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University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

Title: Relationship between dietary quality, determined by DASH score, and cardiometabolic health biomarkers: a cross-sectional analysis in adults

Authors: Catherine M. Phillips[1,2], Janas M Harrington[2] and Ivan J. Perry[2]

Affiliations: [1] HRB Centre for Diet and Health Research, School of Public Health, Physiotherapy and Sports Science, University College Dublin, Belfield, Dublin 4, Ireland. Ireland. [2] HRB Centre for Diet and Health Research, School of Public Health, University College Cork, Western Gateway Building, Western Rd., Cork, Ireland.

Correspondence: Address all correspondence and requests for reprints to: Dr Catherine M. Phillips, HRB Centre for Diet and Health Research, Room F21, Woodview House, School of Public Health, Physiotherapy and Sports Science, University College Dublin, Belfield, Dublin 4, Ireland. E-mail: catherine.phillips@ucd.ie or c.phillips@ucc.ie.

Running title: Dietary quality and cardiometabolic health biomarkers

Key words: dietary quality; inflammation; lipoproteins; insulin resistance; obesity; biomarkers; Mitchelstown cohort; adults;

Abstract

Background and Aims: The relationship between dietary patterns and cardiometabolic disease is of increasing interest. However, limited data regarding the association between dietary quality and biomarkers of cardiometabolic health exist. Therefore the aim of this work was to examine potential associations between dietary quality, assessed using the Dietary Approaches to Stop Hypertension (DASH) dietary quality score, adiposity and biomarkers of glucose homeostasis, lipoprotein metabolism and inflammation in a cross-sectional sample of 1,493 men and women.

Methods: Anthropometric measurements included BMI, hip and waist circumference (WC). Serum acute-phase reactants, adipocytokines, pro-inflammatory cytokines and white blood cell (WBC) counts were determined. Lipoprotein particle size and subclass concentrations were measured using nuclear magnetic resonance (NMR) spectroscopy. Insulin resistance was calculated by homeostasis model assessment (HOMA-IR).

Results: Higher dietary quality was associated with lower BMI ($P < 0.05$), WC ($P < 0.001$), tumour necrosis factor (TNF)-α, interleukin 6 (IL-6), WBC and plasminogen activator inhibitor-1 (PAI-1) concentrations ($P < 0.01$) and reduced insulin resistance ($P < 0.05$). In addition less small low density lipoprotein (LDL) and small high density lipoprotein (HDL) particles and less large very low density lipoprotein (VLDL) particles were observed among those with better dietary quality ($P < 0.001$). Individuals in the top DASH quartile had a 54% and 48% lower likelihood of central obesity and metabolic syndrome (MetS), respectively, than those in the lowest DASH quartile ($P < 0.05$).

Conclusions: Our data suggest that higher quality diet is associated with improved adiposity measures and a less insulin resistant, pro-inflammatory, pro-thrombotic and pro-atherogenic

cardiometabolic profile which may impact on central obesity and MetS risk. These findings, which may be of clinical and public health significance in terms of dietary approaches to promote cardiometabolic health, warrant further examination.

Abbreviations: BMI: Body mass index; C3: Complement component c3; CRP: C reactive protein; CVD: Cardiovascular disease; DASH: Dietary Approaches to Stop Hypertension; FPG: Fasting plasma glucose; GHQ: General health questionnaire; HDL: High-density lipoprotein; HDL-C: High density lipoprotein cholesterol; HOMA-IR: Homeostasis model assessment of insulin resistance; IDL: Intermediate-density lipoprotein; IL-6: interleukin 6; LP-IR: Lipoprotein Insulin Resistance Index; LDL: Low-density lipoprotein; LDL-C: Low density lipoprotein cholesterol; MetS: Metabolic syndrome; MI: Myocardial infarction; NMR: Nuclear magnetic resonance; PAI-1: plasminogen activator inhibitor-1; TNF-α: tumour necrosis factor α; TG: Triglyceride; TRL: Triglyceride-rich lipoprotein; Total-C: Total cholesterol; T2DM: Type 2 diabetes mellitus; VLDL: Very low-density lipoprotein; WBC: White blood cell; WC: Waist circumference; WHR: Waist to hip ratio

1. Introduction

Poor dietary quality contributes to adverse health and mortality. Recent meta-analysis of a range of dietary indices of dietary quality revealed lower risk of all-cause mortality, cardiovascular disease (CVD), type 2 diabetes (T2DM), cancer and neurodegenerative disease among those with higher dietary quality scores [1]. Examination of global dietary quality trends among adults across 187 nations in 1990 and 2010 by the Global Burden of Diseases Nutrition and Chronic Diseases Expert Group reported a modest increase in the consumption of healthy foods, however intake of unhealthy foods has increased to a greater extent during the past two decades [2]. Unhealthy diets, characterized by low intakes of fruits, vegetables, nuts/seeds, wholegrains, seafood and poultry and high intakes of red and processed meats, refined grains, saturated fat and sugar sweetened beverages have been estimated to be associated with a substantial proportion of deaths from heart disease, stroke and T2DM [3, 4].

