

**KOREAN DIETARY PATTERNS AND THE PREVALENCE OF DIABETES, METABOLIC SYNDROME,  
AND SUBCLINICAL ATHEROSCLEROSIS**

by  
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## Abstract

This dissertation investigates the associations between dietary patterns, diabetes, metabolic syndrome, and subclinical atherosclerosis. The literature on Asian dietary patterns and cardiovascular health is limited.

For the first aim, we used a cross sectional design to identify and describe the major dietary patterns in 269,266 adult men and women who underwent a screening examination between January 2011 and December 2013 at the Kangbuk Samsung Total Healthcare Center in Seoul and Suwon, South Korea. Diet was assessed using a validated 103-item food frequency questionnaire. We used principal component analysis to derive three major dietary patterns. These patterns labelled as traditional Korean, modern Korean, and Western Korean, explained 20.7%, 11.4%, and 10.1%, of the total variation in daily dietary intakes. Traditional Korean dietary pattern was characterized by higher intakes of fruits, vegetables, soya and other beans, and fish. Modern Korean dietary pattern was characterized by higher intakes of noodles, raw or salted fish, shellfish, red meat, processed meat, poultry, soda, and alcohol. Western Korean dietary pattern was characterized by higher intakes of bread and cereals, milk and dairy products, snacks, and pizza, and lower intakes of alcohol, rice, and preserved vegetables.

For the second aim, we evaluated the associations between the major Korean dietary patterns and the prevalence of diabetes and metabolic syndrome in 220,979 screening participants without any histories of cardiovascular disease, cancer, diabetes, hypertension, and dyslipidemia. We did not find any significant associations between the traditional Korean pattern and the prevalence of diabetes and metabolic syndrome (both  $P > 0.05$ ). Higher adherence to modern Korean dietary patterns was significantly associated with 32% and 76%

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increase in odds of diabetes (adjusted odds ratio, aOR, P90 vs P10 = 1.32; 95% CI 1.13, 1.55) and metabolic syndrome (aOR P90 vs P10=1.76; 95% CI 1.64, 1.88), respectively. Higher adherence to Western Korean dietary patterns was significantly associated with 22% and 27% decrease in odds of diabetes (aOR P90 vs P10 = 0.78; 95% CI 0.67, 0.91) and metabolic syndrome (aOR P90 vs P10=0.73; 95% CI 0.69, 0.78), respectively. Using those with no metabolic syndrome criteria as the base group, the prevalence ratio of three to five metabolic syndrome criteria comparing the 90<sup>th</sup> to the 10<sup>th</sup> percentiles of modern and Western Korean dietary pattern scores was 2.14 (95%CI 2.00, 2.30) and 0.67 (0.63, 0.72), respectively.

For the third aim, we evaluated the association between the major Korean dietary patterns and prevalent subclinical atherosclerosis. The study population consisted of screening participants who had coronary artery calcium score and diet measured during the same screening visit. We included 27,028 screening participants without any histories of cardiovascular disease, cancer, diabetes, hypertension, and dyslipidemia. We failed to find any significant associations between the three major Korean dietary patterns and the prevalence of subclinical atherosclerosis (all  $P > 0.05$ ).

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## Preface

This dissertation is the culmination of my doctoral studies in the Department of Epidemiology at the Johns Hopkins Bloomberg School of Public Health. This research is a result of an ongoing project on the Kangbuk Samsung Health Study (KSHS) Cohort and was only possible with important contributions from my advisor, co-advisors, co-investigators, and the research team. The general aim of this dissertation is to better understand the role of different diets in maintaining good cardiovascular health.

The first chapter is an introduction to coronary heart disease, coronary artery calcium, and diet. This chapter includes a critical review of the current literature on the associations of diet with coronary heart disease and its risk factors. The second chapter identifies and describes the major dietary patterns in the KSHS cohort. The third chapter then proceeds with investigating the associations between the derived dietary patterns and the prevalence of two risk factors of subclinical atherosclerosis - diabetes and metabolic syndrome. The fourth chapter investigates the association between Korean dietary patterns and prevalent subclinical atherosclerosis that was measured using coronary artery calcium scores. The final chapter provides an overview of the research findings and suggest future research directions.

## Acknowledgements

My PhD has been an interesting journey. The people I met during this journey have enriched my being and taught me more than I anticipated, in ways more diverse than I expected, with more altruism than is required.

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No PhD journey can be complete without the comradery of fellow students, peers and friends including the doctoral seminar group of 2010-2011. I am especially lucky over the years to have interacted with Swaroop Vedula, Yiyi Zhang, Di Zhao, and Edward Hammond. Swaroop has been a dear friend from the time I started my MPH in 2004 and has always been there in times of need. I have also been lucky to have been exposed to the positive energy given out by Yi, Di, and Edward.

These past few years spent on my PhD is but a part of my lifelong scholarly endeavor. I am thankful for the opportunity and support provided by the Department of Social and Preventive Medicine (SPM) and the Faculty of Medicine (FOM) at the University of Malaya, Malaysia. I would like to acknowledge my gratitude to Dato' Dr. Mohd Amin Jalaludin, Dato' Dr. Sirajoon Noor Ghani, Dr. Awang Bulgiba, Dr Maznah Dahlui and all the other faculty and staff from the SPM department. I am thankful to Dato' Dr. Amin and Dato' Dr. Ghani, who were the Dean and the Head of Department, respectively, for offering me an opportunity to contribute to University of Malaya. I am thankful to Dr. Awang who has been an excellent mentor, and Dr. Maznah for her continuing support over these years.



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<i>Om asato maa sad gamaya,</i>	O Supreme Being, lead us from untruth to truth,
<i>Tamaso ma jyotir gamaya,</i>	Lead us from darkness to light,
<i>Mrityor ma mritam gamaya,</i>	Lead us from death to immortality.
<i>Om shaantih shaantih shaantih.</i>	Om, peace, peace, peace.

*Brhadaranyaka Upanishad — I.iii.28*

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## 1. INTRODUCTION

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### 1.1. Overview and specific aims

The relative improvement of life expectancy in the United States in recent decades has been modest compared to the rapid rise in health expenditure. The United States ranks 27th among the OECD countries in life expectancy at birth despite spending two and a half times (US\$8,508) the Organization for Economic Co-operation and Development (OECD) average per capita on healthcare cost.<sup>1</sup>

Diet plays an important role in shaping population health. Analyzed as a cluster of 14 different dietary components, diet was associated with 26% of deaths and 14% of DALYS in the United States.<sup>2</sup> However, a common critique of nutritional research is the difficulty in translating results to effective population interventions.<sup>3</sup> The role of diet as an exposure for health is more complex than individual nutrients acting in isolation. Dietary patterns as an exposure construct acknowledges the complex interactions between the different nutrients and foods in our diet.<sup>4,5</sup> Dietary pattern research in Western countries have resulted in successful implementation of intervention strategies such as the Dietary Approaches to Stop Hypertension (DASH) and Mediterranean type diet.<sup>6-14</sup> However, both DASH and the Mediterranean diets were developed in western populations, which typically consumes higher fat and lower carbohydrate compared to Asians. The literature on dietary patterns in the various Asian countries and its effect on health is more limited.<sup>15-19</sup>

Using a cross sectional study design, we will identify underlying major dietary patterns and assess its associations with prevalent diabetes, metabolic syndrome and subclinical

atherosclerosis in adult Koreans who underwent a comprehensive screening examination at the Kangbuk Samsung Total Healthcare Center in Seoul and Suwon, South Korea,

***Specific Aim 1: To identify and describe the major dietary patterns in a large Korean cohort***

We will identify and describe the major dietary patterns in all participants from 2011 to 2013 using principal components analysis with orthogonal rotation procedure varimax.<sup>20</sup> We will retain the appropriate number of factors based on the Eigen value, Catel's Scree plot (Figure 1), and Velicer's Minimum Average Partial test.<sup>21</sup> We will further describe the characteristics of those with high adherence to these different patterns.

***Specific Aim 2: To evaluate the associations of dietary patterns with the prevalence of diabetes and metabolic syndrome in a large Korean cohort***

Among participants without a history of CVD, cancer, hypertension, diabetes, and dyslipidemia, we will investigate whether high adherence to different Korean dietary patterns are associated with the prevalence of diabetes and metabolic syndrome. We will further evaluate the associations between dietary patterns and different metabolic syndrome criteria.

***Specific Aim 3: To evaluate the association between dietary patterns and the prevalence of subclinical atherosclerosis, measured using coronary artery calcification, in a large Korean cohort***



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The study population for this analysis will be participants who had a coronary artery calcium measurement and completed a food frequency questionnaire. We will also exclude those with any history of CVD, cancer, hypertension, diabetes, or dyslipidemia. We will investigate whether high adherence to different dietary patterns are associated with the prevalence of subclinical atherosclerosis measured using coronary artery calcification.

## 1.2. Coronary heart disease and atherosclerosis

Ischemic heart disease and cerebrovascular disease are responsible for 7.4 (13.2%) and 6.7 (11.9%) million deaths worldwide 2012.<sup>22</sup> Despite a decline in the United States since 1968, major cardiovascular disease remains the leading cause of death accounting for 778,503 (30.9%) of all deaths in 2011.<sup>23, 24</sup> Ischemic heart disease was the leading contributor to years of life lost (15.9% of all years of life lost) and disability-adjusted life-years in the United States in 2010.<sup>25</sup> The 2010 National Health Interview Survey (NHIS) estimated that among the US population aged 18 years and above, 6.7% had a history of either coronary heart disease, angina pectoris, or heart attack.<sup>26</sup> According to the 2014 Update on Heart Disease and Stroke of the American Heart Association (AHA), the prevalence of coronary heart disease, myocardial infarction, and angina pectoris, in 2010 was 15.4, 7.6, and 7.8 million, respectively.<sup>27</sup>

The underlying pathology of coronary heart disease is atherosclerosis, characterized by the development of atherosclerotic plaques, which evolves without any symptoms for decades. There is chronic endothelial injury and accumulation of lipoproteins in the vessel wall. The endothelial dysfunction leads to monocyte adhesion and migration of smooth muscle cells from the media to the intima, followed by macrophage activation. The chronic development of fatty streaks and fibro fatty atheroma usually results in a coronary complication.<sup>28</sup> Atherosclerosis is divided into 6 different types.<sup>29, 30:</sup>

- Type I lesion: lipoprotein accumulation accompanied by macrophage activation and formation of isolated foam cells.

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- Type II lesion (fatty streaks): development of fatty streaks containing foam cells and lipid-containing smooth cells.
- Type III lesion: characterized by increasing amounts of extracellular lipid and development of pre-atheroma lesions.
- Type IV lesion (atheroma): characterized by extracellular lipid accumulation and formation of a lipid core. Type IV lesions result in thickening of the arterial wall but do not decrease the lumen size.
- Type V lesion (Fibro-atheroma): characterized by the development of fibrous tissue around the lipid core and calcification of the lesions.
- Type VI lesion (complicated lesion): characterized by rupture and subsequent hematoma or thrombosis of the vessel. There is increased calcification during this stage.

Type I – III lesions are classified as early stage lesions and type IV – VI lesions are classified as advanced lesions. Subjects with lesion type V are frequently asymptomatic and difficult to detect.

### 1.3. Calcium coronary scoring

#### *Diagnostic imaging of coronary artery calcium*

Computer tomography (CT) imaging techniques have improved since the detection of calcium deposits in 1970. The current generation of electron beam computed tomography (EBCT) and multi-detector computer tomography (MDCT) produce better image quality at lower radiation doses compared to previous generation.<sup>31-33</sup>

EBCT uses scanning electron beam technology instead of X-ray tubes and captures high definition images at a rate of 100-150 ms per image while limiting its slice thickness to 1.5 mm. MDCT scanners are able to produce image slices of 0.5-0.75 mm using rotating X-ray tubes at rates of 260-350 ms per image.<sup>33</sup> The estimated radiation dose from one session of calcium scoring using EBCT was 1.0 mSv for males and 1.3 mSv for females, and 1.5 mSv for males and 1.8 mSv for females with MDCT.<sup>34</sup> Advancement in CT imaging, including reducing the tube voltage, is capable of reducing the estimated radiation dose to < 1.0 mSv.<sup>35, 36</sup> For comparison purposes, this dose is similar to that of one mammographic examination (0.75 mSv), dental x-ray (0.7 mSv), or abdominal x-ray (1 mSv).<sup>33</sup>

#### *Measurement of coronary artery calcium*

The Agatston score is a common metric to quantify coronary artery calcium (CAC). Using an ultrafast CT scanner among 584 high risk subjects, Agatston et al captured 3-mm image slices at 20 sequential levels.<sup>37</sup> They set a threshold of 130 Hounsfield units (HU) within a 1mm<sup>3</sup> area to eliminate imaging noise. Using the density of the calcified lesions, they calculated an overall

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score by summing the individual scores of the 20 levels. Each level density score was based on the largest lesion and was categorized as 0 (<130 HU), 1 (130-199 HU), 2 (200-299 HU), 3 (300-399 HU) or 4 ( $\geq$  400 HU). The level score was then obtained by multiplying the level score by the lesion area.

Other methods of calcium scoring are calcium volume, calcium concentration, and mineral mass. The calcified plaque volume score for each plaque are estimated by multiplying the number of voxels ( $V_n$ ) with the voxel volume ( $V_v$ ,  $\text{mm}^3$ ). The calcium concentration are estimated by measuring the average CT attenuation in calcified plaques. Mineral mass (mg) are determined by multiplying the calcium concentration ( $\text{mg}/\text{cm}^3$ ) by the calcified volume ( $\text{cm}^3$ ). Moselewski et al compared these different methods for quantifying coronary calcium but found no incremental value of calcium concentrations or mineral mass compared with either the Agatston score or the calcified plaque volume.<sup>38</sup>

### *Coronary artery calcium and coronary heart disease*

Coronary calcium was recognized as a feature of atherosclerosis Type V and VI lesions.<sup>30</sup> Though subjects with Type V lesions are frequently asymptomatic, lesion progression, including complications such as surface defects, hematoma, and thrombus formation, increases calcium in the coronary arteries. This calcification process is postulated to be part of a larger inflammatory response to atherosclerotic lesions.<sup>39, 40</sup>

The Multi Ethnic study of Atherosclerosis (MESA) study found that CAC incidence was associated with age, sex, ethnicity, BMI, LDL-C, TG, diabetes and family history of heart attack.

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CAC progression in MESA was associated with age, sex, ethnicity, BMI, systolic blood pressure, diabetes and family history of heart attack. The Epidemiology of Coronary Artery Calcification study (ECAC) found that CAC progression was associated with age, sex, waist to hip ratio, LDL-C, hypertension.<sup>41,42</sup> A study of 5,420 asymptomatic Koreans from 2003 to 2008 found that the adjusted prevalent odds of CAC were higher among males, older subjects, those with a higher pulse pressure, those with higher HbA1C and those who were obese.<sup>43</sup>

A study by Budoff et al from 1998 to 2002 on 16,560 asymptomatic men and women aged  $\geq 35$  years old found that CAC prevalence was higher among males and among non-Hispanic whites (Caucasian male 78%, Hispanic male 72%, African American male 69%, Asian male 69%; Caucasian female 44%, Hispanic female 34%, African American female 36%, Asian female 42%).<sup>44</sup> A similar distribution of CAC prevalence was observed among MESA subjects at baseline (White men 70%, African American men 52%, Hispanic men 56%, Chinese men 59%; White women 45%, African American women 36%, Hispanic women 35%, Chinese women 42%).<sup>45</sup> The lower prevalence of CAC among African American compared to Non-Hispanic White may be an artifact of a shorter duration of disease (due to increased mortality) and of more vulnerable plaques (with less calcification).

In MESA, Chinese were 30% less likely to develop incident CAC compared to whites over an average follow up time of 2.4 years. The median (IQR) annual change in calcium scores (AU) was 20.5 (5.3, 62.4) for whites, 17.9 (4.6, 49.5) for African Americans, 15.0 (3.6, 45.6) for Hispanics, and 12.7 (3.4, 40.2) for Chinese.<sup>42</sup>

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A study of 14,812 asymptomatic subjects, followed for a mean duration of 6.8 years, concluded in 2007 that ethnicity was associated with CAC.<sup>46</sup> Life expectancy for 40 year olds was disproportionately shortened among those with CAC scores of  $\geq 100$  to  $\geq 1000$  for African American (8.3 to 15.0 years), Asians (2.6 to 12.0 years), and Hispanics (6.3 to 15.0 years) compared to NHW (2.0 to 5.9 years). Nasir et al postulated that more inflammation might be present at similar levels of CAC among the ethnic minority. This might lead to different atherosclerosis plaques characteristics for the different ethnicities at similar levels of CAC.

Subjects with an absent or low CAC score are typically at low risk of future coronary events. However, those with a score of 1-10 had three times the risk compared to those with a zero CAC score for future coronary events.<sup>47</sup> In a systematic review by Rumberger of 49,647 asymptomatic individuals in eight studies, those with higher CAC scores were consistently at higher risk of future cardiovascular outcomes (a pooled estimate was not calculated due to substantial heterogeneity in protocols and analytical methods).<sup>48</sup>

#### 1.4. Diet and coronary heart disease

Carbohydrates, protein, alcohol, and fats, are the main sources of energy in our diet and provides 4, 4, 7, and 9 calories of energy per gram, respectively. When energy consumption is constant, a reduction of any macronutrient will result in an increase other components. The National Academy of Science in 2005 recommended that the acceptable range of fat, protein, and carbohydrate intake was 20-35%, 10-35% and 45 to 65% of total energy.<sup>49</sup>

The Dietary Guidelines for Americans 2010, by the US Department of Agriculture (USDA) and Department of Health and Human Services (DHHS), stressed the importance of maintaining calorie balance with physical activity and to consider specific types of macronutrient consumed.<sup>50</sup> Among the key recommendations of this guideline were:

- Limiting saturated fat intake to 10% of total energy.
- Limiting dietary cholesterol to less than 300mg daily.
- Limiting trans-fatty acid consumption to a minimum.
- Limiting the intake of foods high in simple carbohydrates and solid fat (solid fats are fat that are solid at room temperature and are made up primarily of saturated fat).
- A general recommendation to reduce sodium intake to 2.3 gm (6 gm salt) per day. Anyone aged  $\geq 51$  years, with diabetes, hypertension, or chronic kidney disease and all African Americans were to limit sodium intake to 1.5 gm (3.75 gm salt) per day.

*Dietary intake of Americans and Koreans*



## INTRODUCTION

The dietary information of Americans aged  $\geq 20$  years old was collected in the NHANES 2007-2008 cycle with two 24-hour recalls using automated multiple-pass methods. The average American diet consisted of 34% total energy (TE) total fat, 11% TE Saturated Fatty Acids (SFA), 47-50% TE carbohydrate, and 16-18% TE protein.<sup>51</sup> For comparison, the dietary intake of Koreans consisted of 18 %TE total fat, 67 %TE Carbohydrate, and 15 %TE protein.<sup>52</sup> These Korean estimates were based on a 24 hour diet recall collected during the 2001 Korea Health and Nutritional Examination Survey (KHANES).

Another KHANES analysis had used data from 1998, 2001 and 2005 among subjects aged  $\geq 20$  years. Accounting for the diet transition, the dietary intake of Koreans with a traditional diet pattern consisted of 13 %TE total fat, 73 %TE Carbohydrate and 14 %TE protein. The dietary intake of Koreans with a modified diet pattern consisted of 22 %TE total fat, 62 %TE Carbohydrate and 16 %TE protein.<sup>53</sup> Two major dietary patterns were identified and labelled as traditional and modified. The traditional Korean diet pattern was characterized by higher intakes of white rice, legumes, vegetables, kimchi (preserved vegetables) and seaweeds. The modified pattern was characterized by higher intakes of other grains, noodle dumplings, floured bread, pizza, hamburgers, cereals snacks, potatoes, sugared sweets, nuts, fruits, meat products, eggs, fish, dairy products, oils, beverages and seasoning. The modified pattern was more likely to be consumed by Koreans who were younger, resided in metropolitan areas, with higher education and income.

