



## Original Article

# Among young Sri Lankan patients with diabetes, how do lipid profiles differ between those with and without metabolic syndrome?



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## ABSTRACT

**Aims:** Metabolic syndrome (MetS) is a risk factor for cardiovascular disease (CVD). Apolipoproteins are emerging as powerful predictors of CVD. We aimed to study associations of metabolic syndrome and apoB, apoAI, apoB/AI ratio in young Sri Lankans with type 2 diabetes.

**Materials & methods:** Blood samples were available from 690 patients with type 2 diabetes in Sri Lanka Young Diabetes Study, and were analysed for apoB, apoAI, total cholesterol (TC), high-density lipoprotein cholesterol (HDLc), triglycerides (TG) and glycated haemoglobin (HbA<sub>1c</sub>). Their associations with MetS as per NCEP/ATPIII criteria were studied.

**Results:** MetS was present in 60.9% of subjects. Of those with MetS, 76.0% were women. Those with MetS had higher apoB (1.27 v s 1.19 mmol/L;  $p = 0.001$ ), apoB/AI (0.80 v s 0.75;  $p = 0.001$ ), non-HDL cholesterol (NHDLC) (4.15 v s 3.98 mmol/L;  $p = 0.002$ ), and triglycerides (1.51 v s 1.31 mmol/L;  $p < 0.001$ ) and lower apoAI (1.58 v s 1.60 mmol/L;  $p = 0.03$ ) and HDLC (1.02 v s 1.16 mmol/L,  $p < 0.001$ ). ApoB and apoB/AI levels increased significantly as the number of MetS components increased. ApoB and apoB/AI ratio were independently associated with MetS and components.

**Conclusion:** MetS showed a high prevalence among young Sri Lankans with diabetes. Elevated apoB is commonly clustered with other risk indicators in MetS.

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## 1. Background

Metabolic syndrome (MetS) is a constellation of cardiovascular disease (CVD) risk factors (1, 2) used to identify high-risk individuals for type 2 diabetes and CVD [3]. Several observational studies have demonstrated increased risk of developing CVD and of mortality due to CVD in the presence of MetS [4–7]. General features of MetS are abnormal body fat distribution, atherogenic dyslipidemia, elevated blood pressure, insulin resistance, pro-inflammatory state and prothrombotic state [3]. Atherogenic dyslipidemia consists of elevated serum triglycerides and low high density

lipoprotein cholesterol (HDLc). More detailed analysis reveals elevated apolipoprotein B (apoB), increased numbers of small dense low density lipoprotein (sd-LDL) particles, and the presence of small HDL particles also to predict high CVD [3]. Among individuals with diabetes, MetS is associated with a higher risk for future development of CVD [8].

Different criteria for defining MetS have been proposed [2,9]. Almost all include measures of glucose intolerance, central obesity, elevated TG, reduced HDLC and elevated blood pressure. In its 2004 statement, the IDF identified apoB and sd-LDL particles as additional risk predictors of the MetS that should be studied [3].

Diabetes mellitus and metabolic syndrome are increasingly diagnosed among South Asian populations thus increasing the potential burden of CVD. Institution of therapeutic measures to this expanding population has become more and more difficult in these

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countries. Therefore better predictors to identify individuals with increased CVD risk are necessary. Apolipoproteins have emerged as predictors of CVD better than traditional lipid indices. We aimed to study the association of apolipoproteins with other clinical criteria used to identify MetS in a South Asian population with type 2 diabetes with onset in young adults.

