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Lipoprotein particle subclass profiles among metabolically healthy and unhealthy obese and non-obese adults: Does size matter?

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ABSTRACT

Objectives: No data regards lipoprotein particle profiles in obese and non-obese metabolic health subtypes exist. We characterised lipoprotein size, particle and subclass concentrations among metabolically healthy and unhealthy obese and non-obese adults.

Methods: Cross-sectional sample of 1834 middle-aged Irish adults were classified as obese (BMI ≥30 kg/m^2) and non-obese (BMI <30 kg/m^2). Metabolic health was defined using three metabolic health definitions based on various cardiometabolic abnormalities including metabolic syndrome criteria, insulin resistance and inflammation. Lipoprotein size, particle and subclass concentrations were determined using nuclear magnetic resonance (NMR) spectroscopy.

Results: Lipoprotein profiling identified a range of adverse phenotypes among the metabolically unhealthy individuals, regardless of BMI and metabolic health definition, including increased numbers of small low density lipoprotein (LDL) ($P < 0.001$) and high density lipoprotein (HDL) particles ($P < 0.001$), large very low density lipoprotein (VLDL) particles ($P < 0.001$) and greater lipoprotein related insulin resistance ($P < 0.001$). The most significant predictors of metabolic health were lower numbers of large VLDL (ORs 2.72–3.13 and 2.49–3.86, $P < 0.05$ among obese and non-obese individuals, respectively) and small dense LDL particles (ORs 1.78–2.39 and 1.50–1.94, $P < 0.05$) and higher numbers of large LDL (ORs 1.82–2.66 and 2.84–3.27, $P < 0.05$) and large HDL particles (ORs 1.88–2.58 and 1.81–3.49, $P < 0.05$).

Conclusions: Metabolically healthy adults displayed favourable lipoprotein particle profiles, irrespective of BMI and metabolic health definition. These findings underscore the importance of maintaining a healthy lipid profile in the context of overall cardiometabolic health.

1. Introduction

Obesity prevalence is increasing worldwide and is predicted to affect more than one billion people by 2030 [1]. Obesity represents a major public health concern as it promotes insulin resistance (IR) and is associated with increased risk of developing co-morbidities including metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) [2,3], leading to increased risk of premature death and higher all-cause mortality. However not all obese subjects are at increased cardiometabolic risk. Despite their excess body fat a subset of metabolically healthy (MH) individuals have been described [4,5]. Unlike the metabolically unhealthy obese (MUO) phenotype metabolically healthy obesity (MHO) is characterised by favourable lipid and inflammatory profiles, preserved insulin sensitivity and normal blood pressure [6–9]. Despite a more favourable metabolic profile examination of the prevalence of subclinical CVD according to MH and weight status has produced conflicting findings [10–12]. Furthermore prospective data on CVD development and all-cause mortality in MHO is limited and where follow-up has occurred results have been inconsistent [13,14].

Obesity and IR are linked with alterations in the lipoprotein particle profile, which may influence CVD and T2DM risk [15,16]. Lipoprotein particle size, in particular small, dense low density lipoprotein (LDL) and high density lipoprotein (HDL) particles and large very low density lipoprotein (VLDL) particles are associated with increased risk for atherosclerosis and premature CVD [15,17,18]. Traditional lipid tests quantify the cholesterol or triglyceride content of lipoproteins. In contrast, nuclear magnetic resonance (NMR) spectroscopy simultaneously quantifies the number and size of lipoprotein particles [19]. Recent data suggests altered expression of lipid metabolism genes in MHO and MUO

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individuals [20]. Limited data regarding lipoprotein particle profiles in MHO exists. To date the focus has been solely on LDL subclass determined by electrophoretic methods, with the rest of the lipoprofile ignored [21–23]. Therefore the main objective of this paper is to fully examine lipoprotein particle size and concentration, determined by NMR, in a cross-sectional sample of middle-aged metabolically healthy and unhealthy obese and non-obese adults.

2. Methods

2.1. 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 [24]. A population representative random sample was recruited from a large primary care centre in Mitchelstown, County Cork, Ireland (Mitchelstown cohort). Full details have been published elsewhere [24]. In brief 3807 potential Mitchelstown cohort participants were randomly selected from all registered attending patients in the 50–69 year age group. Following exclusion of duplicates, deaths and ineligibles, 3043 were invited to participate in the study and of these 2047 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 taking lipid-lowering medications and those with incomplete lipoprotein particle profiles the remaining 1834 participants were included in the analyses.

2.2. Clinical, anthropometric and lifestyle data

Blood pressure was measured using an Omron M7 Digital BP monitor on the right arm, after a 5 min rest in the seated position. The average of the second and third measurements was used for analyses. Hypertension was defined as average systolic blood pressure (SBP) $\geq$140 mmHg or diastolic blood pressure (DBP) $\geq$90 mmHg or being on hypertensive medication. Body weight was measured in kilogrammes without shoes, to the nearest 100 g, using a Tanita WB100MA weighing scales (Tanita Corporation, IL, USA). Height was measured in centimetres to 1 decimal place using a Seca Leicester height gauge (Seca, Birmingham, UK). Waist circumference (defined as mid-way between lowest rib and iliac crest) was measured in centimetres to 1 decimal place using a Seca 200 measuring tape (Seca, Birmingham, UK). The average of two measures were used for analyses. BMI was calculated and individuals with a BMI $\geq$30 kg/m^2 were defined as obese. Three existing MH definitions [9,25] (Supplemental Table 1) were used to define the MHO, MUO, metabolically healthy non-obese (MHNO) and metabolically unhealthy non-obese (MUNO) subjects. Participants completed a General Health Questionnaire (GHQ), the short form International Physical Activity Questionnaire [26] (IPAQ) and a food frequency questionnaire (FFQ) validated for use in the Irish population. Physical activity levels were determined by frequency, duration and intensity of activity. Smoking status was defined as never, former and current smokers. Alcohol consumption included questions based on weekly intake to define never, moderate and heavy drinkers. A dietary score (the Dietary Approaches to Stop Hypertension (DASH)) was calculated using the FFQ responses, as previously described [27].

