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1 **Title:** Relationship between dietary quality, determined by DASH score, and cardiometabolic

2 health biomarkers: a cross-sectional analysis in adults

3

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16

17 **Running title:** Dietary quality and cardiometabolic health biomarkers

18

19 **Key words:** dietary quality; inflammation; lipoproteins; insulin resistance; obesity; biomarkers;

20 Mitchelstown cohort; adults;

21

22   **Abstract**

23   **Background and Aims:** The relationship between dietary patterns and cardiometabolic disease

24   is of increasing interest. However, limited data regarding the association between dietary quality

25   and biomarkers of cardiometabolic health exist. Therefore the aim of this work was to examine

26   potential associations between dietary quality, assessed using the Dietary Approaches to Stop

27   Hypertension (DASH) dietary quality score, adiposity and biomarkers of glucose homeostasis,

28   lipoprotein metabolism and inflammation in a cross-sectional sample of 1,493 men and women.

29   **Methods:** Anthropometric measurements included BMI, hip and waist circumference (WC).

30   Serum acute-phase reactants, adipocytokines, pro-inflammatory cytokines and white blood cell

31   (WBC) counts were determined. Lipoprotein particle size and subclass concentrations were

32   measured using nuclear magnetic resonance (NMR) spectroscopy. Insulin resistance was

33   calculated by homeostasis model assessment (HOMA-IR).

34   **Results:** Higher dietary quality was associated with lower BMI ($P < 0.05$), WC ($P < 0.001$),

35   tumour necrosis factor (TNF)-α, interleukin 6 (IL-6), WBC and plasminogen activator inhibitor-

36   1 (PAI-1) concentrations ($P < 0.01$) and reduced insulin resistance ($P < 0.05$). In addition less

37   small low density lipoprotein (LDL) and small high density lipoprotein (HDL) particles and less

38   large very low density lipoprotein (VLDL) particles were observed among those with better

39   dietary quality ($P < 0.001$). Individuals in the top DASH quartile had a 54% and 48% lower

40   likelihood of central obesity and metabolic syndrome (MetS), respectively, than those in the

41   lowest DASH quartile ($P < 0.05$).

42   **Conclusions:** Our data suggest that higher quality diet is associated with improved adiposity

43   measures and a less insulin resistant, pro-inflammatory, pro-thrombotic and pro-atherogenic

44 cardiometabolic profile which may impact on central obesity and MetS risk. These findings,

45 which may be of clinical and public health significance in terms of dietary approaches to

46 promote cardiometabolic health, warrant further examination.

47

48 **Abbreviations:** BMI: Body mass index; C3: Complement component c3; CRP: C reactive

49 protein; CVD: Cardiovascular disease; DASH: Dietary Approaches to Stop Hypertension; FPG:

50 Fasting plasma glucose; GHQ: General health questionnaire; HDL: High-density lipoprotein;

51 HDL-C: High density lipoprotein cholesterol; HOMA-IR: Homeostasis model assessment of

52 insulin resistance; IDL: Intermediate-density lipoprotein; IL-6: interleukin 6; LP-IR: Lipoprotein

53 Insulin Resistance Index; LDL: Low-density lipoprotein; LDL-C: Low density lipoprotein

54 cholesterol; MetS: Metabolic syndrome; MI: Myocardial infarction; NMR: Nuclear magnetic

55 resonance; PAI-1: plasminogen activator inhibitor-1; TNF-α: tumour necrosis factor α; TG:

56 Triglyceride; TRL: Triglyceride-rich lipoprotein; Total-C: Total cholesterol; T2DM: Type 2

57 diabetes mellitus; VLDL: Very low-density lipoprotein; WBC: White blood cell; WC: Waist

58 circumference; WHR: Waist to hip ratio

59

60 **1. Introduction**

61 Poor dietary quality contributes to adverse health and mortality. Recent meta-analysis of a range

62 of dietary indices of dietary quality revealed lower risk of all-cause mortality, cardiovascular

63 disease (CVD), type 2 diabetes (T2DM), cancer and neurodegenerative disease among those with

64 higher dietary quality scores [1]. Examination of global dietary quality trends among adults

65 across 187 nations in 1990 and 2010 by the Global Burden of Diseases Nutrition and Chronic

66 Diseases Expert Group reported a modest increase in the consumption of healthy foods, however

67 intake of unhealthy foods has increased to a greater extent during the past two decades [2].