The Dietary Approaches to Stop Hypertension (DASH) diet emphasizes consumption of fruits, vegetables, nuts, beans, wholegrains and low fat dairy and restricting intake of red meat, sugar sweetened beverages, sweets, total fat and saturated fat [5]. Since the development of the DASH diet twenty years ago an increasing body of evidence has demonstrated a consistent reduction in chronic cardiometabolic diseases [1, 5-9]. However the relationships between DASH scores and intermediate biomarkers of cardiometabolic health are unclear. Numerous underlying biological pathways including inflammation, lipid and glucose homeostasis may underlie the positive associations between dietary quality and chronic diseases. However the limited data available on the relationship between DASH scores and select biomarkers of cardiometabolic health [6, 10-12], highlights the need for further investigation. To our knowledge no data exist on the potential associations between DASH scores and NMR derived lipoprotein profiles. Furthermore the focus

of inflammatory profiling in this context has been mainly on C reactive protein (CRP), with little to no information on other inflammatory markers such as interleukin-6 (Il-6), tumour necrosis factor (TNF) α, adiponectin, leptin, resistin or complement component c3 (C3), or thrombotic markers such as plasminogen activator inhibitor-1 (PAI-1). Therefore, the objective of the present study was to comprehensively examine associations between dietary quality using the DASH score and adiposity and a wide range of biomarkers of cardiometabolic health, inflammation, lipoprotein metabolism and glucose homeostasis in a cross-sectional sample of men and women. Such investigation of different potential biological is required to improve our understanding of the relationships between dietary quality and cardiometabolic health.

2. Subjects and Methods

Study design and subject recruitment

The Cork and Kerry Diabetes and Heart Disease Study (Phase II) was a single centre, cross-sectional study conducted between 2010 and 2011 [13]. A population representative random sample was recruited from a large primary care centre in Mitchelstown, County Cork, Ireland (Mitchelstown cohort, clinical trials.gov identifier NCT03191227). The Livinghealth Clinic includes 8 general practitioners and serves a catchment area of approximately 20,000 with a mix of urban and rural residents. Mitchelstown cohort participants were randomly selected from all registered attending patients in the 50-69-year age group. In total, 3,807 potential participants were selected from the practice list. Following exclusion of duplicates, deaths and ineligibles, 3,043 were invited to participate in the study and of these 2,047 White individuals (49.2% male) completed the questionnaire and physical examination components of the baseline assessment (response rate 67%). Ethics committee approval conforming to the Declaration of Helsinki was

obtained from the Clinical Research Ethics Committee of University College Cork. All participants provided written informed consent. Following exclusion of individuals without a DASH score the remaining 1493 participants were used in the analyses. A flow chart outlining the subject selection for the current analysis of the Mitchelstown cohort is presented in **Supplemental Figure S1.**

Clinical and anthropometric data

All participants attended the clinic in the morning after an overnight fast (minimum 8h). Fasting blood samples were taken on arrival. Participants completed a General Health Questionnaire (GHQ), a food frequency questionnaire (FFQ), and the International Physical Activity Questionnaire (IPAQ). Data on age, gender, medical history and medication use was gathered through a self-completed GHQ. The presence of cardiovascular disease (CVD) was obtained from the GHQ by asking study participants if they had been diagnosed with any one of the following seven conditions: Heart Attack (including coronary thrombosis or myocardial infarction), Heart Failure, Angina, Aortic Aneurysm, Hardening of the Arteries, Stroke, or any other Heart Trouble. Subjects who indicated a diagnosis of any one of these conditions were classified as having CVD. Type 2 diabetes was defined according to the American Heart Association guidelines of fasting plasma glucose (FPG) $\geq$ 7 mmol/L or doctor diagnosed diabetes. Blood pressure was measured according to the European Society of Hypertension Guidelines using an Omron M7 Digital BP monitor on the right arm, after a 5-minute rest in the seated position. The average of the second and third measurements was used for analyses. MetS was defined according to the National Cholesterol Education (NCEP) Adult Treatment Panel III (ATP III) [14]. Anthropometric measurements were recorded with calibrated instruments

according to a standardised protocol. Body weight was measured in kilograms without shoes; to the nearest 100g using a Tanita WB100MA® weighing scales (Tanita Corporation, IL, USA). Height was measured in centimetres to one decimal place using a Seca Leicester® height gauge (Seca, Birmingham, UK). BMI was calculated as weight (kg) /height $(m)^2$. Waist circumference (WC) (defined as mid-way between lowest rib and iliac crest) and hip circumference (determined at the maximum perimeter of the hips) were measured in centimetres to 1 decimal place using a Seca 200 measuring tape (Seca, Birmingham, UK). Pelvic width was calculated as the diameter between the right and left iliac crests using callipers. The average of two measures were used for analyses. Individuals with a BMI $\geq 30 kg/m^2$ were defined as obese. Individuals with a waist to hip ratio (WHR) ≥ 0.9 for males and ≥ 0.85 for females were defined as centrally obese [15]. For sensitivity analysis central obesity was alternatively defined according to WC >=94cm for males or average waist >=80cm for females [15] were defined centrally obese..