## 2. Methods

As previously described [10], an observational study was conducted with a consecutive sample of 1007 subjects with diabetes aged less than 45 years (age at diagnosis: 16–40 years) recruited from selected diabetes clinics in Western Province, Sri Lanka from June 2005 to February 2006. Ethical approval was obtained from the Ethics Review Committee, Faculty of Medicine, University of Colombo, Sri Lanka. All participants provided written informed consent. Data on demography, medical history and medication were collected and anthropometric measurements were taken. Blood samples were obtained after an overnight fast (12–14 h) into a plain bottle and serum was separated by centrifugation after leaving at room temperature for 30 min and stored at  $-20^{\circ}\text{C}$ . Total cholesterol (TC), HDLC and triglycerides (TG) were measured by enzymatic photometric methods using a Hitachi 704 chemical auto-analyser (Roche diagnostics, Mannheim, Germany) in the Reproductive and Endocrinology Laboratory, Faculty of Medicine, University of Colombo, Sri Lanka. Serum samples from the cohort were transported to the United Kingdom in dry ice (at  $-80^{\circ}\text{C}$ ) and were stored at  $-80^{\circ}\text{C}$ . ApoB and apoAI were measured by immunoturbidimetric methods traceable to WHO-IFCC reference materials SP3-07 and SP-01 [11,12] on ADVIA 2400 Chemistry Systems (Siemens, Frimley, UK) in the Clinical Biochemistry Department, John Radcliffe Hospital, Oxford, UK. Inter-assay coefficients of variations (CVs) were  $<3.7\%$  for apoB and  $<3.5\%$  for apoA1.

This report is based on 690 participants, after excluding those with incomplete data on lipids and apolipoproteins and those who were on lipid lowering therapy. LDLC levels were calculated using the Friedewald formula in subjects with  $\text{TG} < 4.52 \text{ mmol/L}$  [13]. NHDLC was estimated by subtracting HDLC from TC. HbA<sub>1c</sub> was measured by HPLC (Biorad, Hercules, CA) in National Diabetes Centre, Sri Lanka. ApoB and ApoAI distributions in the United States (results of the National Health and Nutrition Examination Survey III: 1988–1991) were considered as reference distributions [14]. Target concentrations for lipids and apoB were those described in ATP III by NCEP (2) and by Grundy et al. [15] respectively.

### 2.1. Definition of terms

People with established diagnosis of diabetes (based on ADA criteria) and on treatment with insulin or oral antidiabetic agents were recruited in the study. Metabolic syndrome was defined as the presence of 3 or more of impaired glucose tolerance/impaired fasting glycemia, high blood pressure, high waist circumference, high triglycerides and low HDLC. These were defined according to ATP III criteria: waist circumference  $>90 \text{ cm}$  in men and  $> 80 \text{ cm}$  in women, high blood pressure as SBP  $>130 \text{ mmHg}$  and/or diastolic blood pressure  $>85 \text{ mmHg}$ . Triglycerides over  $1.7 \text{ mmol/L}$  ( $150 \text{ mg/dL}$ ) was defined as hypertriglyceridemia and HDLC  $<1.03 \text{ mmol/L}$  ( $40 \text{ mg/dL}$ ) in men and  $<1.30 \text{ mmol/L}$  ( $50 \text{ mg/dL}$ ) in women were defined as low HDLC.

Physical activity was estimated using International Physical Activity Questionnaire and categorized as insufficient, moderately active and active. Smoking status was categorized as never smoked, stopped smoking 1 or more years ago, or current smoking ( $<1$  a day,  $1-10$  a day,  $10-20$  a day or  $> 20$  a day). Alcohol consumption was defined according to the current consumption in units (never

consumed, stopped 1 or more years ago,  $< 3$  units a week,  $< 4$  units a day,  $4-7$  units a day,  $8-14$  units a day,  $15-21$  units a day,  $22-35$  units a day and  $>35$  units a day).

### 2.2. Statistical analysis

Data were analysed using R version 3.1.2 (R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. (URL <http://www.R-project.org/>). Results are shown as mean (standard deviation) or median (interquartile range). TC, HDLC, LDLC, apoB and apoAI were distributed normally and TG was normalised after log transformation. We used *t*-test, Kruskal-Wallis test,  $\chi^2$  test, analysis of variance (ANOVA) with post hoc Tukey test and Spearman's correlation test as appropriate. A *p* value  $< 0.05$  was considered statistically significant.

