



**UNIVERSITI PUTRA MALAYSIA**

**LOW DENSITY LIPOPROTEIN CHOLESTEROL PHENOTYPES AND  
THEIR ASSOCIATION WITH RISK FACTORS OF CARDIOVASCULAR  
DISEASE AMONG SUBJECTS ATTENDING HEALTH SCREENING AT  
A PUBLIC UNIVERSITY IN MALAYSIA**

**NORLIANAH BT MAZALAN**

**FPSK(m) 2020 13**



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UNIVERSITY IN MALAYSIA**

**By**

**NORLIANAH BT MAZALAN**

**Thesis Submitted to the School of Graduate Studies, Universiti Putra  
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Science**

**October 2019**

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in  
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**October 2019**

**Chair : Subashini C. Thambiah, MBBS, MPath**  
**Faculty : Medicine and Health Sciences**

**Background:** Cardiovascular disease (CVD) is the leading cause of death in Malaysia. Dyslipidaemia, a component of both Metabolic Syndrome (MetS) and Framingham Risk Score (FRS), is an established CVD risk factor. However, approximately 50% of individuals with coronary artery disease (CAD) have normal lipid levels and only 30% of all myocardial infarctions can be rationalised on the basis of conventional lipid profile. Low density lipoprotein cholesterol (LDL) particle concentration and size are reported to be important CVD predictors. Individuals with small dense LDL particles are categorised as Pattern B and are at greater risk of developing CAD. This pilot study aimed to determine the prevalence of Pattern B lipoprotein profile and its association with risk factors of CVD, specifically MetS and FRS among selected Malaysian population. This cross-sectional study involving 380 apparently healthy subjects aged  $\geq 30$  years old who attended health screening at Faculty of Medicine and Health Sciences, Universiti Putra Malaysia (FMHS, UPM). Recruitment was by convenience non-random sampling. Sociodemographic factors and clinical characteristics were recorded in the proforma after informed consent. Biochemical analyses on fasting samples (lipid profile, plasma glucose and LDL subfractions) were performed at the Chemical Pathology Laboratory, FMHS, UPM. Data analysis was done using IBM SPSS Statistic version 23.0 for Windows. This study outcomes showed that the prevalence of Pattern B and normolipidaemic Pattern B were 45% and 8.8%, respectively. There was significant association between all sociodemographic factors, clinical characteristics and biochemical parameters (except for ethnicity, waist circumference for females, total cholesterol and LDL) with type of lipoprotein profile pattern. Male gender and MetS are independent predictors of Pattern B. Age, ethnicity and Pattern B independently predict MetS.

Independent predictors of FRS include gender, ethnicity, diastolic blood pressure and Pattern B. The similarity between the independent biochemical predictors of Pattern B, MetS and FRS include LDL1 and LDL3. As conclusion, the prevalence of Pattern B and normolipidaemic Pattern B is relatively high compared to previous studies. Being male with MetS independently predicted Pattern B. By performing LDL subfraction analysis, additional individuals at risk could be identified, that would be missed if their risk were predicted according to their FRS alone. Atherogenic normolipidaemia broadens the population at risk for a CVD event, as these at-risk individuals are not recognised and hence not included in the protective measures of primary CVD prevention.



Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia  
sebagai memenuhi keperluan untuk ijazah Sarjana Sains

**FENOTIP LIPOPROTIN KOLESTEROL KEPADATAN RENDAH DAN  
KAITANNYA DENGAN FAKTOR RISIKO PENYAKIT KARDIOVASKULAR  
DALAM KALANGAN SUBJEK YANG MENGHADIRI SARINGAN  
KESIHATAN DI SEBUAH UNIVERSITI AWAM DI MALAYSIA**