Dietary data

Diet was assessed using a modified version of the self-completed EPIC FFQ [16]. This FFQ was then incorporated into the Irish National Surveys of Lifestyle Attitudes and Nutrition 1998, 2002, 2006 [17-19] and the Cork and Kerry Phase 1 study [20] and has been validated for use in the Irish population. Information on the frequency of consumption of food items during the past 12 months was collected. The daily intake of energy and nutrients was computed from FFQ data using a tailored computer program (FFQ Software Ver 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 [21]. Dietary quality was determined by

calculation of the DASH score using the FFQ responses. The DASH score is a composite score derived from standard food groups within the FFQ as described by Fung et al., [22]. For each food group, consumption was divided into quintiles and participants were classified according to their intake ranking. Consumption of healthy food components were rated on a scale of 1-5, the higher the score the more frequent the consumption of that food, i.e. those in quintile 1 had the lowest consumption and received a score of 1; conversely those in quintile 5 had the highest consumption and received a score of 5. Less healthy dietary constituents, where low consumption is desired, were scored on a reverse scale with lower consumption receiving the higher scores. Component scores were summed and an overall DASH score for each person was calculated. The DASH score was then stratified by quartiles, whereby a lower quartile indicated a poorer dietary quality.

Lifestyle data

Physical activity levels were assessed using the short form IPAQ which provided information on frequency, duration and intensity of physical activity [23]. Using the instrument's scoring protocol, physical activity was categorized into three groups; low, moderate and high, based on a combination of; frequency of activity, duration of each activity bout and metabolic equivalent (MET) minutes per week in all activity types. Smoking status was defined as never (having never smoked at least 100 cigarettes in entire life), former (having smoked at least 100 cigarettes in entire life and do not smoke now), and current smokers (smoking at present). Alcohol consumption included questions based on weekly intake to define non-drinkers (a person who responded to the question "How often do you have a drink containing alcohol" as never), moderate (women and men consuming less than 14 units and 21 units, respectively, in a typical

week) and heavy drinkers (women and men consuming greater than or equal to 14 units and 21 units, respectively, in a typical week).

Biological analyses

Plasma and serum were prepared from fasting blood samples from each subject. Fasting plasma glucose (FPG), serum total, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol and triglyceride (TAG) levels were measured by Cork University Hospital Biochemistry Laboratory using fresh blood samples. FPG concentrations were determined using a glucose hexokinase assay and serum lipids were analyzed using enzymatic colorimetric tests (Olympus Life and Material Science Europa Ltd., Lismeehan, Co. Clare, Ireland) on an Olympus 5400 automatic analyzer (Olympus Diagnostica Gmbh, Hamburg, Germany). Serum insulin, C reactive protein (CRP), tumour necrosis factor α (TNF-α), interleukin 6 (IL-6), adiponectin (ACDC), leptin, resistin, plasminogen activator inhibitor-1 (PAI-1) were determined using a biochip array system (Evidence Investigator; Randox Laboratories, Antrim, UK). Complement component c3 (C3) was determined by immunoturbidimetric assay (Rx Daytona; Randox Laboratories, Antrim, UK). White blood cell (WBC) counts were determined by flow cytometry technology as part of a full blood count by the Cork University Hospital Haematology Laboratory using fresh blood samples. Homeostasis model assessment (HOMA), a measure of insulin resistance, was calculated as [(fasting plasma glucose x fasting serum insulin)/ 22.5] [24]. Quantitative insulin-sensitivity check index (QUICKI), a measure of insulin sensitivity, was calculated as = 1/[log fasting insulin + log fasting glucose][25].

Lipoprotein particle profiling

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). LDL, HDL, and VLDL subclasses were quantified based on the amplitudes of their spectroscopically-distinct lipid methyl group NMR signals [26]. Weighted-average VLDL, LDL, and HDL particle sizes (in nanometer 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 9 subclass categories were investigated: large VLDL (including chylomicrons, if present) (>60 nm), medium VLDL (42 to 60 nm), small VLDL (29 to 42 nm), large LDL (20.5 to 23 nm), small LDL (18 to 20.5 nm), large HDL (9.4 to 14 nm), medium HDL (8.2 to 9.4 nm), and small HDL (7.3 to 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 6 lipoprotein subclass and size parameters most closely associated with IR, was calculated [27].