2.3. Biological analyses

Blood samples were taken following an overnight fast. Fasting plasma glucose (FPG), serum total cholesterol, HDL cholesterol (HDL-C), LDL cholesterol (LDL-C) and triglyceride (TG) levels were measured by Cork University Hospital Biochemistry Laboratory. FPG concentrations were determined using a glucose hexokinase assay and serum lipids were analysed 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, adiponectin and C reactive protein (CRP) were determined using a biochip array system (Evidence Investigator; Randox Laboratories, Antrim, UK). Liver enzymes (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)) were determined were measured by Cork University Hospital Biochemistry Laboratory. Homeostasis model assessment (HOMA), a measure of IR, was calculated [28].

2.4. 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 [19]. 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 9 subclass categories were investigated: large VLDL (including chylomicrons, if present) (>60 nm), medium VLDL (42–60 nm), small VLDL (29–42 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 6 lipoprotein subclass and size parameters most closely associated with IR, was calculated [29].

2.5. Statistical analysis

Statistical analysis was conducted using PASW Statistics version 20 for Windows (SPSS Inc, Chicago, IL). Continuous variables are expressed as means $\pm$ SD and categorical variables as percentages. Lipoprotein variables were assessed for normality of distribution, and skewed variables were normalised as appropriate. Differences between groups were analysed by independent *t*-tests or Mann Whitney U tests for continuous variables and by Chi-Square test for categorical variables. Logistic regression was used to determine associations between lipoprotein status (categorized as below and above median level for each biomarker) and metabolic health among obese and non-obese subjects. Multivariate logistic regression analysis was performed including age, gender, physical activity, dietary quality, smoking status, alcohol consumption, liver enzymes and adiponectin concentrations as confounding factors. For all analyses a *P*-value of <0.05 was considered significant.

3. Results

3.1. Clinical characteristics

The prevalence of metabolically healthy and unhealthy obese and non-obese phenotypes in the sample are presented in Fig. 1. Demographic and clinical characteristics are shown in Table 1. MH individuals were generally younger and more likely to be female than their unhealthy counterparts. Both total cholesterol and LDL-C

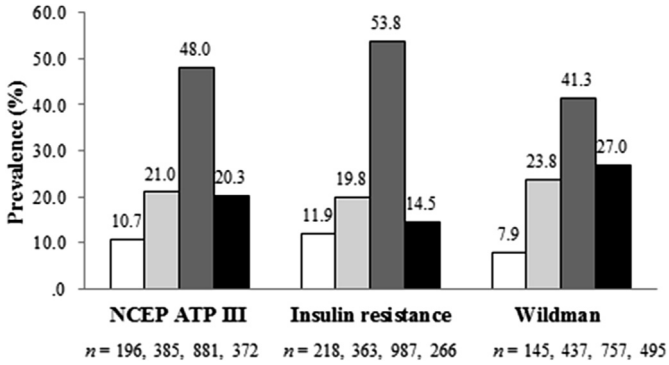

Fig. 1. Prevalence of metabolically healthy and unhealthy obese and non-obese phenotypes in the Mitchelstown cohort according to different metabolic health criteria among all subjects. Results are expressed as the percentage of subjects within each metabolic health definition. The metabolically healthy obese (MHO), metabolically unhealthy obese (MUO), metabolically healthy non-obese (MHNO) and metabolically unhealthy non-obese (MUNO) groups are depicted as white, light grey, dark grey and black bars, respectively.

levels were consistently higher among the MH individuals regardless of BMI status and MH definition. Examination of dietary quality and lifestyle factors including alcohol consumption, smoking and physical activity revealed few differences.

3.2. Lipoprotein profiles according to MH and BMI status

Lipoprotein particle concentrations of the study population according to metabolic health status by BMI category are presented in Table 2. The MH individuals presented with reduced numbers of large and medium VLDL particles ($P < 0.001$), less small LDL ($P < 0.001$) and HDL particles ($P < 0.001$) and greater numbers of large LDL ($P < 0.001$) and HDL particles ($P < 0.001$), relative to their metabolically unhealthy counterparts. Lower lipoprotein insulin resistance scores were noted among all MH subjects ($P < 0.001$). All of these findings were consistent across each of the MH definitions for both obese and non-obese individuals. Fig. 2 illustrates the lipoprotein subclass particle sizes of the study population. MH status was characterised by smaller VLDL particle size and larger LDL and HDL particle size ($P < 0.001$) in both obese and non-obese individuals compared to their metabolically unhealthy counterparts.