*Dietary fat*

## INTRODUCTION

Dietary fatty acids are classified based on its chemical characteristics into saturated, monounsaturated, or polyunsaturated fatty acids. Saturated fatty acids (SFA) consist of fatty acid chains with carbon atoms fully saturated by hydrogen atoms with no double bonds. Examples of saturated fatty acids include myristic acid (C12:0), lauric acid (C14:0), palmitic acid (C16:0) and stearic acid (C18:0).

The mean intake of SFA among Americans  $\geq 20$  years old is 31.6 gm/day (11% TE) for males and 22.3 gm/day (11% TE) for females and is highly prevalent in foods containing solid fats such as coconut oil, palm kernel oil, butter and animal fat.<sup>50</sup> Common sources of stearic fatty acid in the American diet are grain-based desserts (8%), regular cheese (6%), sausage, franks, bacon and ribs (6%), chicken and chicken mixed dishes (6%), pizza (6%) and burgers (5%). Common sources of saturated fatty acid other than stearic acid in the American diet are regular cheese (9%), dairy desserts (6%), pizza (6%), and chicken and chicken mixed dishes (5%).<sup>54</sup>

Mono unsaturated fatty acids (MUFA) consist of a fatty acid molecule with a single double bond. The most common MUFA is oleic acid (C18:1n-9) that is an 18 carbon chain with one double bond located at the 9<sup>th</sup> carbon-carbon bond from the methyl end. The mean intake of MUFA among Americans  $\geq 20$  years old is 35.6 gm/day (13% TE) for males and 24.4 gm/day (12% TE) for females. MUFA is present in vegetable oils such as olive, canola, safflower, sunflower, palm oil and in meats.<sup>50, 55, 56</sup> Common sources of MUFA in American diets are grain based desserts (9%), chicken dishes (8%), sausage, franks, bacons, and ribs (6%), nuts/seeds and nuts/seeds mixed dishes (6%) and pizza (5%).<sup>57</sup>

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Polyunsaturated fatty acids (PUFA) are fatty acid molecules with multiple double bonds. PUFA are commonly classified as omega-3 (n-3) and omega-6 (n-6) based on the position of the double bond with respect to the n-terminal carbon atom. Linoleic acid (LA, 18:2,n-6) is the initial fatty acid of the n-6 family, and can be converted to arachidonic acid (20:4,n-6) and its derivatives. The building block of the n-3 family is  $\alpha$ -linolenic acid (ALA, 18:3,n-3), which is converted by desaturation and elongation to eicosapentanoic (EPA, 20:5,n-3), docosapentanoic (DPA, 22:5,n-3) and docosahexanoic acids (DHA, 22:6,n-3).<sup>58, 59</sup> Linoleic and  $\alpha$ -linolenic acids are considered essential fatty acids because of the human body's inability to create them. With inefficient (5%) internal conversion of ALA to EPA and DHA, dietary intake of foods rich in these long chain PUFA may be needed to maintain higher levels of EPA and DHA.<sup>60</sup>

Common sources of ALA are flaxseed, walnut, rapeseed, soya bean, and oats.<sup>61</sup> The main source for long chain PUFAs are from marine oils whereas DHA from algae source is also commercially available. Common source of n-3 PUFA in the American diet are salad dressing (10%), chicken dishes (7%), grain based desserts (6%), fish and seafood other than tuna and shrimp, and fish mixed dishes (6%) and pizza (5%).<sup>57</sup>

Unsaturated fatty acids are usually liquid oils at room temperature and mostly occur as cis isomers. Trans-isomers of these fatty acids occur naturally through rumination in animals and artificially from food processing techniques of hydrogenation. The structure of trans-fatty acid is functionally closer to that of saturated fatty acid rather than cis isomers of unsaturated fatty acids. Though artificial sources of trans-fat in the diet chain have been reduced with regulation, natural forms still persist mainly through milk and dairy products.

### *Current evidence on dietary fat and risk factors for coronary heart disease*

Saturated fat increases the levels of larger sized low density lipoproteins (LDL), smaller very low density lipoproteins (VLDL), and high density lipoprotein (HDL).<sup>62, 63</sup> A review by Mensink et al in 2003 of 60 trials including 1672 participants summarized that the substitution of carbohydrate intake with saturated fat resulted in an increase of LDL and HDL but there was substantial heterogeneity based on the different sub types of saturated fat intake.<sup>64</sup> However, the replacement of saturated fat in the diet with simple carbohydrate resulted in increased levels of triglycerides, small dense LDL, and decreased levels of HDL.<sup>64, 65</sup> There is no conclusive evidence linking saturated fat with either inflammation, blood pressure, endothelial function, arterial stiffness or insulin resistance.<sup>66</sup>

There is no conclusive evidence linking increased levels of MUFA intake with an increase of serum lipoproteins.<sup>56, 64, 67, 68</sup> A pooled analysis by Mensink et al in 2003 estimated that a 10% energy substitution of carbohydrates with MUFA was associated with a decrease of 0.06 mmol/L in total cholesterol, 0.09 mmol/L in LDL, 0.2 mmol/L of triglycerides and an increase of 0.08 mmol/L in HDL. However, an updated review by Schwingshackl et al in 2011 that included 12 studies with 1,990 participants contrasted interventions high in MUFA intakes to those with low intakes of MUFA. The pooled results found no beneficial association of a high MUFA intervention on total cholesterol, LDL, HDL, triglycerides and C-reactive protein (CRP). The pooled analysis estimated that those on the high MUFA arms had lower systolic (SBP)

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(Weighted Mean Difference, WMD 2.26 mmHg; 95% CI 4.28, 0.25) and diastolic (DBP) (WMD 1.15 mmHg; 95% CI 1.96, 0.34) blood pressures.

The link between fat of marine origin and coronary heart disease was highlighted in the early 1900s with studies on the dietary habits Eskimos.<sup>69</sup> Dietary intakes of west coast Greenlandic Eskimos, high in marine fat, had lower levels of serum LDL and triglycerides compared with Danish controls.<sup>70</sup> Dietary intake of long chain PUFA is associated with a decrease in serum triglyceride and VLDL, accompanied by an increase of larger sized HDL and LDL molecules.<sup>71-73</sup> The postulated mechanism is via reduced levels of sterol regulatory element binding protein (SREBP), stearoyl-CoA desaturase (SCD) and non-esterified fatty acids (NEFA).<sup>74</sup>,<sup>75</sup>. Higher intakes of n-3 long chain PUFA have been associated with decreasing levels of inflammation, heart arrhythmia, arterial stiffness, blood pressure, thrombotic events and improved endothelial function.<sup>58, 59, 61, 75-81</sup> It is suggested that intake of n-3 long chain PUFA increases the activity of PPAR $\alpha/\gamma$ , decreases the activity of nuclear factor  $\kappa\beta$  (NK- $\kappa\beta$ ) and increases levels of the different resolvins and the 3 and 5 series of prostaglandin, prostacylin and thromboxane. The intake of ALA may be beneficial through its conversion to longer chain PUFA and by competing with linoleic acid for the desaturase and elongase enzymes. This enzyme competition reduces production of arachidonic acid and decreases series 2 and 4 of prostaglandins, prostacylin and thromboxane.

The intake of long chain n-3 PUFA was incorporated into the AHA guidelines, as one of the recommendations for lipid management, in the secondary prevention of coronary heart disease since 2006.<sup>82</sup> However, the literature have not been consistent with substantial

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heterogeneity in the design, doses, and types of n-3 PUFA (alpha linolenic acid versus long-chained polyunsaturated fatty acid) investigated.<sup>83-89</sup>

### *Current evidence on dietary fat and coronary heart disease*

In a large study of female nurses, a significant decrease in risk of coronary heart disease was observed with isocaloric substitution of trans-fat with either saturated fat or non-hydrogenated unsaturated fat. Isocaloric substitution of either carbohydrates, trans-fat, or saturated fat with polyunsaturated fat resulted in a significant decrease in risk of CHD. No significant association was seen with substitution of either carbohydrate or saturated fat with mono unsaturated fat.<sup>90</sup> Reviews have shown that increased intakes of trans-fat is associated with a higher TC/HDL ratio, higher LDL and lower HDL.<sup>66, 91</sup> Pooling of four studies examining the association between dietary intake of trans-fat and CHD risk summarized that every 2% TE increase in trans-fat was associated with an estimated 23% increase risk of CHD events (RR 1.23; 95% CI 1.11, 1.37).<sup>92</sup>

Hooper et al limited their review in 2011 to dietary fats and cardiovascular disease in randomized controlled trials. They concluded that dietary saturated fat reduction through either advice, supplement or provided meals, decreases the risk of cardiovascular events by 14% (RR 0.86; 95% CI 0.77 to 0.96; I<sup>2</sup> = 50%; involving 65,508 subjects).<sup>93</sup> This pooled estimate was problematic, as it assumes absolute dietary saturated fat reduction and dietary fat modification interventions are similar. The high between study heterogeneity indicated that 50% of the variation in the various estimates was due to between study factors. They did use

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meta-regression to explore this heterogeneity but the analysis was under powered due to the limited number of studies.

A review of prospective cohort studies in 2010 by Siri-Tarino et al included 16 studies on CHD with 304,485 participants and 8,644 CHD outcomes. They pooled the final multivariate adjusted model estimates comparing the CHD outcomes between those on higher intakes with those with lower intakes of saturated fat. Higher levels of saturated fat intake was not significantly associated with higher risk of outcomes (Pooled Risk Ratio 1.07;95% CI 0.96, 1.19;  $I^2 = 41\%$ ).<sup>94</sup> However, one critique of this analysis has been that one-half of the included studies controlled for serum cholesterol levels in their multivariate estimates.<sup>95</sup> The adjustment for an intermediate would have biased the results towards the null.

The review by Jakobsen et al in 2009 used a fat substitution model and reviewed 11 prospective studies including two randomized primary prevention studies. [jakobsen] Their pooled analysis included 344,696 participants with 5,249 coronary events and 2,155 coronary deaths. A 5% lower energy intake of saturated fat intake replaced by PUFA resulted in 13% decrease hazard of coronary events (Hazard ratio, HR 0.87; 95% CI 0.77, 0.97;  $P_{\text{Heterogeneity}}=0.70$ ) and a 26% decrease in the hazard of coronary deaths (HR 0.74; 95% CI 0.61, 0.89;  $P_{\text{Heterogeneity}}=0.40$ ). There was no benefit of substituting saturated fat intake with mono unsaturated fat. Substituting saturated fat intake with carbohydrate was associated with an increased risk of coronary events (Hazard ratio of a 5% lower energy intake of saturated fat intake replaced by carbohydrates = 1.07; 95% CI 1.01, 1.14;  $P_{\text{Heterogeneity}}=0.51$ ).

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A review by Skeaf in 2009 included 28 cohort studies with 280,000 participants and 6,600 CHD deaths. This pooled analysis estimated that a 5% total energy increase of saturated fats result was not significantly associated with either CHD mortality (RR 1.11; 95% CI 0.75, 1.65) or CHD events (RR 1.03; 95% CI 0.87, 1.22). Similarly, a 5% increase in total energy of MUFA had no significant benefit on either CHD mortality (RR 0.92; 95% CI 0.0.64, 1.34) or CHD events (RR 0.93; 95% CI 0.77, 1.12). A 5% increase in energy intake due to PUFA resulted in a decreased risk of CHD events (RR 0.84; 95% CI 0.70, 1.00) but not CHD mortality.<sup>96</sup>

Recent reviews on the association between saturated fat intake and coronary heart disease have arrived at different conclusions.<sup>93, 94, 96, 97</sup> One reason could be due to the heterogeneous association of the different saturated fatty acids. Micha and Mozaffarian reviewed the association of SFA on CVD risk in 2010, and specifically looked at specific subtypes of the SFA.<sup>66</sup> They highlighted the differential association of stearic acid (C18:0). Replacement of carbohydrates with myristic acid (C12:0), lauric acid (C14:0), palmitic acid (C16:0) resulted in higher levels of LDL and HDL-C. However the replacement of carbohydrate with stearic acid did not have much of an association on LDL-C and HDL-C levels. Thus, further sub classifying saturated fatty acid intake is a better analytical approach.

### *Limitations of current evidence on dietary fat and coronary heart disease*

A major limitation of these nutrient studies is that effect of dietary fat may be heterogeneous depending on the overall diets being consumed. This is due to the simplification of complex dietary intakes into simpler nutrient components, which do not account for how the



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foods are prepared, delivered, and consumed. Analyses ignoring the larger role of diet-nutrient interactions have limited generalizability. A common critique of nutritional research is the difficulty of translating its results into effective population interventions.<sup>3,98</sup>

An example of nutrient based policy having unintended results was the health promotion campaign for a low fat diet.<sup>99</sup> The food industry reacted to this campaign by marketing low-fat products that were high in processed carbohydrates, saturated fat and trans-fat. The public adoption for this campaign temporally coincided with an alarming rise of obesity prevalence. In addition, two trials attempting to limit fat intake showed no significant associations between low fat dietary interventions and cardiovascular disease.<sup>100, 101</sup> The Food and Drug Administration (FDA) is now proposing to remove the reporting of total fat as a mandatory requirement of the nutrition label.<sup>102</sup> As messaging of dietary advice evolves, advice based on dietary patterns rather than specific nutrient may be more robust compared to advice based on nutrients.

Other limitations of the current evidence include: 1) Heterogeneity among pooled studies, possibly to varying amounts of residual confounding; 2) The use of different exposure classification and reference exposure in literature leads to heterogeneous comparisons; 3) The use of absolute dietary exposure reduction compared to using a substitution model; 4) The high correlation between different nutrients makes it difficult to estimate independent effects; 5) Measurement error the exposure that introduces biased estimates, loss of power and possible masking of non-linear associations.<sup>103</sup>

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### *Dietary patterns*

The role of diet as an exposure for health is indeed more complex than individual nutrients acting in isolation. Dietary patterns acknowledges the complex interactions between the different nutrients and foods in our diet.<sup>4,5</sup> Dietary patterns estimate the cumulative effect of multiple different foods, and these associations may have larger effect sizes compared to analyzing single nutrients. Results from dietary pattern research are also easily translatable to dietary interventions. Parikh *et al* broadly classified the different types of diets as low-carbohydrate diets, glycemic-index diets, Mediterranean diet, Dietary Approaches to Stop Hypertension (DASH).<sup>104</sup>

### *Dietary patterns and coronary heart disease*

#### *Low carbohydrate diets*

A feature of low carbohydrate diet is the drastic reduction of total daily energy from all carbohydrates leading to gluconeogenesis from the body's fat storage. Prolonged gluconeogenesis leads to ketosis and ketonuria, which is accompanied by high urine output and rapid loss of weight. The long term effect of this diet has not been sufficiently evaluated. The total daily energy intake of carbohydrate is replaced by protein or fat. Examples of very low carbohydrate diet include the Atkin's diet (68% fat, 27% protein, 5% carbohydrate), Protein power (54% fat, 26% protein, 16% carbohydrate), and zone diet (30% fat, 40% protein, 30% carbohydrates).<sup>104</sup>

A review by Bravata *et al* of 107 low carbohydrate diets including 3,268 participants concluded that there was insufficient evidence of harm or benefit from these diets.<sup>105</sup> Weight

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loss in these studies were associated with increased study duration and decreased caloric intake. However, carbohydrate content was not associated with weight loss.

Bueno *et al* reviewed 13 randomized control trials, with a total 1,577 participants, and concluded that very low carbohydrate ketogenic diet compared to low fat diet was associated with a greater weight loss.<sup>106</sup> However, a major problem of these trials were drop outs that was equally high in studies with follow-up duration of 12 months (n=8 studies; 38.3% dropout), 15 months (n=1 study; 41.7% dropout), and 24 months (n=4 studies; 34.3% dropout). Dropouts following randomization threatens comparability of interventions and may introduce confounding.

### *High protein versus low protein diets*

Schwingshackl and Hoffman reviewed 15 randomized controlled trials comparing high protein ( $\geq 25\%$  total energy intake) with low protein ( $\leq 20\%$  total energy intake) within a low fat diet ( $\leq 30\%$  total energy intake). With total fat being constant, these diets substituted carbohydrates with proteins. They failed to find any significant associations between high protein dietary intervention and weight, waist circumference, fat mass, total cholesterol, LDL-C, HDL-C, triglycerides, fasting glucose, and HbA1c and concluded further research was needed. Though this review had a total of 15 studies with 1,990 participants but the comparison of the individual markers were based on smaller sample sizes.

### *Glycemic-index diets*

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Using the post prandial blood glucose levels after 50 gm carbohydrate portions of different food items, Jenkins et al defined glycemic index as the proportion of a specific food item's area under the curve (AUC) compared to the glucose AUC.<sup>107</sup> A low glycemic index diet does not restrict carbohydrates and contains higher amounts of complex carbohydrates and lower amounts of processed or simple carbohydrates. A lower glycemic index diet is associated with slower absorption of glucose with more sustained peaks and lower likelihood of rebound hunger.

A review by Schwingshackl and Hoffman included 14 randomized controlled trials (RCT) published between 2005 and 2011 with a total of 2,344 participants.<sup>108</sup> They concluded that a low compared with high glycemic index/load diet was associated with lower amounts of serum CRP (Weighted Mean Difference, WMD -0.4 mg/dL; 95% CI -0.8, -0.1), serum insulin (WMD among non-diabetics -5.2 pmol/L; 95% CI -9.0, 1.3) and fat free mass (WMD -1.0 kg; 95% CI -1.7, -0.3). However, they did not find sufficient evidence of an association with weight, waist circumference, total cholesterol, LDL-C, HDL-C, triglycerides, and fasting glucose ( $P > 0.05$ ). Furthermore, a review by Goff et al that included RCTs of shorter duration concluded that low compared to high glycemic index diets were significantly associated with reductions in total cholesterol and LDL-cholesterol in shorter duration studies (0-8 weeks) but the pooled estimates of longer term trials were attenuated and non-significant.<sup>109</sup>

Another review by Ma *et al* included 229,213 participants from 14 cohort studies that were published between 2000 and 2011.<sup>110</sup> They concluded that the pooled RR of fatal and non-fatal cardiovascular disease comparing highest and lowest categories was 13% higher for

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glycemic index (RR=1.13; 95% CI 1.04, 1.22) and 23% higher for glycemic load (RR=1.23; 95% CI 1.18, 1.55).

### *Mediterranean diet*

Keys in his seven countries comparison had summarized the diets of five cohorts in the Mediterranean as having higher intakes of olive oil (15-30% total energy intake), wine (8-20% total energy intake), fresh vegetables and fruits compared to the other cohorts.<sup>111</sup> He also noted that the 15-year CHD age standardized death rates of the Mediterranean sub population was 0.43 times that of the non-Mediterranean European population (284.0 vs 655.1 per 10,000 healthy men aged 40-59 years at entry; P<0.05).

The Lyon Diet Heart Study was a randomized controlled trial enrolling participants following their first myocardial infarction. It compared a Mediterranean-type diet (n=303) with usual post-infarct prudent diet (n=303).<sup>112</sup> Enrollment started in 1988 and was stopped in 1993 after significant interim results. The dietary intervention advised higher intakes of bread, root vegetables and green leafy vegetables, fruits, fish, and lesser intakes of meat with replacement of beef, lamb, and pork with chicken. In addition margarine was to replace butter and cream. The Mediterranean-type dietary intervention was associated with lower risk of overall mortality (Hazard ratio, HR=0.30; 95% CI 0.11, 0.82) and combined cardiovascular endpoint of CVD deaths and no-fatal MI (HR=0.27; 95% CI 0.12, 0.59).

Subsequently, many trials and observational studies have investigated the association between the Mediterranean-type diets and CVD. A recent updated review by Sofi *et al* of 35

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prospective cohorts including 4,172,412 participants used a diet scoring method (range 0-18) to measure adherence to the Mediterranean-type diet.<sup>14</sup> However, the total number of participants appear inflated as multiple publications from a cohort contribute repeatedly to the pooled estimate. The scoring method characterized adherence to Mediterranean diets by higher intakes of fruit, vegetables, legumes, cereals, fish, and olive oil, and lower intakes of meat, meat products, and dairy products, moderate alcohol consumption (12-24gm of alcohol per day). Greater adherence to Mediterranean diet (2-point increase) was associated with 8% reduction in overall mortality (RR=0.92; 95% CI 0.91, 0.93) and a 10% reduction of combined CVD end point of incidence and mortality (RR=0.90; 95% CI 0.87, 0.92).