Statistical analysis

Statistical analysis was conducted using PASW Statistics version 20® for Windows (SPSS Inc., Chicago, IL). Continuous variables were expressed as means ± SEM and categorical variables as percentages. Variables were assessed for normality of distribution and skewed variables were normalized as appropriate. Differences between groups were analysed by ANOVA for continuous variables and by Chi-Square test for categorical variables. Logistic regression analysis determined associations between dietary quality based on DASH quartiles, with a range

of biomarkers and risk of central obesity, MetS, T2DM and CVD. Age, gender, BMI, physical activity, smoking status, alcohol consumption, dietary energy intake, medical history and medication use were considered confounding factors. An alpha level of 0.05 was set to evaluate significance. To correct for the multiple testing performed we calculated false discovery rate (FDR) adjusted *P* values using the method described by Benjamini and Hochberg [28]. In addition sensitivity analyses were conducted using abdominal obesity defined by WC, rather than WHR, as a measure of abdominal obesity in the logistic regression analysis.

3. Results

Clinical and demographic characteristics stratified by DASH quartile

The current analysis included 1,493 Mitchelstown cohort participants (49% male, aged 59.4 ±0.14 years). Mean (SEM) and range of the DASH scores in these individuals were 28.85 (0.15) and 13 to 45. Clinical and demographic characteristics according to DASH quartiles are presented in **Table 1**. Individuals with the highest dietary quality (top quartile of DASH) were marginally older and more likely to be female, with lower BMI, smaller waist circumference, pelvic width, WHR and lower systolic blood pressure (SBP). In terms of lifestyle behaviours, they were also more likely to be non-drinkers, less sedentary and moderate alcohol consumers and less likely to be current smokers ($P < 0.05$). No differences in energy intake were observed according to DASH quartiles. Lower triglyceride and higher HDL-C concentrations ($P < 0.001$) and lower glucose and insulin concentrations ($P < 0.05$), leading to improved insulin sensitivity and reduced insulin resistance ($P < 0.005$) assessed by QUICKI and HOMA respectively, were observed among participants with better dietary quality.

Table 1: Demographic, clinical and lifestyle characteristics stratified by DASH quartiles in the Mitchelstown cohort (*n* = 1493)

	Q 1	**Q 2**	**Q 3**	**Q 4**	***P*** [1]
Age (yrs)	59.1±0.24	59.8±0.24	59.5±0.26	60.1±0.29	0.031
Gender (% male)	70.7	52.1	41.5	24.3	0.001
BMI (kg/m^2)	28.7±0.19	28.5±0.21	28.7±0.23	27.8±0.22	0.021
Waist circumference (cm)	99.38±0.54	97.14±0.58	96.35±0.63	92.91±0.0.65	<0.001
Hip circumference (cm)	99.60±0.43	100.06±0.44	101.14±0.47	100.23±0.47	0.096
WHR	0.99±0.004	0.97±0.004	0.95±0.004	0.92±0.004	<0.001
SBP	131.42±0.73	129.31±0.75	128.53±0.79	128.61±0.87	0.029
DBP	80.70±0.43	79.96±0.44	79.65±0.45	80.28±0.52	0.376
Energy (kcal)	2027±34	2017±34	2077±41	1984±42	0.400
DASH score	23.84±0.22	28.41±0.22	30.85±0.22	34.21±0.27	<0.001
Physical activity (%)					
Low	51.7	50.1	43.6	41.5	0.005
Moderate	24.9	30.0	32.2	36.6	
High	23.4	19.9	24.2	21.9	
Alcohol (%)					
Non-drinker	18.0	18.0	23.1	24.8	<0.001
Moderate	60.6	65.0	66.7	67.3	
Heavy	21.4	17.0	10.2	8.0	
Smoking status (%)					
Never	47.5	48.9	53.4	56.3	<0.001
Former	32.1	36.0	34.0	36.0	
Current	20.4	15.1	12.6	7.8	
TG (mmol/L)	1.49±0.04	1.43±0.04	1.37±0.04	1.20±0.04	<0.001
HDL-C (mmol/L)	1.37±0.02	1.44±0.02	1.47±0.02	1.55±0.02	<0.001
LDL-C (mmol/L)	3.18±0.04	3.16±0.04	3.16±0.04	3.22±0.05	0.78
Total-C (mmol/L)	5.24±0.05	5.29±0.05	5.29±0.05	5.33±0.05	0.67
FPG (mmol/L)	5.29±0.06	5.17±0.05	5.12±0.06	5.08±0.05	0.04
Insulin (µIU/ml)	12.14±0.47	11.78±0.44	11.11±0.47	10.06±0.45	0.014
HOMA	3.04±0.15	2.90±0.15	2.72±0.15	2.40±0.13	0.02
QUICKI	0.27±0.003	0.27±0.003	0.28±0.003	0.28±0.003	0.001

Continuous variables are expressed as means ± SEM; categorical variables are expressed as percentages. [1]*P* was derived from ANOVA for continuous variables and Chi-Square test for categorical variables. Yrs: years; %: percentage; WHR: waist to hip ratio; Kcal: kilocalories.

