UNIVERSITI PUTRA MALAYSIA

ASSOCIATION BETWEEN BONE CHARACTERISTICS AND CARDIOVASCULAR RISK FACTORS AMONG ADULTS IN SELECTED URBAN AREAS IN SELANGOR, MALAYSIA

SAFARINA BINTI MOHAMAD ISMUDDIN

FPSK(m) 2022 12

ASSOCIATION BETWEEN BONE CHARACTERISTICS AND CARDIOVASCULAR RISK FACTORS AMONG ADULTS IN SELECTED URBAN AREAS IN SELANGOR, MALAYSIA

By

SAFARINA BINTI MOHAMAD ISMUDDIN

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

July 2021

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

ASSOCIATION BETWEEN BONE CHARACTERISTICS AND CARDIOVASCULAR RISK FACTORS AMONG ADULTS IN SELECTED URBAN AREAS IN SELANGOR, MALAYSIA

By

SAFARINA BINTI MOHAMAD ISMUDDIN

July 2021

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

Cardiovascular disease (CVD) and osteoporosis (OP) are two significant public health-care issues globally with increased morbidity and mortality. The rising proportion of the ageing population globally indicates that urgent action is required to tackle the projected burden of CVD and OP. Increasing evidence now supports a direct association between these chronic conditions. Understanding this link in pathophysiology is important for the prevention and treatment of these disorders. Previous studies have revealed contradicting associations between CVD and OP. The escalating prevalence of OP and CVD globally with its increased morbidity and mortality notwithstanding the contradictory results on their association stresses the need for further research on this topic. No previous study has evaluated bone characteristics with Pattern B lipoprotein profile, which are individuals with atherogenic small dense low density lipoprotein cholesterol (LDL) particles. Hence this study aimed to determine the associations between bone characteristics and CVD risk factors, including Pattern B among adults in selected urban areas in Selangor, Malaysia. This was a cross sectional study involving 331 healthy subjects aged ≥ 45 years old from three selected residential areas in Puchong, Serdang, and Kajang, who were invited for a health screening at Puchong Specialist Centre. 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 were outsourced to Pantai Premier Laboratory. Data analysis was done using IBM SPSS Statistic version 25.0 for Windows. The prevalence of osteopenia and osteoporosis are 41.4% and 17.2%, respectively. Pattern B is detected in 48.9% with 39.9% having metabolic syndrome (MetS). Waist circumference (WC) and high-density lipoprotein cholesterol (HDL) are associated with abnormal bone mineral density (BMD) status and increased WC, hyperglycaemia, deranged lipid profile and MetS are associated with a higher BMD. The association between WC, fasting blood sugar (FBS), triglyceride (TG) with BMD, respectively is not driven by total fat since the associations remained

highly significant after adjustment for total fat. However, it is gender-specific. For HDL and MetS, however, this association with BMD is driven by total fat in females as it becomes attenuated after adjusting for it. A higher BMD is reported among MetS subjects but the effects of MetS on BMD varied by gender and skeletal site. Apart from the bone resorption marker, c-terminal telopeptide of type 1 collagen (CTX), there was no significant association between Pattern B and bone parameters. However, after adjusting for age, gender, race and total fat, there was no significant difference for CTX between Pattern A (individuals with non-atherogenic large buoyant LDL) and Pattern B. The only significant bone parameter associated with MetS is Mg, which is a protective factor. This study's results suggest that there are skeletal site and gender specific differences in the association between CVD risk factors with abnormal BMD status and BMD per se. The relative contribution of these risk factors would vary with skeletal sites considering that the rate of bone loss at different skeletal sites are diverse due to the variations in the composition of each bone and the heterogeneity in bone microstructure. A higher BMD was demonstrated among MetS subjects but the effects of MetS on BMD varied by gender and skeletal site. The only significant bone parameter associated with MetS in this study is Mg, which is a protective factor. MetS is a combination of CVD risk factors that include obesity, a factor associated with increased BMD, and inflammation, a factor that lowers BMD. In this study, the findings suggest that adiposity may have a protective effect on BMD.

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

PERKAITAN ANTARA CIRI-CIRI TULANG DAN FAKTOR RISIKO KADIOVASKULAR DI KALANGAN DEWASA DI KAWASAN BANDAR TERPILIH DI SELANGOR, MALAYSIA

Oleh

SAFARINA BINTI MOHAMAD ISMUDDIN

Julai 2021

Pengerusi : Subashini C. Thambiah, MBBS, MPath
Fakulti : Perubatan dan Sains Kesihatan

Penyakit kardiovaskular (CVD) dan osteoporosis (OP) merupakan dua isu kesihatan awam global yang signifikan dan menyumbang kepada peningkatan morbiditi dan mortaliti. Peningkatan populasi warga tua di seluruh dunia merupakan indikasi bahawa tindakan segera harus dilakukan bagi mengatasi beban CVD dan OP. Hasil kajian terkini membuktikan kehadiran hubungan langsung di antara kedua-dua penyakit ini. Pemahaman mengenai hubungan patofisiologi adalah penting bagi membolehkan langkah-langkah pencegahan dan rawatan penyakit dilaksanakan. Terdapat percanggahan hubungan di antara CVD dan OP pada kajian-kajian yang terdahulu. Meningkatnya prevalensi OP dan CVD di seluruh dunia termasuk peningkatan morbiditi dan mortaliti menunjukkan perlunya ada penyelidikan lebih lanjut mengenai subjek ini walaupun terdapatnya percanggahan hubungan antara OP dan CVD. Tiada kajian terdahulu yang menilai ciri-ciri tulang dengan profil lipoprotein Pola B, iaitu individu yang mempunyai kolesterol lipoprotein berkepadatan rendah (LDL) dan bersaiz kecil yang aterogenik. Kajian ini bertujuan mengetahui kaitan di antara ciri-ciri kesihatan tulang dan faktor risiko kardiovaskular, termasuk Pola B di kalangan orang dewasa di kawasan bandar terpilih di Selangor, Malaysia. Ia adalah kajian keratan rentas melibatkan 331 subjek sihat berusia 45 tahun dan ke atas dari tiga kawasan perumahan terpilih di Puchong, Serdang, dan Kajang, yang dijemput untuk menjalani pemeriksaan kesihatan di Pusat Pakar Puchong. Pengambilan subjek dilakukan melalui kaedah persampelan konvenien bukan rawak. Faktor sosiodemografi dan ciri-ciri klinikal direkodkan di proforma setelah mendapat persetujuan subjek. Analisis biokimia pada sampel darah subjek berpuasa dilakukan di Makmal Pantai Premier. Analisa data dilakukan menggunakan IBM SPSS Statistic versi 25.0 untuk Windows. Prevalen osteopenia adalah 41.4% manakala prevalen OP adalah 17.2%. Pola B dikesan dikalangan 48.9% subjek dengan 39.9% mengalami sindrom metabolik (MetS). Lingkaran pinggang (WC) dan kolesterol lipoprotein berketumpatan tinggi (HDL) dikaitkan dengan status kepadatan mineral tulang yang tidak normal (BMD) dan