3.3. Lipoprotein predictors of the MH phenotype

Table 3 presents the odds ratios for MH according to lipoprotein particle subclass concentration and size. Obese and non-obese individuals with lower (below the median) concentrations of large VLDL particles were approximately 2.5–4 times more likely to present with MH classified by all definitions. In addition among the non-obese subjects the likelihood of being metabolically healthy was also 2–3 fold greater among individuals with less medium VLDL particles for all MH definitions. Reduced numbers (below the median) of small LDL particles were positively associated with a 1.5–2.5 fold increased likelihood of MH classified by all definitions among both obese and non-obese participants. Similarly, having higher numbers (top 50th percentile) of large LDL and HDL particles increased the odds of being metabolically healthy 2–3.5 fold among all subjects. Examination of particle size revealed that subjects with smaller (below median) VLDL size had approximately 2–4 times greater likelihood of MH, regardless of BMI. Similarly the odds of presenting with MH were 2–3 fold higher among individuals with larger LDL size (above median). No association between HDL particle size and MHO was noted. Among non-obese individuals larger HDL size was positively associated with increased likelihood of presenting with favourable MH.

3.4. Lipoprotein insulin resistance score and metabolic health status

Among the obese subjects, compared to individuals with a LP-IR score in the top 50th percentile, and thus more insulin resistant, those with lower LP-IR values (in the bottom 50th percentile) were more than 3 times more likely to be metabolically healthy (OR 4.45, 95% CI 2.29–8.62, OR 3.28, 95% CI 1.72–6.23 and OR 3.25, 95% CI 1.72–6.23 $P < 0.001$ for MHO defined by MetS, insulin resistance and Wildman). Similarly among the non-obese subjects the odds of presenting with favourable MH status was approximately 2.5–3.5 fold higher among those with a low LP-IR score (OR 2.54, 95% CI 1.68–3.83, OR 3.40, 95% CI 2.16–5.35 and OR 2.66, 95% CI 1.80–3.92 $P < 0.001$ for MHO defined by MetS, insulin resistance and Wildman).

4. Discussion

This study makes an important contribution to our understanding of the molecular mechanisms underlying obesity associated MH subtypes. We demonstrate for the first time that both MHO and MHNO subjects display a range of favourable lipoprotein phenotypes including lower concentrations of small LDL and HDL particles, large and medium VLDL particles and greater numbers of large LDL and HDL particles. Associations between lipoprotein profiles and MH phenotypes were generally not dependent on MH definition.

Despite the inclusion of lipid profiles in most MH definitions, limited data regarding lipoprotein particle profiles in MHO phenotypes exists. Conventional methods of lipid profiling have been employed, and where particle subclasses have been investigated the focus has been on LDL particles [21–23]. Iacobellis et al., examined LDL size by electrophoresis and demonstrated that MHO subjects had lower concentrations of small LDL particles and higher LDL diameter relative to obese subjects with the MetS [21]. Kim et al., also reported larger LDL particle size in metabolically healthy overweight/obese women relative to the normal weight women with MetS [22]. Consistent with these findings Kim et al., demonstrated larger LDL size, less small dense LDL and more large LDL particles in MH overweight/obese Korean subjects [23]. The use of NMR in our study allowed us to examine both the number and size of each of the main lipoprotein subclasses. Consistent with earlier findings [21–23] we also report lower numbers of small LDL particles and higher concentrations of large LDL particles among the MHO subjects. Additionally we demonstrate further novel favourable lipoprotein phenotypes including lower concentrations of large and medium VLDL particles, less small HDL and greater numbers of large HDL particles. These findings were generally consistent across the three MH definitions, regardless of BMI status and independent of a range of confounding factors including markers of liver fat and function. The magnitude of the differences for most of the lipoprotein phenotypes was at least similar, and in many cases greater, than that reported between individuals with and without hypertension, subclinical atherosclerosis, T2DM and CVD [30–33] indicating our data represent both physiologically and clinically significant differences in lipoprotein profiles between metabolically healthy and unhealthy individuals.

However, despite a more favourable metabolic profile, examination of the prevalence and severity of subclinical CVD according to MH and weight status has produced conflicting findings [10–12]. Differences in MH definitions and the transient nature of MH status might partly explain such inconsistencies. Eshtiaghi et al., recently demonstrated the instability of MH status, with more than 40% of

MHO subjects developing the MetS during a 10 year follow-up [34]. Interestingly low HDL-C and HOMA were identified as the most significant predictors of this change. In the study by Kim et al., they identified small, dense LDL as the most significant predictor of the metabolically unhealthy phenotype among overweight/obese subjects [23]. However no other lipoprotein subclasses were investigated. In our study regression analyses identified a range of lipid phenotypes, including lower numbers of large VLDL particles and small dense LDL particles and higher numbers of large LDL and HDL particles, as the most significant predictors of MHO.

Lipoprotein particle size, specifically small, dense LDL and HDL particles and large VLDL particles, has been linked with increased risk for atherosclerosis and premature CVD [15,17,18]. VLDL overproduction is a hallmark of dyslipidemia in obesity and IR [35,36].

Table 1
Demographic and clinical characteristics of the Mitchelstown cohort according to metabolic health and BMI status.