243

244 **Inflammatory and lipoprotein profiles according to DASH quartiles**

245 Supporting the correlation analysis (**Table 2**) examination of a range of inflammatory
246 biomarkers (**Figure 1**) revealed inverse associations between DASH quartiles and TNF-α, IL-6,
247 PAI-1, WBC ($P < 0.01$) and a positive association with adiponectin concentrations ($P < 0.001$).
248 In addition comparison of top versus bottom DASH quartiles revealed differences in CRP and
249 leptin concentrations ($P < 0.05$). No differences were observed for resistin concentrations
250 according to DASH quartiles (data not shown). Lipoprotein particle concentrations and size
251 profiles of the study population according to DASH quartiles are presented in **Table 3**.
252 Increasing dietary quality was associated with a more favourable lipoprotein profile
253 characterised by less total TRL, large and medium VLDL ($P < 0.001$), IDL ($P < 0.05$) and small
254 LDL and HDL particles ($P < 0.001$) and more total HDL ($P < 0.05$), large and medium HDL and
255 large LDL particles ($P < 0.001$). These differences translated into smaller average VLDL particle
256 size and larger average LDL and HDL particle size ($P < 0.001$). In addition there was an inverse
257 association between DASH quartiles and LP-IR scores ($P < 0.001$). All reported findings
258 between DASH scores and both inflammatory and lipoprotein profiles remained significant
259 following adjustment for multiple testing.

260

261 **Table 2:** Spearman correlation coefficients between DASH scores and anthropometric measures and
262 cardiometabolic biomarkers

	Correlation coefficients	***P***

Adiposity measures		
BMI (kg/m^2)	-0.058	<0.05
Waist circumference (cm)	-0.145	<0.01
Hip circumference (cm)	-0.006	0.530
WHR	-0.200	<0.01
Pelvic width (cm)	-0.082	<0.01
Inflammatory and thrombotic markers		
IL-6 (pg/mL)	-0.073	<0.01
TNF-α (pg/mL)	-0.057	<0.05
CRP (ng/mL)	-0.076	<0.01
C3 (mg/dL)	-0.071	<0.01
ACDC (ng/mL)	0.106	<0.01
Leptin (ng/mL)	0.007	0.791
Resistin (ng/mL)	-0.035	0.181
WBC ($10^9/L$)	-0.122	<0.01
PAI-1 (ng/mL)	-0.077	<0.01
Glucose homeostasis biomarkers		
HOMA	-0.061	<0.05
QUICKI	0.055	<0.05
Insulin (μIU/ml)	-0.072	<0.01
Glucose (mmol/L)	-0.023	0.373
Lipoprotein profile parameters		
Total TRL (nmol/L)	-0.054	<0.05
Large VLDL (nmol/L)	-0.084	<0.01
Medium VLDL (nmol/L)	-0.096	<0.01
Small VLDL (nmol/L)	0.014	0.595
Total LDL (nmol/L)	-0.106	<0.01
IDL (nmol/L)	-0.096	<0.01
Large LDL (nmol/L)	0.093	<0.01
Small LDL (nmol/L)	-0.152	<0.01
Total HDL (μmol/L)	0.022	0.411
Large HDL (μmol/L)	0.153	<0.01

Medium HDL (μmol/L)	0.037	0.158 263
Small HDL (μmol/L)	-0.125	<0.01
VLDL (nm)	-0.072	<0.05
LDL (nm)	0.138	<0.01
HDL (nm)	0.160	<0.01
LP -IR score	-0.175	<0.01

264

265 Values are presented as Spearman correlation coefficients between continuous DASH scores and a range
266 of adiposity measures and cardiometabolic biomarkers among the Mitchelstown cohort (*n*=1493).

267

268 **Table 3:** Lipoprotein profiles of the Mitchelstown cohort (*n*=1493) according to DASH quartiles