## 3. Results

Among 1007 participants recruited for SLYDS, 903 (89.7%) had type 2 diabetes of which, 202 were on lipid lowering therapy. Lipid data were not available in 11 participants. This analysis is therefore based on 690 patients with type 2 diabetes who were not on lipid lowering therapy. Mean age was 38 years and 307 were men (44.7%). MetS was diagnosed in 420 (60.9%) subjects. Women were more likely to have MetS (76% versus 42%,  $p < 0.001$ ). There was no significant difference in age between those with and without MetS once sex was taken into account. Table 1 summarizes the characteristics of the population and comparison between those with and without MetS.

HbA<sub>1c</sub>, TC and LDLC did not differ between those with and without MetS after adjusting for age and sex. Insignificant HbA<sub>1c</sub> difference is expected as all participants had diabetes. HDLC was lower ( $p < 0.001$ ), log (TG) higher ( $p < 0.001$ ), ApoB higher ( $p < 0.001$ ), ApoA1 lower ( $p = 0.027$ ), ApoB/ApoAI higher ( $p < 0.001$ ), and non-HDL cholesterol higher ( $p = 0.002$ ) in those with MetS, and the differences increased with increasing number of criteria met for MetS.

Fig. 1(a–f) shows the change of different lipid levels against the number of MetS criteria. HDLC, TG, apoB, apoAI (not shown), apoB:A1 ratio and NHDLC showed significant associations ( $p < 0.005$ ) whereas the associations with LDLC and TC (not shown) were insignificant. Furthermore, ApoB showed a linear association with LDLC as well as NHDLC in both men and women irrespective of presence or absence of metabolic syndrome. (Fig. 1 (g) and (h))

Tables 2 and 3 summarize the associations of ApoB and ApoB:A1 ratio with MetS and MetS components. Both apoB and apoB:A1 ratio showed a significant association with MetS and hypertriglyceridemia. ApoB and apoB:A1 ratio showed a consistent association with high blood pressure and low HDL respectively. Although apoB and apoB:A1 ratio was significantly higher in those with high WC, their association in linear regression model were insignificant. Association patterns did not change after correcting for age, sex, physical activity, smoking status and alcohol consumption.

## 4. Discussion

Metabolic syndrome represents a constellation of risk factors that predict diabetes and cardiovascular disease risk [1]. However, several recent studies have shown that MetS is a weak predictor of CVD outcomes in patients with type 2 diabetes [16].

**Table 1**  
Demographic, anthropometric, lipid profile and glycemic data of study participants (N = 690).

	All patients	No MetS	MetS	P
No of patients (%)	690	270 (39.1)	420 (60.9)	–
Males (%)	307 (44.5)	177 (65.6)	130 (31.0)	<0.001
Age (years)	38 (34–41)	37 (33–40)	38 (35–41)	0.059
WC (cm)	87.8 (9.4)	81.3 (7.7)	91.0 (8.0)	<0.001 <sup>a</sup>
BMI (kg/m <sup>2</sup> )	24.8 (3.9)	22.1 (2.8)	26.5 (3.6)	<0.001
HbA <sub>1c</sub> %	8.00 (1.97)	7.97 (2.10)	8.03 (1.88)	0.090
TC (mmol/l)	5.15 (1.07)	5.14 (1.12)	5.13 (1.04)	0.210
HDLC (mmol/l)	1.07 (0.31)	1.16 (0.37)	1.02 (0.26)	<0.001 <sup>a</sup>
TG (mmol/l) <sup>b</sup>	1.46 (1.07–2.07)	1.31 (0.99–1.97)	1.51 (1.14–2.15)	<0.001 <sup>a</sup>
LDLC (mmol/l)	3.31 (0.93)	3.27 (1.01)	3.34 (0.88)	0.120
NHDL (mmol/l)	4.08 (1.06)	3.98 (1.12)	4.15 (1.01)	0.045
ApoB (g/l)	1.25 (0.28)	1.19 (0.30)	1.27 (0.28)	<0.001
ApoA1 (g/l)	1.58 (0.28)	1.60 (0.29)	1.58 (0.27)	0.027
TC/HDL	4.84 (4.01–5.93)	4.41 (3.58–5.59)	5.01 (4.24–6.08)	<0.001 <sup>a</sup>
ApoB/apoA1	0.79 (0.68–0.92)	0.75 (0.64–0.89)	0.80 (0.70–0.94)	<0.001
NHDL/apoB	3.32 (2.99–3.60)	3.03 (3.03–3.62)	3.32 (2.98–3.59)	0.055
LDLC/apoB	2.70 (2.36–2.98)	2.75 (2.40–3.04)	2.66 (2.34–2.95)	0.040
HDLC/apoA1	0.66 (0.56–0.78)	0.71 (0.61–0.83)	0.64 (0.55–0.74)	<0.001