		NCEP ATP III[a]	*P*	Insulin resistance[b]	*P*	Wildman	*P*
Age (yrs)	MHO	59.23 ± 5.66	**0.034**	60.08 ± 5.64	**0.041**	60.00 ± 6.06	0.958
	MUO	60.25 ± 5.33		59.85 ± 5.30		60.03 ± 5.27	
	MHNO	58.63 ± 5.35	**0.000**	59.23 ± 5.53	**0.018**	58.41 ± 5.25	**0.000**
	MUNO	61.22 ± 5.58		60.14 ± 5.55		60.88 ± 5.66	
Gender (% male)	MHO	50.5	0.242	44.2	**0.000**	47.2	**0.000**
	MUO	56.8		60.7		57.1	
	MHNO	45.8	0.162	42.5	**0.000**	41.0	**0.043**
	MUNO	49.6		63.0		56.0	
BMI (kg/m^2)	MHO	33.00 ± 2.93	**0.000**	32.78 ± 2.92	**0.000**	32.72 ± 3.07	**0.000**
	MUO	34.13 ± 4.00		34.34 ± 3.73		34.22 ± 3.88	
	MHNO	25.62 ± 2.64	**0.000**	25.62 ± 2.64	**0.000**	25.54 ± 2.62	**0.000**
	MUNO	27.08 ± 2.34		27.67 ± 1.93		26.77 ± 2.49	
SBP (mm Hg)	MHO	130.72 ± 16.69	**0.005**	132.26 ± 17.25	0.218	128.80 ± 18.00	**0.000**
	MUO	134.70 ± 16.10		134.02 ± 16.04		135.06 ± 15.53	
	MHNO	124.62 ± 15.95	**0.000**	126.54 ± 16.96	**0.000**	122.68 ± 15.03	**0.000**
	MUNO	134.90 ± 16.10		132.26 ± 15.20		135.20 ± 16.20	
DBP (mm Hg)	MHO	81.80 ± 10.06	0.165	81.98 ± 10.10	0.299	80.47 ± 10.48	**0.002**
	MUO	82.97 ± 10.15		82.85 ± 10.20		83.17 ± 9.92	
	MHNO	77.74 ± 9.12	**0.000**	78.41 ± 9.43	**0.000**	76.91 ± 8.90	**0.000**
	MUNO	82.38 ± 9.38		81.97 ± 8.98		82.45 ± 9.26	
FPG (mmol/L)	MHO	4.97 ± 0.44	**0.000**	4.98 ± 0.55	**0.025**	4.86 ± 0.35	**0.000**
	MUO	5.72 ± 1.71		5.78 ± 1.70		5.68 ± 1.62	
	MHNO	4.85 ± 0.55	**0.000**	4.85 ± 0.51	**0.000**	4.78 ± 0.42	**0.000**
	MUNO	5.40 ± 1.44		5.67 ± 1.63		5.38 ± 1.32	
TG (mmol/L)	MHO	1.17 ± 0.38	**0.000**	1.40 ± 0.66	**0.000**	1.15 ± 0.35	**0.000**
	MUO	1.88 ± 1.00		1.79 ± 1.00		1.80 ± 0.97	
	MHNO	1.13 ± 0.55	**0.000**	1.16 ± 0.64	**0.000**	1.05 ± 0.47	**0.000**
	MUNO	1.66 ± 1.01		1.77 ± 0.98		1.63 ± 0.96	
Total-C (mmol/L)	MHO	5.34 ± 0.75	**0.000**	5.30 ± 0.91	**0.000**	5.32 ± 0.79	**0.026**
	MUO	5.05 ± 1.11		5.05 ± 1.07		5.10 ± 1.07	
	MHNO	5.53 ± 0.94	**0.000**	5.47 ± 0.97	**0.005**	5.54 ± 0.95	**0.000**
	MUNO	5.11 ± 1.14		5.19 ± 1.07		5.20 ± 1.08	
HDL-C (mmol/L)	MHO	1.44 ± 0.28	**0.000**	1.41 ± 0.33	**0.000**	1.45 ± 0.27	**0.000**
	MUO	1.23 ± 0.33		1.24 ± 0.32		1.25 ± 0.33	
	MHNO	1.56 ± 0.37	**0.000**	1.58 ± 0.37	**0.000**	1.61 ± 0.82	**0.000**
	MUNO	1.41 ± 0.37		1.31 ± 0.32		1.39 ± 0.98	
LDL-C (mmol/L)	MHO	3.35 ± 0.64	**0.000**	3.22 ± 0.81	**0.000**	3.34 ± 0.68	**0.000**
	MUO	2.91 ± 0.98		2.95 ± 0.96		2.98 ± 0.95	
	MHNO	3.44 ± 0.82	**0.000**	3.35 ± 0.86	**0.001**	3.44 ± 0.83	**0.000**
	MUNO	2.93 ± 1.01		3.06 ± 1.01		3.06 ± 0.98	
Dietary quality	MHO	28.41 ± 5.98	0.997	28.41 ± 5.48	0.921	28.43 ± 5.16	0.839
	MUO	28.40 ± 5.78		28.36 ± 5.16		28.34 ± 5.33	
	MHNO	29.02 ± 5.29	0.950	28.26 ± 5.97	0.060	28.69 ± 5.95	0.129
	MUNO	29.05 ± 5.29		29.15 ± 5.65		29.26 ± 5.87	
Physical activity							
Low/moderate/high	MHO	51.3/28.9/19.8	0.530	47.0/31.8/21.0	**0.017**	50.3/31.4/18.1	0.491
	MUO	55.8/27.5/16.7		59.6/25.1/15.3		55.7/26.8/17.5	
	MHNO	44.5/30.7/24.7	0.661	44.7/30.3/24.9	0.185	43.4/33.4/23.1	**0.037**
	MUNO	46.9/30.6/22.5		48.0/32.6/19.4		48.1/26.5/25.4	
Alcohol consumption							
Non-drinker/drinker/heavy	MHO	21.0/65.6/13.2	0.641	25.0/61.0/13.9	0.854	23.4/65.3/11.2	0.532
	MUO	24.0/60.6/15.4		22.6/62.1/15.2		22.9/61.3/15.8	
	MHNO	19.1/66.4/14.4	0.305	18.1/67.1/14.6	0.773	18.9/68.3/12.8	0.078
	MUNO	17.0/66.3/16.7		19.0/64.6/16.4		18.0/63.5/18.5	
Smoking status							
Never/former/current	MHO	51.0/41.8/7.2	0.280	50.2/40.5/9.1	0.821	47.6/46.9/5.4	0.061
	MUO	47.6/41.1/11.3		48.3/41.0/10.7		49.1/39.4/11.5	
	MHNO	53.7/29.6/16.6	0.602	53.1/29.7/17.1	0.094	54.3/29.1/16.6	0.199
	MUNO	49.3/33.7/17.0		51.0/36.0/13.0		49.5/33.5/17.0	