	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	***P* [1] *trend***	***P* [2] *Q4 vs Q1***
Lipoprotein particle concentration						
Total TRL	69.85±2.05	71.09±2.02	64.62±1.97	58.85±2.02	<0.001	<0.001
Large VLDL	3.14±0.23	2.82±0.20	2.59±0.22	1.53±0.12	<0.001	<0.001
Medium VLDL	30.80±1.25	30.73±1.19	25.67±1.05	21.95±1.00	<0.001	<0.001
Small VLDL	35.91±1.23	37.54±1.14	36.36±1.30	35.37±1.51	0.675	0.776
Total LDL	1301.68±18.50	1259.68±19.00	1239.86±19.22	1241.26±21.00	0.077	0.035
IDL	119.25±4.10	117.17±3.98	114.04±4.38	99.87±4.33	0.011	0.007
Large LDL	538.74±12.86	587.09±13.92	612.66±14.14	683.21±15.47	<0.001	<0.001
Small LDL	643.72±18.77	555.40±19.20	513.17±19.67	458.14±20.01	<0.001	<0.001
Total HDL	37.79±0.27	38.71±0.29	38.32±0.30	38.86±0.30	0.042	0.012
Large HDL	5.95±0.17	6.99±0.19	7.39±0.20	8.17±0.24	<0.001	<0.001
Medium HDL	12.96±0.27	13.81±0.29	13.66±0.30	14.03±0.31	0.056	0.013
Small HDL	18.87±0.26	17.92±0.28	17.27±0.26	16.65±0.31	<0.001	<0.001
Lipoprotein particle size						
VLDL (nm)	45.69±0.31	44.90±0.27	45.14±0.32	43.75±0.31	<0.001	<0.001
LDL (nm)	20.73±0.02	20.85±0.03	20.94±0.03	21.04±0.03	<0.001	<0.001
HDL (nm)	9.19±0.02	9.29±0.02	9.34±0.02	9.41±0.03	<0.001	<0.001
LP -IR score	39.33±0.99	34.29±0.99	31.91±1.05	26.85±1.11	<0.001	<0.001

269

Values are expressed as means ± SEM. [1]*P* for trend was derived from ANOVA comparing across all DASH quartiles.

[2]*P* for Q4 vs Q1 was derived from ANOVA comparing DASH quartile 4 to DASH quartile 1.

DASH and cardiometabolic disease risk

Among all subjects in the current analysis the prevalence of central obesity (defined by WHR), MetS, T2DM and CVD was 87.3%, 21.25%, 14.9% and 10.44%, respectively. When stratified by DASH quartiles the prevalence of central obesity and MetS decreased with increasing dietary quality (93.7, 90.0, 84.5, 79.8%, P <0.001 and 25.6, 21.1, 18.6, 18.3%, P <0.05 in DASH quartiles 1-4, for central obesity and MetS, respectively. Logistic regression analysis (**Table 4**) revealed that likelihood of central obesity (defined by WHR) was lower among those with the highest DASH scores compared to those among the bottom DASH quartile (P < 0.001, unadjusted model). This association persisted after adjustment for potential confounders (OR 0.46, 95% CI (0.25, 0.84), P =0.01, adjusted model). Sensitivity analysis using abdominal obesity defined by WC, rather than WHR, did not reveal any association with DASH score quartiles (data not shown). MetS risk was also predicted to be lower among those in the top DASH quartile relative to those among the lowest DASH quartile (P = 0.005 unadjusted model). This association persisted after controlling for potential confounders whereby individuals with the highest dietary quality had a 48% lower likelihood of MetS than those with the lowest dietary quality (OR 0.52, 95% CI 0.28-0.94, P < 0.05). No associations were noted between DASH score and either T2DM or CVD, which may be due to their lower prevalence. All reported findings remained significant following adjustment for multiple testing.

289 **Table 4:** Logistic regression analysis of the association between DASH quartiles and cardiometabolic disease

	Central obesity		**Metabolic Syndrome**		**T2DM**		**CVD**	
Model 1		***p***		***p***		***p***		***p***
Quartile 1	1 [reference]		1 [reference]		1 [reference]		1 [reference]	
Quartile 2	0.63 (0.40, 0.98)	0.044	0.84 (0.63, 1.12)	0.24	1.16 (0.75, 1.78)	0.51	1.18 (0.80, 1.75)	0.40
Quartile 3	0.46 (0.30, 0.72)	0.001	0.69 (0.51, 0.94)	0.018	0.89 (0.56, 1.42)	0.63	1.01 (0.68, 1.53)	0.93
Quartile 4	0.29 (0.19, 0.45)	< 0.001	0.62 (0.44, 0.87)	0.005	0.73 (0.43, 1.23)	0.24	0.71 (0.44, 1.15)	0.17
Model 2								
Quartile 1	1 [reference]		1 [reference]		1 [reference]		1 [reference]	
Quartile 2	0.78 (0.47, 1.28)	0.32	0.83 (0.53, 1.29)	0.41	1.12 (0.57, 2.18)	0.75	1.08 (0.60, 1.93)	0.80
Quartile 3	0.67 (0.40, 1.12)	0.12	0.74 (0.46, 1.16)	0.19	0.96 (0.47, 1.94)	0.90	1.06 (0.58, 1.94)	0.84
Quartile 4	0.46 (0.25, 0.84)	0.01	0.52 (0.28, 0.94)	0.03	0.72 (0.28, 1.87)	0.49	1.01 (0.47, 2.09)	0.98

290

291 Data is presented as OR (95% CI). DASH scores were stratified by quartiles. Central obesity defined according to waist hip ratio Reference group refers to lowest
292 DASH quartile within the same comparative group. Model 1: Unadjusted. Model 2: Adjusted for age, gender, BMI, physical activity, smoking status, alcohol
293 consumption, dietary energy intake, anti-inflammatory and lipid lowering medication use.