peningkatan WC, hiperglisemia, dan profil lipid tidak normal. MetS dikaitkan dengan BMD yang lebih tinggi. Perkaitan masing-masing di antara WC, paras gula darah puasa (FBS), trigliserida (TG) dengan BMD tidak dipengaruhi oleh jumlah lemak memandangkan hubungkait tetap signifikan setelah penyesuaian terhadap jumlah lemak. Walau bagaimanapun, ianya bergantung pada jantina. Untuk HDL dan MetS, perkaitan dengan BMD adalah dipengaruhi oleh jumlah lemak pada wanita kerana hubungkait berkurangan setelah pelarasan dilakukan. BMD yang lebih tinggi dilaporkan pada subjek MetS tetapi kesan MetS pada BMD adalah berbeza mengikut jantina dan lokasi rangka tulang. Selain dari penanda penyerapan semula tulang, *c-terminal telopeptide of type 1 collagen* (CTX), tidak ada hubungan yang signifikan antara Pola B dan parameter tulang. Walau bagaimanapun, setelah penyesuaian umur, jantina, bangsa dan jumlah lemak, tidak ada perbezaan yang signifikan untuk CTX di antara Pola A (individu dengan LDL bersaiz besar dan *buoyant* yang bukan aterogenik) dan Pola B. Satu-satunya parameter tulang yang signifikan yang berkait dengan MetS adalah Mg, yang merupakan faktor pelindung. Hasil kajian ini menunjukkan terdapat perbezaan struktur tulang dan jantina dalam hubungan di antara faktor risiko CVD dengan status BMD dan BMD yang tidak normal. Sumbangan relatif faktor-faktor risiko ini dipengaruhi lokasi rangka tulang disebabkan oleh perbezaan kadar kehilangan struktur tulang di tempat yang berbeza mengikut komposisi tulang dan heterogeniti dalam struktur mikro tulang. BMD yang lebih tinggi ditunjukkan dikalangan subjek MetS tetapi kesan MetS pada BMD berbeza mengikut jantina dan lokasi rangka tulang. Satu-satunya parameter tulang yang signifikan yang berkaitan dengan MetS dalam kajian ini adalah Mg, yang merupakan faktor pelindung. MetS adalah gabungan faktor risiko kardiovaskular merangkumi obesiti, iaitu faktor yang berkait dengan peningkatan BMD dan juga keradangan, iaitu faktor yang menurunkan BMD. Penemuan kajian ini menunjukkan bahawa adipositi mungkin mempunyai kesan perlindungan terhadap BMD.

ACKNOWLEDGEMENTS

In these difficult and challenging times of the Covid-19 era, my utmost gratitude and humble prostrations to Allah S.W.T for giving me the resilience and strength to complete this project as scheduled. I would like to thank my main supervisor, Assoc. Prof. Dr. Subashini C. Thambiah, who tirelessly monitored my progress and guided me every step of the way. My appreciation to Assoc. Prof. Dr. Intan Nureslyna Samsudin and Dr. Siti Yazmin Zahari Sham, my co-supervisors who also ensured the smooth running of this project. Thanks to Assoc. Prof. Dr. Salmiah Md. Said and Assoc. Prof. Dr. Geeta Appannah for their invaluable input in the statistical analysis of this project.

With sincere gratitude, I would also like to acknowledge all staff of the Chemical Pathology laboratory, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia (FMHS, UPM) – the late En. Norazmie Ramly, Pn. Rossalyna Rokmat, Pn Noorelina Muhammad, En Mohd Khairul Anwar and Pn Elisha Freda Edham and the late Miss Cherynn Lai and Dr Hailoon Low from All Eights (M) Sdn Bhd., for their help during the collection, processing and analysis of samples. Not forgetting my project colleagues, Nurunnaim bin Zainudin, Norlianah bt. Mazalan, Nasrin Shahifar, Dr. Noor Ayuni bt. Mohamed Pesri and Dr. Lai Yin Ye who were also working on different aspects of this large project. This project would not have been successfully completed without their support and cooperation.

My heartfelt love and appreciation to my pillars of strength, my husband, Shahrizan bin Redwan and children, Suffyya Nur Humaira, Muhammad Ummair Mukhriz and Suffyya Nur Hannah for their understanding, patience and constant support throughout this journey. My dear father, Mohammad Ismuddin Mat Saiman, my late mother, Wan Latifah Sulaiman, and my late father-in-law, Redwan Mohd Tab and mother-in-law, Aziah Yob Manan, thank you for your endless prayers. Likewise, my siblings who have been a moral support, my deepest gratitude to all of you. Last but not least, may Allah S.W.T bless all of you who were involved, either directly or indirectly in my journey.

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:

Subashini a/p Chellappah C. Thambiah, MBBS, MPath, AM
Associate Professor (Medical)
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Intan Nureslyna binti Samsudin, MB Bch Bao, MPath, AM
Associate Professor (Medical)
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

Siti Yazmin Zahari Sham, BM, MPath, AM
Medical Lecturer
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

_____
ZALILAH MOHD SHARIFF,PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

Date:14 April 2022

Declaration by Members of the Supervisory Committee

This is to confirm that:

- the research and the writing of this thesis were done under our supervision;
- supervisory responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2015-2016) are adhered to.

Signature: _____
Name of Chairman of Supervisory Committee: _____

Signature: _____
Name of Member of Supervisory Committee: _____

Signature: _____
Name of Member of Supervisory Committee: _____

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

$1,25(OH)_2D$	1,25-dihydroxyvitamin D
25(OH)D	25-hydroxyvitamin D
ACS	acute coronary syndrome
ALP	alkaline phosphatase
Apo	apolipoprotein
BMD	bone mineral density
BMI	body mass index
BP	blood pressure
C/EBPα	CCAAT/enhancer-binding protein α
Ca	calcium
CAD	coronary artery disease
CI	confidence interval
CTX	c-terminal telopeptide of type 1 collagen
CV	coefficient of variation
CVD	cardiovascular disease
DBP	diastolic blood pressure
DM	diabetes mellitus
DXA	dual-energy x -ray absorptiometry
FDA	Food and Drug Administration
FMHS	Faculty of Medicine and Health Sciences
FSL	fasting serum lipid
HDL	high density lipoprotein cholesterol
IDF	International Diabetes Federation
IDL	intermediate density lipoprotein cholesterol

IQR	interquartile range
L-FN	left femoral neck
L-TH	left total hip
lbLDL	large buoyant low-density lipoprotein
LDL	low density lipoprotein cholesterol
LS	lumbar spine
MetS	metabolic syndrome
Mg	magnesium
NCEP ATP III	National Cholesterol Education Program Adult Treatment Panel III
OP	osteoporosis
OPe	osteopenia
OPG	osteoprotegerin
P1NP	procollagen type 1 n-propeptide
PAGE	polyacrylamide gel electrophoresis
PGGE	polyacrylamide gradient gel electrophoresis
PO_4	phosphate
PPAR-γ	peroxisome proliferator-activated receptor-γ
PTH	parathyroid hormone
RANK	receptor activator of nuclear factor-kb
RANKL	receptor activator of nuclear factor-kb ligand
Runx2	runt-related transcription factor 2
SBP	systolic blood pressure
SD	standard deviation
sdLDL	small dense low-density lipoprotein cholesterol
sFRP-1	secreted frizzled-related protein 1

T2DM	type 2 diabetes mellitus
TB	total body
TBS	trabecular bone score
TC	total cholesterol
TG	triglycerides
UPM	Universiti Putra Malaysia
VLDL	very low-density lipoprotein cholesterol
WC	waist circumference
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Background

The population worldwide is ageing at a rapid pace. The global world's population aged 60 years and older is estimated to be 2 billion by 2050 and majority of the elderly will be living in low- and middle-income countries. This proportion has doubled from 12% in 2015 to 22% in 2050 (World Health Organization, 2018). Malaysia is well on its way to becoming an ageing society by 2030 when it is projected that 15% of its population will be 60 years old and above (Malaysian Healthy Aging Society, 2019). This demographic shift is a major challenge for all countries in ensuring that their healthcare and social systems are equipped to face it.

Cardiovascular disease (CVD) and osteoporosis (OP) are two significant public health-care issues globally with increased morbidity and mortality (Warburton, Nicol, Gatto, & Bredin, 2007). The rising proportion of the ageing population globally indicates that urgent action is required to tackle the projected burden of CVD and OP. The high morbidity and mortality associated with these two diseases can result in an increase in healthcare demand and hence marked financial pressure on the government.

