoyant, lipid-rich HDL particles [58]. It should be noted, however, that uncertainty exists with regard to which lipoprotein characteristic derived from NMR spectroscopy is most strongly associated with CVD risk, with some studies suggesting small VLDL particles to be pro-atherogenic and smaller HDL subclasses to be cardioprotective [59,60]. Nevertheless, dietary strategies which improve dyslipidaemia characterised by large VLDL and small dense HDL particles may have the potential to attenuate atherogenesis and progression towards overt type 2 diabetes and related CVD.

We observed notable sex differences in lipoprotein profiles in this study, findings which have also been reported in previous research [13]. In particular, it has been observed that as women age, post-menopausal total cholesterol and LDL cholesterol concentrations surpass those in men [61]. Nevertheless, although women experience an escalation in the incidence of CVD after menopause, they continue to have significantly lower CVD morbidity and mortality relative to age-matched men [62]. Notably, we found concentrations of large VLDL and small HDL to be significantly greater among males in this study. The factors influencing the sex-specific regulation of plasma lipid kinetics and concentrations are not clear [63], although the effect of sex steroids is believed to be a factor [64]. However, sex differences in lipoprotein profiles are difficult to interpret because of potential confounding due to changes in total body fat, body fat distribution and insulin sensitivity that accompany menopause [63]. In addition, factors such as the length of exposure to hyperlipidaemia and biological/genetic susceptibility are thought to be similarly important determinants of sex-related differences in CVD risk [65]. As the underlying physiological modulators of plasma lipid metabolism responsible for the differences between men and women remain to be determined, future research should examine possible sex-specific direct or indirect modulators of lipid metabolism, including dietary patterns.

4.1. Strengths and limitations

This study has several strengths. With the elderly population growing [66] it is to be expected that the number of individuals with non-communicable diseases will increase. Modifications in certain lifestyle behaviours and adopting a healthier diet may help prevent chronic conditions, and this may be of particular importance to older adults who often have low energy requirements and poor diets [67–69]. As far as we are aware, this research is the first to compare DASH, HEI-2015, MD and E-DII score relationships with a range of plasma lipids, lipoprotein particle concentrations and sizes in a middle-to older-aged population; thus, our study has examined the largest number of biomarkers in this context. Research on dietary indices is important for public health in terms of providing better insights into disease causation and informing public health nutrition policy. Other strengths include the large number of middle-to older-aged study participants, equal representation by sex (49% male) and the use of validated questionnaires to collect data. Furthermore, to address the potential issue of multiple testing, we applied a stringent Romano-Wolf multiple hypothesis correction [41], which is more powerful than earlier multiple testing procedures.

Despite these strengths, several limitations should be noted. The cross-sectional study design, which precludes drawing conclusions regarding the temporal direction of relationships, limits inference with respect to causality. This should be considered in light of decades of work on the association between diet and serum lipids which suggest that relationships may be discernible only using longitudinal data [70]. In addition, the use of self-reported questionnaires is subject to potential inaccuracies. Thus, it should be noted that as a structured dietary assessment technique, the FFQ is less precise than 24-h recall and food records; furthermore, as a method based on long-term memory it can introduce recall and reporting biases [71,72]. However, this approach has been shown to provide valid estimates of food intake in older adults [73]. In addition, the FFQ used in this study was developed specifically for use in an Irish population and was further validated by dietitians in a random sample [31]. Another potential limitation of this study is the non-availability of information on the remaining 18 food parameters for the E-DII calculation. Nevertheless, on average, we have had data on 27 food parameters for E-DII score calculations and previous research reported no significant change in relationships when going from 45 to less than 30 food parameters [74,75].

Finally, the generalisability of our findings may be limited. Our data were collected from a single primary care-based sample which may not be representative of the general population. However, Ireland represents a generally ethnically homogeneous population [76]. In addition, previous research suggests that approximately 98% of Irish adults are registered with a GP and that, even in the absence of a universal patient registration system, it is possible to perform population-based epidemiological studies that are representative using our methods [77]. As random sampling of subjects and the use of validated methods for data collection ensured internal sample validity, it is equally possible that the relationships described may be generalisable to a similar middle-to older-aged, white European population. Nevertheless, future studies utilising longitudinal data in different populations will be needed to confirm these findings. In particular, it will be important to determine whether the DASH score demonstrates stronger associations with CVD outcomes and mortality in a middle-to older-aged population compared to other dietary indices, and whether these relationships are mediated by the lipoprotein particle subclass markers identified in this research.

5. Conclusions

In conclusion, the results from this research suggest that better quality diet is associated with more favourable cardiometabolic health characterised by a less pro-atherogenic cardiometabolic profile. Notably, our findings imply that the DASH score may be more closely associated with lipoprotein profile parameters in middle-to older-aged adults than the HEI-2015, MD and E-DII scores. As an unfavourable lipoprotein profile may precede many non-communicable diseases, in particular CVD, these data highlight the potential benefits of adopting a healthy diet. Improving our understanding of the relationships between diet and biomarkers of health is warranted, with a view to informing public health nutrition policy and promotion of healthy eating to improve dietary quality and ultimately overall health and well-being.

Author contributions

S.R.M: Conceptualization, methodology, formal analysis, investigation, data curation, writing—original draft preparation, and writing—review and editing.

P.N: methodology, investigation, data curation and writing—review and editing.

J.M.H: methodology, investigation, data curation, writing—review and editing, project administration and funding acquisition.

N.S: methodology, investigation and writing—review and editing.

J.R.H: methodology, investigation and writing—review and editing.

I.J.P: Conceptualization, writing—review and editing, project administration and funding acquisition.

C.M.P: Conceptualization, methodology, investigation, writing—review and editing, supervision, project administration and funding acquisition.

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Conflicts of interest

We wish to disclose that Dr. James R. Hébert 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 counselling and dietary intervention in clinical settings. Dr. Nitin Shivappa 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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