Oleh

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**Oktober 2019**

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**Latar belakang:** Penyakit kardiovaskular (CVD) merupakan penyebab utama kematian di Malaysia. Dislipidemia, iaitu komponen kepada *Metabolic Syndrome* (MetS) dan *Framingham Risk Score* (FRS), merupakan factor risiko utama bagi CVD. Walau bagaimanapun, dianggarkan 50% individu yang menghidap penyakit arteri koronari (CAD) mempunyai tahap kolesterol yang normal, manakalannya 30% serangan jantung boleh dijelaskan dengan profil kolesterol konvensional. Kajian menunjukkan bahawa konsentration partikel dan saiz kepadatan rendah kolesterol lipoprotein (LDL) merupakan penentu risiko CVD. Individu dengan lipoprotein berkepadatan rendah dan bersaiz kecil (sdLDL) diklasifikasikan sebagai Profil Pola B dan mempunyai risiko yang tinggi untuk menghidap CAD. Tujuan utama kajian perintis ini adalah untuk mengenalpasti prevalen Profil Pola B lipoprotein dan kaitannya dengan factor risiko CVD, khususnya MetS dan FRS di kalangan populasi rakyat Malaysia yang terpilih. Ini merupakan kajian kaedah keratan rentas melibatkan seramai 380 subjek sihat berusia 30 tahun ke atas yang hadir pada saringan kesihatan di Fakulti Perubatan dan Sains Kesihatan, Universiti Putra Malaysia (FPSK, UPM). Pemilihan subjek dilakukan melalui kaedah sampel bukan-rawak. Faktor sosiodemografi dan kriteria klinikal direkodkan di dalam pro-forma selepas persetujuan dimaklumkan. Analisis biokimia ke atas sampel puasa (profil lipid, plasma glukos dan subfraks LDL) telah dilakukan di Makmal Patologi Kimia, FPSK, UPM. Data telah dianalisa dengan menggunakan IBM SPSS Statistik versi 23.0 untuk Windows. Hasil kajian ini menunjukkan prevalen keseluruhan bagi Pola B adalah 45% manakala Pola B dengan paras lipid normal adalah 8.8%. Terdapat hubungan signifikan di antara semua factor sosiodemografik, kriteria klinikal dan parameter biokimia [kecuali etnik, ukur lilit pinggang bag iperempuan, jumlah keseluruhan kolesterol dan LDL] dengan profil lipoprotein. Jantina lelaki dan MetS merupakan predictor utama untuk Profil Pola B. Umur, etnik dan Pola B dapat meramalkan MetS secara bebas. Prediktor utama FRS adalah jantina, etnik, tekanan darah diastolik dan Pola B. Persamaan antara

predictor utama biokimia bagi Pola B, MetS dan FRS adalah LDL1 dan LDL3. Kesimpulannya, prevalen Pola B secara relatifnya adalah tinggi berbanding kajian sebelum ini. Lelaki yang mempunyai MetS adalah secara bebas meramal kepada Pola B. Analisa subfraks LDL dapat mengenalpasti lebih ramai individu berisiko, yang gagal dikenalpasti sekiranya hanya menggunakan FRS. Aterogenik normolipidemia meluaskan lagi populasi yang berisiko untuk episod CVD, yang lazimnya gagal dikenalpasti dan oleh itu tidak dapat perlindungan pencegahan awal CVD.



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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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## LIST OF ABBREVIATIONS

ACS	Acute Coronary Syndrome
AGE	Advanced Glycation End Products
AHA	American Heart Association
AIR	Atherosclerosis and Insulin Resistance
AMI	Acute Myocardial Infarction
ApoB	Apolipoprotein B
ApoA-I	Apolipoprotein A-I
ApoB-100	Apolipoprotein B100
ApoCIII	Apolipoprotein C3
ARIC	Atherosclerosis Risk in Communities
BMI	Body Mass Index
BP	Blood Pressure
CAD	Coronary Artery Disease
CE	Cholesteryl Ester
CETP	Cholesteryl Ester Transfer Protein
CV	Cardiovascular
CVD	Cardiovascular disease
CMR	Chylomicron remnants
CHD	Coronary Heart Disease
IHD	Ischemic Heart Disease
CI	Confidence Interval
CPG	Clinical Practice Guidelines
DBP	Diastolic Blood Pressure
DM	Diabetes Mellitus
FDA	United States Food and Drug Administration
FFA	Free Fatty Acid
FSL	Fasting Serum Lipid
GGE	Gradient Gel Electrophoresis
HDL	High Density Lipoprotein
HOCL	Hypochlorous Acid
HOSCN	Hypothiocyanous Acid
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
IgG	Immunoglobulin G
IHD	Ischemic Heart Disease
IL-8	Interleukin-8
IDF	International Diabetes Federation
IQR	Interquartile Range
IR	Insulin Resistance
IbLDL	Large Buoyant Low Density Lipoprotein
LDL	Low Density Lipoprotein
LDL-P	LDL Particles
LDL-R	LDL Receptor
LOX-1	LDL Receptor-1
Lp(a)	Lipoprotein(a)
LPL	Lipoprotein Lipase
MetS	Metabolic Syndrome