CVD is the leading cause of mortality in Malaysia (Lu et al., 2014). In Malaysia, coronary artery disease (CAD) is the major cause of national mortality, contributing to 15.6% of all deaths in 2018 (Department of Statistics, Malaysia, 2019). OP, on the other hand, is a silent disease and the health and economic impact of the disease results from fractures. In Malaysia, it is estimated that over 1 million people are at risk from OP, out of which 20% are men (Yeap et al, 2016).

Body composition can be evaluated precisely with dual-energy x-ray absorptiometry (DXA) and bone mineral density (BMD) indicates bone status over time while circulating bone turnover markers (BTMs) define the present bone remodelling stage (Pirilä et al., 2014). Although DXA is the gold-standard method for OP diagnosis, BMD alone by DXA is not adequate for assessment of bone strength. Trabecular bone score (TBS) is an indirect textural index of trabecular microarchitecture, which assesses pixel gray-level variations in the lumbar spine (LS) DXA image. In some situations, like glucocorticoid-induced OP and in diabetes mellitus (DM), the TBS out-performs the DXA (Silva & Leslie, 2017).

Traditionally, major cardiovascular factors include age, obesity, dyslipidaemia, smoking, DM and hypertension (Bugan, 2014; Veeranna, Pradhan, Niraj, Fakhry, & Afonso, 2010). Several shared pathophysiological factors in both CVD and OP have been advocated such as comparable molecular pathways linking vascular and bone mineralisation, oestrogen deficiency, vitamin D and K, lipid oxidation products, parathyroid hormone (PTH), inflammation and homocysteine (Lampropoulos, Papaioannou, & D'Cruz, 2012). A possible explanation is that a common underlying mechanism elicits both OP and CVD by affecting bone and blood vessels concurrently. The most likely contributing factor is lipids (Lello, Capozzi, & Scambia, 2015).

Dyslipidaemia is an established CVD risk factor. A possible association between lipid profile and OP has also been investigated. Some researchers have demonstrated that an atherogenic lipid profile is associated with a BMD (Lekamwasam, Weerarathna, Rodrigo, Arachchi, & Munidasa, 2009). However, others report no relationship between lipid profile and BMD (Solomon, Avorn, Canning, & Wang, 2005). Studies have shown that low-density lipoprotein cholesterol (LDL) particle size and concentration are significant predictors of CVD (El Harchaoui et al., 2007). Atherogenic dyslipidaemia consists of reduced high-density lipoprotein cholesterol (HDL), raised triglyceride (TG) and small dense LDL (sdLDL) particles. On conventional lipid profile measurement, the LDL levels are typically normal but there is a higher amount of atherogenic sdLDL particles, which are not detected (Zambahari et al, 2017). Thus, the need for LDL subfraction by an alternative method to determine CVD risk in individuals with a 'normal' lipid profile. Typically, individuals with large, buoyant LDL particles (LDL-1 and LDL-2 subfractions) are categorised as Pattern A (non-atherogenic), whereas individuals with atherogenic sdLDL particles (LDL-3 through LDL-7) are categorised as Pattern B and are at a higher risk for CVD (Krauss & Siri, 2004).

1.2 Problem Statement

CVD and OP are considered independent non-communicable diseases that increase significantly with advancing age. Nevertheless, a direct relationship between these chronic diseases is now supported by increasing evidence. Understanding this link in pathophysiology is important for the prevention and treatment of these disorders. Both conditions are reliant on hormonal, nutritional, genetic, lifestyle and metabolic factors. Several studies have demonstrated that OP share similar risk factors and pathogenesis with CVD including sedentary way of life, raised oxidative stress, inflammation, deficiency of sex hormones and smoking. Abdominal obesity, dyslipidaemia, hypertension and hyperglycaemia, components of Metabolic Syndrome (MetS) are also associated with the manifestation of OP. Each component has a distinct impact on bone health (Wong et al, 2016; Chin et al., 2020).

Previous studies have revealed contradicting associations between BMD & MetS as a precursor of CVD. In vivo studies in animal models demonstrate that obesity, dyslipidaemia, hypertension and hyperglycaemia are contributory factors in OP

pathogenesis. In contrast, human epidemiological research data are inconclusive on the association between MetS and bone health (Wong et al, 2016). The escalating prevalence of OP and CVD globally with its increased morbidity and mortality notwithstanding the contradictory results on their association stresses the need for further research on this topic.

1.3 Significance of this Study

Common pathophysiology and shared risk factors indicate an interaction between these conditions (Pirilä et al., 2014). Understanding this link in pathophysiology is significant for the prevention and management of these disorders. Common biomarkers can be used as tools for early identification of subjects at higher risk for both CVD and OP. Hence, patients with one of these diseases could be assessed and treated for the other. This study aims to determine the associations between bone characteristics such as BMD, TBS, and biochemical parameters involved in bone homeostasis [25-hydroxyvitamin D [25(OH)D], BTMs, PTH, adjusted calcium (Ca), phosphate (PO_4) and magnesium (Mg)] and CVD risk factors, including Pattern B lipoprotein profile in Malaysian subjects attending health screening in a specialist clinic. In addition, associations with demographic, clinical and biochemical variables will be determined between groups in relation to BMD status, LDL lipoprotein profile pattern and MetS status. To date, no previous investigation has evaluated bone characteristics with Pattern B and LDL subfractions.

1.4 Objectives

1.4.1 General Objectives

To determine the associations between bone characteristics and CVD risk factors in study population.

1.4.2 Specific Objectives

To determine the:

i. association of sociodemographic factors, DXA measurements and biochemical parameters with gender, BMD status [normal BMD, osteopenia (OPe) and OP], lipoprotein profile pattern (Pattern A and Pattern B) and MetS status (with and without MetS);

ii. relationship between abnormal BMD (OPe + OP) and CVD risk factors [MetS status and its components [waist circumference (WC), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood sugar (FBS),

TG, HDL], Pattern B status and its components [sdLDL (LDL-3, LDL -4) and mean LDL size] and lipid status (dyslipidaemia versus normolipidaemia)];

iii. relationship between TBS and BMD at all skeletal sites [lumbar spine ((LS), left total hip (L-TH), left femoral neck (L-FN), total body (TB)] with MetS status and its components (WC, SBP, DBP, FBS, TG, HDL), Pattern B status and its components [LDL-3, LDL-4 and mean LDL size] and lipid status (dyslipidaemia versus normolipidaemia);

iv. relationship between MetS with bone parameters [adjusted Ca, PO_4, Mg, PTH, 25(OH)D, alkaline phosphatase (ALP), c-terminal telopeptide of type 1 collagen (CTX), procollagen type 1 n-propeptide (P1NP), TBS, BMD at all skeletal sites (LS, L-TH, L-FN, TB)] and BMD status.

1.5 Research Hypotheses

The alternative hypotheses of this study are:

i. there is significant difference in sociodemographic factors, DXA measurements and biochemical parameters between male and female, subjects with normal BMD, osteopenia and osteoporosis, subjects with Pattern A and Pattern B and subjects with and without MetS;

ii. there is significant association between abnormal BMD status (OPe + OP) and CVD risk factors [MetS status and its components (WC, SBP, DBP, FBS, TG, HDL), Pattern B status and its components (LDL-3, LDL-4 and mean LDL size) and lipid status (dyslipidaemia versus normolipidaemia)] after adjusting for confounders;

iii. there is significant association between TBS and BMD at all skeletal sites (LS, L-TH, L-FN, TB) with MetS status and its components (WC, SBP, DBP, FBS, TG, HDL), Pattern B status and its components (LDL-3, LDL-4 and mean LDL size) and lipid status (dyslipidaemia versus normolipidaemia) after adjusting for confounders;

iv. there is significant association between MetS with bone parameters [(adjusted Ca, PO_4, Mg, PTH, 25(OH)D, ALP, CTX, P1NP, TBS, BMD at all skeletal sites (LS, L-TH, L-FN, TB)] and BMD status after adjusting for confounders.