### *Dietary Approaches to Stop Hypertension (DASH)*

The Dietary Approaches to Stop Hypertension (DASH) randomized controlled trial was a 8-week feeding trial designed to compare the blood pressure changes in two interventional diets with a control diet.<sup>6</sup> The 'ideal' interventional diet had higher intakes of fruits, vegetables, legumes, seeds, low-fat dairy products, fish, chicken, and lean meat. The other interventional diet had higher intakes of fruits and vegetables with similar but had similar fat intake with the controls as butter was used. The fruits and vegetable enriched diet reduced the systolic and diastolic blood pressure by 2.8 and 1.1 mm Hg ( $P<0.001$  and  $P=0.07$ ). Compared to controls, the combination (also termed ideal/DASH) diet reduced the systolic and diastolic blood pressure by 11.4 and 5.5 mm Hg in hypertensives ( $P<0.001$  for each) and 3.5 and 2.1 mm Hg in normotensives ( $P<0.001$  and  $P=0.003$ ).<sup>7</sup>

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The DASH diet resulted in greater blood pressure reductions among those with high sodium intakes. Sodium intake was held constant through the trial duration at the individual level and was further categorized into high, intermediate, and low. When the association between the DASH diets was stratified by salt intake, a greater reduction was seen among those with higher salt intakes and among African Americans. The DASH and low salt combination diet compared with the control high salt combination diet reduced systolic and diastolic blood pressure by 11.5 and 7.1 mm Hg diets.<sup>113</sup>

Though DASH diet had been associated with short term outcomes,<sup>114</sup> the evidence between DASH diets and various long term cardiovascular outcomes are inconclusive. The Premier Trial enrolled pre-hypertensive participants aged  $\geq 25$  years old and randomized them into one of three arms for 18 months.<sup>11</sup> Participants in the control arm received advice to follow the National High Blood Pressure Education Program lifestyle recommendations for blood pressure control. Participants in the established arm received active counselling and group session to meet recommended goals. The established plus DASH arm participants additionally received dietary advice. Comparing the advice only, established group, and established plus DASH group, the change from baseline for systolic blood pressure was -7.4, -8.6 ( $P > 0.05$ ), and -9.5 ( $P < 0.05$ ) mm Hg, respectively, and for diastolic blood pressure was -5.2, -6.0 ( $P > 0.05$ ), and -6.2 ( $P > 0.05$ ) mm Hg, respectively.

There was no evidence of an association between adherence to a DASH type diet and incident hypertension, CHD deaths, Stroke deaths or all CVD deaths ( $P > 0.05$ ) in an analysis of 20,993 women from the Iowa Women Health Study.<sup>8</sup> A suggestive non-significant beneficial

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association was seen when comparing the highest to the lowest quintiles of DASH adherence for CHD deaths (adjusted HR=0.86; 0.67, 1.12), stroke deaths (aHR=0.82; 95% CI 0.55, 1.23), and all CVD death (aHR=0.93; 95% CI 0.76, 1.12). The study concluded that high adherence of the DASH diet might be needed to change long term CVD outcomes.

DASH diet scores were calculated in 88,517 women from the Nurses' Health Study and followed up for 24 years.<sup>9</sup> Higher DASH scores were associated with lower incidences of CHD and stroke. The highest compared to the lowest quintile of DASH scores were associated with a 24% reduction of total CHD (aHR=0.76; 95% CI 0.67, 0.85; P trend<0.001) and a 17% reduction of total stroke (aHR=0.83; 95% CI 0.71, 0.96; P trend=0.007).

### *Hypothesis driven dietary patterns- dietary scores or index*

Hypothesis driven, a priori defined, dietary patterns builds upon current cumulative knowledge of the associations between diet and CHD. However, these scores and indexes typically use broad definitions of foods and subtle differences may be lost.<sup>115</sup> An example is the use of vegetables as a larger food group compared to sub-categorizing vegetable intake to green-leafy, other-colored, and non-colored vegetables that may differ in their phytochemical profiles.

The Healthy Eating Index and Diet Quality Index are examples of a priori defined dietary scores. The Healthy Eating Index measures adherence to the major recommendations of the original food pyramid and the Dietary Guidelines for Americans.<sup>116</sup> The Diet Quality Index (DQI) was initially developed to measure adherence to dietary recommendations from the 1989 Diet



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and Health publication of the National Academy of Science.<sup>117</sup> It was later revised to incorporate changes in nutrition policy in the 1990's incorporating changes in food pyramid, 1995 dietary guidelines and the Dietary Reference Intakes. The DQI was revised following principles of moderation, variety, and proportionality.<sup>118</sup> Another two dietary pattern scores were created using diet data from 5,089 MESA participants and compared with CVD risk factors and markers of subclinical atherosclerosis. The two scores were labelled Comprehensive Healthy Dietary Pattern and the Simplified Healthy Dietary Pattern. These two scores were significantly associated with CRP, IL-6, homocysteine, fibrinogen, fasting insulin, waist circumference, and BMI. However, no significant association was seen between these patterns and carotid intima media thickness, coronary artery calcium scores, blood pressure, and ankle brachial index.

### *Dietary patterns derived using either cluster or principal component analysis*

Post hoc dietary patterns derived by either cluster or principal component analysis uses correlations within the diet data. Food items are usually categorized into larger groups based on nutrient profiles and how these foods are prepared. These patterns may be more powerful at detecting diet associations by capturing a larger cumulative effect across many food items. However, limitations of these methods include unknown generalizability of derived patterns to other populations and that it lacks any theoretical basis.

Nettleton investigated the association between dietary patterns and subclinical atherosclerosis in 5,089 participants aged 45-84 years from the MESA cohort. Subclinical

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atherosclerosis was measured using coronary artery calcium and carotid intima media thickness. A total of four dietary patterns were derived using principal component analysis and labelled as “Fats and Processed Meat”, “Vegetables and Fish”, “Beans, Tomatoes, and Refined Grains”, and “Whole grain and Fruit”. There was no evidence of an association between any of these derived dietary patterns and prevalent coronary artery calcium and carotid intima media thickness.<sup>119</sup>

She further investigated the role of dietary patterns and risk of incident CVD in 5,316 MESA participants that were followed up for an average duration of 4 years. The fully adjusted hazard ratios of any incident CVD event comparing the fifth to the first quintile for Fats and Processed Meat pattern and Whole grain and fruit were 1.82 (95%CI 0.99, 3.35; P trend=0.10) and 0.54 (95% CI 0.33, 0.91;P trend=0.007), respectively.<sup>120</sup>

In the Whitehall II cohort, the healthy pattern (fruit, vegetables, whole-meal bread, low-fat dairy and little alcohol) decreased the adjusted hazard of CVD events by 29% (95% CI 0.51, 0.98) compared to the unhealthy pattern (white bread, processed meat, fries, and full-cream milk) but no associations were seen with all-cause mortality.<sup>121</sup> The associations of the sweet patterns and Mediterranean type patterns were inconsistent and not significant.

Five dietary patterns were derived from the Framingham nutrition studies: heart healthy, light eating, wine and moderate eating, high fat, and empty calorie. However, only the empty calorie pattern was associated with carotid atherosclerosis (aOR=2.28; 95% CI 1.12, 4.62) compared to the heart healthy pattern.<sup>122</sup>

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Two major dietary patterns were identified in the Nurse Health Study. Participants with higher adherence to the prudent pattern had higher intakes of vegetables, fruits, legumes, fish, poultry, and whole grains. Participants with higher adherence to the Western pattern had higher intakes of red meat, processed meat, refined grains, French fries, and sweets or desserts. The adjusted hazard ratio comparing the fifth to first quintile for CVD and all-cause mortality was 0.72 (95% CI 0.60, 0.87) and 0.83 (95% CI 0.76, 0.90), respectively for prudent diet, and 1.22 (95% CI 1.01, 1.48) and 1.21 (95% CI 1.12, 1.32), respectively for Western diets.<sup>123</sup>

The latent construct of derived dietary patterns in non-Western populations are likely to be different because of different methods in food preparation and local diet. For example, though traditional East Asian diets are high in vegetables and fruits but they also have higher intakes of sodium. This is a result of higher intakes of soya sauce, preserved soya or bean paste, preserved vegetables, or pickled vegetables. The latent construct for patterns with higher intakes of meats and alcohol are more consistent with those found in Western populations.

Three patterns were derived from the Japanese Ohsaki National Health Insurance cohort and labelled as Japanese, 'animal food', and high-dairy, high-fruit-and-vegetable, low-alcohol (DFA) patterns. The adjusted hazard ratio for CVD mortality comparing the fourth to the first quartile of the Japanese, 'animal food', and DFA patterns were 0.73 (95% CI 0.59, 0.90; P trend=0.003), 1.22 (95% CI 0.99, 1.51; P trend=0.03), and 0.88 (95% CI 0.68, 1.13; P trend=0.14), respectively.<sup>19</sup>

A more recent Japanese cohort with a larger sample that included the Ohsaki cohort identified the same three patterns. The adjusted hazard ratio of CVD mortality comparing the

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fifth to the first quintile of the vegetable, animal food, and dairy product patterns were 0.93 (95% CI 0.78, 1.13; P trend=0.73), 0.88 (95% CI 0.73, 1.05; P trend=0.50), and 0.89 (95% CI 0.74, 1.08; P trend=0.23), respectively for men, and 0.82 (95% CI 0.67, 1.00; P trend=0.04), 1.08 (95% CI 0.87, 1.34; P trend=0.42), and 0.76 (95% CI 0.61, 0.94; P trend=0.01), respectively for women.<sup>16</sup>

### *Diet and diabetes*

In a review of 10 studies comprising 190,301 participants, Esposito et al summarized that adherence to a healthy type dietary pattern was associated with a 32% decreased risk for diabetes (95% CI 0.58, 0.79).<sup>124</sup> They healthy type dietary patterns as ones with higher intakes of fruits and vegetables, whole grains, fish, and poultry, and by lower intakes of red meat, processed foods, sugar-sweetened beverages, and starchy foods.

In the Nurses Health Studies (NHS) II, the relative risks comparing the highest and lowest quintile for intakes of whole grain and bran were 0.68 (95%CI 0.57, 0.81) and 0.64 (95 CI% 0.54, 0.76), respectively.<sup>125</sup> The Women's Health Initiative was a large randomized control trial in 48,835 post-menopausal women aged 50 to 79 years.<sup>100</sup> It investigated the effect of a dietary intervention that advised lower total dietary fat and higher intakes of vegetables, fruits and grains. There were no significant associations between the lower fat diet intervention and incidence of CHD, stroke, or CVD. Furthermore, in spite of decreasing total fat intake and increasing intakes of vegetables, fruits and grains, there was no significant difference in mean

changes of glucose at Year 3 post randomization between the intervention and comparison group.

The heterogeneity in the associations of grain intake and diabetes may be explained by stratifying grain intake into whole and refined grains. Whole grains contain the endosperm, germ, and bran, whereas refined grains only contain the endosperm. The removal of the germ and bran during the milling process leads to a simpler carbohydrate, which has a higher glycemic index compared to whole grains. In a recent review of sixteen cohorts, the relative risks for diabetes comparing high versus low intakes of total whole grain and refined grain were 0.74 (95% CI 0.71, 0.78) and 0.94 (95% CI 0.82, 1.09), respectively.<sup>126</sup>

### *Diet and metabolic syndrome*

Recent publications on dietary patterns in South Korea have investigated the associations between dietary patterns and metabolic syndrome. Cho *et al* measured dietary intake using FFQs in 4,984 women screened at the National Cancer Center, South Korea, between August 2002 and May 2007.<sup>17</sup> They summarized the food items into 16 food groups and derived three dietary patterns using factor analysis. They labelled these patterns as Western, healthy, and traditional. The age adjusted odds ratio of metabolic syndrome comparing the highest to the lowest quartiles of the Western, healthy, and traditional was 0.87 (95% CI 0.54, 1.20; P trend=0.304), 0.58 (95% CI 0.50, 0.91; P trend=0.012), and 1.05 (95% CI 0.79, 1.40; P trend=0.873), respectively. Residual confounding was a limitation as the multivariable model only adjusted for age.

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Song *et al* used cluster analysis of 23 food groups to derive three dietary patterns of 4,730 subjects who had completed 24-hr recall in the Korean National Health and Nutrition Examination Survey III (KNHANES III) in 2005.<sup>18</sup> They labelled these patterns as Traditional, Meat & Alcohol, and Korean Healthy. The odds ratio of metabolic syndrome, adjusting for age, gender, region, smoking, and physical activity, was 1.21 (95% CI 0.92, 1.58) for the Meats & Alcohol group, and 0.92 (95% CI 0.75, 1.13) for the Korean Healthy group compared to the traditional group.

Oh *et al* derived three dietary patterns, Traditional Korean (37.5%), Westernized Korean (42.9%), and Meat and Alcohol (19.7%), from 1,435 subjects aged  $\geq 65$  years old interviewed in the KHANES 2011.<sup>127</sup> Dietary information was collected using 24-hr recall and the food items were categorized into 23 groups. Cluster analysis was used to derive the dietary patterns. The high proportion of Westernized diet in this elderly population was unexpected. There was many typographical errors in the tables and manuscript that made interpretation difficult.

Kastorini *et al*, pooling the results of eight studies with 10,399 subjects, summarized that adherence to a Mediterranean Diet was associated with a 50% reduction in the hazard of metabolic syndrome.<sup>128</sup> However, there was a typographical error in their results that was presented as “log-hazard ratio= -0.69, 95% CI: -1.24 to – 1.16”.

### 1.5. Significance

This asymptomatic Korean cohort, with diet intakes higher in carbohydrate and lower in fat compared to typical western diets, provides an opportunity to explore the association between diet and CHD. The derivation of dietary patterns in a very large Asian cohort is novel. This study adds to the evidence base on diet associations with diabetes, metabolic syndrome, and subclinical atherosclerosis. Assuming that these dietary patterns represent different stages of dietary transition, the patterns may help explain the downstream effect of the current diet transition in South Korea.

To summarize, this study derives the major dietary patterns in a large South Korean cohort and evaluates the associations between dietary patterns and diabetes, metabolic syndrome, and subclinical atherosclerosis.

## 1.6. Kangbuk Samsung Health Study

### *Study population*

The Kangbuk Samsung Health Study is a cohort of Korean men and women 18 years of age or older who underwent a comprehensive annual or biennial examination at the Kangbuk Samsung Total Healthcare Center in Seoul and Suwon, South Korea. Annual or biennial health screening exams are widely performed in Korea, as health exams are mandatory for all workers under the Industrial Safety and Health Law. Dietary information was collected routinely in the health screening examinations from 2011 onwards.

This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital that exempted the requirement for informed consent as we only accessed de-identified data routinely collected as part of health screening exams.

### *Data collection*

Comprehensive health screening examinations were conducted at the clinics of the Kangbuk Samsung Hospital Total Healthcare Center in Seoul and Suwon. Socio demographic characteristics, smoking status, physical activity patterns, and history of comorbidities were collected using a self-administered questionnaire. Height, weight, and sitting blood pressure was measured by trained nurses. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squares.

### *Dietary assessment*

Dietary intake was assessed using a 103-item self-administered FFQ designed to measure usual dietary habits in Korea. In the validation study, FFQ were administered twice



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with a one year interval between these administrations, and was validated against 12-days of dietary record information that consisted of three day dietary records administered four times during the different seasons in the same year.<sup>129</sup> The sex, age, energy-adjusted and de-attenuated correlations for protein, fat, and carbohydrate was 0.43, 0.40, and 0.64, respectively. We used the first FFQ administration if participants had repeat FFQ information.

The FFQ asked participants about their usual consumption of 103 items that was further categorized into the following food groups: rice and rice based noodles (3), noodles (6), bread (6), kimchi and preserved vegetables (5), non-colored vegetables (4), green leafy vegetables (8), other colored vegetables (7), mushrooms (2), potato (3), soya bean, soya bean products and other beans (4), nuts (1), fruits (11), raw or salted fish (2), oily fish (4), non-oily fish (4), shellfish (5), seaweed (2), meat (8), processed meat (1), poultry (1), eggs (1), milk and dairy products (4), snacks (3), pizza (1), coffee and tea (5), soda and cola (1). We ignored one item on fats due to the non-specific nature of the question.

The FFQ had three predefined categories of portion size, ranging from small to large, and nine predefined categories of frequency, ranging from never to three times per day for foods and from never to five times per day or more for beverages. The average daily nutrient intakes were estimated using a food composition table derived from the Korean Nutrient Society Database.<sup>130</sup> Daily alcohol intake was measured in the general self-administered questionnaire and included weekly frequency, amount consumed, and type of alcohol consumed.

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## Abstract

### Introduction

Dietary risk factors are associated with 26% of deaths and 14% of DALYS in the United States in 2010. Dietary patterns are preferred over single nutrient because it acknowledges the complex interactions between nutrients and foods, it estimates a larger cumulative effect, and may be easier to translate into effective interventions. We aim to identify and describe the major dietary patterns in a large cohort of asymptomatic Koreans.

### Methods

We conducted a cross sectional study in 269,266 adult men and women who underwent a screening examination between January 2011 and December 2013 at the Kangbuk Samsung Total Healthcare Center in Seoul and Suwon, South Korea. Diet was assessed using a validated 103-item food frequency questionnaire that was further categorized into 27 food groups based on their nutrient profile and culinary preference. We used principal component analysis with varimax rotation to derive three major dietary patterns. The Traditional Korean, Modern Korean, and Western Korean dietary patterns explained 20.7%, 11.4%, and 10.1%, of the total variation in the food group intakes.

### Results

The Traditional Korean patterns had higher intakes of vegetables, mushrooms, potatoes, soya and other beans, fruits, oily and non-oily fish, shellfish, and seaweed. Modern Korean patterns had higher intakes of noodles, raw or salted fish, shellfish, red meat, processed meat, poultry, soda, and alcohol. Western Korean patterns had higher intakes of bread and cereals, milk and dairy products, snacks, and pizza, and lower intakes of alcohol, rice, and preserved



vegetables. Participants with higher adherence to Modern Korean compared to Traditional Korean patterns were more likely younger, male, have higher education, currently smoke, and be physically inactive. Participants with higher adherence to Western Korean compared to Traditional Korean patterns were more likely younger, female, have higher education, and less likely to currently smoke, be physically active, or have any history of hypertension, diabetes, and dyslipidemia.

### **Conclusion**

We were able to identify three distinct dietary patterns in a large sample of apparently healthy adult Korean men and women. These dietary patterns may represent the different phases of the ongoing nutrition transition of the Korean society.

## Introduction

The relative improvement of life expectancy in the United States has been modest compared to the rapid rise in health expenditure in recent decades. The United States ranks 27<sup>th</sup> among the Organization for Economic Co-operation and Development (OECD) countries in life expectancy at birth despite spending two and a half times (US\$8,508) the OECD average per capita on healthcare cost.<sup>1</sup> This high cost contrasts with other better ranked countries that have a substantially lower gross domestic product and lower health expenditure per capita. For example, South Korea ranks 16 among the OECD countries in life expectancy at birth and has a health expenditure per capita of US\$2,198. The United States also ranks higher than South Korea in terms of dietary risks of the age-standardized attributable disability-adjusted life years.

Diet plays an important role in shaping population health. Diet composition, analyzed as a cluster of 14 different dietary components, was associated with 26% of deaths and 14% of DALYS in the United States.<sup>2</sup> However, a critique of nutritional research is the difficulty of translating results to effective population interventions.<sup>3</sup> The role of diet in maintaining good health is indeed more complex than individual nutrients acting in isolation. Dietary patterns acknowledges the complex interactions between the different nutrients and foods in our diet.<sup>4</sup> <sup>5</sup> Dietary pattern research have successfully been translated into intervention strategies such as the Mediterranean type diet and the Dietary Approaches to Stop Hypertension (DASH). The DASH diet has been associated with various short term cardiovascular benefits but the scientific evidence on long term benefits are inconclusive.<sup>6-11</sup> The Mediterranean pattern has also been consistently associated with cardiovascular benefits.<sup>12-14</sup>

However, both DASH and the Mediterranean diets were developed in western populations, which typically consumes a higher fat and lower carbohydrate diet compared to Asians. The literature on dietary patterns among the various Asian countries and its role on health is more limited.<sup>15-18</sup> We aim to identify and describe the major dietary patterns in a large cohort of asymptomatic Koreans, which consumes a higher carbohydrate lower fat diet compared to western populations.