Data presented as mean (SD) or median (interquartile range).

<sup>a</sup> Included in the NCEP ATPIII definition of MetS.

<sup>b</sup> Log of triglyceride level used for calculation.

#### 4.1. Significance of ApoB and ApoA1 in predicting cardiovascular risk

The role of small-dense LDL in atherogenesis and as a risk factor for CVD is well recognized [2,17], and reduction of sd-LDL is associated with clinical benefit [18].

When triglyceride levels are high, sd-LDL becomes the dominant LDL fraction. This is a result of two processes. First, the liver produces greater amounts of larger, TG rich VLDL particles, which are progressively hydrolysed to produce more LDL. Secondly, there is increased exchange and transfer of triglyceride and cholesterol ester among VLDL, LDL and HDL particles by cholesterol ester transfer protein (CETP), leading to formation of more triglyceride-rich LDL particles. The triglyceride in the particles is hydrolysed by hepatic lipase to produce sd-LDL particles with less cholesterol ester per particle and therefore a lower cholesterol/apoB ratio. The formation of sd-LDL is enhanced in diabetes mellitus and metabolic syndrome since the clearance of VLDL is further impaired in the presence of insulin resistance. LDL concentration is not a reliable indicator of sd-LDL as normocholesterolemic subjects can have sd-LDL as their predominant fraction of LDL. At present, sd-LDL can only be measured using gradient gel electrophoresis or ultracentrifugation, methods that are not suited for routine clinical care. ApoB is a better indicator of risk in this situation, because each LDL particle has 1 apoB molecule, and the apoB concentration is therefore proportional to the number of particles, which is directly related to risk of atherogenesis [19].

ApoB and apoA1 predict CVD more accurately than traditional risk factors such as total cholesterol (TC), HDL cholesterol (HDLC), LDL cholesterol (LDLC), triglycerides (TG) and the ratio of TC/HDLC [20]. ApoB:A1 ratio has proven to be an independent predictor of CVD risk in different populations [21]. HDL particles contain at least one apoA1 molecule, while there is a one to one correspondence between apoB and the total number of atherogenic particles, of which 90% or more are LDL particles (except in familial dysbetalipoproteinemia and hepatic lipase deficiency).

#### 4.2. Association of metabolic syndrome and apolipoprotein abnormalities

The present study shows that young Sri Lankans with type 2 diabetes have a high prevalence of MetS (60.9% overall, 42.3% in

men, 75.7% in women) when defined by the NCEP/ATPIII criteria. This is comparable to the rate of 60.8% reported in the UKPDS population of 4542 subjects [22]. UKPDS population had a higher proportion of males (58% Vs 44.5% in SLYDS) and 48.9% of men and 77.6% of women had metabolic syndrome.

In our study population, participants with metabolic syndrome had significantly higher apoB in addition to high TG and low HDLC, which are components in the diagnostic criteria of the syndrome, while the other lipid indices such as LDLC and TC did not differ. Therefore, elevated apoB seems to be a characteristic feature of the atherogenic dyslipidaemia seen in metabolic syndrome.

The LDLC/apoB was significantly lower in those with MetS. Because of the 1:1 relationship between ApoB and LDL particles, a low LDLC/apoB suggests the presence of sd-LDL particles [23].