68 Unhealthy diets, characterized by low intakes of fruits, vegetables, nuts/seeds, wholegrains,

69 seafood and poultry and high intakes of red and processed meats, refined grains, saturated fat and

70 sugar sweetened beverages have been estimated to be associated with a substantial proportion of

71 deaths from heart disease, stroke and T2DM [3, 4].

72 The Dietary Approaches to Stop Hypertension (DASH) diet emphasizes consumption of fruits,

73 vegetables, nuts, beans, wholegrains and low fat dairy and restricting intake of red meat, sugar

74 sweetened beverages, sweets, total fat and saturated fat [5]. Since the development of the DASH

75 diet twenty years ago an increasing body of evidence has demonstrated a consistent reduction in

76 chronic cardiometabolic diseases [1, 5-9]. However the relationships between DASH scores and

77 intermediate biomarkers of cardiometabolic health are unclear. Numerous underlying biological

78 pathways including inflammation, lipid and glucose homeostasis may underlie the positive

79 associations between dietary quality and chronic diseases. However the limited data available on

80 the relationship between DASH scores and select biomarkers of cardiometabolic health [6, 10-

81 12], highlights the need for further investigation. To our knowledge no data exist on the potential

82 associations between DASH scores and NMR derived lipoprotein profiles. Furthermore the focus

83   of inflammatory profiling in this context has been mainly on C reactive protein (CRP), with little

84   to no information on other inflammatory markers such as interleukin-6 (Il-6), tumour necrosis

85   factor (TNF) α, adiponectin, leptin, resistin or complement component c3 (C3), or thrombotic

86   markers such as plasminogen activator inhibitor-1 (PAI-1). Therefore, the objective of the

87   present study was to comprehensively examine associations between dietary quality using the

88   DASH score and adiposity and a wide range of biomarkers of cardiometabolic health,

89   inflammation, lipoprotein metabolism and glucose homeostasis in a cross-sectional sample of

90   men and women. Such investigation of different potential biological is required to improve our

91   understanding of the relationships between dietary quality and cardiometabolic health.

92

2. Subjects and Methods

Study design and subject recruitment

95   The Cork and Kerry Diabetes and Heart Disease Study (Phase II) was a single centre, cross-

96   sectional study conducted between 2010 and 2011 [13]. A population representative random

97   sample was recruited from a large primary care centre in Mitchelstown, County Cork, Ireland

98   (Mitchelstown cohort, clinical trials.gov identifier NCT03191227). The Livinghealth Clinic

99   includes 8 general practitioners and serves a catchment area of approximately 20,000 with a mix

100   of urban and rural residents. Mitchelstown cohort participants were randomly selected from all

101   registered attending patients in the 50-69-year age group. In total, 3,807 potential participants

102   were selected from the practice list. Following exclusion of duplicates, deaths and ineligibles,

103   3,043 were invited to participate in the study and of these 2,047 White individuals (49.2% male)

104   completed the questionnaire and physical examination components of the baseline assessment

105   (response rate 67%). Ethics committee approval conforming to the Declaration of Helsinki was

106   obtained from the Clinical Research Ethics Committee of University College Cork. All

107   participants provided written informed consent. Following exclusion of individuals without a

108   DASH score the remaining 1493 participants were used in the analyses. A flow chart outlining

109   the subject selection for the current analysis of the Mitchelstown cohort is presented in

110   **Supplemental Figure S1.**

111

112   **Clinical and anthropometric data**

113   All participants attended the clinic in the morning after an overnight fast (minimum 8h). Fasting

114   blood samples were taken on arrival. Participants completed a General Health Questionnaire

115   (GHQ), a food frequency questionnaire (FFQ), and the International Physical Activity

116   Questionnaire (IPAQ). Data on age, gender, medical history and medication use was gathered

117   through a self-completed GHQ. The presence of cardiovascular disease (CVD) was obtained

118   from the GHQ by asking study participants if they had been diagnosed with any one of the

119   following seven conditions: Heart Attack (including coronary thrombosis or myocardial

120   infarction), Heart Failure, Angina, Aortic Aneurysm, Hardening of the Arteries, Stroke, or any

121   other Heart Trouble. Subjects who indicated a diagnosis of any one of these conditions were

122   classified as having CVD. Type 2 diabetes was defined according to the American Heart