1.6 Conceptual Framework

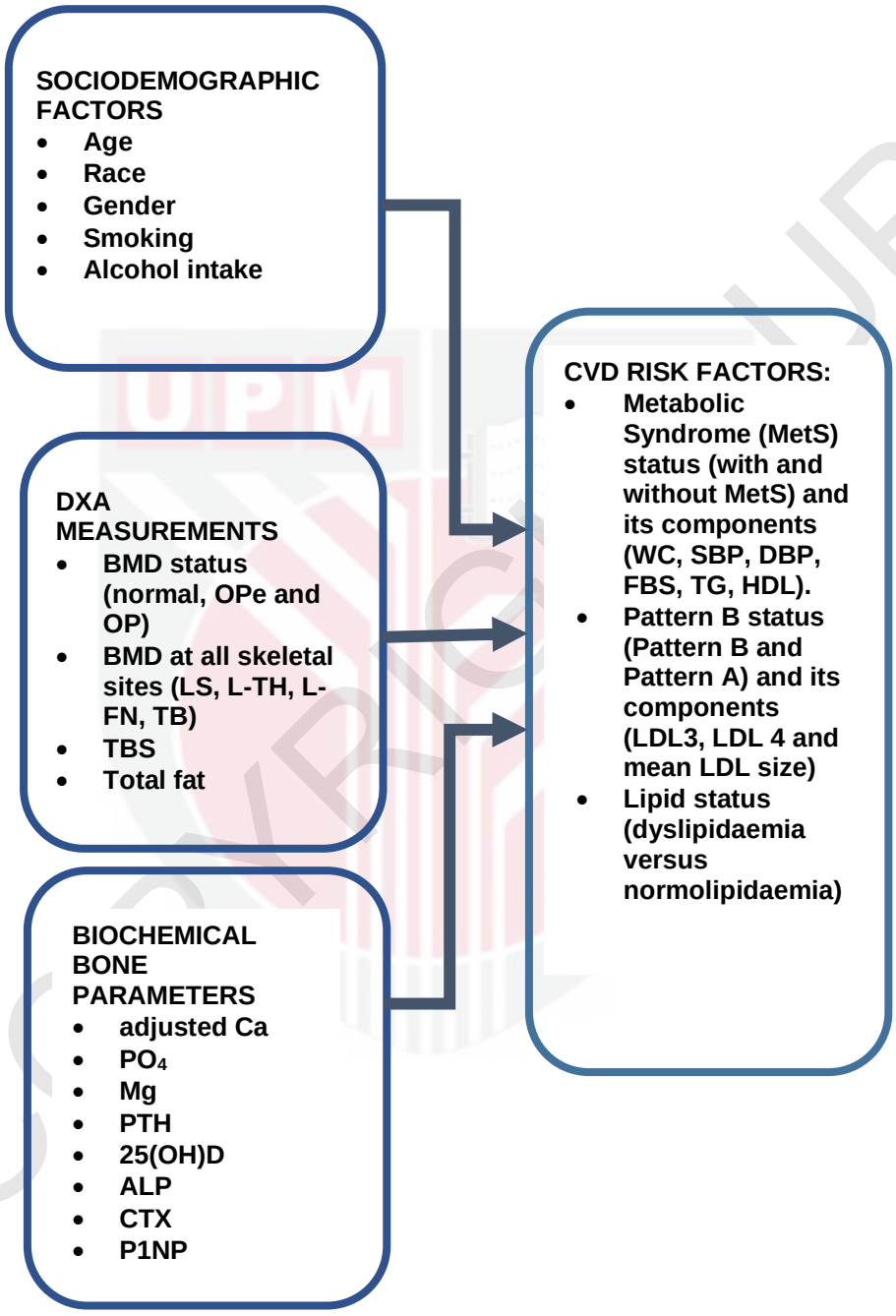

Figure 1.1: Conceptual framework of the study

REFERENCES

Abdul Rahman A.R, Rosman, A., Chin C.Y., ….. Rahana A. R. (2018). Management of Hypertension 5th edition. *Clinical Practice Guidelines*, *5th edition*, 1–160. https://doi.org/10.1080/00325481.1947.11691709

Adami S., Braga, V., Zamboni, M., Gatti, D., Rossini, M., Bakri, J., Battaglia, E. (2004). Relationship Between Lipids and Bone mass in 2 Cohorts of Healthy Women and Men. *Calcified Tissue International*; 74: 136-142.

Akkawi, I., & Zmerly, H. (2018). *Osteoporosis : Current Concepts*. 122–127.

Alberti, K. G. M. M., Eckel, R. H., Grundy, S. M., Zimmet, P. Z., Cleeman, J. I., Donato, K. A., … Smith, S. C. (2009). Harmonizing the metabolic syndrome: A joint interim statement of the international diabetes federation task force on epidemiology and prevention; National heart, lung, and blood institute; American Heart Association; World heart federation; International . *Circulation*, *120*(16), 1640–1645. https://doi.org/10.1161/CIRCULATIONAHA.109.192644

Anis Safura, R., Aqil Mohammad, D., Mohamed Noor Khan Nor-Ashikin, Nafiza Mat-Nasir, Kien Keat Ng, Maizatullifah Miskan, … Yusoff, K. (2013). JIS definition identified more malaysian adults with metabolic syndrome compared to the NCEP-ATP III and IDF criteria. *BioMed Research International*, *2013*, 1–10.

Anuurad, E., Shiwaku, K., Enkhmaa, B., Nogi, A., Kitajima, K., Yamasaki, M., & Yamane, Y. (2004). Ethnic differences in the formation of small LDL particles in Asians: A comparison of Koreans, Japanese and Mongolians. *European Journal of Clinical Investigation*, 34(11), 738-746.

Au Yeung, S. L., Xu, L., Lam, T. H., Leung, G. M., Schooling, C. M., Jiang, C., … Cheng, K. K. (2017). Age at menarche and cardiovascular risk factors using Mendelian randomization in the Guangzhou Biobank Cohort Study. *Preventive Medicine*, *101*, 142–148. https://doi.org/10.1016/j.ypmed.2017.06.006

Baigent, C., Blackwell, L., Emberson, J., Holland, L.E., Reith, C., Bhala, N., …..Collins R: Cholesterol Treatment Trialists' (CTT) Collaboration. (2010). Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*, *376,* 1670–1681.

Bañuls, C., Bellod, L., Jover, A., Martínez-Triguero, M. L., Víctor, V. M., Rocha, M., & Hernández-Mijares, A. (2012). Comparability of two different polyacrylamide gel electrophoresis methods for the classification of LDL pattern type. *Clinica Chimica Acta*. https://doi.org/10.1016/j.cca.2011.09.047

Barret-Connor, E, Kritz-Silverstein, D. (1996). Does Hyperinsulinaemia preserve bone? *Diabetes Care*. 19(12): 1388 – 1392.

Bilen, O., Kamal, A., & Virani, S. S. (2016). Lipoprotein abnormalities in South Asians and its association with cardiovascular disease: Current state and future directions. *World Journal of Cardiology*, *8*(3), 247. https://doi.org/10.4330/wjc.v8.i3.247

Bugan, B. (2014). Risk Factors for Coronary Artery Disease. *Journal of Clinical and Analytical Medicine*, *5*(2), 1–5. https://doi.org/10.4328/jcam.1304

Chaturvedi, N. (2003). Ethnic differences in cardiovascular disease. *Heart*, *89*(6), 681–686.

Chan C.Y., Subramaniam S., Mohamed N., Ima-Nirwana S., Muhammad N., Fairus A., et al. (2020). Determinants of bone health status in a multi-ethnic population in Klang Valley, Malaysia. *Int J Environ Res Publ Health*, 17:1e16.