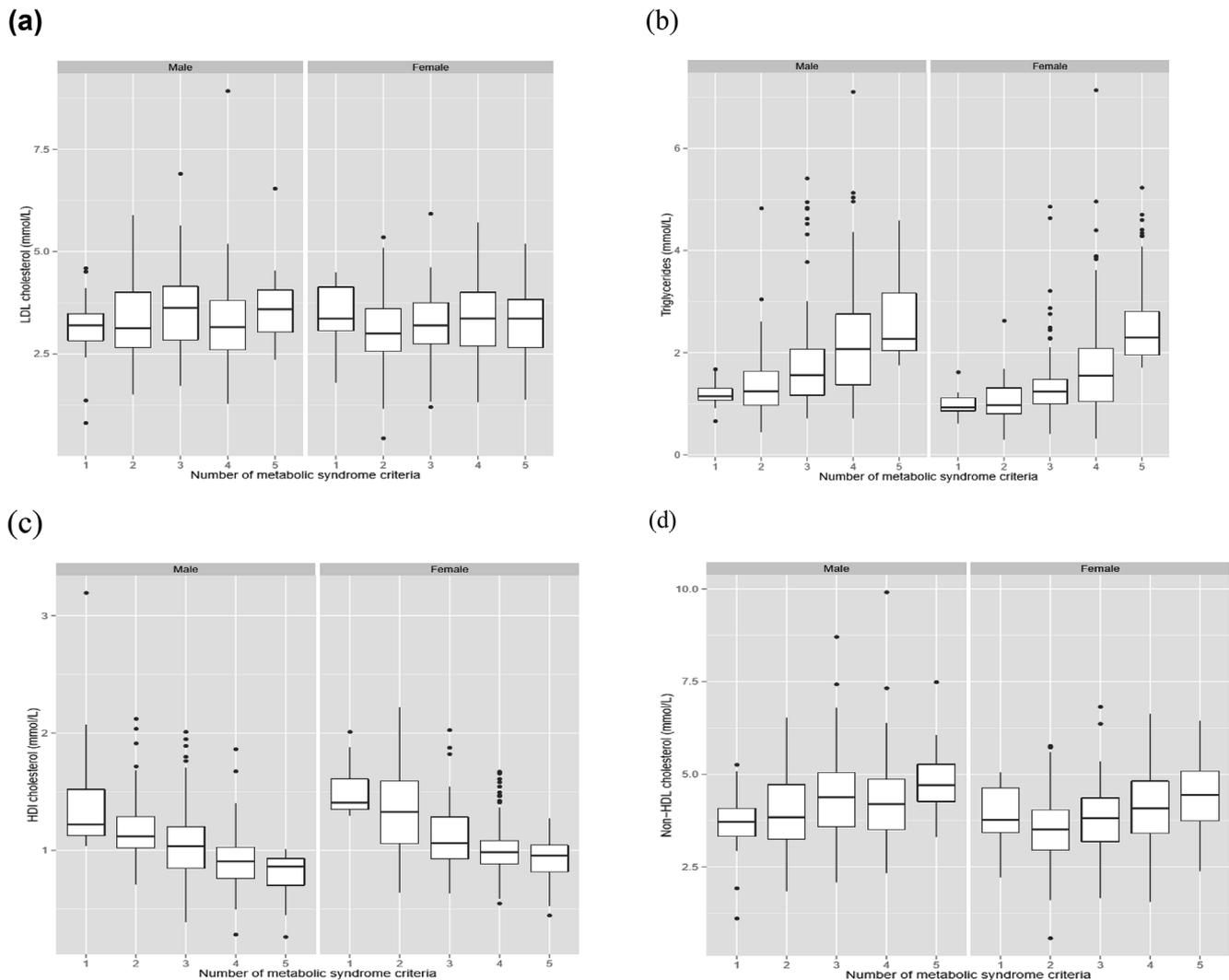
Comparison of our study population with NHANES-III(14, 24), INTERHEART [25,26] study group and with studies from Saudi Arabia [27] and Georgia [28] is summarized in Table 4.