123   Association guidelines of fasting plasma glucose (FPG) $\geq$ 7 mmol/L or doctor diagnosed

124   diabetes. Blood pressure was measured according to the European Society of Hypertension

125   Guidelines using an Omron M7 Digital BP monitor on the right arm, after a 5-minute rest in the

126   seated position. The average of the second and third measurements was used for analyses. MetS

127   was defined according to the National Cholesterol Education (NCEP) Adult Treatment Panel III

128   (ATP III) [14]. Anthropometric measurements were recorded with calibrated instruments

129   according to a standardised protocol. Body weight was measured in kilograms without shoes; to

130   the nearest 100g using a Tanita WB100MA® weighing scales (Tanita Corporation, IL, USA).

131   Height was measured in centimetres to one decimal place using a Seca Leicester® height gauge

132   (Seca, Birmingham, UK). BMI was calculated as weight (kg) /height (m)^2. Waist circumference

133   (WC) (defined as mid-way between lowest rib and iliac crest) and hip circumference (determined

134   at the maximum perimeter of the hips) were measured in centimetres to 1 decimal place using a

135   Seca 200 measuring tape (Seca, Birmingham, UK). Pelvic width was calculated as the diameter

136   between the right and left iliac crests using callipers. The average of two measures were used for

137   analyses. Individuals with a BMI $\geq$ 30kg/m^2 were defined as obese. Individuals with a waist to

138   hip ratio (WHR) $\geq$0.9 for males and $\geq$0.85 for females were defined as centrally obese [15]. For

139   sensitivity analysis central obesity was alternatively defined according to WC >=94cm for males

140   or average waist >=80cm for females [15] were defined centrally obese..

141

142   **Dietary data**

143   Diet was assessed using a modified version of the self-completed EPIC FFQ [16]. This FFQ was

144   then incorporated into the Irish National Surveys of Lifestyle Attitudes and Nutrition 1998, 2002,

145   2006 [17-19] and the Cork and Kerry Phase 1 study [20] and has been validated for use in the

146   Irish population. Information on the frequency of consumption of food items during the past 12

147   months was collected. The daily intake of energy and nutrients was computed from FFQ data

148   using a tailored computer program (FFQ Software Ver 1.0; developed by the National Nutrition

149   Surveillance Centre, School of Public Health, Physiotherapy and Sports Science, University

150   College Dublin, Belfield, Dublin 4, Ireland), which linked frequency selections with the food

151   equivalents in McCance and Widdowson Food Tables [21]. Dietary quality was determined by

152   calculation of the DASH score using the FFQ responses. The DASH score is a composite score

153   derived from standard food groups within the FFQ as described by Fung et al., [22]. For each

154   food group, consumption was divided into quintiles and participants were classified according to

155   their intake ranking. Consumption of healthy food components were rated on a scale of 1-5, the

156   higher the score the more frequent the consumption of that food, i.e. those in quintile 1 had the

157   lowest consumption and received a score of 1; conversely those in quintile 5 had the highest

158   consumption and received a score of 5. Less healthy dietary constituents, where low

159   consumption is desired, were scored on a reverse scale with lower consumption receiving the

160   higher scores. Component scores were summed and an overall DASH score for each person was

161   calculated. The DASH score was then stratified by quartiles, whereby a lower quartile indicated

162   a poorer dietary quality.

163

164   **Lifestyle data**

165   Physical activity levels were assessed using the short form IPAQ which provided information on

166   frequency, duration and intensity of physical activity [23]. Using the instrument's scoring

167   protocol, physical activity was categorized into three groups; low, moderate and high, based on a

168   combination of; frequency of activity, duration of each activity bout and metabolic equivalent

169   (MET) minutes per week in all activity types. Smoking status was defined as never (having never

170   smoked at least 100 cigarettes in entire life), former (having smoked at least 100 cigarettes in

171   entire life and do not smoke now), and current smokers (smoking at present). Alcohol

172   consumption included questions based on weekly intake to define non-drinkers (a person who

173   responded to the question "How often do you have a drink containing alcohol" as never),

174   moderate (women and men consuming less than 14 units and 21 units, respectively, in a typical

175 week) and heavy drinkers (women and men consuming greater than or equal to 14 units and 21

176 units, respectively, in a typical week).