## Methods

### *Study population*

The Kangbuk Samsung Health Study is a cohort of Korean men and women aged 18 years or older who underwent a comprehensive screening examination at the Kangbuk Samsung Total Healthcare Center in Seoul and Suwon, South Korea. Annual or biennial health screening examinations are widely performed in South Korea as these are mandatory for all workers under the Industrial Safety and Health Law. Dietary information was collected routinely in the health screening examinations from 2011 onwards using a Food Frequency Questionnaire (FFQ). We used the first FFQ administration if participants had repeat FFQ information.

Of the 277,667 participants screened at these centers from 2011 to 2013, we excluded 8,401 participants with histories of either cardiovascular disease (n=3,399) or cancer (n=6,600) from this analysis. Of the remaining 269,266 participants, dietary patterns could not be derived on a further 72,173 (26.8%) participants for the following reasons: no FFQ data (n=32,024; 11.9%); participants who reported extreme intakes of total energy defined as more than 2 interquartile ranges above the 75th percentile or below the 25th percentile of log transformed

intake, corresponding to <338 and >5209 kcal/day for females, and <503 and >4906 kcal/day for males (n=6,604; 2.5%), and insufficient FFQ data to derive dietary pattern scores (n=33,545; 12.5%).

Dietary patterns was available in 197,093 (73.2%) of the 269,266 participants. The proportion of availability for dietary factor information was similar by categories of sex, smoking status, and physical activity status, and dyslipidemia (Table 2.1). The mean waist and BMI was similar in those with and without dietary factor information. However, the missingness of dietary information was associated with age, education, history of hypertension, diabetes, and dyslipidemia. Participants with missing dietary information was relatively older compared to those with available information (42.6±10.5 vs 39.4±8.6 years) The availability of dietary factor information of those with educations levels of university or higher, technical college, and high school or lower was 76.6%, 74.3%, 69.1%, respectively. The availability of dietary factor information was also lower among those with hypertension (69.9%) and diabetes (66.8%).

This study was reviewed and approved by the Institutional Review Board of Kangbuk Samsung Hospital. The requirement for informed consent was waived as we only accessed de-identified data that was routinely collected as part of health screening exams.

#### *Data collection*

Comprehensive health screening examinations were routinely conducted at the clinics of the Kangbuk Samsung Hospital Total Healthcare Center in Seoul and Suwon. Information on socio demographic characteristics, smoking status, physical activity patterns, and history of comorbidities, were collected using a self-administered questionnaire. Height, weight, and

sitting blood pressure was measured by trained nurses. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squares.

*Dietary assessment*

Dietary intake was assessed using a 103-item self-administered Korean FFQ, which was designed to measure usual dietary habits in Korea. In a prior study, FFQ were administered twice with a one year interval between these administrations and was validated against 12-days of diet records.<sup>19</sup> The dietary record information consisted of three-day dietary records, including two weekdays and one weekend, administered four times during the different seasons of the year. The sex, age, energy-adjusted and de-attenuated correlations for protein, fat, and carbohydrate was 0.43, 0.40, and 0.64, respectively.

The FFQ asked participants about their usual consumption of 103 items that was further categorized into the following food groups: rice and rice based noodles (3), noodles (6), bread (6), kimchi and preserved vegetables (5), non-colored vegetables (4), green leafy vegetables (8), other colored vegetables (7), mushrooms (2), potato (3), soya bean, soya bean products and other beans (4), nuts (1), fruits (11), raw or salted fish (2), oily fish (4), non-oily fish (4), shellfish (5), seaweed (2), meat (8), processed meat (1), poultry (1), eggs (1), milk and dairy products (4), snacks (3), pizza (1), coffee and tea (5), soda and cola (1). We ignored one question on fat intake because of its non-specific nature and added daily alcohol intake as an additional food group for consideration. The FFQ had three predefined categories of portion size, ranging from small to large, and nine predefined categories of frequency, ranging from never to three times per day for foods and from never to five times per day or more for beverages. The average daily

nutrient intakes were estimated using a food composition table derived from the Korean Nutrient Society Database.<sup>20</sup>

### *Statistical Methods*

The primary outcome of this analysis was the unique major dietary patterns of this cohort. We combined the daily energy intake of individual food items into 27 food groups based on similarities in the nutrient profile and culinary preference. We used principal components analysis with orthogonal rotation procedure varimax to create independent factors representing latent diet patterns.<sup>21</sup> We identified three factors, labelled as Traditional Korean, Modern Korean, and Western Korean, based on the Eigen value (greater $>$ 2), Catel's Scree plot (Figure 2.1), and Velicer's Minimum Average Partial test.<sup>22</sup> The factor loadings of each food group represents the correlation between daily energy intake of the food group and the specific factor. Factor scores were estimated using Bartlett's approach (Figure 2.2) and were standardized to have means and standard deviation of 0 and 1, respectively.

We defined high adherence to a specific dietary pattern as being in the upper fifth quintile of the dietary factor scores. Descriptive statistics was used to summarize the distribution of characteristics in the overall sample and in those with high adherence to specific dietary patterns. Quantile regression was used to model median daily energy intake because of its skewed distribution. A multivariable quantile regression model with all three continuous factor scores was used to estimate the change in daily food or nutrient intake associated with substitution of different dietary pattern adherence. The change in median intakes associated with a lower adherence to Traditional Korean patterns substituted with a higher adherence to either Modern Korean or Western Korean was estimated by substituting a 1 SD factor score of

Traditional Korean dietary pattern with 1 SD factor score of either Modern Korean or Western Korean patterns.

## Results

Three major dietary patterns were identified that explained 42.2% of the variation in daily dietary energy intakes (Table 2.2). The first factor, labelled as Traditional Korean dietary pattern, was characterized by higher loadings of preserved vegetables, non-colored, green leafy and other colored vegetables, mushroom, potato and sweet potato, soya and other beans, fruits, oily and non-oily fish, shellfish, and seaweed. The second factor, labelled as Modern Korean dietary pattern, was characterized by higher intakes of noodles, raw or salted fish, shellfish, red meat, processed meat, poultry, soda, and alcohol. The third factor, labelled as Western Korean dietary pattern, was characterized by higher intakes of bread and cereals, milk and dairy products, snacks, and pizza. These three dietary patterns, Traditional Korean, Modern Korean, and Western Korean explained 20.7%, 11.4% and 10.1%, respectively, of the total variation of these food group intakes.

The mean $\pm$ SD age of the 197,093 participants with dietary pattern information was 39.4 $\pm$ 8.6 years (Table 2.3). The proportion of males, those with at least a university education, current smokers, and those with health enhancing physical activity patterns was 54.8%, 67.5%, 24.6%, and 17.4%, respectively. The prevalence of hypertension, diabetes, and dyslipidemia, was 8.3%, 2.4%, and 11.0%, respectively. Those with high adherence to Traditional Korean dietary patterns compared to those with high adherence of Modern Korean dietary patterns were more likely to be female, older, have lower levels of education, increased physical activity,

and less likely to be a current smoker. Compared to Western Korean dietary patterns, those with high adherence to the Traditional Korean dietary patterns were more likely to be male, older, have lower levels of education, be a current smoker, physically active, and have a history of hypertension, diabetes, or dyslipidemia.

Those with a higher adherence of Traditional Korean dietary patterns, defined as 1 SD higher than the mean factor scores, had median intakes (SE) of rice and rice cake, noodles, breads and cereals, any vegetables, fruits, any fish, and red meat, corresponding to 760.6 (1.1), 126.5 (0.3), 60.2 (0.2), 61.7 (0.1), 100.3 (0.2), 50.1 (0.1), and 134.1 (0.2) Kcal/day, respectively (Table 2.4). A higher adherence (1 SD increase) of Modern Korean dietary patterns with a concurrent lower adherence (1 SD decrease) to Traditional Korean dietary pattern was associated with increased daily energy intakes of noodles, red meat, processed meat, poultry, pizza, soda, and alcohol by 34.7%, 20.5%, 42.3%, 21.3%, 42.0%, 87.7%, and 69.6%, respectively. It was also associated with decreased intakes of non-colored, green leafy, and other colored vegetables, mushroom, potato, soya and other beans, nuts, fruits, oily fish, and seaweeds by 29.8%, 35.3%, 44.2%, 40.2%, 39.6%, 32.3%, 41.9%, 41.9%, 21.4%, and 33.3%. Likewise, a higher adherence (1 SD increase) of Western Korean dietary patterns with a concurrent lower adherence (1 SD decrease) to Traditional Korean dietary pattern was associated with increased daily energy intakes of breads and cereals, processed meat, snacks, pizza, and soda, by 41.5%, 28.2%, 58.5%, 65.1%, and 57.6%, respectively. This change in adherence was also associated with decreased intakes of preserved vegetables, non-colored, green leafy, and other colored vegetables, mushroom, soya and other beans, fruits, raw or salted fish, oily fish, non-oily fish, shellfish, seaweed, and alcohol.



Those with higher adherence of Traditional Korean dietary patterns had a median (SE) total energy intake of 1,834.3 (1.5) Kcal/day with a diet of 66.1% carbohydrates, 13.8% protein, 16.0% total fat, and a daily fiber intake of 10.6 gm/1000 Kcal (Table 2.5). A higher adherence of Modern Korean dietary patterns with a concurrent lower adherence to Traditional Korean dietary pattern was associated with lower intakes of total energy (-1.7%), carbohydrate (-4.6%), protein (-5.8%), and fiber (-23.4%), and with higher intakes of total fat (3.0%) and alcohol (79.3%). Likewise, a higher adherence of Western Korean dietary patterns with a concurrent lower adherence to Traditional Korean dietary pattern was associated with lower intakes of total energy (-7.8%), carbohydrate (-0.4%), protein (-4.3%), alcohol (-35.0%), and fiber (-20.0%), and with higher intakes of total fat (13.9%).

## Discussion

In this large cohort of South Korean men and women, consuming a diet higher in carbohydrates and lower in fats compared to Western diets, we identified three major dietary patterns that we labelled as Traditional Korean, Modern Korean, and Western Korean. These three dietary patterns explained 42.3% of the total variation in daily dietary intakes.

The Traditional Korean dietary pattern had higher intakes of vegetables, mushrooms, potatoes, soya and other beans, fruits, oily and non-oily fish, shellfish, and seaweed. This is the typical diet consumed by previous generations Koreans. A sustained public health campaign in Korea over the past decades had advocated for retention of traditional diet as a healthy alternative.<sup>23</sup> The Traditional Korean dietary pattern appears to be the healthiest dietary pattern among the three different patterns. This diet has similarities with the Mediterranean

type diet, DASH diet, prudent, healthy and previously derived traditional Japanese and Korean patterns.<sup>6, 14, 16, 17, 24-27</sup> However, the label “traditional” that is typically used in non-Western populations may differ from one another and with other “healthy” diets because of heterogeneous food preparations and local diet culture. Another major difference in traditional East Asian diets is the high sodium intake that may be due to the higher intakes of soya sauce, preserved soya or bean paste, preserved vegetables, or pickled vegetables.

Mediterranean type diets are characterized by higher intakes of legumes, cereals, fruit and vegetables, fish, olive oil, and lower intakes of meat and pork.<sup>14</sup> However, olive oil was poorly measured in this version of the FFQ and was not considered in our analysis. The DASH diet is characterized by a diet rich in fruit, vegetables, legumes, seeds, low-fat dairy products, fish, chicken, and lean meat with reduced intakes of saturated and total fat.<sup>6</sup> Interestingly, the DASH diet was associated with larger reductions of blood pressure among those with high compared to low sodium intakes.<sup>28</sup> This is relevant here because diets in South Korea typically have high intakes of sodium. The healthy pattern from the Whitehall II study had higher intakes of fruit, vegetables, whole-meal bread, low-fat dairy and little alcohol.<sup>25</sup> In comparison, the prudent diet is characterized by higher intakes vegetables, fruits, legumes, fish, poultry, and whole grains.<sup>27</sup>

The Modern Korean dietary pattern had higher intakes of noodles, raw or salted fish, shellfish, red meat, processed meat, poultry, soda, and alcohol. This pattern closely resembles the Korean meat & alcohol pattern, and the common meat pattern in the west. The higher intakes of meat, soda and alcohol results in diets with more amounts of total fat and lower amounts of fiber, vitamin A, vitamin C, folate, and phosphorous compared to the traditional

diet. This diet may be a result of the dietary transition occurring in Korea in recent decades with urbanization and globalization.<sup>29</sup>

The Western Korean dietary pattern had higher intakes of bread and cereals, milk and dairy products, snacks, and pizza, and lower intakes of alcohol, rice, and preserved vegetables. Compared to traditional Korean and Asian diets, these food groups are perceived to be a result of western influence. Those with higher adherence to this Western Korean diet are very much younger compared those with higher adherence to the Traditional patterns. Due to a possible lag period, the effect of this dietary pattern on CVD may be appreciated with a longer follow up duration.

There are several limitations of this study that needs to be considered. First, dietary intakes are difficult to measure and measurement error is a possible source of bias. However, dietary patterns compared to nutrients are less susceptible to this bias as it uses the inter-correlations among the different food items and estimates a larger cumulative effect of several food groups. Second, missingness of dietary intakes are missing at random and are associated with age, education, history of hypertension, diabetes, and dyslipidemia. As this is a descriptive paper, we used list wise deletion for missing covariate information. We will use multiple imputation with chained equations to address missingness when further evaluating diet-outcome associations. Third, the generalization of these results to other populations are unknown as our study population consists of asymptomatic healthy young and middle-aged Koreans who participated in a screening program.

Our study al has several strengths. The Kangbuk Samsung Health Study will be one of the largest cohorts with dietary pattern exposures. We will able to evaluate association of small

effect sizes and perform detailed multivariable dose response modeling. Data collection involved the use of high-quality clinical and imaging equipment. The central laboratory routinely followed quality-assurance programs. The data management and analysis were documented with audit trails of major version changes.

South Korea is undergoing a nutrition transition amidst further urbanization and epidemiological transition. Using the Kangbuk Samsung Health Study cohort, we were able to identify three distinct dietary patterns, labeled as traditional Korean, Modern Korean, and Western Korean, in asymptomatic apparently healthy young and middle-aged Koreans. Participants with higher adherence to Modern Korean compared to Traditional Korean patterns were more likely younger, male, have higher education, currently smoke, and be physically inactive. Participants with higher adherence to Western Korean compared to Traditional Korean patterns were more likely younger, female, have higher education, and less likely to currently smoke, be physically active, or have any history of hypertension, diabetes, and dyslipidemia. These dietary patterns may represent the different phases of the ongoing nutrition transition, urbanization and Westernization of the Korean society.

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Table 2.1 Cohort participant characteristics by availability of dietary factor information (N=269,266)

Characteristics	n	Overall n (column %)	Dietary factor information, n (row %)	
			Not available (n=72,173)	Available (n=197,093)
Age, mean±SD	269,266	40.3±9.2	42.6±10.5	39.4±8.6
Sex	269,266			
Female.		122,833 (45.6)	33,836 (27.5)	88,997 (72.5)
Male		146,433 (54.4)	38,337 (26.2)	108,096 (73.8)
Education	222,841			
University or higher		146,814 (65.9)	34,327 (23.4)	112,487 (76.6)
Technical college		29,914 (13.4)	7,670 (25.6)	22,244 (74.4)
High school or lower		46,113 (20.7)	14,157 (30.7)	31,956 (69.3)
Smoking status	226,668			
Never		130,233 (57.5)	30,675 (23.6)	99,558 (76.4)
Former		40,078 (17.7)	9,225 (23)	30,853 (77)
Current		56,357 (24.9)	13,777 (24.4)	42,580 (75.6)
Physical activity patterns	261,086			
Inactive		123,210 (47.2)	31,790 (25.8)	91,420 (74.2)
Minimally active		92,713 (35.5)	22,682 (24.5)	70,031 (75.5)
Health-enhancing		45,163 (17.3)	11,171 (24.7)	33,992 (75.3)
Comorbid history				
Hypertension	269,266			
No		245,871 (91.3)	65,142 (26.5)	18,079 (73.5)
Yes		23,395 (8.7)	7,031 (30.1)	16,364 (69.9)
Diabetes	269,266			
No		262,290 (97.4)	69,857 (26.6)	192,433 (73.4)
Yes		6,976 (2.6)	2,316 (33.2)	4,660 (66.8)
Dyslipidemia	269,266			
No		240,134 (89.2)	64,689 (26.9)	175,445 (73.1)
Yes		29,132 (10.8)	7,484 (25.7)	21,648 (74.3)
Waist (cm), mean±SD	228,828	81.6±9.4	81.9±9.3	81.5±9.5
BMI (kg/m <sup>2</sup> ), mean±SD	268,835	23.2±3.3	23.3±3.2	23.2±3.3



Table 2.2 Factor loading matrix for the three major dietary patterns (N = 197,093)

Food groups	Dietary food patterns			Uniqueness
	Traditional Korean	Modern Korean	Western Korean	
Rice & rice cake				0.8458
Noodles		0.5600		0.6313
Bread and cereals			0.7059	0.4826
Preserved Vegetables	0.4691			0.6454
Vegetables – non colored	0.7394			0.4267
Vegetables – green leafy	0.7706			0.3973
Vegetables – other color	0.7269			0.4529
Mushroom	0.6546			0.5674
Potato and sweet potato	0.5754			0.5707
Soya and other beans	0.6234			0.5983
Nuts				0.7568
Fruits	0.593			0.5613
Raw or salted fish		0.5429		0.5924
Oily fish	0.6655			0.4824
Non-oily fish	0.6634			0.4721
Shellfish	0.5549	0.4221		0.492
Seaweed	0.5819			0.6608
Red meat		0.6629		0.457
Processed meat		0.5231		0.5612
Poultry		0.4915		0.6381
Eggs				0.79
Milk and dairy products			0.5490	0.6305
Snacks			0.7047	0.4699
Pizza			0.6163	0.4911
Coffee & Tea				0.8005
Soda		0.5641		0.5509
Alcohol		0.5983		0.5665

\* Only factor loading with absolute values larger than 0.40 are shown for better interpretability

Table 2.3 Participants characteristics in highest quintile of major dietary patterns (N = 197,093)

	n	Overall	Quintile 5 (Higher adherence)		
			Traditional Korean	Modern Korean	Western Korean
Age	197,093	39.4±8.6	42.3±9.3	37.2±6.8	35.4±6.2
Male	197,093	108,096 (54.8)	18,690 (47.4)	34,804 (88.3)	16,399 (41.6)
Education	166,687				
University or higher		112,487 (67.5)	22,242 (67.8)	23,409 (72.5)	24,757 (75.7)
Technical college		22,244 (13.3)	4,023 (12.3)	4,131 (12.8)	4,079 (12.5)
High school or lower		31,956 (19.2)	6,555 (20.0)	4,736 (14.7)	3,859 (11.8)
Smoking status	172,991				
Never		99,558 (57.6)	19,670 (60.6)	11,876 (32.1)	25,342 (72.4)
Former		3,0853 (17.8)	5,822 (17.9)	8,096 (21.9)	4,322 (12.3)
Current		42,580 (24.6)	6,979 (21.5)	17,048 (46.1)	5,357 (15.3)
Physical activity patterns	195,443				
Inactive		91,420 (46.8)	14,063 (36.1)	17,671 (45.0)	19,126 (49.0)
Minimally active		70,031 (35.8)	15,119 (38.8)	15,112 (38.5)	13,865 (35.5)
Health-enhancing		33,992 (17.4)	9,764 (25.1)	6,475 (16.5)	6,069 (15.5)
Comorbid history					
Hypertension	197,093	16,364 (8.3)	4,099 (10.4)	3,815 (9.7)	1690 (4.3)
Diabetes	197,093	4,660 (2.4)	1,315 (3.3)	855 (2.2)	340 (0.9)
Dyslipidemia	197,093	21,648 (11.0)	4,626 (11.7)	5,382 (13.7)	3,201 (8.1)
Waist, cm	167,526	81.5±9.5	81.6±9.3	86±8.9	79.8±9.8
BMI	196,866	23.2±3.3	23.3±3.3	24.5±3.3	22.7±3.4