Key differences are higher ApoB, higher ApoA1 and lower ApoB:A1 ratios in our population. Data from other regional countries on apolipoprotein levels are lacking [29]. Apolipoprotein parameters of our population appear to match those in the Saudi Arabian study. This is probably because all participants in those studies had diabetes. However, diabetes is associated with low HDLC and therefore a low ApoA1 is expected. The reason for the observed high ApoA1 level in these two populations remains unclear. Comparisons across these studies should however be made with caution as they differ from each other in age distribution, prevalence of diabetes, geographies and ethnicities and had been conducted in different periods of time.

Based on NHANES-III, sex specific ApoB:A1 cut offs have been formulated to determine high CVD risk (0.97 in men, 0.86 in women) [24]. According to those cut offs 25.3% of our population had high risk of CVD (30.1% of those with metabolic syndrome and 18.5% of those without).

MetS had a weaker association with low apoA1 than with low HDLC. The significantly lower HDLC/apoA1 in those with MetS indicated the presence of smaller subclasses of HDL in MetS.

When individual risk factors of MetS were considered, those with hypertriglyceridemia, hypertension and high WC had significantly higher apoB indicating their association with increased number of LDL particles. The risk of CVD is assumed to be more



**Fig. 1.** Association of lipid parameters with number of criteria in metabolic syndrome defined according to NCEP/ATPIII (a–f) and association of ApoB with LDL cholesterol and non HDL cholesterol (g and h). (a) LDLc, (b) triglycerides (c) HDL cholesterol; (d) non-HDL cholesterol; (e) ApoB; (f) apoB:A1 ratio; (g) ApoB and LDL Cholesterol; (h) ApoB and HDL cholesterol.

directly related to the number of circulating atherogenic particles that come into contact with and enter the arterial wall than to the measured concentration of cholesterol [30].

#### 4.3. Implications, strengths and weaknesses

These findings imply that young Sri Lankans with diabetes have a high prevalence of MetS and this is associated with high levels of apoB and higher apoB:A1 ratio indicating higher risk of atherosclerotic cardiovascular disease than would be predicted by traditional risk factors. This observation may be a consequence of unique genetic predispositions leading to altered lipid metabolism. This also highlights the importance of utilising apoB levels and apoB:A1 ratio in cardiovascular risk prediction and treatment.

This is the first study on apolipoprotein patterns among people with diabetes in Sri Lanka. Strengths of the study include its large sample size and detailed assessment of correlations. Limitations are exclusion of older adults, and not having prospective data to accurately estimate the cardiovascular event risk which could be potential areas for further studies.

## 5. Conclusions

Metabolic syndrome affects about 60% of young Sri Lankans with type 2 diabetes. These individuals also have higher levels of apoB and apoB:A1 ratios, predicting high cardiovascular disease risk. This suggests that early CVD risk assessment, including apolipoprotein level estimation is essential in young people with diabetes. There is a need for further studies on apolipoproteins in older adults with diabetes to assess their predictive power for cardiovascular disease. Combining apolipoproteins with other criteria of metabolic syndrome may improve prediction of cardiovascular risk.

## Declarations

### Author contributions

GWK, PK, BS and DRM conceived the research question and designed the study. GWK, PK, BS and DRM developed the proposal and supervised the conduct of the study. GWK and BS supervised the laboratory studies and quality control. GWK, BS and HAD