Chin, K. Y., Chan, C. Y., Subramaniam, S., Muhammad, N., Fairus, A., Ng, P. Y., … Mohamed, N. (2020). Positive association between metabolic syndrome and bone mineral density among malaysians. *International Journal of Medical Sciences*, *17*(16), 2585–2593. https://doi.org/10.7150/ijms.49030

Chin, K. Y., Low, N. Y., Dewiputri, W. I., & Ima-Nirwanaa, S. (2017). Factors associated with bone health in Malaysian middle-aged and elderly women assessed via quantitative ultrasound. *International Journal of Environmental Research and Public Health*, *14*(7), 1–13. https://doi.org/10.3390/ijerph14070736

Chin KY, Wong SK, Ekeuku SO, Pang KL (2020). Relationship Between Metabolic Syndrome and Bone Health – An Evaluation of Epidemiological Studies and Mechanisms Involved. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, 13: 3667–3690.

Clarke, B. (2008). Normal bone anatomy and physiology. *Clinical Journal of the American Society of Nephrology : CJASN*, *3 Suppl 3*, 131–139. https://doi.org/10.2215/CJN.04151206

Cui, L-H., Shin, M-H., Kweon, S-S., …. Choi, J-S. (2007). Relative contribution of body composition to bone mineral density at different sites in men and women of South Korea. *J Bone Miner Metab*. 25:165–171.

Dennison EM, Syddall HE, Sayer AA, Martin HJ, Cooper C, and the Hertfordshire Cohort Study Group. (2007). Lipid profile, obesity and bone mineral density: the Hertfordshire Cohort Study. QJM. 2007 May ; 100(5): 297–303.

Department of Statistics, Malaysia (2017). Retrieved from https://www.dosm.gov.my/v1/index.php?r=column/ctheme&menu_id=L0pheU4 3

Department of Statistics, Malaysia. Press release: Statistics on causes of death, Malaysia, 2019. Retrieved from https://dosm.gov.my/v1/index.php?r=column/pdfPrev&id=RUxlSDNkcnRVazJnakNCNVN2VGgrdz09

Di Angelantonio E., Sarwar N., Perry, P., Kaptoge, S., Ray, K.K., Thompson, A.,... Danesh J: Emerging Risk Factors Collaboration. (2009). Major lipids, apolipoproteins, and risk of vascular disease. *JAMA, 302,* 1993–2000.

Duan, Y., Parfitt, A. M., & Seeman, E. (1999). Vertebral bone mass, size, and volumetric density in women with spinal fractures. *Journal of Bone and Mineral Research*, *14*(10), 1796–1802. https://doi.org/10.1359/jbmr.1999.14.10.1796

Dutheil, F., Walther, G., Chapier, R., Mnatzaganian, G., Lesourd, B., Naughton, G., … Lac, G. (2014). Atherogenic subfractions of lipoproteins in the treatment of metabolic syndrome by physical activity and diet - The RESOLVE trial. *Lipids in Health and Disease*, *13*(1), 1–9. https://doi.org/10.1186/1476-511X-13-112

El Harchaoui, K., van der Steeg, W. A., Stroes, E. S. G., Kuivenhoven, J. A., Otvos, J. D., Wareham, N. J., … Boekholdt, S. M. (2007). Value of Low-Density Lipoprotein Particle Number and Size as Predictors of Coronary Artery Disease in Apparently Healthy Men and Women. The EPIC-Norfolk Prospective Population Study. *Journal of the American College of Cardiology*, *49*(5), 547–553. https://doi.org/10.1016/j.jacc.2006.09.043

Finkelstein, J. S., Brockwell, S. E., Mehta, V., Greendale, G. A., Sowers, M. R., Ettinger, B., Neer, R. M. (2008). Bone mineral density changes during the menopause transition in a multiethnic cohort of women. *Journal of Clinical Endocrinology and Metabolism*, *93*(3), 861–868. https://doi.org/10.1210/jc.2007-1876

Fisher, A., Srikusalanukul, W., Davis, M., & Smith, P. (2013). Cardiovascular diseases in older patients with osteoporotic hip fracture: Prevalence, disturbances in mineral and bone metabolism, and bidirectional links. *Clinical Interventions in Aging*, *8*, 239–256. https://doi.org/10.2147/CIA.S38856

Franklin, S. S., & Wong, N. D. (2013). Hypertension and cardiovascular disease: Contributions of the Framingham Heart Study. *Global Heart*, *8*(1), 49–57. https://doi.org/10.1016/j.gheart.2012.12.004

Galesanu, C., & Mocanu, V. (2015). Vitamin D Deficiency and the Clinical Consequences. *Revista Medico-Chirurgicală a Societăţii de Medici Şi Naturalişti Din Iaşi*, *119*(2), 310–318.

Gallo, L., Maria C. Faniello, M.C., Canino, G., Tripolino, C., Gnasso, A., Cuda, G., Costanzo, F.S., & Irace, C. (2016). Serum Calcium Increase Correlates With Worsening of Lipid Profile: An Observational Study on a Large Cohort From South Italy. *Medicine 95(8),* 1–5.

Gazi, I., Tsimihodimos, V., Filippatos, T., Bairaktari, E., Tselepsi, A.D., and Elisaf, M. (2006). Concentration and relative distribution of low-densitiy lipoproteins subfractions in patients with metabolic syndrome defined according to the National Cholesterol Education Program criteria. *Metabolism Clinical and Experimental* 55: 885-891.

Ghee, L. K., & Kooi, C. W. (2016). A review of metabolic syndrome research in Malaysia. *Medical Journal of Malaysia*, 71, 20–28.

Grundy, S. M., Balady, G. J., Criqui, M. H., Fletcher, G., Greenland, P., Hiratzka, L. F., … Smith, S. C. (1998). Primary Prevention of Coronary Heart Disease: Guidance From Framingham. *Circulation*, *97*(18), 1876–1887. https://doi.org/10.1161/01.cir.97.18.1876

Grundy, S. M., Pasternak, R., Greenland, P., Smith, S., & Fuster, V. (1999). Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: A statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *Circulation*, *100*(13), 1481–1492. https://doi.org/10.1161/01.CIR.100.13.1481

Guerrero-Romero F, Jaquez-Chairez FO, Rodríguez-Morán M (2016). Magnesium in metabolic syndrome: a review based on randomized, double-blind clinical trials. *Magnesium Research*, 29 (4): 146-53.

Harvey, N. C., Glüer, C. C., Binkley, N., McCloskey, E. V., Brandi, M. L., Cooper, C., … Kanis, J. A. (2015). Trabecular bone score (TBS) as a new complementary approach for osteoporosis evaluation in clinical practice. *Bone*, *78*, 216–224. https://doi.org/10.1016/j.bone.2015.05.016

Hernandez JL, JM Olmos, E.Pariente, J. Martínez, C.Valero, P. García-Velasco, D.Nan, Javier L., J.González-Macías (2010). Metabolic syndrome and bone metabolism: the Camargo Cohort Study. Menopause: *The Journal of The North American Menopause Society,* 17(5): 955-961.

Hernández JL, Olmos JM, González-Macías J. (2011). Metabolic syndrome, fractures and gender. *Maturitas,* 68: 217–223.