177

178 **Biological analyses**

179 Plasma and serum were prepared from fasting blood samples from each subject. Fasting plasma

180 glucose (FPG), serum total, high density lipoprotein (HDL) cholesterol, low density lipoprotein

181 (LDL) cholesterol and triglyceride (TAG) levels were measured by Cork University Hospital

182 Biochemistry Laboratory using fresh blood samples. FPG concentrations were determined using

183 a glucose hexokinase assay and serum lipids were analyzed using enzymatic colorimetric tests

184 (Olympus Life and Material Science Europa Ltd., Lismeehan, Co. Clare, Ireland) on an Olympus

185 5400 automatic analyzer (Olympus Diagnostica Gmbh, Hamburg, Germany). Serum insulin, C

186 reactive protein (CRP), tumour necrosis factor α (TNF-α), interleukin 6 (IL-6), adiponectin

187 (ACDC), leptin, resistin, plasminogen activator inhibitor-1 (PAI-1) were determined using a

188 biochip array system (Evidence Investigator; Randox Laboratories, Antrim, UK). Complement

189 component c3 (C3) was determined by immunoturbidimetric assay (Rx Daytona; Randox

190 Laboratories, Antrim, UK). White blood cell (WBC) counts were determined by flow cytometry

191 technology as part of a full blood count by the Cork University Hospital Haematology

192 Laboratory using fresh blood samples. Homeostasis model assessment (HOMA), a measure of

193 insulin resistance, was calculated as [(fasting plasma glucose x fasting serum insulin)/ 22.5] [24].

194 Quantitative insulin-sensitivity check index (QUICKI), a measure of insulin sensitivity, was

195 calculated as = 1/[log fasting insulin + log fasting glucose][25].

196

197 **Lipoprotein particle profiling**

198 Lipoprotein subclass particle concentrations and average VLDL, LDL, and HDL particle

199 diameters were measured on serum specimens by NMR spectroscopy at LipoScience, Inc

200 (Raleigh, NC). LDL, HDL, and VLDL subclasses were quantified based on the amplitudes of

201 their spectroscopically-distinct lipid methyl group NMR signals [26]. Weighted-average VLDL,

202 LDL, and HDL particle sizes (in nanometer diameter units) were computed as the sum of the

203 diameter of each subclass multiplied by its relative mass percentage as estimated from the

204 amplitude of its NMR signal. The following 9 subclass categories were investigated: large VLDL

205 (including chylomicrons, if present) (>60 nm), medium VLDL (42 to 60 nm), small VLDL (29

206 to 42 nm), large LDL (20.5 to 23 nm), small LDL (18 to 20.5 nm), large HDL (9.4 to 14 nm),

207 medium HDL (8.2 to 9.4 nm), and small HDL (7.3 to 8.2 nm). Particle concentrations are

208 expressed as nanomoles per litre (VLDL and LDL) and micromoles per litre (HDL). A

209 Lipoprotein Insulin Resistance score (LP-IR), ranging from 0 (least) to 100 (most) insulin

210 resistant, which is a weighted combination of the 6 lipoprotein subclass and size parameters most

211 closely associated with IR, was calculated [27].

212

213 **Statistical analysis**

214 Statistical analysis was conducted using PASW Statistics version 20® for Windows (SPSS Inc.,

215 Chicago, IL). Continuous variables were expressed as means ± SEM and categorical variables as

216 percentages. Variables were assessed for normality of distribution and skewed variables were

217 normalized as appropriate. Differences between groups were analysed by ANOVA for

218 continuous variables and by Chi-Square test for categorical variables. Logistic regression

219 analysis determined associations between dietary quality based on DASH quartiles, with a range

220 of biomarkers and risk of central obesity, MetS, T2DM and CVD. Age, gender, BMI, physical

221 activity, smoking status, alcohol consumption, dietary energy intake, medical history and

222 medication use were considered confounding factors. An alpha level of 0.05 was set to evaluate

223 significance. To correct for the multiple testing performed we calculated false discovery rate

224 (FDR) adjusted P values using the method described by Benjamini and Hochberg [28]. In

225 addition sensitivity analyses were conducted using abdominal obesity defined by WC, rather

226 than WHR, as a measure of abdominal obesity in the logistic regression analysis.