MI	Myocardial Infarction
NCEP ATP III	National Cholesterol Education Program Adult Treatment Panel III
NF-Kb	NF-kappaB
NHBLI	National Heart, Lung, and Blood Institute
NHMS	National Health and Morbidity Survey
NMR	Nuclear Magnetic Resonance
PAGE	Polyacrylamide Gel Electrophoresis
PGGE	Polyacrylamide Gradient Gel Electrophoresis
RAGE	Receptor for Advanced Glycation End
Rf	Retardation Factor
ROS	Reactive Oxygen Species
RR	Relative Risk
SBP	Systolic Blood Pressure
sdLDL	Small Dense Low Density Lipoprotein
SHBG	Sex Hormone Binding Globulin
SMC	Smooth Muscle Cell
TC	Total Cholesterol
T2DM	Type 2 Diabetes Mellitus
TG	Triglycerides
TLC	Therapeutic lifestyle changes
UPM	Universiti Putra Malaysia
VAP	Vertical Auto Profile
VLDL	Very Low Density Lipoprotein
WC	Waist Circumference
WHO	World Health Organization

## CHAPTER 1

### INTRODUCTION

#### 1.1 Background

Cardiovascular disease (CVD) is the foremost cause of death in Malaysia. In 2012, CVD was the cause of 31% of all global death, of which approximately 7.4 million and 6.7 million were due to coronary heart disease (CHD) and stroke, respectively. In Malaysia, CVD is estimated to account for 36% of total deaths [World Health Organization (WHO), 2014].

Traditionally, major CVD risk factors include age, obesity, hyperlipidaemia, smoking, diabetes mellitus (DM) and hypertension (Yusof et al., 2013). Metabolic syndrome (MetS), a constellation of these CVD risk factors is also common in Malaysia, with a prevalence of 42%, using the harmonised criteria (Yeow et al., 2012). MetS is characterised by atherogenic dyslipidaemia, which consists of elevated small dense low density lipoprotein (sdLDL) levels, raised triglycerides (TG) and reduced high density lipoprotein (HDL) levels (Nikolic et al., 2013).

These risk factors also form the Framingham Risk Score (FRS), a coronary prediction tool that estimates a patient's 10-year risk of developing CVD event, which subsequently dictates management (Ridker, Buring, Rifai & Cook, 2007). It categorises patients into low (< 10%), intermediate (10 - 20%) and high risk (> 20%) groups [Khanna et al., 2013].

Dyslipidaemia, a component of both MetS and FRS, is an established risk factor in CVD. Previous research has demonstrated that LDL particle concentration and size are important predictors of CVD (El Harchaoui et al., 2007). On conventional lipid profile measurement, the LDL levels are typically normal in atherogenic dyslipidaemia but there is a higher fraction of sdLDL, which is not detected (CPG Management of Dyslipidaemia, 2017). Hence, the necessity for a more specific diagnostic tool for atherogenic dyslipidaemia.

In this study, measurement of LDL particle size and quantification of sdLDL fractions will be performed using polyacrylamide gel electrophoresis (PAGE). Characteristically, Pattern A includes large, buoyant LDL (lbLDL) particles (LDL1 and LDL2 subfractions) and Pattern B, the atherogenic profile has sdLDL particles (LDL3 through LDL7) [Krauss & Siri, 2004].

## **1.2 Problem Statement**

Persons with MetS normally do not have elevated levels of LDL. However, it is hypothesised that the CVD risk associated with MetS may be attributable to sdLDL particles. These sdLDL particles are more susceptible to oxidation than lbLDL (Kathiresan et al., 2006), hence more atherogenic. Despite the widespread use of FRS, which is a conventional algorithm to assess 10-year CHD risk in middle-aged, asymptomatic persons (Vekic, Topic, Zeljkovic, Jelic-Ivanovic & Spasojevic-Kalimanovska, 2007), there is evolving concern for novel CHD risk prediction biomarkers.

It is established that race has an impact on conventional CHD risk factors. Since LDL subfractions are the promising predictors of CHD, further research is required to determine the distribution of these subfractions among diverse ethnicities. Current research on LDL subfractions is based on western populations with inadequate data on Asians (Vekic et al., 2007).

Although several studies have demonstrated the predictive power of LDL subfractions in CHD risk assessment, National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) still does not recommend its use in routine practice because methods available for measurement are complicated and inaccurate (Vekic et al., 2007). Furthermore, LDL subfraction as an independent predictor of CHD risk is questioned as it is highly correlated with TG and HDL (Pasternak, 2002). Hence, more studies are required to establish the role of sdLDL as a risk marker in CVD.

This study will use the FDA approved semi-automated Lipoprint Lipoprotein Subfractions Testing System from Quantimetrix that utilises the PAGE method to separate the LDL subfractions on the basis of size. To date, there are limited studies on sdLDL in South East Asia and to our knowledge, none in Malaysia. Thus, the aim of this study is to determine the prevalence of Pattern B lipoprotein profile and its association with risk factors of CVD, specifically MetS and FRS among selected apparently healthy Malaysian subjects.