Table 2.4 Major dietary patterns and daily food group intakes (N =197,093)

Food groups	Dietary food patterns		
	Traditional Korean Median intake*, kcal/day (SE)	Modern Korean Change in daily energy intake**, % (SE)	Western Korean Change in daily energy intake**, % (SE)
Rice & rice cake	760.6 (1.1)	1.1 (0.1)	-17.4 (0.1)
Noodles	126.5 (0.3)	34.7 (0.3)	12.3 (0.2)
Bread and cereals	60.2 (0.2)	-11.2 (0.3)	41.5 (0.3)
Preserved Vegetables	29.5 (0.1)	-12.1 (0.2)	-41.1 (0.2)
Vegetables – non colored	6.1 (0.1)	-29.8 (0.1)	-38.8 (0.1)
Vegetables – green leafy	8.8 (0.1)	-35.3 (0.1)	-40.2 (0.1)
Vegetables – other color	17.3 (0.1)	-44.2 (0.1)	-34.0 (0.1)
Mushroom	1.6 (0.1)	-40.2 (0.2)	-36.0 (0.2)
Potato and sweet potato	12.3 (0.1)	-39.6 (0.2)	-17.3 (0.2)
Soya and other beans	33.7 (0.1)	-32.3 (0.1)	-28.2 (0.1)
Nuts	4.7 (0.1)	-41.9 (0.3)	-8.3 (0.3)
Fruits	100.3 (0.2)	-41.9 (0.2)	-20.3 (0.2)
Raw or salted fish	4.1 (0.1)	15.8 (0.2)	-29.6 (0.2)
Oily fish	24.4 (0.1)	-21.4 (0.1)	-29.6 (0.1)
Non-oily fish	13.6 (0.1)	-19.7 (0.1)	-34.1 (0.1)
Shellfish	8.0 (0.1)	-7.1 (0.2)	-24.5 (0.2)
Seaweed or sea mustard	1.2 (0.1)	-33.3 (0.2)	-32.5 (0.2)
Red meat	134.1 (0.2)	20.5 (0.2)	-8.3 (0.1)
Processed meat	4.3 (0.1)	42.3 (0.4)	28.2 (0.4)
Poultry	12.2 (0.1)	21.3 (0.2)	5.3 (0.2)
Eggs	18.2 (0.1)	-13.9 (0.2)	-8.2 (0.2)
Dairy products	83.6 (0.2)	-17.5 (0.2)	13.6 (0.3)
Snacks	31.0 (0.1)	10.6 (0.3)	58.5 (0.4)
Pizza	15.0 (0.1)	42.0 (0.4)	65.1 (0.5)
Coffee & Tea	60.5 (0.2)	8.0 (0.3)	-11.2 (0.3)
Soda	5.2 (0.1)	87.7 (0.8)	57.6 (0.7)
Alcohol	56.6 (0.2)	69.6 (0.5)	-37.0 (0.3)

\* Higher adherence to Traditional Korean dietary pattern defined as 1 SD higher than the mean factor scores

\*\* Change in daily food intake associated with a 1 SD substitution of Traditional Korean dietary pattern with 1 SD of either Modern Korean or Western Korean dietary patterns. This reflects a change of adherence from one dietary pattern to another dietary pattern. All differences significant with P<0.001

Table 2.5 Major dietary patterns and daily nutrient intake (N =197,093)

Food groups	Dietary food patterns		
	Traditional Korean Median intake*, kcal/day (SE)	Modern Korean Change in daily energy intake**, % (SE)	Western Korean Change in daily energy intake**, % (SE)
Energy (kcal)	1834.3 (1.5)	-1.7 (0.1)	-7.8 (0.1)
Carbohydrate (%total energy)	66.1 (0.1)	-4.6 (0.1)	-0.4 (0.1)
Protein (%total energy)	13.8 (0.1)	-5.8 (0.1)	-4.3 (0.1)
Total Fat (%total energy)	16.0 (0.1)	3.0 (0.1)	13.9 (0.1)
Alcohol (%total energy)	3.0 (0.1)	79.3 (0.6)	-35.0 (0.3)
Fiber (gm/1000kcal)	10.6 (0.1)	-23.4 (0.1)	-20.0 (0.1)
Vit A (ugRE/1000kcal)	346.6 (0.3)	-29.7 (0.1)	-24.6 (0.1)
Retinol (ug/1000kcal)	57.2 (0.1)	-6.6 (0.2)	12.8 (0.2)
Vit C (mg/1000kcal)	61.0 (0.1)	-32.5 (0.1)	-24.9 (0.1)
Vit B1 (mg/1000kcal)	0.6 (0.1)	-3.9 (0.1)	-7.2 (0.1)
Folate (ug/1000kcal)	279.8 (0.2)	-24.2 (0.1)	-24.1 (0.1)
Calcium (mg/1000kcal)	270.7 (0.3)	-24.1 (0.1)	-13.7 (0.1)
Phosphorous (mg/1000kcal)	511.1 (0.3)	-11.6 (0.1)	-8.5 (0.1)
Sodium (mg/1000kcal)	1544.7 (2.3)	-7.6 (0.1)	-21.8 (0.1)

\* Higher adherence to Traditional Korean dietary pattern defined as 1 SD higher than the mean factor scores

\*\* Change in daily food intake associated with a 1 SD substitution of Traditional Korean dietary pattern with 1 SD of either Modern Korean or Western Korean dietary patterns. This reflects a change of adherence from one dietary pattern to another dietary pattern.

\*\*\* All differences significant with  $P < 0.001$

Figure 2.1. Scree Plot

The Eigen values of the factors (dietary patterns) are ordered from high to low and are plotted. One method to determine the number of factors to retain is to visually examine the plot to locate the point where the slope levels off. The slope here levels off after the third factor (see text for details).

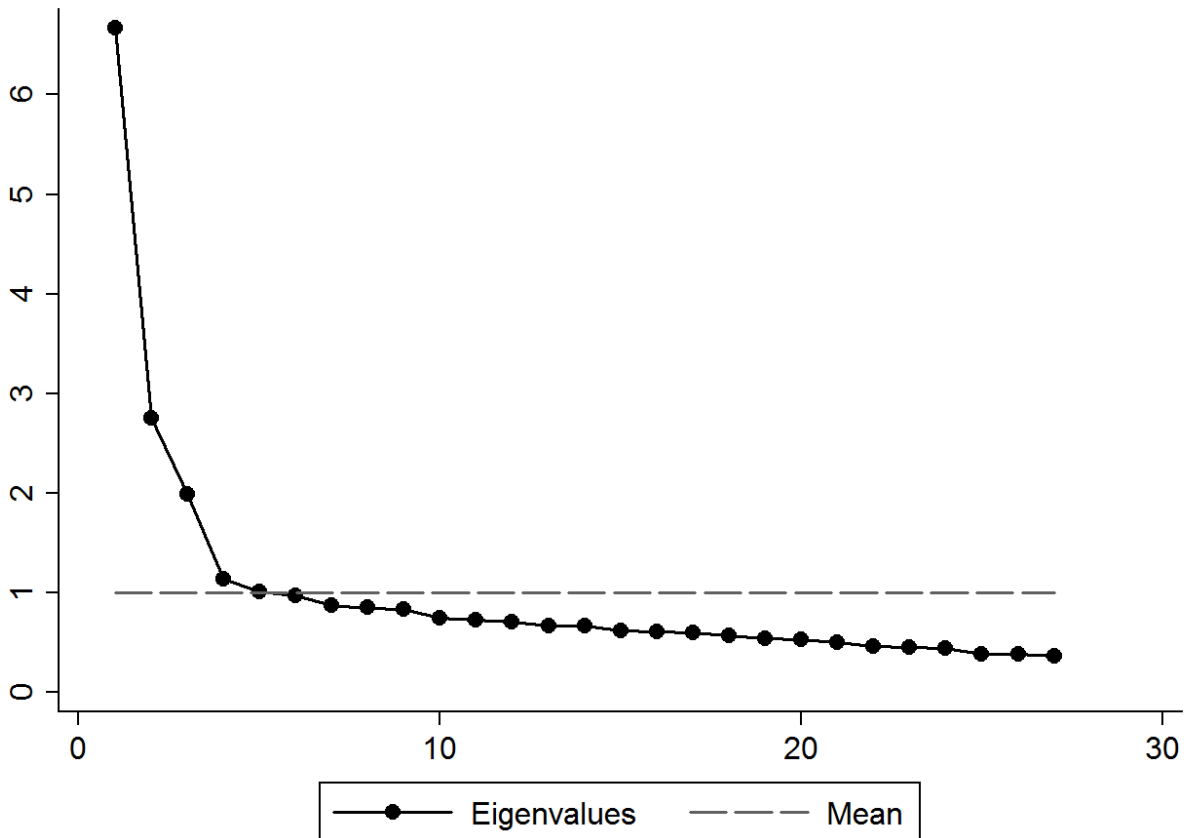
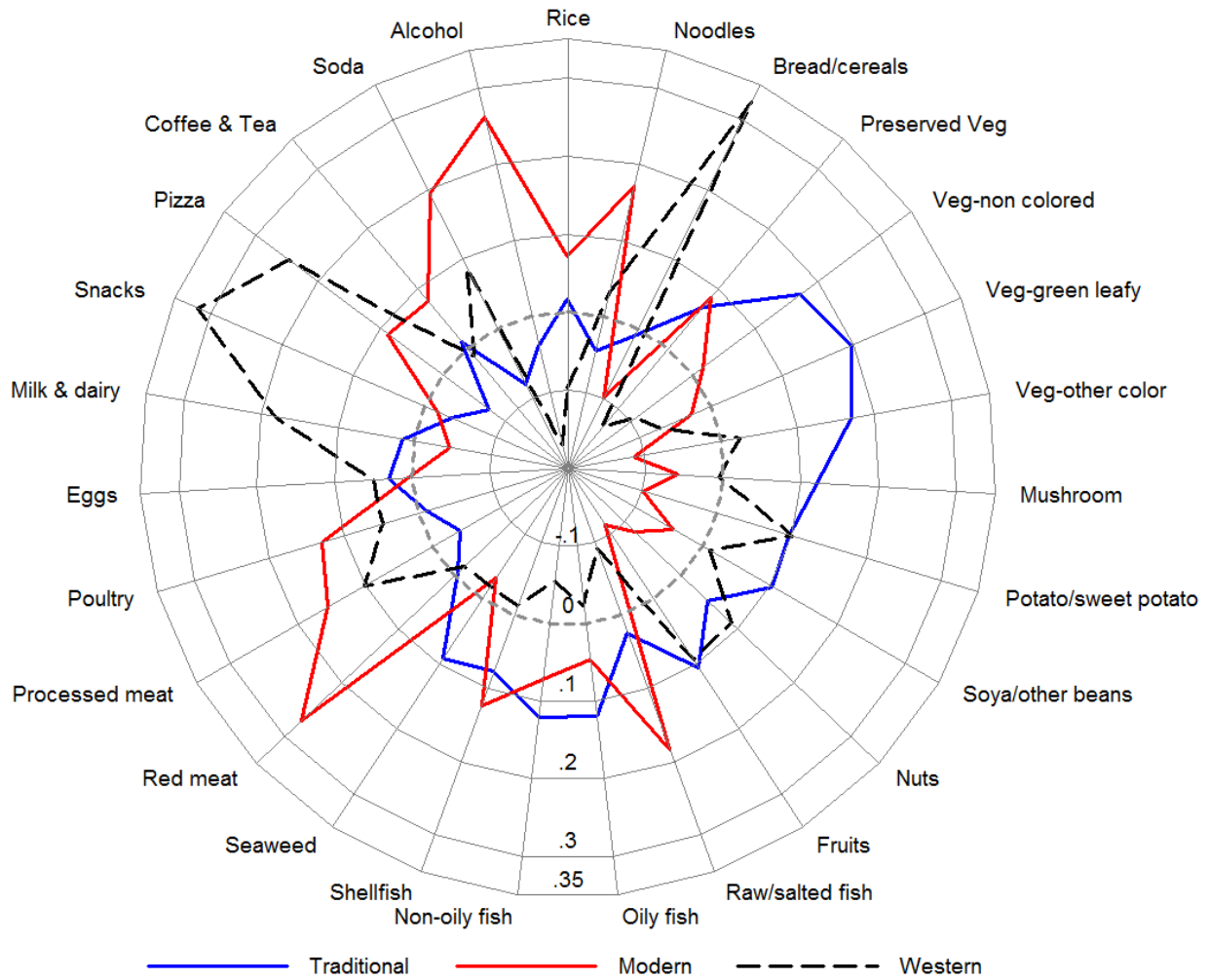


Figure 2.2. Bartlett scoring coefficients for the food groups

The Bartlett scoring coefficients for the food groups are based on a principal component analysis with varimax rotated factors (see text for details).





## Abstract

### Introduction

We evaluated the associations between the major Korean dietary patterns and the prevalence of diabetes and metabolic syndrome.

### Methods

We conducted a cross sectional study of the Kangbuk Samsung Health Study cohort who underwent a screening examination between January 2011 and December 2013 at the Kangbuk Samsung Total Healthcare Center in Seoul and Suwon, South Korea. We included 220,979 adult men and women who did not have any history of cardiovascular disease, cancer, diabetes, hypertension, and dyslipidemia. Diet was assessed using a validated 103-item food frequency questionnaire and principal component analysis was used to derive three major dietary patterns: traditional, modern, and Western Korean.

### Results

The crude prevalence of diabetes and metabolic syndrome was 1.4% and 8.3%, respectively. In the fully adjusted multivariable models, the odds ratio of diabetes comparing the 90<sup>th</sup> to the 10<sup>th</sup> percentile of dietary scores was 1.01 (95% CI 0.88, 1.16) for traditional, 1.32 (95% CI 1.13, 1.55) for modern, and 0.78 (95%CI 0.67, 0.91) for Western Korean dietary patterns. Likewise, the adjusted odds ratio of metabolic syndrome comparing the 90<sup>th</sup> to the 10<sup>th</sup> percentile of dietary scores was 1.01 (95% CI 0.95, 1.07) for traditional, 1.76 (95% CI 1.64, 1.88) for modern, and 0.73 (95% CI 0.69, 0.78) for Western Korean dietary patterns.



Compared to those without any metabolic syndrome criteria, the relative prevalent ratios of having one to two criteria for metabolic syndrome comparing the 90<sup>th</sup> to the 10<sup>th</sup> percentile of dietary scores were 1.02 (95%CI 0.99, 1.06) for traditional, 1.43 (95%CI 1.38, 1.48) for modern, and 0.85 (0.83, 0.88) for Western dietary patterns. The corresponding relative prevalent ratios of having three to five metabolic syndrome criteria comparing the 90<sup>th</sup> to the 10<sup>th</sup> percentile of dietary scores were 1.02 (95%CI 0.96, 1.09) for traditional, 2.14 (95%CI 2.00, 2.30) for modern, and 0.67 (0.63, 0.72) for Western dietary patterns.

### **Conclusion**

In this large cross-sectional study of young and middle-aged Korean men and women, we found no evidence of any associations between traditional Korean dietary patterns and the prevalence of diabetes or metabolic syndrome. Transition of diet to a more modern type pattern, characterized by higher intakes of meats and alcohol, were associated with higher odds of diabetes and metabolic syndrome. Higher adherence to Western Korean dietary patterns were associated with lower odds of diabetes and metabolic syndrome. We are uncertain on the benefits of this Western Korean dietary pattern and longer term studies are needed to better evaluate these associations.

## Introduction

The global prevalence of diabetes is rapidly increasing. The number of diabetics was predicted to increase from 171 to 366 million between 2000 and 2030.<sup>1</sup> However, rapid urbanization, nutrition and epidemiologic transition, and increasingly sedentary lifestyles have been associated with an exponential increase in prevalence estimates resulting in revised global projections of 382 (8.3%) to 592 million diabetics between 2013 and 2035.<sup>2-5</sup> In the United States, the 2012 prevalence of diabetes was estimated to be 12.3% among those aged  $\geq 20$  years olds resulting in total direct medical and indirect cost of \$176 and \$69 billion, respectively.<sup>6</sup>

Metabolic syndrome is a clustering of cardiovascular risk factors characterized by raised fasting glucose levels, central obesity, raised systolic blood pressure, raised triglyceride levels, and lowered high density lipoprotein cholesterol (HDL-C) levels.<sup>7</sup> These criteria represent different pathways of insulin resistance, low-grade inflammation, atherogenic dyslipidemia, oxidative stress, and endothelial dysfunction, which lead to cardiovascular disease and may be modified by diet.<sup>8-13</sup> The global prevalence of metabolic syndrome in adults is between 20-30%.<sup>14</sup> While the prevalence of central obesity increased from 45.4% to 56.1%, the prevalence of metabolic syndrome decreased slightly from 25.5% to 22.9% in the United States between 1999-2000 and 2009-2010.<sup>15</sup>

Dietary factors and physical inactivity was associated with 10% of the global disability-adjusted life-years (DALYS) in 2010.<sup>16</sup> In the United States, dietary factors was associated with 26% and 14% of deaths and DALYs, respectively, in 2010.<sup>17</sup> Dietary patterns compared to

individual dietary factors is a better exposure construct of diet because it acknowledges the complex interactions between nutrient, food, and food preparation.<sup>18</sup> Higher intakes of healthy food patterns, like the Mediterranean diet, and lower intakes of unhealthy patterns, like the meat based Western diet, have been associated with lower risk of diabetes and metabolic syndrome.<sup>19-23</sup> However the evidence on diet patterns and diabetes and metabolic syndrome in East Asia is more limited.<sup>24,25</sup> The aim of this study was to evaluate the associations between the major dietary patterns and the prevalence of diabetes and metabolic syndrome in a large asymptomatic Korean population.

## Methods

### *Study population*

The Kangbuk Samsung Health Study is a cohort of Korean men and women 18 years of age or older who underwent a comprehensive screening examination at the Kangbuk Samsung Total Healthcare Center in Seoul and Suwon, South Korea. Annual or biennial health screening examinations are widely performed in Korea, as health exams are mandatory for all workers under the Industrial Safety and Health Law.

A total of the 277,667 participants were screened at these centers from 2011 to 2013. We excluded 56,688 participants with any of the following comorbidities: history of cardiovascular disease (N=3,399), cancer (N=6,600), hypertension (N=23,395), diabetes (N=6,976), and dyslipidemia (N=29,132). The final sample size for this analysis was 220,979 participants.

This cross sectional study was approved by the Institutional Review Board of Kangbuk Samsung Hospital that exempted the requirement for informed consent because we only accessed de-identified data routinely collected as part of health screening examinations.

#### *Dietary assessment*

Dietary intake was collected routinely in the health screening examinations from 2011 onwards using a validated Food Frequency Questionnaire (FFQ). We used the first FFQ administration if participants had repeat FFQ information. The 103-item self-administered Food Frequency Questionnaire (FFQ) was designed to measure usual dietary habits in Korea.<sup>26</sup> The FFQ asked participants about their usual consumption of food items in the following food groups: rice and rice based noodles (3 items), noodles (6 items), bread (6 items), kimchi and preserved vegetables (5 items), non-colored vegetables (4 items), green leafy vegetables (8 items), other colored vegetables (7 items), mushrooms (2 items), potato (3 items), soya bean, soya bean products and other beans (4 items), nuts (1 items), fruits (11 items), raw or salted fish (2 items), oily fish (4 items), non-oily fish (4 items), shellfish (5 items), seaweed (2 items), meat (8 items), processed meat (1 items), poultry (1 items), eggs (1 items), milk and dairy products (4 items), snacks (3 items), pizza (1 items), coffee and tea (5 items), and soda and cola (1 items). We did not use the question on fat because it was non-specific in nature.