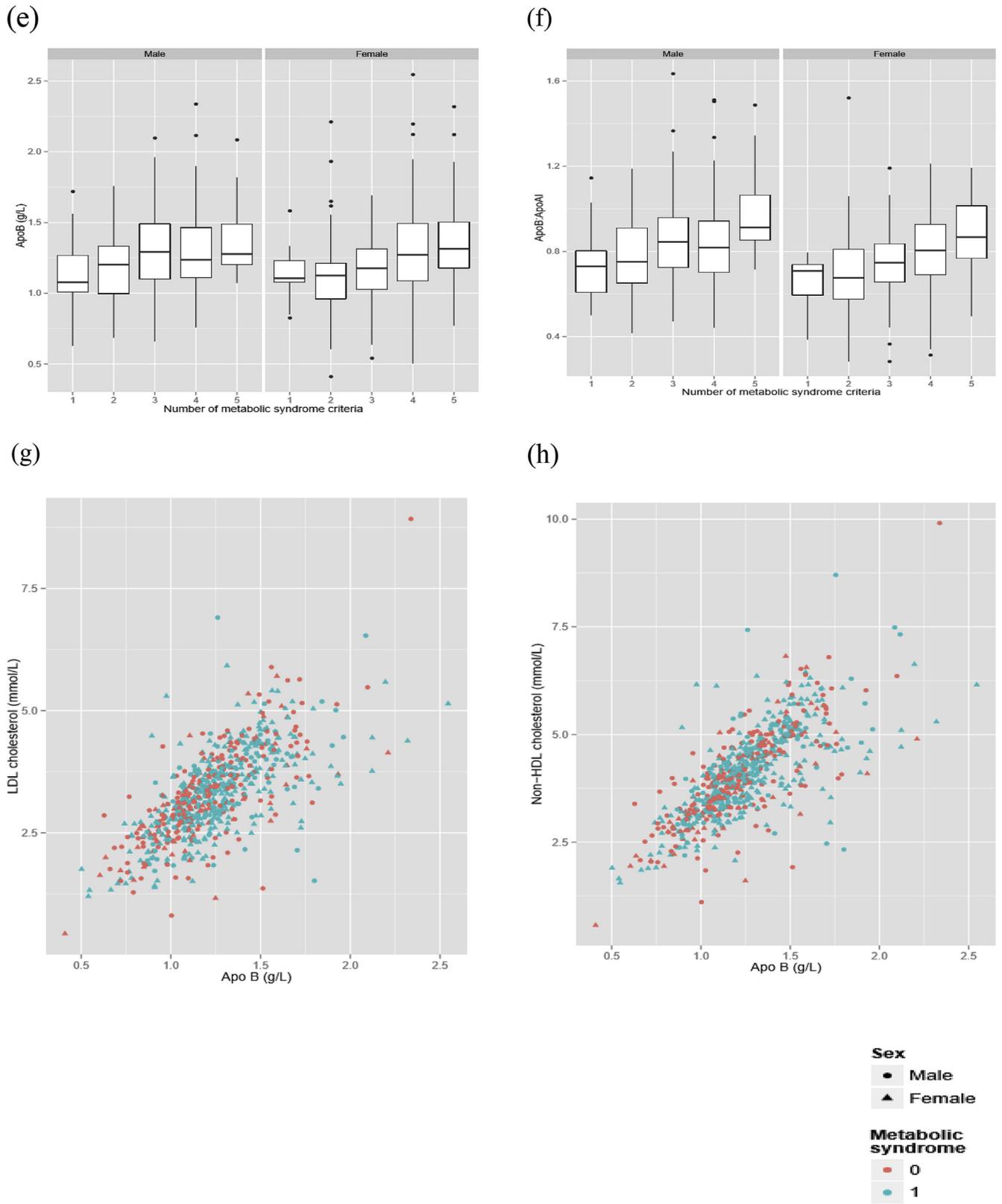


Fig. 1. (continued).

**Table 2**  
Mean and median distributions of ApoB and apoB/apoAI ratio in participants with and without MetS components/MetS.

Polio proteins		Metabolic syndrome component								Metabolic syndrome	
		High BP		High WC		High TG		Low HDLC		Present	Absent
		Present	Absent	Present	Absent	Present	Absent	Present	Absent		
ApoB (g/l)	Mean	1.27	1.21	1.26	1.22	1.36	1.18	1.25	1.22	1.27	1.20
	SD	0.28	0.29	0.28	0.29	0.28	0.26	0.30	0.26	0.28	0.28
	P	0.02		0.04		<0.001		0.24		0.002	
ApoB: ApoA	Med	0.79	0.78	0.79	0.76	0.86	0.74	0.81	0.74	0.80	0.78
	IQR	0.69–1.11	0.67–1.11	0.69–1.10	0.65–1.12	0.75–1.18	0.64–1.03	0.70–1.15	0.63–1.05	0.70–1.16	0.67–1.09
	P	0.08		0.04		<0.01		<0.001		0.003	

BP: blood pressure; HDLC: high density lipoprotein cholesterol; MetS: Metabolic syndrome; TG: triglyceride; WC: waist circumference. Abnormalities are defined in Table 1.