227

228 **3. Results**

229 **Clinical and demographic characteristics stratified by DASH quartile**

230 The current analysis included 1,493 Mitchelstown cohort participants (49% male, aged 59.4

231 ±0.14 years). Mean (SEM) and range of the DASH scores in these individuals were 28.85 (0.15)

232 and 13 to 45. Clinical and demographic characteristics according to DASH quartiles are

233 presented in **Table 1**. Individuals with the highest dietary quality (top quartile of DASH) were

234 marginally older and more likely to be female, with lower BMI, smaller waist circumference,

235 pelvic width, WHR and lower systolic blood pressure (SBP). In terms of lifestyle behaviours,

236 they were also more likely to be non-drinkers, less sedentary and moderate alcohol consumers

237 and less likely to be current smokers ($P < 0.05$). No differences in energy intake were observed

238 according to DASH quartiles. Lower triglyceride and higher HDL-C concentrations ($P < 0.001$)

239 and lower glucose and insulin concentrations ($P < 0.05$), leading to improved insulin sensitivity

240 and reduced insulin resistance ($P < 0.005$) assessed by QUICKI and HOMA respectively, were

241 observed among participants with better dietary quality.

242

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 $\pm$ 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

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.

270 **DASH and cardiometabolic disease risk**

271 Among all subjects in the current analysis the prevalence of central obesity (defined by WHR),

272 MetS, T2DM and CVD was 87.3%, 21.25%, 14.9% and 10.44%, respectively. When stratified

273 by DASH quartiles the prevalence of central obesity and MetS decreased with increasing dietary

274 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

275 quartiles 1-4, for central obesity and MetS, respectively. Logistic regression analysis (**Table 4**)

276 revealed that likelihood of central obesity (defined by WHR) was lower among those with the

277 highest DASH scores compared to those among the bottom DASH quartile ($P < 0.001$,

278 unadjusted model). This association persisted after adjustment for potential confounders (OR

279 0.46, 95% CI (0.25, 0.84), *P* =0.01, adjusted model). Sensitivity analysis using abdominal

280 obesity defined by WC, rather than WHR, did not reveal any association with DASH score

281 quartiles (data not shown). MetS risk was also predicted to be lower among those in the top

282 DASH quartile relative to those among the lowest DASH quartile ($P = 0.005$ unadjusted model).

283 This association persisted after controlling for potential confounders whereby individuals with

284 the highest dietary quality had a 48% lower likelihood of MetS than those with the lowest dietary

285 quality (OR 0.52, 95% CI 0.28-0.94, $P < 0.05$). No associations were noted between DASH

286 score and either T2DM or CVD, which may be due to their lower prevalence. All reported

287 findings remained significant following adjustment for multiple testing.

288

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.

294 **4. Discussion**

295 To our knowledge, the current study is the largest investigation of the associations between

296 dietary quality assessed by DASH and a range of intermediate biomarkers of cardiometabolic

297 health in an adult population. We provide evidence for associations between higher quality diet

298 and more favourable cardiometabolic health characterized by improved anthropometric measures

299 and a less pro-inflammatory, less pro-thrombotic, less pro-atherogenic and less insulin resistant

300 cardiometabolic profile, which after adjustment for a range of confounding factors translated into

301 a 54% reduced risk of central obesity and a 48% reduced risk of MetS among those with the

302 highest dietary quality relative those in the bottom DASH quartile.

303 Evidence to date regarding the link between DASH and inflammation is inconsistent and has

304 been based on selected biomarkers. Cross-sectional analysis of 775 healthy women in the

305 Women's Lifestyle Validation Study which was conducted within the Nurses' Health Study

306 (NHS) and NHS II longitudinal revealed associations between DASH and leptin, but not with

307 adiponectin [10]. Findings from the Multiethnic Cohort involving five ethnic groups ($n = 166$,

308 550) revealed associations with adiponectin, but not with leptin [11]. Such disparities may have

309 arisen due to differences in study design, gender, sample sizes or ethnic differences. CRP has

310 been the most widely investigated pro-inflammatory marker in the context of dietary quality. A

311 recent systematic review and meta-analysis of the effect of the DASH diet on CRP

312 concentrations demonstrated that compared to the usual or unhealthy diet, adherence to the

313 DASH diet was associated with more favourable CRP levels [12]. Importantly the current work

314 expands the knowledge base by examining a broader range of inflammatory biomarkers

315 including acute-phase reactants, adipocytokines, white blood cell counts and additional pro-

316 inflammatory cytokines. We report inverse associations between DASH quartiles and TNF-

317   α, IL-6, PAI-1, WBC and a positive association with adiponectin concentrations. In addition