The FFQ had three predefined categories of portion size, ranging from small to large, and nine predefined categories of frequency, ranging from never to three times per day for foods and from never to five times per day or more for beverages. The average daily nutrient

intakes were estimated using a food composition table derived from the Korean Nutrient Society Database.<sup>27</sup> Daily alcohol intake was measured in the general self-administered questionnaire that included weekly frequency, amount consumed, and type of alcohol consumed. We derived three dietary pattern scores from the daily intake of the different food groups using post hoc principal components analysis and labelled them as traditional Korean, modern Korean, and Western Korean.

The traditional Korean dietary pattern was characterized by higher intakes of vegetables, mushrooms, potatoes, soya and other beans, fruits, oily and non-oily fish, shellfish, and seaweed. The modern Korean dietary pattern was characterized by higher intakes of noodles, raw or salted fish, shellfish, red meat, processed meat, poultry, soda, and alcohol. Western Korean patterns had higher intakes of bread and cereals, milk and dairy products, snacks, and pizza, and lower intakes of alcohol, rice, and preserved vegetables.

#### *Data collection*

Comprehensive health screening examinations were conducted at the clinics of the Kangbuk Samsung Hospital Total Healthcare Center in Seoul and Suwon. Socio demographic characteristics, smoking status, physical activity patterns, and history of comorbidities were collected using a self-administered questionnaire. Body height and weight was measured using a digital scale. Trained nurses measured sitting blood pressure using standard mercury sphygmomanometer.<sup>28</sup> Body mass index (BMI) was calculated as weight in kilograms divided by

height in meters square. Physical activity was assessed using a validated Korean version of the short form International Physical Activity Questionnaire (IPAQ).<sup>29</sup>

A phlebotomist collected blood from the ante-cubital veins of the participants after at least a 10-hour fast. Blood specimens were analyzed in the hospital central laboratory. The Laboratory Medicine Department at Kangbuk Samsung Hospital was accredited biannually by the Korean Society of Laboratory Medicine and participated in quality assurance programs of the Korean Society of Quality Assurance for Clinical Laboratories and the College of American Pathologist.

Serum total cholesterol and triglycerides were determined using an enzymatic colorimetric assay. Serum low- and high-density lipoprotein cholesterol (LDL-C and HDL-C, respectively) were directly measured using homogeneous enzymatic colorimetric assays. Serum fasting glucose and HbA1c was measured using the hexokinase and turbidimetric inhibition immunoassay methods, respectively. HbA1C measurements were standardized to the Diabetes Control and Complications Trials (DCCT) and the National Glycohemoglobin Standardization Program standards.

Metabolic syndrome represents an abnormal clustering of multiple metabolic risk factors. Participants with three or more of the following five factors are classified as having metabolic syndrome : 1) Central obesity, defined for Korean populations as having a waist circumference of  $\geq 90$ cm for males and  $\geq 85$ cm for females<sup>30</sup>; 2) Raised serum triglycerides, defined as  $\geq 1.7$  mmol/L (150 mg/dL); 3) Low high density lipoprotein cholesterol (HDL-C), defined as  $\leq 1.0$  mmol/L (40 mg/dL) for males and  $\leq 1.3$  mmol/L (50 mg/dL) for females; 4)

Raised blood pressure, defined as a systolic blood pressure of  $\geq 130$  mmHg, or a diastolic blood pressure  $\geq 85$  mmHg; and 5) Raised fasting blood sugar, defined as  $\geq 5.6$  mmol/L (100 mg/dL).<sup>7</sup>

Medication history was not used to classify any outcomes because the study population excluded anyone with a history of hypertension, diabetes, or dyslipidemia.

### *Statistical methods*

Descriptive statistics was used to summarize the distribution of characteristics in all participants and in those with high adherence to specific dietary patterns. We defined those in the third tertile as having high adherence to a specific dietary pattern. The prevalence of diabetes and metabolic syndrome were dichotomous outcomes and modeled using binary logistic regression. Participants were further categorized based on the number of metabolic syndrome criteria into three groups: nil, 1 to 2, and 3 to 5. We used multinomial logistic regression to model this three category outcome and estimated the relative prevalence ratio using those without any criteria for metabolic syndrome as the base group.

In these regression analyses, we fitted two hierarchical models: Model 1 adjusting for age (restricted cubic splines), sex, center, year of screening, and daily log transformed energy intake (restricted cubic splines of log energy), and Model 2 that further adjusts for education level (university or higher, college graduate, high school or lower), physical activity (inactive, minimally active, health-enhancing), smoking (never, former, current), and history of hormone replacement therapy. Restricted cubic splines for age and log-energy were created with knots at the 5<sup>th</sup>, 27.5<sup>th</sup>, 50<sup>th</sup>, 72.5<sup>th</sup>, and 95<sup>th</sup> percentile. We further explored a more flexible dose

response model between the different outcomes and the dietary scores using restricted cubic spline of each dietary pattern scores. We created splines with knots at the 5th, 35th, 65th, and 95th percentile.

We were not able to obtain dietary pattern scores in 58,593 (26.5%) of the 220,979 participants for the following reasons: no FFQ data (n=29,184; 13.2%); participants who reported extreme intakes of total energy defined as more than 2 interquartile ranges above the 75th percentile or below the 25th percentile of log transformed intake, corresponding to <338 and  $\geq$ 5209 kcal/day for females, and <503 and >4906 kcal/day for males (n=4,428; 2.0%), and insufficient FFQ data to derive diet scores (n=24,981; 11.3%). The proportion of missing information on education level, smoking status, and physical activity patterns was 42.1, 8.0, 2.0, and 1.1%, respectively. We used multiple imputations using chained equations to address missing data in the analysis.<sup>31, 32</sup> Missing covariate patterns were explored and imputation models refined to create 40 imputation sets with a burn-in of 10 iterations. Imputation diagnostics included graphical exploration of the mean and standard deviations of the imputed data across different iterations and sets. Two sided P-value < 0.05 were considered statistically significant. Statistical analyses were performed using Stata version 12 (StataCorp, Texas, USA).

## Results

The mean ( $\pm$ SD) age of the 220,979 participants was 39.9 $\pm$ 0.1 years (Table 3.1). The proportion of males, those with at least a university education, current smokers, and those with health enhancing physical activity patterns was 50.6%, 67.5%, 22.1%, and 16.8%, respectively.



Compared to those with high adherence to traditional Korean patterns, participants with high adherence to modern Korean patterns were more likely to be male, younger, have higher education levels, and currently smoke; they were also more likely to have higher intakes of alcohol and meat, and lower intakes of carbohydrate, vegetables, and fruits. Those with high adherence to Western Korean compared to traditional Korean dietary patterns were more likely to be female, younger, have higher education levels, have higher intakes of total fat and less likely to currently smoke and have lower intakes of vegetables and fruits.

Compared to an overall prevalence of 1.4%, the crude prevalence of diabetes in those with high adherence to traditional, modern, and Western Korean patterns was 1.8%, 1.6%, and 0.7%, respectively. (Table 3.2) In the fully adjusted multivariable models, the odds ratio of diabetes comparing the third to the first tertile for traditional, modern, and Western Korean dietary patterns were 1.02 (95%CI 0.91, 1.16;P trend=0.615), 1.24 (95% CI 1.09, 1.41;P trend=0.001), and 0.77 (95% CI 0.67, 0.88; P trend<0.001), respectively. The odds ratio of diabetes comparing the 90<sup>th</sup> to the 10<sup>th</sup> percentile of dietary scores was 1.01 (95% CI 0.88, 1.16) for traditional, 1.32 (95% CI 1.13, 1.55) for modern, and 0.78 (95%CI 0.67, 0.91) for Western Korean dietary patterns.

Compared to an overall prevalence of 8.3%, the crude prevalence of metabolic syndrome in those with high adherence to traditional, modern, and Western Korean patterns was 8.6%, 12.4%, and 5.4%, respectively.(Table 3.3) In fully adjusted multivariable models, the odds ratio of metabolic syndrome comparing the third to the first tertile of traditional, modern, and Western dietary patterns were 1.01 (95% CI 0.95, 1.06; P trend=0.727), 1.58 (95% CI 1.49,

1.68;  $P$  trend<0.001), and 0.75 (95% CI 0.71, 0.79;  $P$  trend<0.001), respectively. The odds ratio of metabolic syndrome comparing the 90<sup>th</sup> to the 10<sup>th</sup> percentile of dietary scores was 1.01 (95% CI 0.95, 1.07) for traditional, 1.76 (95% CI 1.64, 1.88) for modern, and 0.73 (95% CI 0.69, 0.78) for Western Korean dietary patterns.

Among those without metabolic syndrome, 52.9% did not meet any criteria and 38.8% met one to two criteria for metabolic syndrome. Using those with no metabolic syndrome criteria as the base referent group, the relative prevalent ratios of having one to two criteria for metabolic syndrome criteria comparing the third to the first tertile of traditional, modern, and Western dietary patterns were 1.01 (95% CI 0.98, 1.04;  $P$  trend=0.398), 1.31 (95% CI 1.27, 1.36;  $P$  trend<0.001), and 0.87 (95% CI 0.85, 0.90;  $P$  trend<0.001), respectively (Table 3.4). The corresponding relative prevalent ratios comparing the 90<sup>th</sup> to the 10<sup>th</sup> percentile of dietary scores were 1.02 (95%CI 0.99, 1.06) for traditional, 1.43 (95%CI 1.38, 1.48) for modern, and 0.85 (0.83, 0.88) for Western dietary patterns. Using those with no metabolic syndrome criteria as the base referent group, the relative prevalent ratio of having three to five metabolic syndrome criteria comparing the third to the first tertile of traditional, modern, and Western dietary patterns were 1.01 (95% CI 0.96, 1.07;  $P$  trend=0.572), 1.83 (95% CI 1.72, 1.94;  $P$  trend<0.001), and 0.70 (95% CI 0.66, 0.73;  $P$  trend<0.001), respectively. The corresponding relative prevalent ratios comparing the 90<sup>th</sup> to the 10<sup>th</sup> percentile of dietary scores were 1.02 (95%CI 0.96, 1.09) for traditional, 2.14 (95%CI 2.00, 2.30) for modern, and 0.67 (0.63, 0.72) for Western dietary patterns.

Using flexible dose response models, we further investigated the associations between dietary pattern scores and the individual criteria for metabolic syndrome – raised serum triglycerides (TG), low high density cholesterol (HDL-C), raised systolic blood pressure (SBP), raised fasting glucose, and central obesity (Figure 3.1). Comparing the 90<sup>th</sup> to the 10<sup>th</sup> percentile of traditional Korean dietary pattern scores, the fully adjusted odds ratio for raised TG was 0.91 (95% CI 0.87, 0.95); low HDL-C was 0.97 (95% CI 0.92, 1.02); raised SBP was 1.09 (95% CI 1.03, 1.15); raised fasting glucose was 1.11 (95% CI 1.06, 1.15); central obesity was 1.01 (95% CI 0.96, 1.05). Comparing the 90<sup>th</sup> to the 10<sup>th</sup> percentile of modern Korean dietary pattern scores, the fully adjusted odds ratio for raised TG was 1.55 (95% CI 1.47, 1.63); low HDL-C was 0.87 (95% CI 0.82, 0.91); raised SBP was 1.47 (95% CI 1.38, 1.57); raised fasting glucose was 1.63 (95% CI 1.56, 1.70); and central obesity was 1.69 (95% CI 1.62, 1.77). Comparing the 90<sup>th</sup> to the 10<sup>th</sup> percentile of Western Korean dietary pattern scores, the fully adjusted odds ratio for raised TG was 0.91 (95% CI 0.87, 0.95); low HDL-C was 0.97 (95% CI 0.92, 1.02); raised SBP was 1.09 (95% CI 1.03, 1.15); raised fasting glucose was 1.11 (95% CI 1.06, 1.15); and central obesity was 1.01 (95% CI 0.96, 1.05).

## Discussion

In this large cross-sectional study of young and middle-aged Korean men and women who participated in a health screening program, higher adherence to modern Korean dietary patterns were significantly associated with higher odds of diabetes, insulin resistance, metabolic syndrome, raised triglycerides, systolic blood pressure, fasting glucose, and central

obesity, and lower odds of low HDL-C. Higher adherence to traditional Korean dietary patterns was only significantly associated with lower odds of insulin resistance, raised triglycerides, and higher odds of raised systolic blood pressure and fasting glucose. Higher adherence to Western Korean dietary patterns were significantly associated with lower of diabetes, metabolic syndrome, raised triglycerides, systolic blood pressure, fasting glucose, low HDL-C, and higher odds of central obesity.

The association between diet and cardiovascular health was highlighted in large population based studies in the mid-1950s by Ancel Keys.<sup>33,34</sup> The use of dietary patterns as an exposure construct is more recent and intuitive compared to nutrient analysis. Though there are many different opinions on what constitutes a healthy diet, it typically has higher intakes of whole grain, fresh fruits and vegetables, vegetable oils high in mono- or poly-unsaturated fat, moderate intakes of seafood (8-12 oz. per week), low-fat milk and dairy, and lower intakes of refined grain or processed carbohydrates, red and processed meat, fast food, alcohol, sugar sweetened beverages, and foods high in saturated and trans fats.

Diets like the Mediterranean and DASH have been associated with lower risk of diabetes and metabolic syndrome. In a review of 10 studies comprising 190,301 participants, adherence to a healthy type dietary pattern was associated with a 32% decrease in risk for diabetes (95% CI 0.58, 0.79).<sup>20</sup> Healthy type dietary patterns were defined as ones with higher intakes of fruits and vegetables, whole grains, fish, and poultry, and by lower intakes of red meat, processed foods, sugar-sweetened beverages, and starchy foods. In the Nurses Health Studies (NHS) II, the relative risks comparing the highest and lowest quintile for intakes of whole grain and bran,

were 0.68 (95%CI 0.57, 0.81) and 0.64 (95 CI% 0.54, 0.76), respectively.<sup>21</sup> The Women's Health Initiative, a large randomized control trial in 48,835 post-menopausal women, found no significant associations between incidence of CHD, stroke, or CVD, and a dietary intervention that advised lower intakes of total dietary fat and higher intakes of vegetables, fruits, and grains.<sup>22</sup> In spite of decreasing total fat intake and increasing intakes of vegetables, fruits and grains, there was no significant difference in mean changes of glucose at Year 3 post randomization between the intervention and comparison group. The heterogeneity in the associations of grain intake and diabetes may be a result of the differential effect of whole and refined grains. In a recent review of sixteen cohorts, the relative risks for diabetes comparing high versus low intakes of total whole grain and refined grain were 0.74 (95% CI 0.71, 0.78) and 0.94 (95% CI 0.82, 1.09), respectively.<sup>23</sup>

A meta-analysis, pooling results from 8 studies with 10,399 subjects, summarized that a higher adherence to Mediterranean type diets was associated with a 50% decreased risk for metabolic syndrome.<sup>19</sup> The estimates for the individual criteria were not pooled because of substantial heterogeneity, however, higher adherence to Mediterranean type diet was consistently associated with lower levels of waist circumference, serum triglycerides, fasting glucose, and higher levels of HDL-C. No association was seen with blood pressure levels. A Korean study of 4,984 women between August 2002 and May 2007 summarized that the age-adjusted odds ratio of Metabolic syndrome comparing the highest to the lowest quartiles of the Western, healthy, and traditional was 0.87 (95% CI 0.54, 1.20; P trend=0.304), 0.58 (95% CI 0.50, 0.91; P trend=0.012), and 1.05 (95% CI 0.79, 1.40; P trend=0.873), respectively.<sup>24</sup>

However, residual confounding was an important limitation. In a cluster analysis of 4,730 subjects from the Korean National Health and Nutrition Examination Survey III (KNHANES III) in 2005 concluded that adjusted odds ratio of metabolic syndrome was 1.21 (95% CI 0.92, 1.58) for the Meats & Alcohol group, and 0.92 (95% CI 0.75, 1.13) for the Korean Healthy group compared to the traditional group.<sup>25</sup>

This study has a few limitations. First, causation cannot be inferred because cross-sectional study designs limits the assumption of exposure temporality. However, we excluded anyone with history of hypertension, diabetes, or dyslipidemia, to reduce the possibility of reverse causation. Second, although we controlled for several important confounders in the multivariable models, these associations are still susceptible to residual confounding due to unmeasured confounders or incomplete adjustment. Third, measurement error of diet is a problem and non-differential misclassification bias may dilute the associations. However, an advantage of using dietary patterns over single nutrients as an exposure is that it estimates a larger effect. Fourth, our study population was asymptomatic young and middle-aged Korean men and women, the extrapolation of these results to other populations are unknown. Fifth, the much younger age distribution of those with high adherence to Western Korean dietary patterns makes interpretation of its associations more difficult. The lower prevalence of diabetes and metabolic syndrome among those with high adherence to the Western Korean dietary patterns may be due to a combination of the younger age distribution and the latency of the diet exposure. Further follow-up of this group is required to better investigate the associations of the Western Korean dietary patterns with diabetes and metabolic syndrome.

Our study has some strengths. This is one of the largest population-based study investigating the associations between major dietary patterns and the prevalence of diabetes and metabolic syndrome. The large sample size results in precise estimates of the associations. Second, data from participants were collected using standardized methods and all blood were analyzed in an accredited central laboratory in the hospital. Third, data management and analysis were documented with audit trails of major version changes. Fourth, we used multiple imputations to address the issue of missing data.

In this large cross-sectional study of young and middle-aged Korean men and women, we found no evidence of any associations between traditional Korean dietary patterns and the prevalence of diabetes or metabolic syndrome. Transition of diet patterns to a more modern type pattern, characterized by higher intakes of meats and alcohol, were associated with higher odds of diabetes and metabolic syndrome. Higher adherence to Western Korean dietary patterns were associated with lower odds of diabetes and metabolic syndrome but longer term studies are needed to better evaluate this specific pattern.

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Table 3.1 Characteristics of study participants (N=220,979)

	Overall	Traditional pattern*	Modern pattern*	Western pattern*
	% (SE) or Mean±SE			
Male	50.6 (0.1)	45.1 (0.2)	81.2 (0.2)	41.3 (0.2)
Age (years)	39±0.1	41.2±0.1	37.2±0.1	35.9±0.1
Education level				
University or higher	67.5 (0.1)	69.2 (0.2)	72.8 (0.2)	74.8 (0.2)
Technical college	14.0 (0.1)	13.0 (0.1)	13.1 (0.2)	13.1 (0.1)
High school or lower	18.5 (0.1)	17.8 (0.2)	14.1 (0.2)	12.1 (0.1)
Smoking status				
Never	62.6 (0.1)	65.8 (0.2)	39.5 (0.2)	73.3 (0.2)
Former	15.3 (0.1)	15.1 (0.2)	20.5 (0.2)	11.7 (0.1)
Current	22.1 (0.1)	19.1 (0.2)	40.0 (0.2)	15.0 (0.1)
Physical activity patterns				
Inactive	47.9 (0.1)	39.2 (0.2)	45.9 (0.2)	49.0 (0.2)
Minimally active	35.4 (0.1)	38.6 (0.2)	38.1 (0.2)	35.7 (0.2)
Health-enhancing	16.8 (0.1)	22.2 (0.2)	16.1 (0.2)	15.3 (0.1)
Body mass index (kg/m <sup>2</sup> )	22.9±0.1	23.0±0.1	23.9±0.1	22.5±0.1
Daily dietary intake				
Total energy, Kcal/day	1589±2	1904±3	1888±3	1757±3
Carbohydrate, %TE	65.8 (0.1)	65.4 (0.1)	61.8 (0.1)	64.7 (0.1)
Protein, %TE	13.1 (0.1)	14.1 (0.1)	13.2 (0.1)	13.4 (0.1)
Total fat, %TE	16.2 (0.1)	16.7 (0.1)	17.2 (0.1)	18.9 (0.1)
Alcohol, %TE	5.0 (0.1)	3.9 (0.1)	7.8 (0.1)	3.0 (0.1)
Vegetable, Kcal/day	53±1	80±1	58±1	49±1
Fruit, Kcal/day	89±1	133±1	76±1	103±1
Meat, Kcal/day	138±1	166±1	210±1	155±1

\* Characteristics of participants in the third tertile of dietary pattern scores; representing those with high adherence to the dietary pattern

\*\*Age and sex had no missing information. The availability of other covariates was: education (N=181,833), smoking (N=185,765), physical activity (N=213,686), body mass index (N=220,581), daily dietary intakes and dietary pattern information (N=162,386), metabolic syndrome (N=185,758), and diabetes (N=220,795). We use multiple imputation to address missingness in this analysis.