Herrmann, M., Farrell, C. J. L., Pusceddu, I., Fabregat-Cabello, N., & Cavalier, E. (2017). Assessment of Vitamin D status - A changing landscape. *Clinical Chemistry and Laboratory Medicine*, *55*(1), 3–26. https://doi.org/10.1515/cclm-2016-0264

Hill, T. R., Aspray, T. J., & Francis, R. M. (2013). Vitamin D and bone health outcomes in older age. *Proceedings of the Nutrition Society*, *72*(4), 372–380. https://doi.org/10.1017/S0029665113002036

Holick, M. F., Binkley, N. C., Bischoff-Ferrari, H. A., Gordon, C. M., Hanley, D. A., Heaney, R. P., … Weaver, C. M. (2011). Evaluation, treatment, and prevention of vitamin D deficiency: An endocrine society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism*, *96*(7), 1911–1930. https://doi.org/10.1210/jc.2011-0385

Hulthe, J, Bokemark, L Wikstrand, J and Fagerberg, B. (2000). The Metabolic Syndrome, LDL Particle Size and Atherosclerosis. *Arteriosclerosis Thrombosis and Vascular Biology*. 20: 2140-2147.

Jeddi, M., Roosta, M. J., Dabbaghmanesh, M. H., Omrani, G. R., Ayatollahi, S. M. T., Bagheri, Z., … Bakhshayeshkaram, M. (2013). Normative data and percentile curves of bone mineral density in healthy Iranian children aged 9-18 years. *Archives of Osteoporosis*, *8*(1–2). https://doi.org/10.1007/s11657-012-0114-z

Jeon YK, Lee JG, Kim SS, Kim BH, Kim SJ, Kim YK, Kim IJ. (2011). Association between bone mineral density and metabolic syndrome in pre- and postmenopausal women. *Endocrine Journal,* 58 (2), 87-93.

Jousilahti, P., Vartiainen, E., Tuomilehto, J., & Puska, P. (1999). Sex, Age, Cardiovascular Risk Factors, and Coronary Heart Disease. *Circulation*, *99*(9), 1165–1172. https://doi.org/10.1161/01.cir.99.9.1165

Ju SY, Jeong HS, Kim Do H. Blood vitamin D status and metabolic syndrome in the general adult population: a dose response meta-analysis. J*. Clin. Endocrinol. Metab*. 99(3), 1053–1063 (2014).

Kahan, T. (2014). Focus on blood pressure as a major risk factor. *The Lancet*, *383*(9932), 1866–1868. https://doi.org/10.1016/S0140-6736(14)60896-5

Kautzky-Willer, A., Baggio, G., Rossi, M. C., Lapolla, A., & Russo, G. T. (2017). Type 2 Diabetes and Cardiovascular Risk in Women 2016. *International Journal of Endocrinology*, *2017*. https://doi.org/10.1155/2017/6905697

Khor, G. L. (2001). Cardiovascular epidemiology in the Asia-Pacific region. *Asia Pacific Journal of Clinical Nutrition*, *10*(2), 76–80. https://doi.org/10.1111/j.1440-6047.2001.00230.x

Khosla, S., & Riggs, B. L. (2005). Pathophysiology of age-related bone loss and osteoporosis. *Endocrinology and Metabolism Clinics of North America*, *34*(4), 1015–1030. https://doi.org/10.1016/j.ecl.2005.07.009

Kim, J. H., Choi, H. J., Kim, M. J., Shin, C. S., & Cho, N. H. (2012). Fat mass is negatively associated with bone mineral content in Koreans. *Osteoporosis International*, *23*(7), 2009–2016. https://doi.org/10.1007/s00198-011-1808-6

Kim, B. J., Ahn, S. H., Bae, S. J., Kim, E. H., Kim, T. H., Lee, S. H., Kim, H. K., Choe, J. W., Kim, S. Y., Koh, J. M., & Kim, G. S. (2013). Association between metabolic syndrome and bone loss at various skeletal sites in

postmenopausal women: a 3-year retrospective longitudinal study. *Osteoporosis International: 24*(8), 2243–2252.

Kim, H., Oh, H. J., Choi, H., Choi, W. H., Lim, S. K., & Kim, J. G. (2013). The association between bone mineral density and metabolic syndrome: a Korean population-based study. *J Bone Miner Metab*, 19: 1-8.

Kinjo M, Setoguchi S, Soloman DH. (2007). Bone Mineral Density in Adults with the Metabolic Syndrome: Analysis in a Population-Based U.S. Sample. *The Journal of Clinical Endocrinology & Metabolism* 92(11):4161–4164.

Klein, S., Allison, D. B., Heymsfield, S. B., Kelley, D. E., Leibel, R. L., Nonas, C., & Kahn, R. (2007). Waist circumference and cardiometabolic risk: A consensus statement from Shaping America's Health: Association for Weight Management and Obesity Prevention; NAASO, the Obesity Society; the American Society for Nutrition; and the American Diabetes Associat. *Diabetes Care*, *30*(6), 1647–1652. https://doi.org/10.2337/dc07-9921

Kolovou, G. D., Anagnostopoulou, K. K., & Cokkinos, D. V. (2005). Pathophysiology of dyslipidaemia in the metabolic syndrome. *Postgraduate Medical Journal*, *81*(956), 358–366. https://doi.org/10.1136/pgmj.2004.025601

Kotseva, K., De Backer, G., De Bacquer, D., Rydén, L., Hoes, A., Grobbee, D., … Wood, D. (2019). Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: Results from the European Society of Cardiology ESC-EORP EUROASPIRE V registry. *European Journal of Preventive Cardiology*, *26*(8), 824–835. https://doi.org/10.1177/2047487318825350

Kranioti, E. F., Bonicelli, A., & García-donas, J. G. (2019). Bone-mineral density : clinical signi fi cance , methods of quanti fi cation and forensic applications. *Dovepress*, *9*, 9–21.

Krauss, R. M., & Siri, P. W. (2004). Metabolic abnormalities: Triglyceride and low-density lipoprotein. *Endocrinology and Metabolism Clinics of North America*, *33*(2), 405–415. https://doi.org/10.1016/j.ecl.2004.03.016

Kulanuwat, S., Tungtrongchitr, R., Billington, D., & Davies, I. G. (2015). Prevalence of plasma small dense LDL is increased in obesity in a Thai population. *Lipids in Health and Disease*, *14*(1), 1–8. https://doi.org/10.1186/s12944-015-0034-1

Lampropoulos, C. E., Papaioannou, I., & D'Cruz, D. P. (2012). Osteoporosis - A risk factor for cardiovascular disease? *Nature Reviews Rheumatology*, *8*(10), 587–598. https://doi.org/10.1038/nrrheum.2012.120

Lee, S. J., Lee, E. Y., Lee, J. H., Kim, J. E., Kim, K. J., Rhee, Y., Kim, H. C., Youm, Y., & Kim, C. O. (2019). Associations of serum 25-hydroxyvitamin D with metabolic syndrome and its components in elderly men and women:

the Korean Urban Rural Elderly cohort study. BMC geriatrics, 19(1), 102.

Lekamwasam, S., Weerarathna, T., Rodrigo, M., Arachchi, W. K., & Munidasa, D. (2009). Association between bone mineral density, lean mass, and fat mass among healthy middle-aged premenopausal women: A cross-sectional study in southern Sri Lanka. *Journal of Bone and Mineral Metabolism*, *27*(1), 83–88. https://doi.org/10.1007/s00774-008-0006-x

Lello, S., Capozzi, A., & Scambia, G. (2015). Osteoporosis and cardiovascular disease: An update. *Gynecological Endocrinology*, *31*(8), 590–594. https://doi.org/10.3109/09513590.2015.1041908

Lu, H. T., Nordin, R., Wan Ahmad, W. A., Lee, C. Y., Zambahari, R., Ismail, O., Liew, H. B., Sim, K. H., & NCVD Investigators (2014). Sex differences in acute coronary syndrome in a multiethnic asian population: results of the malaysian national cardiovascular disease database-acute coronary syndrome (NCVD-ACS) registry. *Global heart,* 9(4), 381–390.

Maas, A. H. E. M., & Appelman, Y. E. A. (2010). Gender differences in coronary heart disease. *Netherlands Heart Journal*, *18*(12), 598–603. https://doi.org/10.1007/s12471-010-0841-y

Mafauzy, M. (2000). The problems and challenges of the aging population of malaysia. *The Malaysian Journal of Medical Sciences. 7*(1), 1–3. PMID: 22844207; PMCID: PMC3406209.