Figures are expressed as % or means ± SD. *P* value for comparison to metabolically unhealthy within same BMI category.
Bold indicates a P value < 0.05.
[a] Using NCEP ATP III MetS criteria.
[b] Using homeostasis model.

Predominance of large VLDL may reflect hepatic overproduction of TG packaged into VLDL particles overloaded with TG. Microsomal triglyceride transfer protein (MTP) is responsible for hepatic and intestinal TRL assembly. We have previously demonstrated increased MTP expression in animal models of IR, obesity and diabetes [37,38] and in human T2DM subjects [39]. Recent data suggests altered expression of lipid metabolism genes in MHO and MUO individuals [20]. Although that study did not examine MTP expression, compared to MHO subjects the at-risk obese subjects displayed lower expression of peroxisome proliferator-activated receptor delta (PPARδ). Activation of PPARδ has been linked with protection from dyslipidemia via hepatic removal of VLDL particles [40], thus it may be speculated that MUO subjects may have impaired VLDL metabolism relative to their MHO counterparts. Large VLDL particles may be more important for atherogenic risk than medium and small VLDL particles [15] as they are associated with the small dense LDL phenotype [41,42]. Lipid enriched VLDL particles are more efficiently hydrolysed by lipoprotein lipase [43], thereby generating smaller particles with greater capacity to penetrate the endothelial wall thereby enhancing intimal accumulation of TG and cholesterol ester. Furthermore hepatic overproduction of large VLDL is thought to initiate diabetic dyslipidemia [44,45]. The pathway from obesity and insulin resistance towards overt T2DM represents a progressive phenotype, with dyslipidemia

Table 2
Lipoprotein particle concentration in the obese and non-obese Mitchelstown participants according to different metabolic health definitions.