Table 3.2. Association between Korean dietary patterns and diabetes (N=220,979)

	Tertile 1	Tertile 2	Tertile 3	P trend	P90 vs P10	P
	Adjusted odds ratio (95% CI) or Prevalence, % (SE)					
Traditional pattern						
Prevalence	1.1 (0.1)	1.3 (0.1)	1.8 (0.1)			
Model 1	1.00 (ref)	0.94 (0.84, 1.05)	0.97 (0.86, 1.10)	0.725	0.95 (0.83, 1.09)	0.449
Model 2	1.00 (ref)	0.96 (0.86, 1.07)	1.02 (0.91, 1.16)	0.615	1.01 (0.88, 1.16)	0.867
Modern pattern						
Prevalence	1.3 (0.1)	1.4 (0.1)	1.6 (0.1)			
Model 1	1.00 (ref)	1.12 (1.00,1.26)	1.35 (1.19, 1.53)	<0.001	1.45 (1.24, 1.68)	<0.001
Model 2	1.00 (ref)	1.09 (0.97, 1.22)	1.24 (1.09, 1.41)	0.001	1.32 (1.13, 1.55)	0.001
Western pattern						
Prevalence	2.4 (0.1)	1.3 (0.1)	0.7 (0.1)			
Model 1	1.00 (ref)	0.83 (0.75, 0.91)	0.7 (0.61, 0.8)	<0.001	0.71 (0.61, 0.82)	<0.001
Model 2	1.00 (ref)	0.87 (0.79, 0.97)	0.77 (0.67, 0.88)	<0.001	0.78 (0.67, 0.91)	0.002

\* Overall prevalence of diabetes=1.4%; Model 1 adjusted for age, sex, center, year of screening, and total daily energy intake. Model 2 additionally adjusted for education level (university or higher, college graduate, or high school or lower), physical activity (inactive, minimally active, health-enhancing), smoking status (never, former, or current), and history hormone replacement therapy.

Table 3.3. Association between Korean dietary patterns and metabolic syndrome (N=220,979)

	Tertile 1	Tertile 2	Tertile 3	P trend	P90 vs P10	P
	Adjusted odds ratio (95% CI) or Prevalence, % (SE)					
<b>Traditional pattern</b>						
Prevalence	7.8 (0.1)	8.3 (0.1)	8.6 (0.1)			
Model 1	1.00 (ref)	0.95 (0.91, 0.99)	0.94 (0.89, 0.99)	0.030	0.93 (0.88, 0.99)	0.019
Model 2	1.00 (ref)	0.98 (0.94, 1.03)	1.01 (0.95, 1.06)	0.727	1.01 (0.95, 1.07)	0.724
<b>Modern pattern</b>						
Prevalence	5.0 (0.1)	7.6 (0.1)	12.4 (0.1)			
Model 1	1.00 (ref)	1.20 (1.14, 1.27)	1.74 (1.64, 1.85)	<0.001	1.96 (1.84, 2.1)	<0.001
Model 2	1.00 (ref)	1.16 (1.09, 1.22)	1.58 (1.49, 1.68)	<0.001	1.76 (1.64, 1.88)	<0.001
<b>Western pattern</b>						
Prevalence	12.0 (0.1)	8.1 (0.1)	5.4 (0.1)			
Model 1	1.00 (ref)	0.82 (0.78, 0.85)	0.68 (0.64, 0.71)	<0.001	0.66 (0.62, 0.70)	<0.001
Model 2	1.00 (ref)	0.87 (0.83, 0.91)	0.75 (0.71, 0.79)	<0.001	0.73 (0.69, 0.78)	<0.001

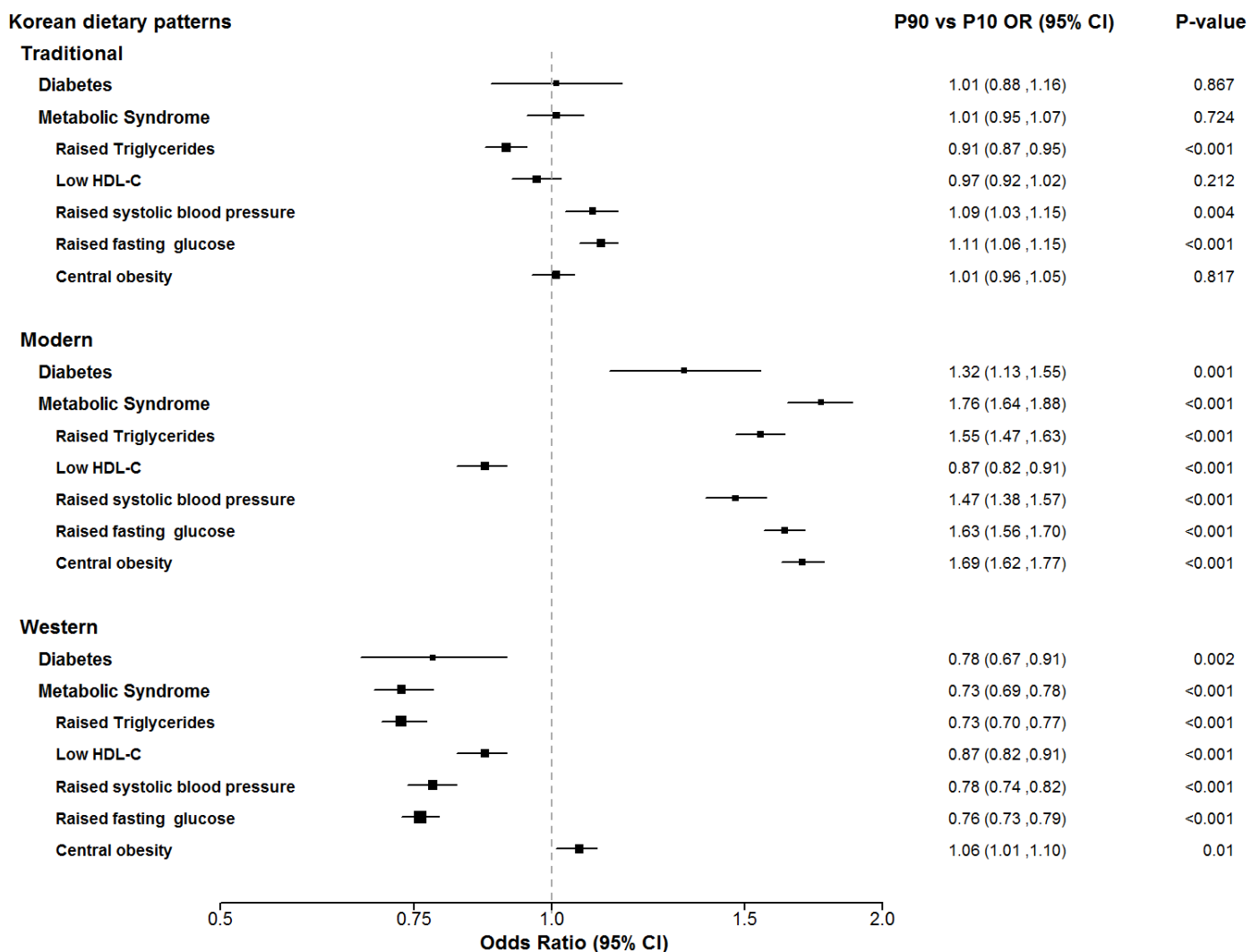
\* Overall prevalence of metabolic syndrome=8.3%; Model 1 adjusted for age, sex, center, year of screening, and total daily energy intake. Model 2 additionally adjusted for education level (university or higher, college graduate, or high school or lower), physical activity (inactive, minimally active, health-enhancing), smoking status (never, former, or current), and history hormone replacement therapy.

Table 3.4. Association between Korean dietary patterns and number of metabolic syndrome criteria (N=220,979)

	Tertile 1	Tertile 2	Tertile 3	P trend	P90 vs P10	P
	Adjusted odds ratio (95% CI) or Prevalence, % (SE)					
No MS criteria	Base group	Base group	Base group	-	Base group	-
1-2 MS criteria						
Traditional pattern						
Prevalence	37.4 (0.1)	39.1 (0.1)	39.8 (0.1)			
Model 1	1.00 (ref)	0.99 (0.96, 1.02)	0.98 (0.95, 1.01)	0.134	0.98 (0.95, 1.01)	0.206
Model 2	1.00 (ref)	1.01 (0.98, 1.04)	1.01 (0.98, 1.04)	0.398	1.02 (0.99, 1.06)	0.198
Modern pattern						
Prevalence	33.5 (0.1)	38.4 (0.1)	44.6 (0.1)			
Model 1	1.00 (ref)	1.12 (1.09, 1.15)	1.37 (1.33, 1.42)	<0.001	1.50 (1.45, 1.56)	<0.001
Model 2	1.00 (ref)	1.10 (1.07, 1.13)	1.31 (1.27, 1.36)	<0.001	1.43 (1.38, 1.48)	<0.001
Western pattern						
Prevalence	44.4 (0.1)	38.8 (0.1)	33.9 (0.1)			
Model 1	1.00 (ref)	0.89 (0.87, 0.91)	0.82 (0.8, 0.84)	<0.001	0.80 (0.77, 0.82)	<0.001
Model 2	1.00 (ref)	0.92 (0.90, 0.95)	0.87 (0.85, 0.9)	<0.001	0.85 (0.83, 0.88)	<0.001
3-5 MS criteria						
Traditional pattern						
Prevalence	7.8 (0.1)	8.3 (0.1)	8.8 (0.1)			
Model 1	1.00 (ref)	0.94 (0.90, 0.99)	0.93 (0.88, 0.98)	0.012	0.92 (0.87, 0.98)	0.011
Model 2	1.00 (ref)	0.99 (0.94, 1.04)	1.01 (0.96, 1.07)	0.572	1.02 (0.96, 1.09)	0.464
Modern pattern						
Prevalence	5.0 (0.1)	7.6 (0.1)	12.4 (0.1)			
Model 1	1.00 (ref)	1.28 (1.21, 1.35)	2.07 (1.95, 2.19)	<0.001	2.46 (2.29, 2.63)	<0.001
Model 2	1.00 (ref)	1.22 (1.15, 1.29)	1.83 (1.72, 1.94)	<0.001	2.14 (2.00, 2.30)	<0.001
Western pattern						
Prevalence	12.0 (0.1)	8.1 (0.1)	5.4 (0.1)			
Model 1	1.00 (ref)	0.76 (0.73, 0.80)	0.61 (0.58, 0.64)	<0.001	0.58 (0.55, 0.62)	<0.001
Model 2	1.00 (ref)	0.83 (0.79, 0.86)	0.70 (0.66, 0.73)	<0.001	0.67 (0.63, 0.72)	<0.001

\* Overall prevalence of fulfilling no metabolic syndrome criteria=52.9%, 1 to 2 metabolic syndrome criteria=38.8%, and 3 to 5 metabolic syndrome criteria = 8.3%; Model 1 adjusted for age, sex, center, year of screening, and total daily energy intake. Model 2 additionally adjusted for education level (university or higher, college graduate, or high school or lower), physical activity (inactive, minimally active, health-enhancing), smoking status (never, former, or current), and history hormone replacement therapy.

Figure 3.1. Association between Korean dietary patterns and prevalence of diabetes and metabolic syndrome (N=220,979)



\*\* Adjusted for age, sex, center, year of screening, total daily energy intake, education level (university or higher, college graduate, or high school or lower), physical activity (inactive, minimally active, health-enhancing), smoking status (never, former, or current), and history hormone replacement therapy.





## Abstract

### Introduction

The literature on the associations between dietary patterns and subclinical atherosclerosis is limited and inconclusive. Our objective was to evaluate the associations between major dietary patterns and subclinical atherosclerosis in a large Korean screening population.

### Methods

We conducted a cross sectional analysis of the Kangbuk Samsung Health Study cohort who had their coronary artery calcium score and diet measured during a screening examination between January 2011 and December 2013 at the Kangbuk Samsung Total Healthcare Center in Seoul and Suwon, South Korea. We included 27,028 adult men and women who were did not have any history of cardiovascular disease, cancer, diabetes, hypertension, and dyslipidemia. Diet was assessed using a validated 103-item food frequency questionnaire and principal component analysis was used to derive three major dietary patterns: traditional, modern, and Western Korean.

### Results

The prevalence of CACS 1-10 AU and CACS>10 was 3.6% (n=985) and 4.6% (n=1,250), respectively. The adjusted CACS ratio comparing the third to the first tertile for the traditional, modern, and Western Korean patterns were 0.88 (95% CI 0.58, 1.34; P trend=0.539), 1.16 (95% CI 0.75, 1.80; P trend=0.483), and 0.86 (95%CI 0.59, 1.25; P trend=0.405), respectively. The adjusted CACS ratio comparing the 90<sup>th</sup> to the 10<sup>th</sup> percentile for the traditional, modern, and

Western Korean patterns were 0.93 (95% CI 0.57, 1.50; P=0.759), 1.19 (95% CI 0.70, 2.05; P=0.518), and 0.84 (95%CI 0.54, 1.29; P=0.420), respectively.

### **Conclusion**

In this large cross-sectional study of asymptomatic young to middle aged Korean men and women, we failed to find any significant associations between traditional, modern, and Western dietary patterns, and subclinical atherosclerosis measured using coronary artery calcium scores.

## Introduction

Ischemic heart disease and cerebrovascular disease were responsible for 12.7% and 11.3% of the 55 million worldwide deaths in 2011.<sup>1</sup> Despite a decline in the United States since 1968, major cardiovascular disease remains the leading cause of death accounting for 778,503 (30.9%) of all deaths in 2011.<sup>2, 3</sup> Ischemic heart disease was the leading contributor to years of life lost (15.9% of all years of life lost) and disability-adjusted life-years in the United States in 2010.<sup>4</sup> Coronary artery calcium (CAC) is a marker of subclinical atherosclerosis and CAC score progression is associated with higher risk of cardiac events and all-cause mortality.<sup>5-8</sup> In a pooled analysis of eight studies (n=6,521), the relative risk for all-cause mortality or cardiovascular events among those with a CAC score of  $\geq 10$  was 5.47 times those with scores  $< 10$ .<sup>9</sup>

Keys in the 1950's made the argument that diets high in fat, specifically saturated fats, was associated with higher rates of CHD.<sup>10, 11</sup> However, recent reviews of the associations of dietary fat and CVD have been inconclusive with substantial heterogeneity in the pooled estimates.<sup>12-16</sup> The difficulty in translating nutritional epidemiological research was highlighted when two trials reported no significant associations between low-fat diet interventions and CVD risk.<sup>17, 18</sup> Other limitations of nutritional research include a lack of reproducibility and generalizability, small effect sizes, residual confounding, and measurement error.<sup>19, 20</sup> Food items strongly correlate and it is difficult to estimate the independent association of a nutrient that is present in multiple foods. Dietary patterns, as an alternative exposure construct of diet, acknowledges the complex interactions between nutrients and food items, are easily interpreted, and may be easier to translate to effective interventions using food substitution.

The Mediterranean diet pattern has been consistently associated with cardiovascular benefits.<sup>21-23</sup> The DASH diet is another promising dietary intervention that has been associated with short term benefits, however, evidence on longer term cardiovascular benefits have been inconclusive.<sup>24-29</sup> The literature on dietary patterns and subclinical atherosclerosis is more limited.<sup>30-32</sup> We aimed to evaluate the associations of three major dietary patterns and prevalence of subclinical atherosclerosis in a large Korean asymptomatic screening population.

## Methods

### *Study population*

The Kangbuk Samsung Health Study is a cohort of Korean men and women 18 years of age or older who underwent a comprehensive annual or biennial examination at the Kangbuk Samsung Total Healthcare Center in Seoul and Suwon, South Korea. Annual or biennial health screening exams are widely performed in Korea, as health exams are mandatory for all workers under the Industrial Safety and Health Law.

A total of 38,466 participants had their coronary calcium measured and completed a Food Frequency Questionnaire during the same visit between January 2011 and December 2013). If participants had repeated CAC measurements or FFQ administrations, we only used the first measurement for this analysis. We further excluded 11,438 participants with any of the following comorbidities: history of cardiovascular disease (N=442), cancer (N=894), hypertension (N=4,686), diabetes (N=1,440), and dyslipidemia (N=7,119). The final sample size for this analysis was 27,028 participants.

This study cross sectional study was approved by the Institutional Review Board of Kangbuk Samsung Hospital that exempted the requirement for informed consent as we only accessed de-identified data routinely collected as part of health screening exams.

#### *Data collection*

Comprehensive health screening examinations were conducted at the clinics of the Kangbuk Samsung Hospital Total Healthcare Center in Seoul and Suwon. Socio demographic characteristics, smoking status, physical activity patterns, and history of comorbidities were collected using a self-administered questionnaire. Height, weight, and sitting blood pressure was measured by trained nurses. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squares.

#### *Dietary assessment*

Dietary intake was collected routinely in the health screening examinations from 2011 onwards using a validated Food Frequency Questionnaire (FFQ). We used the first FFQ administration if participants had repeat FFQ information. The 103-item self-administered Food Frequency Questionnaire (FFQ) was designed to measure usual dietary habits in Korea.<sup>33</sup> The FFQ asked participants about their usual consumption of food items in the following food groups: rice and rice based noodles (3 items), noodles (6 items), bread (6 items), kimchi and preserved vegetables (5 items), non-colored vegetables (4 items), green leafy vegetables (8 items), other colored vegetables (7 items), mushrooms (2 items), potato (3 items), soya bean, soya bean products and other beans (4 items), nuts (1 items), fruits (11 items), raw or salted fish (2 items), oily fish (4 items), non-oily fish (4 items), shellfish (5 items), seaweed (2 items), meat (8 items), processed meat (1 items), poultry (1 items), eggs (1 items), milk and dairy

products (4 items), snacks (3 items), pizza (1 items), coffee and tea (5 items), and soda and cola (1 items). We ignored one item on fats due to the non-specific nature of the question.

The FFQ had three predefined categories of portion size, ranging from small to large, and nine predefined categories of frequency, ranging from never to three times per day for foods and from never to five times per day or more for beverages. The average daily nutrient intakes were estimated using a food composition table derived from the Korean Nutrient Society Database.<sup>34</sup> Daily alcohol intake was measured in the general self-administered questionnaire and included weekly frequency, amount consumed, and type of alcohol consumed. We derived three dietary pattern scores from the daily intake of the different food groups, labelled as traditional Korean, modern Korean, and Western Korean, using principal component analysis with varimax rotation. These three dietary patterns explained 42.2% of the variation in daily dietary intakes.

The traditional Korean dietary pattern was characterized by higher intakes of vegetables, mushrooms, potatoes, soya and other beans, fruits, oily and non-oily fish, shellfish, and seaweed. The modern Korean dietary pattern was characterized by higher intakes of noodles, raw or salted fish, shellfish, red meat, processed meat, poultry, soda, and alcohol. Western Korean patterns had higher intakes of bread and cereals, milk and dairy products, snacks, and pizza, and lower intakes of alcohol, rice, and preserved vegetables.

#### *Measurement of Coronary Artery Calcium*

All coronary artery calcium scores were measured from multi detector computed tomography scans. These scans were obtained with a Lightspeed VCT XTe-64 slice MDCT scanner (GE Healthcare, Tokyo, Japan) with the same standard scanning protocol using 32\*2.5-

mm section collimation, 400 ms rotation time, 120 kV tube voltage, and 124 mAS (310 mA\*0.4 second) tube current under ECG-gated dose modulation. Quantitative CAC scores were calculated by the method proposed Agatston et al.<sup>35</sup> The inter-observer and intra-observer intraclass correlation coefficient for CAC measurements at these centers were excellent (0.99 for both).<sup>36</sup>

### *Statistical Methods*

Descriptive statistics was used to summarize the distribution of participant characteristics by CAC score categories and in those with high adherence to specific dietary patterns. We defined those in the third tertile as having high adherence to a specific dietary pattern.