Makovey J, Naganathan V, Sambrook P. (2005). Gender differences in relationships between body composition components, their distribution and bone mineral density: a cross-sectional opposite sex twin study. *Osteoporos Int* 16: 1495–1505.

Malaysian Healthy Aging Society (2019). Are we ready for an ageing Malaysia? https://healthyageing.org/index.php/are-we-ready-for-an-ageing-malaysia

Martineau, P., & Leslie, W. D. (2017). Trabecular bone score (TBS): Method and applications. *Bone*, *104*, 66–72. https://doi.org/10.1016/j.bone.2017.01.035

McCloskey, E. V., Odén, A., Harvey, N. C., Leslie, W. D., Hans, D., Johansson, H., … Kanis, J. A. (2016). A Meta-Analysis of Trabecular Bone Score in Fracture Risk Prediction and Its Relationship to FRAX. *Journal of Bone and Mineral Research*, *31*(5), 940–948. https://doi.org/10.1002/jbmr.2734

McClung, M. R. (2005). The relationship between bone mineral density and fracture risk. *Current Osteoporosis Reports*, *3*(2), 57–63. https://doi.org/10.1007/s11914-005-0005-y

Miller, M., Stone, N. J., Ballantyne, C., Bittner, V., Criqui, M. H., Ginsberg, H. N., … Pennathur, S. (2011). Triglycerides and cardiovascular disease: A scientific statement from the American Heart Association. *Circulation*, *123*(20), 2292–2333. https://doi.org/10.1161/CIR.0b013e3182160726

Mottillo, S., Filion, K. B., Genest, J., Joseph, L., Pilote, L., Poirier, P., … Eisenberg, M. J. (2010). The metabolic syndrome and cardiovascular risk: A systematic review and meta-analysis. *Journal of the American College of Cardiology*, *56*(14), 1113–1132. https://doi.org/10.1016/j.jacc.2010.05.034

Muka, T., Trajanoska, K., Kiefte-de Jong, J. C., Oei, L., Uitterlinden, A. G., Hofman, A., Dehghan, A., Zillikens, M. C., Franco, O. H., & Rivadeneira, F. (2015). The Association between Metabolic Syndrome, Bone Mineral Density, Hip Bone Geometry and Fracture Risk: The Rotterdam Study. *PloS one*, *10*(6), e0129116. https://doi.org/10.1371/journal.pone.0129116

Mulukutla, S. R., Venkitachalam, L., Marroquin, O. C., Kip, K. E., Aiyer, A., Edmundowicz,
D., & Reis, S. E. (2008). Population variations in atherogenic dyslipidemia: A report from the HeartSCORE and IndiaSCORE Studies*. Journal of Clinical Lipidology*, *2*(6), 410–417.

Mussolino ME, Gillum RF. (2006). Bone mineral density and hyper tension prevalence in postmenopausal women: results from the Third National Health and Nutrition Examination Survey. *Ann. Epidemiol.* 16(5), 395–399.

Nikolic, D., Katsiki, N., Montalto, G., Isenovic, E. R., Mikhailidis, D. P., & Rizzo, M. (2013). Lipoprotein subfractisons in metabolic syndrome and obesity: Clinical significance and therapeutic approaches. *Nutrients*. https://doi.org/10.3390/nu5030928

Nishida, C., Uauy, R., Kumanyika, S., & Shetty, P. (2004). The Joint WHO/FAO Expert Consultation on diet, nutrition and the prevention of chronic diseases: process, product and policy implications. *Public Health Nutrition*, *7*(1a), 245–250. https://doi.org/10.1079/phn2003592

Nordestgaard ,B.G,. Varbo, A. (2014). Triglycerides and cardiovascular disease. *Lancet, 384,* 626–635.

Ogston, S. A., Lemeshow, S., Hosmer, D. W., Klar, J., & Lwanga, S. K. (1991). Adequacy of Sample Size in Health Studies. *Biometrics*, *47*(1), 347. https://doi.org/10.2307/2532527

Ohira, T., & Iso, H. (2013). Cardiovascular disease epidemiology in Asia - An overview. *Circulation Journal*, *77*(7), 1646–1652. https://doi.org/10.1253/circj.CJ-13-0702

Oravec, S., Dukat, A., Gavornik, P., Kucera, M., Gruber, K., Gaspar, L., & Banach, M. (2014). Atherogenic versus non-atherogenic lipoprotein profiles in healthy individuals. Is there a need to change our approach to diagnosing dyslipidemia? *Current Medicinal Chemistry*, *21*(25), 2892–2901. http://doi.org/10.2174/09298673216661403031530 48

Pajunen, P., Rissanen, H., Härkänen, T., Jula, A., Reunanen, A., & Salomaa, V. (2010). The metabolic syndrome as a predictor of incident diabetes and cardiovascular events in the Health 2000 Study. *Diabetes and Metabolism*, *36*(5), 395–401. https://doi.org/10.1016/j.diabet.2010.04.003

Park KK, Kim, SJ, Moon ES. (2010). Association between Bone Mineral Density and Metabolic Syndrome in Postmenopausal Korean Women. *Gynecol Obstet Invest* 2010;69:145–152.

Pirilä, S., Taskinen, M., Turanlahti, M., Kajosaari, M., Mäkitie, O., Saarinen-Pihkala, U. M., & Viljakainen, H. (2014). Bone health and risk factors of cardiovascular disease - A cross-sectional study in healthy young adults. *PLoS ONE*, *9*(10). https://doi.org/10.1371/journal.pone.0108040

Pothuaud, L., Barthe, N., Krieg, M. A., Mehsen, N., Carceller, P., & Hans, D. (2009). Evaluation of the Potential Use of Trabecular Bone Score to Complement Bone Mineral Density in the Diagnosis of Osteoporosis: A Preliminary Spine BMD-Matched, Case-Control Study. *Journal of Clinical Densitometry*, *12*(2), 170–176. https://doi.org/10.1016/j.jocd.2008.11.006

Quantimetrix lipoprint system. (2005). *Quantimetrix Corporation*.

Quantrimetrix corporation. (2005). Lipoprint System. *User's Manual Clinical Research*.

Rapsomaniki, E., Timmis, A., George, J., Pujades-Rodriguez, M., Shah, A. D., Denaxas, S., … Hemingway, H. (2014). Blood pressure and incidence of twelve cardiovascular diseases: Lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people. *The Lancet*, *383*(9932), 1899–1911. https://doi.org/10.1016/S0140-6736(14)60685-1

Reis JP, von Mühlen D, Kritz-Silverstein D, Wingard DL, Barrett-Connor E. (2007). Vitamin D, Parathyroid Hormone Levels, and the Prevalence of Metabolic Syndrome in Community-Dwelling Older Adults. *Diabetes Care* 30:1549–1555.

Rizzo, M., Barbagallo, C. M., Severino, M., Polizzi, F., Onorato, F., Noto, D., Averna, R. M. (2003). Low-density-lipoprotein peak particle size in a Mediterranean population. *European Journal of Clinical Investigation*, 33(2), 126–133.

Rizzo, M., & Berneis, K. (2006). Low-density lipoprotein size and cardiovascular risk
assessment. *QJM - Monthly Journal of the Association of Physicians*, *99*(1), 1–14. https://doi.org/10.1093/qjmed/hci154

Robinson, J. G. (2012). What is the role of advanced lipoprotein analysis in practice? *Journal of the American College of Cardiology*, *60*(25), 2607–2615. https://doi.org/10.1016/j.jacc.2012.04.067

Roche package inserts for Ca, PO_4, Mg, ALP Glucose, TC, HDL, TG, P1NP and CTX. (2017). *Roche Diagnostics, Germany.*

Samitz, G., Egger, M., Zwahlen, M. (2011). Domains of physical activity and all-cause mortality: systematic review and dose–response meta-analysis of cohort studies. *Int J Epidemiol. 40*, 1382–1400.