4. Discussion

To our knowledge, the current study is the largest investigation of the associations between dietary quality assessed by DASH and a range of intermediate biomarkers of cardiometabolic health in an adult population. We provide evidence for associations between higher quality diet and more favourable cardiometabolic health characterized by improved anthropometric measures and a less pro-inflammatory, less pro-thrombotic, less pro-atherogenic and less insulin resistant cardiometabolic profile, which after adjustment for a range of confounding factors translated into a 54% reduced risk of central obesity and a 48% reduced risk of MetS among those with the highest dietary quality relative those in the bottom DASH quartile.

Evidence to date regarding the link between DASH and inflammation is inconsistent and has been based on selected biomarkers. Cross-sectional analysis of 775 healthy women in the Women's Lifestyle Validation Study which was conducted within the Nurses' Health Study (NHS) and NHS II longitudinal revealed associations between DASH and leptin, but not with adiponectin [10]. Findings from the Multiethnic Cohort involving five ethnic groups (n = 166, 550) revealed associations with adiponectin, but not with leptin [11]. Such disparities may have arisen due to differences in study design, gender, sample sizes or ethnic differences. CRP has been the most widely investigated pro-inflammatory marker in the context of dietary quality. A recent systematic review and meta-analysis of the effect of the DASH diet on CRP concentrations demonstrated that compared to the usual or unhealthy diet, adherence to the DASH diet was associated with more favourable CRP levels [12]. Importantly the current work expands the knowledge base by examining a broader range of inflammatory biomarkers including acute-phase reactants, adipocytokines, white blood cell counts and additional pro-inflammatory cytokines. We report inverse associations between DASH quartiles and TNF-

α, IL-6, PAI-1, WBC and a positive association with adiponectin concentrations. In addition comparison of top versus bottom DASH quartiles revealed differences in CRP and leptin concentrations. The observed differences in IL-6 and CRP concentrations (45% and 30% comparing top vs bottom DASH quartiles, respectively) were greater than those reported between non-cases and cases of CVD and T2DM in the Caerphilly study [29], and for IL-6 between survivors of a first myocardial infarction (MI) and age and gender matched controls [30] and cases of stroke and no CVD events [31]. Differences in TNF-α concentrations (9% Q1 vs Q4 DASH) were similar to those reported between cases of congestive heart failure and no CVD events [31]. Similarly the observed differences in adiponectin concentrations (21% Q1 vs Q4 DASH) exceeded those between patients with and without CVD in the Cardiovascular Health Study and the British Regional Heart Study [32, 33]. Differences in WBCs (16% Q1 vs Q4 DASH) were greater than those reported between non-cases and cases of CVD [29]. Furthermore the differences in PAI-1 concentrations between top and bottom DASH quartiles were comparable to those noted in several MI case control studies [30, 34]. Collectively these data suggest both physiologically and clinically significant differences in pro-inflammatory profiles according to DASH status.

Examination of adherence to the DASH diet and impact on lipid profiles has demonstrated associations with HDL-C, LDL-C and triglyceride concentrations [10, 35, 36]. Scant data on lipoprotein profiles exist. 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 particle concentrations determined by ion mobility. They reported that the DASH diet, but not the HF-DASH diet, significantly reduced LDL-C, HDL-C, apolipoprotein A-I, IDL and large LDL particles, and

LDL peak diameter compared with the control diet [37]. No study to date has examined DASH in the context of lipoprotein particle subclass determined by NMR. We report a more favourable lipoprotein profile characterized by less large VLDL and small LDL and HDL particles and more total, large and medium HDL and large LDL particles among those with the highest dietary quality. These changes translated into smaller average VLDL particle size and larger average LDL and HDL particle size. Lipoprotein particle size, in particular large VLDL and small, dense LDL and HDL particles are associated with increased risk for atherosclerosis and premature CVD [38-41]. Large VLDL particles are important in terms of CVD risk as they are associated with the pro-atherogenic small dense LDL phenotype [39]. Relative to LDL particles these 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 [42]. VLDL particles may also be directly taken up by macrophages (without any modifications like LDL) to create foam cells, the hallmark cells of atherosclerotic plaque. Hepatic overproduction of large triglyceride-rich VLDL is a hallmark of dyslipidemia in obesity and insulin resistance [43, 44] which may initiate diabetic dyslipidemia [45]. Thus dietary strategies which improve dyslipidemia characterised by elevated triglycerides, large VLDL particles and small dense LDL and HDL particles have the potential to attenuate atherogenesis and progression towards overt T2DM and related cardiometabolic disease.