318   comparison of top versus bottom DASH quartiles revealed differences in CRP and leptin

319   concentrations. The observed differences in IL-6 and CRP concentrations (45% and 30%

320   comparing top vs bottom DASH quartiles, respectively) were greater than those reported

321   between non-cases and cases of CVD and T2DM in the Caerphilly study [29], and for IL-6

322   between survivors of a first myocardial infarction (MI) and age and gender matched controls [30]

323   and cases of stroke and no CVD events [31]. Differences in TNF-α concentrations (9% Q1 vs Q4

324   DASH) were similar to those reported between cases of congestive heart failure and no CVD

325   events [31]. Similarly the observed differences in adiponectin concentrations (21% Q1 vs Q4

326   DASH) exceeded those between patients with and without CVD in the Cardiovascular Health

327   Study and the British Regional Heart Study [32, 33]. Differences in WBCs (16% Q1 vs Q4

328   DASH) were greater than those reported between non-cases and cases of CVD [29]. Furthermore

329   the differences in PAI-1 concentrations between top and bottom DASH quartiles were

330   comparable to those noted in several MI case control studies [30, 34]. Collectively these data

331   suggest both physiologically and clinically significant differences in pro-inflammatory profiles

332   according to DASH status.

333   Examination of adherence to the DASH diet and impact on lipid profiles has demonstrated

334   associations with HDL-C, LDL-C and triglyceride concentrations [10, 35, 36]. Scant data on

335   lipoprotein profiles exist. A randomised crossover trial of 36 participants who consumed in

336   random order, a control diet, a standard DASH diet, and a higher-fat, lower carbohydrate

337   modified DASH (HF-DASH) diet for 3 weeks each, examined lipoprotein particle concentrations

338   determined by ion mobility. They reported that the DASH diet, but not the HF-DASH diet,

339   significantly reduced LDL-C, HDL-C, apolipoprotein A-I, IDL and large LDL particles, and

340   LDL peak diameter compared with the control diet [37]. No study to date has examined DASH

341   in the context of lipoprotein particle subclass determined by NMR. We report a more favourable

342   lipoprotein profile characterized by less large VLDL and small LDL and HDL particles and more

343   total, large and medium HDL and large LDL particles among those with the highest dietary

344   quality. These changes translated into smaller average VLDL particle size and larger average

345   LDL and HDL particle size. Lipoprotein particle size, in particular large VLDL and small, dense

346   LDL and HDL particles are associated with increased risk for atherosclerosis and premature

347   CVD [38-41]. Large VLDL particles are important in terms of CVD risk as they are associated

348   with the pro-atherogenic small dense LDL phenotype [39]. Relative to LDL particles these large

349   lipid-enriched VLDL particles are more efficiently hydrolysed by lipoprotein lipase, have greater

350   capacity to penetrate the endothelial wall and be preferentially retained in the arterial intima [42].

351   VLDL particles may also be directly taken up by macrophages (without any modifications like

352   LDL) to create foam cells, the hallmark cells of atherosclerotic plaque. Hepatic overproduction

353   of large triglyceride-rich VLDL is a hallmark of dyslipidemia in obesity and insulin resistance

354   [43, 44] which may initiate diabetic dyslipidemia [45]. Thus dietary strategies which improve

355   dyslipidemia characterised by elevated triglycerides, large VLDL particles and small dense LDL

356   and HDL particles have the potential to attenuate atherogenesis and progression towards overt

357   T2DM and related cardiometabolic disease.

358   The DASH diet has been associated with improved insulin sensitivity and reduced risk of insulin

359   resistance and T2DM [6, 7, 46]. In keeping with those findings we report improved insulin

360   sensitivity and reduced insulin resistance among participants with better dietary quality as well

361   as an inverse association between DASH quartiles and LP-IR scores. Although we did not detect

362   any association between DASH and T2DM or CVD risk, most likely due to relatively small

363   number of cases, we did report lower risk of central obesity and metabolic syndrome among

364   those with the highest dietary quality. Previous data on dietary patterns and dietary quality

365   (dietary guideline adherence) suggest associations between better dietary quality and healthy

366   dietary patterns with more favourable anthropometric measures of cardiometabolic health [47]. It

367   is interesting to note that in the current study BMI decreased across DASH quartiles and the risk

368   of central obesity, assessed by WHR, was lower among those in the top DASH quartile.