Seibel, M. J. (2005). *Biochemical Markers of Bone Turnover Part I : Biochemistry and Variability Markus*. *26*(November), 97–122.

Sharrett, A.R., Ballantyne, C.M., Coady, S.A., Heiss, G., Sorlie, P.D., Catellier, D., Patsch, W: Atherosclerosis Risk in Communities Study Group. (2011). Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density subfractions: The Atherosclerosis Risk in Communities (ARIC) Study. *Circulation, 104,* 1108–1113.

Siemens package inserts for 25(OH)D and PTH. (2016) *Siemens Healthcare Diagnostics Inc., Germany*.

Silva, B. C., & Leslie, W. D. (2017). Trabecular Bone Score: A New DXA–Derived Measurement for Fracture Risk Assessment. *Endocrinology and Metabolism Clinics of North America*, *46*(1), 153–180. https://doi.org/10.1016/j.ecl.2016.09.005

Silva, B. C., Leslie, W. D., Resch, H., Lamy, O., Lesnyak, O., Binkley, N., … Bilezikian, J. P. (2014). Trabecular bone score: A noninvasive analytical method based upon the DXA image. *Journal of Bone and Mineral Research*, *29*(3), 518–530. https://doi.org/10.1002/jbmr.2176

Solomon, D. H., Avorn, J., Canning, C. F., & Wang, P. S. (2005). Lipid levels and bone mineral density. *American Journal of Medicine*, *118*(12), 1414.e1-1414.e5. https://doi.org/10.1016/j.amjmed.2005.07.031

Srikanthan, P., Horwich, T. B., & Tseng, C. H. (2016). Relation of Muscle Mass and Fat Mass to Cardiovascular Disease Mortality. *American Journal of Cardiology*, *117*(8), 1355–1360. https://doi.org/10.1016/j.amjcard.2016.01.033

Strong, A., Rader, D.J. (2010). Clinical Implications of Lipid Genetics for Cardiovascular Disease. *Curr Cardiovasc Risk Re*p, 4, 461–468.

Superko, M. (2009). Are advanced lipoprotein testing and subfractionation clinically useful. *Circulation*, *119*(17), 2383–2395. https://doi.org/10.1161/CIRCULATIONAHA.108.809582

Szulc P, Varennes A, Delmas PD, Goudable J, Chapurlat R (2010). Men with metabolic syndrome have lower bone mineral density but lower fracture risk–the MINOS study. *J Bone Miner Res* 25:1446–1454.

Tian H, Pan J, Qiao D, Dong X, Li R, Wang Y, Tu R, Abdulai T, Liu X, Hou J, Zhang G, Wang C. (2020). Adiposity reduces the risk of osteoporosis in Chinese rural population: the Henan rural cohort study. *BMC Public Health* 20:285.

Van, J., Pan, J., Charles, M.A., Krauss, R., Wong, N., Wu, X. (2007) Atherogenic lipid phenotype in a general group of subjects. *Archives of Pathology Laboratory Medicine*, 131(11):1679-85.

Vasikaran, S., Eastell, R., Bruyère, O., Foldes, A. J., Garnero, P., Griesmacher, A., … Kanis, J. A. (2011). Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: A need for international reference standards. *Osteoporosis International*, *22*(2), 391–420. https://doi.org/10.1007/s00198-010-1501-1

Veeranna, V., Pradhan, J., Niraj, A., Fakhry, H., & Afonso, L. (2010). Traditional Cardiovascular Risk Factors and Severity of Angiographic Coronary Artery Disease in the Elderly. *Preventive Cardiology*, *13*(3), 135–140. https://doi.org/10.1111/j.1751-7141.2009.00062.x

von Muhlen D, Safii, S, Jassal SK, Svartberg J, Barrett-Connor E. (2007). Associations between the metabolic syndrome and bone health in older men and women: the Rancho Bernardo Study. *Osteoporos Int* 18:1337–1344.

W Chun, W., Sano, A., Nishida, H., Urano, S., Sakagami, K. (1997). *Effect of cigarette smoking on lipid profile: Analysis of mass screening of 29 519 middle-aged Japanese men.* In: MD RL, MD JM, MD SN, MD RP, editors. In Proceedings of the 10th World congress on Tobacco or Health. 24th - 28th August 1997, Beijing, China. Ed Lu R, Mackay J, Niu S and Peto R. Springer. pp. 137–137.

Warburton, D. E. R., Nicol, C. W., Gatto, S. N., & Bredin, S. S. D. (2007). Cardiovascular disease and osteoporosis: Balancing risk management. *Vascular Health and Risk Management*, *3*(5), 673–689.

Wheater, G., Elshahaly, M., Tuck, S. P., Datta, H. K., & van Laar, J. M. (2013). The clinical utility of bone marker measurements in osteoporosis. *Journal of Translational Medicine*, *11*(1). https://doi.org/10.1186/1479-5876-11-201

Wong, S. K., Chin, K. Y., Suhaimi, F. H., Ahmad, F., & Ima-Nirwana, S. (2016). The Relationship between Metabolic Syndrome and Osteoporosis: A Review. *Nutrients* 2016, 8, 347.

World Health Organization. (1994). Assessment of fracture risk and its application to screening for postmenopausal osteoporosis- who technical report series 843. *WHO, Geneva 1994*, Vol. 25, pp. 1–130.

World Health Organization. (2007). Who Scientific Group on the Assessment of Osteoporosis At Primary Health. *World Health*, (May 2004), 1–13. https://doi.org/10.1016/S0140-6736(02)08761-5

World Health Organization. (2011). Global Health and Aging. In *World Health Organization*. Retrieved from https://www.who.int/ageing/publications/global_health.pdf

World Health Organization, (2018).Ageing and health. In *World Health Organization*.
Retrieved from https://www.who.int/news-room/fact-sheets/detail/ageing-and-health

Wright, R.S. (2013). Recent clinical trials evaluating benefit of drug therapy for modification of HDL cholesterol. *Curr Opin Cardiol, 28*, 389–398.

Yeap, S. S., Hew, F. L., Damodaran, P., Chee, W., Lee, J. K., Goh, E., Mumtaz, M., Lim, H. H., & Chan, S. P. (2016). A summary of the Malaysian Clinical Guidance on the management of postmenopausal and male osteoporosis, 2015. *Osteoporosis and sarcopenia*, *2*(1), 1–12.

Yeap, S. S., Thambiah, S. C., Samsudin, I. N., Appannah, G., Zainuddin, N., Mohamad-Ismuddin, S., Shahifar, N., Md-Said, S., Zahari-Sham, S. Y., Suppiah, S., & Hew, F. L. (2020). Different reference ranges affect the prevalence of osteoporosis and osteopenia in an urban adult Malaysian population. *Osteoporosis and sarcopenia*, *6*(4), 168–172. https://doi.org/10.1016/j.afos.2020.11.005

Zambahari, R., Rajadurai, J., Rahman, A.R.A., Omar, AF., Yip F.Y., Chandran A., Pheng C.S., Hassan H.A., Easaw M., Yusoff M.R., Jagan N., Lin O.M., Ahmad W.A.W., Hussein Z., (2017). Management of Dyslipidaemia 5th edition. *Clinical Practice Guidelines*, *17*(July), 1–107. https://doi.org/10.1136/hrt.2003.021287

Zhou, J., Zhang, Q., Yuan, X., Wang, J., Li, C., Sheng, H., … Li, H. (2013). Association between metabolic syndrome and osteoporosis: A meta-analysis. *Bone*, *57*(1), 30–35. https://doi.org/10.1016/j.bone.2013.07.013