		NCEP ATP III[a]	*P*	Insulin resistance[b]	*P*	Wildman	*P*
Total TRL (nmol/L)	MHO	58.02 ± 33.00	**0.000**	68.31 ± 38.72	**0.004**	60.55 ± 34.93	**0.000**
	MUO	83.63 ± 42.88		78.84 ± 42.64		79.74 ± 42.51	
	MHNO	55.63 ± 38.75	**0.000**	57.55 ± 40.07	**0.000**	51.86 ± 35.05	**0.000**
	MUNO	80.72 ± 48.97		84.21 ± 49.62		80.29 ± 49.37	
Large VLDL (nmol/L)	MHO	1.65 ± 1.62	**0.000**	2.46 ± 4.41	**0.000**	1.52 ± 1.77	**0.000**
	MUO	5.25 ± 6.84		4.93 ± 6.35		4.86 ± 6.51	
	MHNO	1.47 ± 2.61	**0.000**	1.48 ± 2.48	**0.000**	1.21 ± 2.16	**0.000**
	MUNO	3.41 ± 5.29		4.16 ± 5.51		3.32 ± 5.03	
Medium VLDL (nmol/L)	MHO	23.61 ± 16.32	**0.000**	29.29 ± 22.80	**0.000**	23.21 ± 16.00	**0.000**
	MUO	39.77 ± 25.77		37.10 ± 24.37		37.97 ± 25.37	
	MHNO	34.28 ± 20.53	**0.000**	21.05 ± 20.54	**0.000**	18.39 ± 18.20	**0.000**
	MUNO	20.65 ± 29.96		38.53 ± 32.30		34.37 ± 29.35	
Small VLDL (nmol/L)	MHO	32.77 ± 25.58	**0.014**	36.55 ± 23.64	0.995	35.82 ± 28.41	0.675
	MUO	38.61 ± 23.99		36.80 ± 25.21		36.90 ± 23.34	
	MHNO	33.51 ± 26.35	**0.000**	35.01 ± 27.17	**0.001**	32.25 ± 24.44	**0.000**
	MUNO	43.02 ± 31.10		41.50 ± 31.37		42.59 ± 32.08	
Total LDL (nmol/L)	MHO	1294.10 ± 340.24	0.699	1286.70 ± 377.45	0.485	1255.53 ± 315.15	0.103
	MUO	1307.83 ± 429.81		1311.11 ± 415.72		1318.93 ± 425.39	
	MHNO	1280.79 ± 376.33	**0.032**	1250.53 ± 386.12	**0.012**	1261.74 ± 370.46	0.741
	MUNO	1227.00 ± 469.10		1321.32 ± 475.54		1269.51 ± 456.98	
IDL (nmol/L)	MHO	115.00 ± 82.33	0.671	117.65 ± 97.07	0.992	117.90 ± 89.63	0.915
	MUO	118.33 ± 94.33		117.58 ± 86.62		116.98 ± 90.74	
	MHNO	117.62 ± 85.56	0.054	112.68 ± 86.72	0.186	112.60 ± 83.29	0.366
	MUNO	106.96 ± 96.03		120.91 ± 95.91		117.29 ± 96.88	
Large LDL (nmol/L)	MHO	622.43 ± 221.63	**0.000**	579.36 ± 262.03	**0.000**	615.48 ± 232.48	**0.000**
	MUO	440.33 ± 272.67		454.74 ± 264.64		464.35 ± 271.88	
	MHNO	707.88 ± 290.57	**0.000**	697.99 ± 296.52	**0.000**	735.04 ± 281.46	**0.000**
	MUNO	513.70 ± 287.48		470.21 ± 257.72		520.10 ± 288.21	
Small LDL (nmol/L)	MHO	556.61 ± 359.00	**0.000**	589.64 ± 389.84	**0.000**	522.08 ± 327.92	**0.000**
	MUO	749.20 ± 396.24		738.80 ± 383.05		737.64 ± 400.21	
	MHNO	455.26 ± 388.87	**0.000**	439.84 ± 381.13	**0.000**	414.07 ± 369.02	**0.000**
	MUNO	606.35 ± 446.72		730.18 ± 447.39		632.14 ± 440.35	
Total HDL (μmol/L)	MHO	37.73 ± 5.43	0.176	38.38 ± 5.92	**0.001**	37.76 ± 5.30	0.253
	MUO	37.03 ± 6.04		36.68 ± 5.72		37.11 ± 6.02	
	MHNO	38.39 ± 5.59	0.072	38.87 ± 5.81	0.075	38.75 ± 5.43	0.888
	MUNO	39.52 ± 6.77		38.14 ± 6.61		38.70 ± 6.76	
Large HDL (μmol/L)	MHO	6.64 ± 3.35	**0.000**	6.33 ± 3.38	**0.000**	6.77 ± 3.20	**0.000**
	MUO	4.80 ± 3.04		4.85 ± 3.02		4.98 ± 3.17	
	MHNO	8.22 ± 4.41	**0.000**	8.37 ± 4.35	**0.000**	8.66 ± 4.37	**0.000**
	MUNO	6.57 ± 3.87		5.31 ± 3.18		6.30 ± 3.83	
Medium HDL (μmol/L)	MHO	13.23 ± 5.29	0.883	13.89 ± 5.99	**0.043**	13.26 ± 5.30	0.861
	MUO	13.16 ± 6.07		12.83 ± 5.68		13.16 ± 5.97	
	MHNO	13.61 ± 5.95	0.576	13.71 ± 6.05	0.552	13.70 ± 6.01	0.816
	MUNO	13.81 ± 6.68		13.45 ± 6.48		13.62 ± 6.42	
Small HDL (μmol/L)	MHO	17.84 ± 5.34	**0.015**	18.14 ± 5.91	0.088	17.73 ± 5.37	**0.025**
	MUO	19.07 ± 5.48		18.99 ± 5.15		18.97 ± 5.46	
	MHNO	16.56 ± 5.34	**0.000**	16.80 ± 5.85	**0.000**	16.38 ± 5.81	**0.000**
	MUNO	19.13 ± 5.85		19.38 ± 6.09		18.77 ± 6.01	
LP −IR score	MHO	32.49 ± 17.83	**0.000**	34.43 ± 19.64	**0.000**	30.11 ± 16.29	**0.000**
	MUO	49.99 ± 20.47		49.89 ± 19.95		48.69 ± 20.73	
	MHNO	25.37 ± 19.42	**0.000**	24.74 ± 18.93	**0.000**	23.03 ± 18.11	**0.000**
	MUNO	37.71 ± 22.54		45.23 ± 21.37		38.24 ± 22.16	

Figures are expressed as means ± SD. *P* value for comparison to metabolically unhealthy within same BMI category.
Bold indicates a P value < 0.05.
[a] Using NCEP ATP III MetS criteria.
[b] Using homeostasis model.

frequently preceding T2DM by many years. While we await prospective studies investigating the impact of tailored anti-atherosclerotic therapies based on an individuals' lipoprotein profile, it is tempting to speculate that early identification of dyslipidemia and implementation of effective interventions to improve lipid profiles may have the potential to attenuate progression from obesity and IR towards overt T2DM.