## **1.3 Significance of This Study**

Conventional lipid profile, which reports LDL, HDL, TG and total cholesterol (TC) levels, does not identify sdLDL particles. Approximately 50% of individuals diagnosed with coronary artery disease (CAD) have normal lipid levels and only 30% of all myocardial infarctions (MI) can be rationalised on the basis of conventional lipid profile (The Lipoprint System Quantimetrix Manual, 2006). Hence, LDL subfractions testing convey a level of CVD risk not possible with conventional lipid profile. To date, there are no data related to the association of Pattern B lipoprotein profile with risk factors of CVD, specifically MetS and FRS in Malaysia. Therefore, this study will help identify subjects with an atherogenic profile where on conventional lipid profile measurement, the LDL levels are typically normal but there is a higher fraction of sdLDL, which is not

detected. In turn, this data could be used to strategise effective prevention and therapeutic programmes to reduce associated cardiovascular morbidity and mortality in the Malaysian population.

## **1.4 Objectives**

### **1.4.1 General Objective**

To determine Pattern B lipoprotein profile and its association with risk factors of CVD (MetS and FRS) in subjects attending health screening at FMHS, UPM.

### **1.4.2 Specific Objectives**

To determine the:

- i. baseline characteristics (sociodemographic factors, clinical characteristics and biochemical parameters) of study subjects;
- ii. prevalence of Pattern A and Pattern B, and normolipidaemic and dyslipidaemic Pattern B lipoprotein profiles, and its associations with sociodemographic factors, clinical characteristics and biochemical parameters, respectively, in study subjects;
- iii. prevalence of MetS and FRS values, and its associations with sociodemographic factors, clinical characteristics and biochemical parameters, respectively, in study subjects;
- iv. correlation between LDL subfractions (LDL1 to LDL5) with components of MetS (WC, TG, HDL, SBP, DBP & FBG) and FRS (WC, TC, HDL, SBP, FBG, total FRS, age) in study subjects;
- v. independent predictors of Pattern B, normolipidaemic Pattern B, MetS and FRS, respectively;

## **1.5 Hypotheses**

The alternative hypotheses of this study are:

- i. There are significant differences in sociodemographic factors, clinical characteristics and biochemical parameters between Pattern A and Pattern B, and normolipidaemic and dyslipidaemic Pattern B lipoprotein profiles, respectively in study subjects;
- ii. There are significant differences in sociodemographic factors, clinical characteristics and biochemical parameters between subjects with and without MetS, and among subjects with Low, Intermediate and High FRS values, respectively, in study subjects;

- iii. There are significant correlation between LDL subfractions (LDL1 to LDL5) with components of MetS (WC, TG, HDL, SBP, DBP & FBG) and FRS (WC, TC, HDL, SBP, FBG, total FRS, age) in study subjects;
- vi. There are significant independent predictors of Pattern B, normolipidaemic Pattern B, MetS and FRS, respectively;



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## BIODATA OF STUDENT

Norlianah bt Mazalan was born in Sandakan, Sabah. Her primary education was in two local government schools, SK Sg Manila and SK St Mary Convent, Sandakan, Sabah. She then completed her secondary education in SMK St Cecilia, Sabah in 2009. After that, she continued with the local pre-university programme, The Malaysian Matriculation Programme in Labuan Matriculation College with the aim of pursuing biomedicine. She graduated from Universiti Kuala Lumpur Institute of Medical Science Technology (UniKL MESTECH) in 2016 with Bachelor of Clinical Laboratory Science (Honours). She then completed her internship training at Faculty of Medicine and Health Sciences, Universiti Putra Malaysia (FMHS, UPM), Serdang, Selangor for one semester. In 2016, Norlianah applied to further her postgraduate studies at FMHS, UPM and is currently in her final year of the Master of Science (Chemical Pathology).

## LIST OF PUBLICATIONS

Subashini C. Thambiah, Noor Ayuni Mohamed Pesri, **Norlianah Mazalan**, Intan Nureslyna Samsudin, Safarina Mohamad Ismuddin, Geeta Appannah, Malina Osman and Siti Yazmin Zahari Sham. A Pilot Study on Pattern B Lipoprotein Profile in Malaysia. *Submitted to The Malaysian Journal of Pathology*. 2019.

Subashini C. Thambiah, **Norlianah Mazalan**, Intan Nureslyna Samsudin, Geeta Appannah, Siti Yazmin Zahari Sham, Salmiah Md. Said. (2020). Low Density Lipoprotein Cholesterol (LDL) Subfraction Profiles and Its Association with Risk Factors of Cardiovascular Disease Among Subjects Attending Health Screening at Faculty of Medicine and Health Sciences, Universiti Putra Malaysia. *Writing in Progress*. 2020.



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