369   Individuals with the lowest dietary quality had the greatest WHR suggesting that they carried

370   more weight around the abdomen relative to the hip area. Consistent with our observations of

371   more favourable metabolic profile (including lower WHR) among those with higher DASH

372   scores are the findings that leg fat is linked with more favorable inflammatory and metabolic

373   profiles [48, 49] whereas visceral, but not abdominal subcutaneous fat, has been associated with

374   higher plasma concentrations of IL-6 and CRP [50]. Substituting WC for WHR did not result in

375   any significant associations between DASH quartiles and central obesity risk, suggesting perhaps

376   that body fat distribution or body shape, rather than abdominal obesity per say may be more

377   related to dietary quality. Findings from a recent systematic review suggesting that dietary

378   patterns as described by diet index scores, mainly affect visceral adipose tissue, whereas

379   subcutaneous adipose tissue may be determined more by excessive energy intake support this

380   concept [51].

381   Among the strengths of our study are the large number of participants aged 50 to 69 years old

382   with evaluable data; equal representation by gender (49.2% male); assessment of a wide range of

383   clinical and cardiometabolic, endocrine, lipid and inflammatory parameters; information on a

384   wide range of confounding factors including diet and lifestyle behaviours, medical history and

385   use of medications. Despite these strengths, a number of limitations can be identified. The cross-

386   sectional study design limits inference regards causality and precludes drawing conclusions

387   regarding the temporal direction of the relationship between dietary quality and biomarkers and

388   health status. Prospective studies investigating whether lower dietary quality arises from non-

389   optimal cardiometabolic health profiles or status or is a causative factor are required. The

390   recently completed follow-up of the Mitchelstown cohort, which will allow longitudinal analysis

391   of the reported diet-biomarker-cardiometabolic health associations to be examined in an aging

392   population, will undoubtedly be important in this regard. Although we controlled for

393   confounding factors we cannot exclude the possibility that unmeasured confounders, such as

394   genotype, may also influence our observations. Moreover residual confounding arising from

395   imprecise measurement of dietary intake should also be considered. As a structured dietary

396   assessment method, the use of an FFQ can introduce recall and reporting biases related to

397   psychosocial factors (response sets) [52, 53] . Generalisability of our findings may also be

398   limited. The Mitchelstown cohort (response rate 67%) was a random sample of middle-aged

399   adults from an area representative of both urban and rural population in Ireland. Our previous

400   research suggests that approximately 98% of Irish adults are registered with a general

401   practitioner and that, even in the absence of a universal patient registration system, it is possible

402   to perform population based epidemiological studies that are representative of the general

403   population using these methods [54].

404   In conclusion, these novel results provide further evidence regarding the relationship between

405   dietary quality and intermediate biomarkers of cardiometabolic health. Importantly, they expand

406   on the previously described diet-biomarker associations and highlight the potential of higher

407   dietary quality in the context of a more favourable cardiometabolic risk profile and reduced

408   likelihood of central obesity and MetS. These data suggest that the potential benefits of

409   following a DASH diet, in terms of CVD prevention, extend beyond the well known blood

410   pressure lowering effects. Improving our understanding of the relationship between such dietary

411   indices and biomarkers of cardiometabolic health is warranted, with a view to informing public

412   health planning and policy to improve and maintain optimal cardiometabolic health at the

413   population level.

414

420

421   **Author Contributions**

422   All authors contributed to the conception and design of the study, or analysis of the data, drafting

423   of the manuscript or critical revision of the manuscript for important intellectual input. All

424   authors approved the final version.

425

426   **Conflict of Interest Statement**

427   We have no conflicts of interest to declare.

428

429   **Supplementary Information**

430   **Supplementary Figure S1 (pdf)** presents a flow chart outlining the subject selection for the

431   current analysis of the Mitchelstown cohort. Supplementary information is available at the

432   International Journal of Obesity's website.

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593

594   **Figure Legend**

595   **Figure 1.** Concentrations of inflammatory and thrombotic markers stratified by DASH quartiles.

596   Results are expressed as mean concentrations ± SEM for IL-6, TNF-α, CRP, C3, WBC, PAI-1,

597   ACDC and leptin according to DASH quartiles in the Mitchelstown cohort ($n = 1493$). *P* for

598   trend was derived from ANOVA comparing across all DASH quartiles. *P* for Q1 vs Q4 was

599   derived from ANOVA comparing DASH quartile 4 to DASH quartile 1.

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