A surprising finding was that conventional lipid profile analysis revealed higher total cholesterol and LDL-C levels among the MHO and MHNO individuals. Although not all MHO studies include total or LDL-C data, our findings are in contrast to those which have detailed these measures [21–23,46,47]. It is possible that differences in the measurement of LDL-C might partly account for these disparities. Interestingly our NMR data did not reflect the findings with the traditional measures. Of note in patients with discordance between cholesterol and particle measures of LDL and HDL, CVD risk tracks with the particle measures [48,49]. Furthermore we report lower LP-IR scores among all MH subjects irrespective of BMI and MH definition. The LP-IR score is an alternative means of assessing a patient's IR status based on lipoprofile data [29] which may help predict risk of future T2DM, independent of glucose concentration, before they become overtly pre-diabetic, so that effective lifestyle modification could theoretically prevent, not just delay, onset of the disease.

Our study has several strengths including a high participation rate (67%), inclusion of questionnaires to assess dietary and lifestyle behaviours, and use of NMR to perform the largest characterisation of lipoprotein particle size and concentration among MH obese and non-obese phenotypes to date. Several limitations can be identified. The cross-sectional study design and complex interrelationships between each of the lipoporotein classes limited our ability to make an inference about the causal relationships between lipoprotein profiles and MHO. Obesity was classified according to BMI which does not discriminate between lean and fat body mass. Thus persons of short stature or muscular build may be misclassified. Future work may benefit from direct measurement of body fat. We have demonstrated that combined assessment of BMI and body fat percentage to classify obesity may help identify individuals at greater cardiometabolic risk than BMI alone [50]. Those identified as obese using both measures had a more metabolically unhealthy profile and were unresponsive to dietary intervention. We speculate that the MUO subjects are metabolically overburdened and thus no longer dietary responsive, whereas the MHO subjects have greater metabolic flexibility to adapt to dietary challenges. Supporting this concept Perez-Martinez et al. [51], recently demonstrated that MH subjects display lower postprandial TG and large TRL-TG responses compared to MUO and MUNO subjects. Such data emphasize the potential benefits of stratification based on an individual's MH phenotype with a view to ascertaining the appropriate therapeutic or intervention strategy.

In conclusion, our data which may be of public health and clinical significance, suggest that favourable lipoprotein profiles characterised by reduced numbers of large VLDL particles and more large LDL and HDL particles are associated with MH, particularly among obese subjects. Considering the relationship between atherogenic dyslipidaemia and CVD, improving our understanding

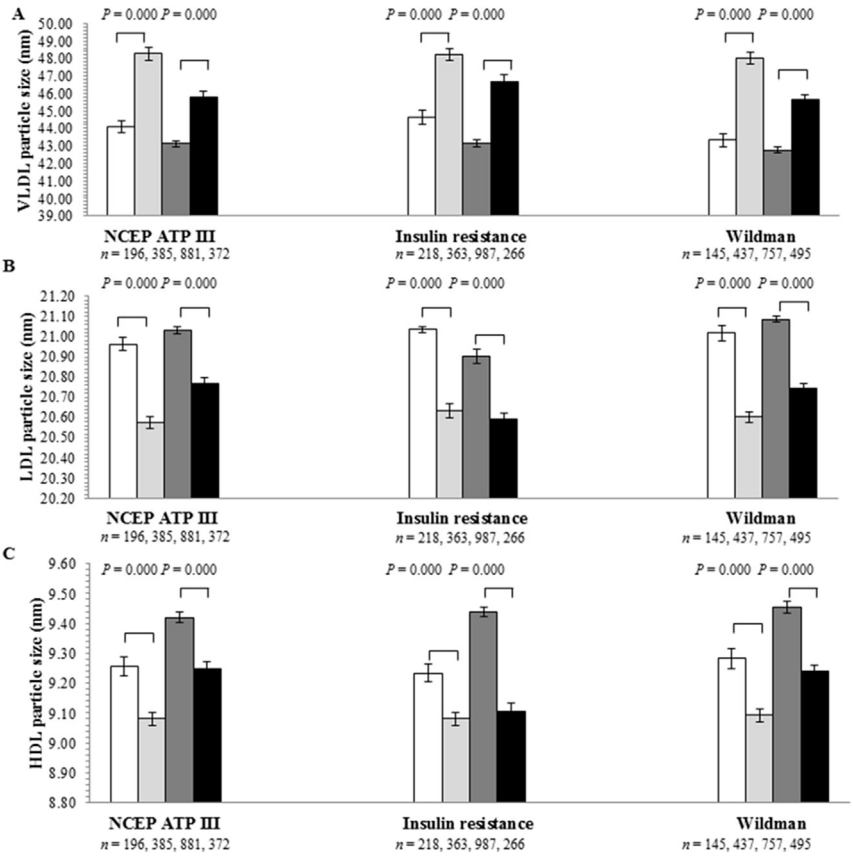

Fig. 2. Lipoprotein particle size according to metabolic health and BMI status. Mean VLDL (A), LDL (B), and HDL (C) particle sizes are expressed as nm ± SEM. The metabolically healthy obese (MHO), metabolically unhealthy obese (MUO), metabolically healthy non-obese (MHNO) and metabolically unhealthy non-obese (MUNO) groups are depicted as white, light grey, dark grey and black bars, respectively.

Table 3
Multivariate-adjusted odds ratios for the metabolically healthy phenotype associated with lipoprotein particle number and size among the obese and non-obese subjects.