The DASH diet has been associated with improved insulin sensitivity and reduced risk of insulin resistance and T2DM [6, 7, 46]. In keeping with those findings we report improved insulin sensitivity and reduced insulin resistance among participants with better dietary quality as well as an inverse association between DASH quartiles and LP-IR scores. Although we did not detect any association between DASH and T2DM or CVD risk, most likely due to relatively small

number of cases, we did report lower risk of central obesity and metabolic syndrome among those with the highest dietary quality. Previous data on dietary patterns and dietary quality (dietary guideline adherence) suggest associations between better dietary quality and healthy dietary patterns with more favourable anthropometric measures of cardiometabolic health [47]. It is interesting to note that in the current study BMI decreased across DASH quartiles and the risk of central obesity, assessed by WHR, was lower among those in the top DASH quartile. Individuals with the lowest dietary quality had the greatest WHR suggesting that they carried more weight around the abdomen relative to the hip area. Consistent with our observations of more favourable metabolic profile (including lower WHR) among those with higher DASH scores are the findings that leg fat is linked with more favorable inflammatory and metabolic profiles [48, 49] whereas visceral, but not abdominal subcutaneous fat, has been associated with higher plasma concentrations of IL-6 and CRP [50]. Substituting WC for WHR did not result in any significant associations between DASH quartiles and central obesity risk, suggesting perhaps that body fat distribution or body shape, rather than abdominal obesity per say may be more related to dietary quality. Findings from a recent systematic review suggesting that dietary patterns as described by diet index scores, mainly affect visceral adipose tissue, whereas subcutaneous adipose tissue may be determined more by excessive energy intake support this concept [51].

Among the strengths of our study are the large number of participants aged 50 to 69 years old with evaluable data; equal representation by gender (49.2% male); assessment of a wide range of clinical and cardiometabolic, endocrine, lipid and inflammatory parameters; information on a wide range of confounding factors including diet and lifestyle behaviours, medical history and use of medications. Despite these strengths, a number of limitations can be identified. The cross-

sectional study design limits inference regards causality and precludes drawing conclusions regarding the temporal direction of the relationship between dietary quality and biomarkers and health status. Prospective studies investigating whether lower dietary quality arises from non-optimal cardiometabolic health profiles or status or is a causative factor are required. The recently completed follow-up of the Mitchelstown cohort, which will allow longitudinal analysis of the reported diet-biomarker-cardiometabolic health associations to be examined in an aging population, will undoubtedly be important in this regard. Although we controlled for confounding factors we cannot exclude the possibility that unmeasured confounders, such as genotype, may also influence our observations. Moreover residual confounding arising from imprecise measurement of dietary intake should also be considered. As a structured dietary assessment method, the use of an FFQ can introduce recall and reporting biases related to psychosocial factors (response sets) [52, 53] . Generalisability of our findings may also be limited. The Mitchelstown cohort (response rate 67%) was a random sample of middle-aged adults from an area representative of both urban and rural population in Ireland. Our previous research suggests that approximately 98% of Irish adults are registered with a general practitioner and that, even in the absence of a universal patient registration system, it is possible to perform population based epidemiological studies that are representative of the general population using these methods [54].

In conclusion, these novel results provide further evidence regarding the relationship between dietary quality and intermediate biomarkers of cardiometabolic health. Importantly, they expand on the previously described diet-biomarker associations and highlight the potential of higher dietary quality in the context of a more favourable cardiometabolic risk profile and reduced likelihood of central obesity and MetS. These data suggest that the potential benefits of

following a DASH diet, in terms of CVD prevention, extend beyond the well known blood pressure lowering effects. Improving our understanding of the relationship between such dietary indices and biomarkers of cardiometabolic health is warranted, with a view to informing public health planning and policy to improve and maintain optimal cardiometabolic health at the population level.

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Author Contributions

All authors contributed to the conception and design of the study, or analysis of the data, drafting of the manuscript or critical revision of the manuscript for important intellectual input. All authors approved the final version.

Conflict of Interest Statement

We have no conflicts of interest to declare.

Supplementary Information

Supplementary Figure S1 (pdf) presents a flow chart outlining the subject selection for the current analysis of the Mitchelstown cohort. Supplementary information is available at the International Journal of Obesity's website.

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Figure Legend

Figure 1. Concentrations of inflammatory and thrombotic markers stratified by DASH quartiles. Results are expressed as mean concentrations ± SEM for IL-6, TNF-α, CRP, C3, WBC, PAI-1, ACDC and leptin according to DASH quartiles in the Mitchelstown cohort (*n* = 1493). *P* for trend was derived from ANOVA comparing across all DASH quartiles. *P* for Q1 vs Q4 was derived from ANOVA comparing DASH quartile 4 to DASH quartile 1.