**Table 3**  
Association between individual components of MetS and MetS as a whole with apoB level and apoB/AI ratio.

Component of metabolic syndrome	ApoB				ApoB/AI ratio			
	Unadjusted		Adjusted <sup>a</sup>		Unadjusted		Adjusted <sup>a</sup>	
	B	P	B	P	B	P	B	P
High BP	6.37	0.01	4.7	0.021	0.02	0.11	0.01	0.31
High WC	3.38	0.08	−1.4	0.75	0.01	0.47	0.01	0.72
High TG	17.1	<0.001	17.5	<0.001	0.12	<0.001	0.11	<0.001
Low HDL	2.8	0.16	0.02	0.99	0.07	<0.001	0.07	<0.001
MetS <sup>b</sup>	5.7	0.02	6.85	0.01	0.03	0.008	0.06	<0.001

<sup>a</sup> Adjusted for age, sex, smoking status, alcohol status, physical activity level and other components of MetS criteria.

<sup>b</sup> Adjusted values derived by adjusting for age, sex, smoking status and alcohol status, physical activity as the dependent variable in a continuous scale and presence or absence of MetS or MetS criteria as independent binomial variables.

**Table 4**  
Comparison of ApoB, ApoAI and ApoB:AI ratios in different studies.

Study/country	Population <sup>a</sup>	ApoB	ApoAI	ApoB:AI	Reference
NHANES– III, metabolic syndrome	USA, 1988–94 N = 2964, 5.5% had diabetes	1.03 (0.01)	1.51 (0.51)	0.68 (0.65–0.71)	Sierra-Johnson et al., 2006 [24],
Present				0.90 (0.78–1.06)	Bachorik et al., 1997 [14]
Absent				0.69 (0.56–0.84)	
Saudi Arabia	N = 250 Age 52 (±9.5) All with diabetes	1.1 (0.30)	1.4 (0.30)	0.81 (0.25)	Alfadda AA et al., 2008 [27]
Georgia	N = 1522, Age 45 (±18) years, all without diabetes	0.81 (0.34)	1.06 (0.42)	0.79 (0.3)	Makaridze Z et al., 2014 [28]
SLYDS (current study)	N = 690 Age 38 (33–41) All with diabetes	1.25 (0.28)	1.58 (0.28)	0.79 (0.68–0.92)	–
INTERHEART	52 countries Age 58 (49–67)				Yusuf S et al., 2004 [25]
Cases	N = 12461 (7.4% diabetes)	1.02 (0.27)	1.13 (0.24)	0.90 (0.85–0.93)	
Controls	N = 14637 (18.4% diabetes)	0.95 (0.25)	1.22 (0.28)	0.78 (0.71–0.84)	
INTERHEART South Asian cohort	5 countries Age 52 (45–60)				Karthikeyan et al., 2009 [26]
Cases	N = 2171	0.95 (0.26)	1.01 (0.23)	0.94 (0.89–0.97)	
Controls	N = 2573	0.90 (0.24)	1.08 (0.23)	0.83 (0.78–0.87)	

All lipid values are mean (SD) except apoB:AI in SLYDS (median and IQR).

In INTERHEART cases were people who had had an acute myocardial infarction and controls were age and sex matched for cases.

NR: data not reported.

<sup>a</sup> Age expressed as median (IQR) or mean (SD).

analysed data and wrote the manuscript and was critically reviewed by PK. All authors approved the final manuscript.

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#### Ethics

Ethical approval was obtained from the Ethics Review

Committee, Faculty of Medicine, University of Colombo.

#### Consent for study and publication

All participants provided informed written consent for participation and for publication of clinical data.

#### Conflicts of interest

None of the authors have conflicts of interests to declare in relation to this paper.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.dsx.2018.07.002>.

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