	NCEP ATP III[a]	*P*	Insulin resistance[b]	*P*	Wildman	*P*
Large VLDL (nmol/L)						
Above median	1 [reference]		1 [reference]		1 [reference]	
Below median (obese)	2.84 (1.56–5.18)	**0.001**	2.72 (1.85–3.99)	**0.000**	3.13 (1.64–5.97)	**0.001**
Below median (non-obese)	2.49 (1.62–3.83)	**0.000**	3.86 (1.96–7.58)	**0.000**	2.53 (1.75–3.64)	**0.000**
Medium VLDL (nmol/L)						
Above median	1 [reference]		1 [reference]		1 [reference]	
Below median (obese)	1.78 (0.98–3.22)	0.058	1.56 (0.84–2.92)	0.161	2.45 (1.24–4.84)	**0.010**
Below median (non-obese)	2.02 (1.36–2.95)	**0.000**	2.46 (1.57–3.86)	**0.000**	2.93 (2.02–4.24)	**0.000**
Small VLDL (nmol/L)						
Above median	1 [reference]		1 [reference]		1 [reference]	
Below median (obese)	1.57 (0.90–2.75)	0.114	1.21 (0.63–2.01)	0.701	1.10 (0.58–2.08)	0.768
Below median (non-obese)	1.40 (0.97–2.04)	0.070	1.49 (0.98–2.25)	0.061	1.55 (1.10–2.19)	0.013
Large LDL (nmol/L)						
Below median	1 [reference]		1 [reference]		1 [reference]	
Above median (obese)	2.66 (1.45–4.88)	**0.002**	1.82 (1.05–3.12)	**0.025**	1.84 (1.05–3.56)	**0.035**
Above median (non-obese)	3.00 (2.02–4.45)	**0.000**	2.84 (2.84–4.38)	**0.000**	3.27 (2.25–4.76)	**0.000**
Small LDL (nmol/L)						
Above median	1 [reference]		1 [reference]		1 [reference]	
Below median (obese)	2.07 (1.13–4.82)	**0.019**	1.78 (1.02–3.30)	**0.042**	2.39 (1.22–4.66)	**0.011**
Below median (non-obese)	1.50 (1.02–2.22)	**0.042**	1.83 (1.19–2.81)	**0.006**	1.94 (1.35–2.82)	**0.001**
Large HDL (μmol/L)						
Below median	1 [reference]		1 [reference]		1 [reference]	
Above median (obese)	2.35 (1.24–4.43)	**0.009**	1.88 (1.02–3.35)	**0.042**	2.58 (1.30–5.13)	**0.007**
Above median (non-obese)	1.81 (1.21–2.73)	**0.004**	3.49 (2.20–5.53)	**0.000**	2.53 (1.71–3.74)	**0.000**
Medium HDL (μmol/L)						
Above median	1 [reference]		1 [reference]		1 [reference]	
Below median (obese)	1.06 (0.60–1.88)	0.839	1.13 (0.63–2.00)	0.586	1.33 (0.70–2.53)	0.383
Below median (non-obese)	1.53 (1.05–2.23)	**0.028**	1.38 (0.91–2.07)	0.127	1.54 (1.08–2.21)	**0.018**
Small HDL (μmol/L)						
Above median	1 [reference]		1 [reference]		1 [reference]	
Below median (obese)	1.43 (0.80–2.56)	0.234	1.05 (0.58–1.88)	0.882	1.44 (0.75–2.77)	0.276
Below median (non-obese)	1.48 (1.02–2.15)	**0.040**	1.32 (0.87–1.98)	0.189	1.41 (1.02–2.00)	**0.035**
VLDL size (nm)						
Above median	1 [reference]		1 [reference]		1 [reference]	
Below median (obese)	2.57 (1.37–4.82)	**0.003**	3.03 (1.59–5.77)	**0.001**	4.04 (2.00–8.16)	**0.000**
Below median (non-obese)	2.33 (1.54–3.52)	**0.000**	1.80 (1.16–2.79)	**0.009**	2.34 (1.58–3.48)	**0.000**
LDL size (nm)						
Below median	1 [reference]		1 [reference]		1 [reference]	
Above median (obese)	3.10 (1.65–5.81)	**0.000**	1.40 (0.80–2.58)	0.075	3.12 (1.56–6.23)	**0.001**
Above median (non-obese)	1.75 (1.16–2.65)	**0.008**	3.20 (2.00–5.10)	**0.000**	2.08 (1.41–3.09)	**0.000**
HDL size (nm)						
Below median	1 [reference]		1 [reference]		1 [reference]	
Above median (obese)	1.57 (0.84–2.66)	0.162	1.41 (0.74–2.67)	0.295	1.41 (0.71–2.83)	0.330
Above median (non-obese)	1.49 (1.05–2.22)	**0.040**	3.58 (2.23–5.75)	**0.000**	1.76 (1.21–2.57)	**0.003**

Figures are expressed as OR (95%CI). Adjusted for gender, age, smoking, physical activity, dietary quality, alcohol intake, adiponectin, ALT and AST concentrations. Reference group is metabolically unhealthy within same BMI category.
Bold indicates a P value < 0.05.
[a] Using NCEP ATP III MetS criteria.
[b] Using homeostasis model.

of the association between obesity associated MH subtypes and lipoprotein metabolism may be useful in the development of targeted screening to identify those at greatest risk of developing the most serious obesity and cardiovascular related complications.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2015.07.040.

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