Coronary artery calcium is estimated using the Agatston score, which multiplies the lesion area by its density. The density of a lesion is based on the CT attenuation and measured using Hounsfield units. Densities below a threshold of 130 Hounsfield units (HU) within a 1mm<sup>3</sup> area are ignored to decrease imaging noise. We assumed that CAC scores followed a log-normal distribution with left censored values at 0 Agatston Units (AU). We investigated the association between dietary patterns and CAC scores by modelling the outcome continuously and categorically. For the primary analysis, we modeled the natural log (CAC score + 1) using Tobit regression to estimate CAC score ratios comparing the second and third tertile of the dietary pattern scores to the first.<sup>37</sup> To test for a linear trend in the dietary pattern, we included the median values of each tertile as a continuous variable in the regression models. We used logistic regression to model the prevalence of detectable CAC (CAC score >0AU). Based on the distribution of CAC score in this low risk study population, we categorized CAC score into three



categories 0 AU, 1 to 10 AU, and >10 AU. The relative prevalence of CAC 1 to 10 AU and >10 AU was modeled using multinomial logistic regression with CAC score=0 AU as the base group.

In these regression analyses, we fitted two models: a model adjusting for age (restricted cubic splines), sex, center, year of screening, and daily energy intake (restricted cubic splines of log energy), and a model that further adjusted for education level (university or higher, college graduate, high school or lower), physical activity (inactive, minimally active, health-enhancing), and smoking (never, former, current). Restricted cubic splines for age and log-energy were created with knots at the 5<sup>th</sup>, 27.5<sup>th</sup>, 50<sup>th</sup>, 72.5<sup>th</sup>, and 95<sup>th</sup> percentile. We further explored a more flexible shape of the dose response relationship between the dietary scores and CAC scores using restricted cubic spline of each dietary pattern scores. We created splines with knots at the 5<sup>th</sup>, 35<sup>th</sup>, 65<sup>th</sup>, and 95<sup>th</sup> percentile.

We were not able to obtain dietary pattern scores in 11,372 participants (42.1%) because participants either reported extreme intakes of total energy defined as more than 2 interquartile ranges above the 75th percentile or below the 25th percentile of log transformed intake (n=558; 2.1%), or there was insufficient FFQ data to derive the dietary pattern scores (n=10,814; 40.0%). The proportion of participants with missing information on education level, smoking status, and physical activity patterns was 8.0, 2.0, and 1.1%, respectively. We used multiple imputations to address missing data in the analysis.<sup>38, 39</sup> Missing covariate patterns were explored and imputation models refined to create 50 imputation sets with a burn in of 10 iterations. Imputation diagnostics included graphical exploration of the mean and standard deviations of the imputed data across different iterations and sets. Two sided P-value <0.05

were considered statistically significant. Statistical analyses were performed using Stata version 12 (StataCorp, Texas, USA).

## Results

The mean ( $\pm$ SD) age of the 27,028 participants were  $39.9\pm 6.4$  years (Table 4.1). The proportion of males, those with at least a university education, current smokers, and those with health enhancing physical activity patterns was 77.0%, 73.4%, 27.9%, and 16.4%, respectively. Participants with CAC scores  $>10$  AU compared to those with undetectable CAC scores were more likely to be male, older, have higher BMI, currently smoke and have health-enhancing physical activity patterns. The total energy intake and proportion of energy from carbohydrate, protein were similar in those with undetectable CAC, CAC score 1 to 10 AU, and CAC score  $>10$  AU.

Those with high adherence to traditional compared to modern Korean dietary patterns were more likely to be female, older, have lower levels of education, increased physical activity, and less likely to be current smokers. (Table 4.2) Those with high adherence to Western compared to traditional Korean dietary patterns were more likely to be younger and have higher levels of education, and less likely to be current smokers and physically active. The proportion of total energy for those with high adherence to traditional, modern, and Western dietary patterns from carbohydrate was 64.4%, 61.7%, and 64.3%, respectively; from protein was 14.0%, 13.3%, and 13.5%, respectively; from total fat was 16.6%, 17.0%, and 18.3%, respectively; and from alcohol was 5.0%, 8.0%, and 3.8%, respectively.

The fully adjusted CAC score ratio comparing the third to the first tertile for the traditional, modern, and Western Korean patterns were 0.88 (95% CI 0.58, 1.34; P trend=0.539), 1.16 (95% CI 0.75, 1.80; P trend=0.483), and 0.86 (95%CI 0.59, 1.25; P trend=0.405), respectively. (Table 4.3) We also used multivariable adjusted models with restricted cubic splines for the dietary patterns scores to allow a more flexible representation of the dose-response associations. The fully adjusted CAC score ratio comparing the 90<sup>th</sup> to the 10<sup>th</sup> percentile for the traditional, modern, and Western Korean patterns were 0.93 (95% CI 0.57, 1.50), 1.19 (95% CI 0.70, 2.05), and 0.84 (95% CI 0.54, 1.29), respectively.

The fully adjusted odds ratio of detectable CAC (CACS>0) comparing the third to the first tertile for the traditional, modern, and Western Korean patterns were 0.94 (95% CI 0.79, 1.13; P trend=0.514), 1.06 (95% CI 0.89, 1.28; P trend=0.500), and 0.95 (95%CI 0.81, 1.11; P trend=0.500), respectively. (Table 4.4) The fully adjusted relative prevalence ratio of CACS 1-10 AU comparing the third to the first tertile for the traditional, modern, and Western Korean patterns were 0.96 (95% CI 0.76, 1.21; P trend=0.742), 1.02 (95% CI 0.81, 1.29; P trend=0.877), and 0.96 (95%CI 0.77, 1.21; P trend=0.876), respectively. The corresponding relative prevalence ratio of CACS>10 AU comparing the third to the first tertile for the traditional, modern, and Western Korean patterns were 0.93 (95% CI 0.73, 1.18; P trend=0.532), 1.10 (95% CI 0.86, 1.40; P trend=0.423), and 0.94 (95%CI 0.76, 1.16; P trend=0.413), respectively.

## Discussion

In this large cross-sectional study of young and middle-aged asymptomatic men and women who participated in a screening program, we did not find any significant association

between the traditional, modern, and Western Korean dietary patterns and coronary artery calcium scores. Higher adherence to the traditional and Western Korean dietary pattern was associated with a 12% and 14% non-significant decrease in CAC score ratios, whereas, higher adherence to the modern Korean dietary pattern was associated with a 16% non-significant increase in CAC score ratios (all  $P > 0.05$ ).

The null findings of our study was similar to the only other study that investigated the association between empirically derived dietary patterns and coronary artery calcium scores. Four dietary patterns were derived in 5,089 participants aged 45-84 years from the MESA cohort using principal component analysis and labelled as “Fats and Processed Meat”, “Vegetables and Fish”, “Beans, Tomatoes, and Refined Grains”, and “Whole grain and Fruit”. There was no evidence of an association between any of these derived dietary patterns and coronary artery calcium and carotid intima media thickness.<sup>31</sup>

A more common research question has been the association between diet patterns and cardiovascular disease. A recent review estimated that higher adherence to a Mediterranean type diet was associated with pooled reductions of 8% and 10% in overall mortality and CVD events, respectively.<sup>23</sup> In the Whitehall II cohort, the healthy pattern (fruit, vegetables, whole-meal bread, low-fat dairy and little alcohol) reduced the adjusted hazard of CVD events by 29% (95% CI 0.51, 0.98) compared to the unhealthy pattern (white bread, processed meat, fries, and full-cream milk) but no significant associations were seen with all-cause mortality.<sup>40</sup> The associations of the sweet patterns and Mediterranean type patterns were inconsistent and not significant.

Whole grain and fruits have been associated with 46% reductions with incident CVD events (Q5 vs Q1 HR=0.54; 95% CI 0.33, 0.91; P trend=0.007) in MESA.<sup>41</sup> The fully adjusted hazard ratios comparing fifth to first quintiles for the “Fat and Processed Meat”, “Vegetables and Fish”, “Beans, Tomatoes, and Refined Grains” patterns were 1.82 (95% CI 0.99, 3.35; P trend=0.10), 0.98 (95% CI 0.54, 1.79; P trend=0.38), and 0.80 (95% CI 0.45, 1.42; P trend=0.79).

Five dietary patterns were derived from the Framingham nutrition studies: heart healthy, light eating, wine and moderate eating, high fat, and empty calorie. However, only the empty calorie pattern was associated with carotid atherosclerosis (aOR=2.28; 95% CI 1.12, 4.62) compared to the heart healthy pattern.<sup>32</sup>

Two major dietary patterns were identified in the Nurse Health study. Participants with higher adherence to the prudent pattern had higher intakes of vegetables, fruits, legumes, fish, poultry, and whole grains. Participants with higher adherence to the Western pattern had higher intakes of red meat, processed meat, refined grains, French fries, and sweets or desserts. The adjusted hazard ratio comparing the fifth to first quintile for CVD and all-cause mortality was 0.72 (95% CI 0.60, 0.87) and 0.83 (95% CI 0.76, 0.90), respectively for prudent diet, and 1.22 (95% CI 1.01, 1.48) and 1.21 (95% CI 1.12, 1.32), respectively for Western diets.<sup>42</sup>

Three patterns were derived from the Japanese Ohsaki National Health Insurance cohort and labelled as Japanese, ‘animal food’, and high-dairy, high-fruit-and-vegetable, low-alcohol (DFA) patterns. The adjusted hazard ratio for CVD mortality comparing the fourth to the first quartile of the Japanese, ‘animal food’, and DFA patterns were 0.73 (95% CI 0.59, 0.90; P trend=0.003), 1.22 (95% CI 0.99, 1.51; P trend=0.03), and 0.88 (95% CI 0.68, 1.13; P trend=0.14), respectively.<sup>43</sup>

A more recent Japanese cohort with a larger sample that included the Ohsaki cohort identified the same three patterns. The adjusted hazard ratio of CVD mortality comparing the fifth to the first quintile of the vegetable, animal food, and dairy product patterns were 0.93 (95% CI 0.78, 1.13; P trend=0.73), 0.88 (95% CI 0.73, 1.05; P trend=0.50), and 0.89 (95% CI 0.74, 1.08; P trend=0.23), respectively, for men and 0.82 (95% CI 0.67, 1.00; P trend=0.04), 1.08 (95% CI 0.87, 1.34; P trend=0.42), and 0.76 (95% CI 0.61, 0.94; P trend=0.01), respectively, for women.<sup>44</sup>

This study has a few limitations. First, we cannot infer causation in this cross-sectional study because temporality between exposure and outcome cannot be established. However, to reduce the possibility of reverse causation we excluded participants with any history of cardiovascular disease, cancer, hypertension, diabetes, or dyslipidemia. Second, the prevalence of coronary artery calcium was low in this young to middle aged asymptomatic population. Smaller number of outcomes may result in lower precision. Third, although we controlled for several important confounders in the multivariable adjusted, the associations are still susceptible to residual confounding due to unmeasured confounders or incomplete adjustment. Fourth, measurement error of diet is a problem and non-differential misclassification bias may attenuate the associations. However, an advantage of dietary pattern over single nutrient analysis is that it estimates a larger cumulative effect. Fifth, our study population consisted of asymptomatic young and middle-aged Koreans and the extrapolation of these results to other populations are unknown. Six, the younger age distribution of those with high adherence to Western Korean dietary patterns makes interpretation of its associations difficult. The suggested lower CAC ratio among those with high adherence to the Western

Korean patterns may be due to a combination of the younger age distribution and the latency of the diet exposure. Further follow-up of this group is required to fully investigate the role of a Western Korean diet and subclinical atherosclerosis.

Our study has some strengths. This is one of the largest population-based study investigating the association between dietary patterns and coronary artery calcium scores. Second, data from participants were collected using standardized methods. Though this was only a screening program but its long standing duration resulted in the implementation of standardized protocols during the visits. All blood were sent to an accredited central laboratory in the hospital for analysis. Third, data management and analysis were documented with audit trails of major version changes. Fourth, we used multiple imputations to address the issue of missing data.

In this large cross-sectional study of asymptomatic young to middle aged Korean men and women, we failed to find any significant evidence for an association between the traditional, modern, and Western dietary patterns, and subclinical atherosclerosis measured using coronary artery calcium scores.

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Table 4.1 Characteristics of KSHS screening participants by coronary artery calcium scores (N=27,028)

	Overall (N=27,028)	Undetectable (N=24,793)	CACS 1-10AU (N=985)	CACS >10AU (N=1,250)
	mean±SD or median (interquartile range) or %(SE)			
Male (N=27,028)	20,823 (77.0)	18,745 (75.6)	916 (93.0)	1,162 (93.0)
Age, years (N=27,028)	39.9±6.4	39.5±6.3	44.2±6.1	45.7±6.2
Body mass index, kg/m <sup>2</sup> (N=27,011)	23.9±3.1	23.9±3.1	24.7±2.8	24.7±2.9
Education level (N=24,877)				
University or higher	18,263 (73.4)	16,720 (73.4)	679 (73.7)	864 (73.3)
Technical college	2,838 (11.4)	2,601 (11.4)	117 (12.7)	120 (10.2)
High school or lower	3,776 (15.2)	3,457 (15.2)	125 (13.6)	194 (16.5)
Smoking status (N=26,484)				
Never	12,934 (48.8)	12,278 (50.5)	305 (31.6)	351 (28.7)
Former	6,154 (23.2)	5,456 (22.5)	306 (31.7)	392 (32.0)
Current	7,396 (27.9)	6,560 (27)	354 (36.7)	482 (39.3)
Physical activity patterns (N=26,730)				
Inactive	12,136 (45.4)	11,248 (45.9)	390 (40.1)	498 (40.4)
Minimally active	10,197 (38.1)	9,322 (38.0)	394 (40.5)	481 (39.0)
Health-enhancing	4,397 (16.4)	3,955 (16.1)	188 (19.3)	254 (20.6)
Daily dietary intake (N=15,656)				
Total energy, Kcal/day	1,603 (1,282-1,987)	1,606 (1,284-1,989)	1,595 (1,290-1,964)	1,557 (1,242-1,918)
% Total energy carbohydrate	66.2 (0.1)	66.3 (0.1)	65 (0.1)	66.2 (0.1)
% Total energy protein	12.6 (0.1)	12.6 (0.1)	12.3 (0.1)	12.1 (0.1)
% Total energy total fat	15.4 (0.1)	15.5 (0.1)	14.4 (0.1)	13.5 (0.1)
% Total energy alcohol	3.4 (0.1)	3.3 (0.1)	5.1 (0.1)	5.7 (0.1)
Vegetable, Kcal/day	44 (26-69)	44 (26-69)	47 (28-74)	47 (29-73)
Fruit, Kcal/day	54 (26-104)	54 (26-104)	48 (24-102)	49 (24-100)
Fish, Kcal/day	34 (19-57)	34 (19-56)	35 (20-60)	35 (20-57)
Meat, Kcal/day	121 (71-196)	122 (71-197)	116 (70-194)	110 (66-171)

\* CACS-Coronary artery calcium score; AU- Agatston score. CACS, age, and sex had complete information. The following covariates had some missing information: body mass index (N=17), education level (N=2,151), smoking status (N=544), physical activity patterns (N=298), and daily dietary intake covariates (N=11,372). We used multiple imputation to address missingness.

Table 4.2 Characteristics of KSHS participants with high adherence to dietary patterns (N=27,028)

	Traditional Korean	Modern Korean mean±SE or %(SE)	Western Korean
Male	71.4 (0.6)	95.8 (0.2)	72.6 (0.6)
Age, years	41.2±0.1	38.4±0.1	37.5±0.1
Body mass index, kg/m <sup>2</sup>	24±0.1	24.7±0.1	23.9±0.1
Education level			
University or higher	75.5 (0.5)	78.0 (0.5)	82.2 (0.5)
Technical college	10.2 (0.4)	10.7 (0.4)	9.4 (0.4)
High school or lower	14.2 (0.5)	11.3 (0.4)	8.4 (0.3)
Smoking status			
Never	51.1 (0.6)	32.8 (0.6)	59.7 (0.6)
Former	23.3 (0.6)	25.5 (0.5)	19.2 (0.5)
Current	25.6 (0.5)	41.8 (0.6)	21.1 (0.5)
Physical activity patterns			
Inactive	37.2 (0.6)	45.2 (0.6)	44.7 (0.6)
Minimally active	40.6 (0.6)	40.1 (0.6)	40.1 (0.6)
Health-enhancing	22.1 (0.5)	14.7 (0.4)	15.2 (0.4)
Daily dietary intake			
Total energy, Kcal/day	1941±9	1919±8	1825±8
% Total energy carbohydrate	64.4 (0.1)	61.7 (0.1)	64.3 (0.1)
% Total energy protein	14.0 (0.1)	13.3 (0.1)	13.5 (0.1)
% Total energy total fat	16.6 (0.1)	17 (0.1)	18.3 (0.1)
% Total energy alcohol	5 (0.1)	8 (0.1)	3.8 (0.1)
Vegetable, Kcal/day	73±1	57±1	49±1
Fruit, Kcal/day	112±1	72±1	93±1
Fish, Kcal/day	73±1	60±1	47±1
Meat, Kcal/day	175±2	209±2	168±2

\* High adherence defined as being in the upper tertile of dietary pattern scores.

\* CAC scores, age and sex had complete information, multiple imputation was used to account for missing information in following covariates: body mass index (N=27,011), education level (N=24,877), smoking status (N=26,484), physical activity patterns (N=26,730), and daily dietary intake covariates (N=15,656)

Table 4.3. Association between coronary artery calcium and dietary patterns (N=27,028)

	CAC score ratio (95% CI)			P trend	P90 vs P10	P
	Tertile 1	Tertile 2	Tertile 3			
Traditional Korean						
Model 1	1.00 (ref)	1.10 (0.78, 1.56)	0.94 (0.62, 1.42)	0.748	1.01 (0.63, 1.61)	0.982
Model 2	1.00 (ref)	1.07 (0.75, 1.52)	0.88 (0.58, 1.34)	0.539	0.93 (0.57, 1.50)	0.759
Modern Korean						
Model 1	1.00 (ref)	1.11 (0.76, 1.63)	1.29 (0.84, 1.98)	0.225	1.37 (0.81, 2.29)	0.238
Model 2	1.00 (ref)	1.06 (0.72, 1.56)	1.16 (0.75, 1.80)	0.483	1.19 (0.70, 2.05)	0.518
Western Korean						
Model 1	1.00 (ref)	0.86 (0.63, 1.16)	0.81 (0.56, 1.17)	0.237	0.78 (0.51, 1.20)	0.264
Model 2	1.00 (ref)	0.88 (0.65, 1.19)	0.86 (0.59, 1.25)	0.405	0.84 (0.54, 1.29)	0.420

Model 1 adjusted for age, sex, center, year of screening, and daily log-energy intake.

Model 2 additionally adjusted for education level (university or higher, college graduate, high school or lower), physical activity (inactive, minimally active, health-enhancing), and smoking status (never, former, current)

Table 4.4. Association between detectable coronary artery calcium and dietary patterns (N=27,028)

Coronary artery calcium score (CACS)	Odds or relative prevalence ratio (95% CI)					
	Tertile 1	Tertile 2	Tertile 3	P trend	P90 vs P10	P
CACS>0 AU						
Traditional pattern						
Model 1	1.00 (ref)	1.03 (0.89, 1.19)	0.97 (0.82, 1.15)	0.719	1.00 (0.82, 1.21)	0.963
Model 2	1.00 (ref)	1.01 (0.87, 1.18)	0.94 (0.79, 1.13)	0.514	0.96 (0.79, 1.18)	0.712
Modern pattern						
Model 1	1.00 (ref)	1.04 (0.88, 1.21)	1.11 (0.93, 1.33)	0.244	1.13 (0.91, 1.40)	0.269
Model 2	1.00 (ref)	1.02 (0.86, 1.19)	1.06 (0.89, 1.28)	0.500	1.07 (0.86, 1.34)	0.548
Western pattern						
Model 1	1.00 (ref)	0.95 (0.84, 1.08)	0.92 (0.79, 1.08)	0.312	0.92 (0.76, 1.10)	0.363
Model 2	1.00 (ref)	0.96 (0.84, 1.10)	0.95 (0.81, 1.11)	0.500	0.94 (0.78, 1.14)	0.536
CACS 1-10 AU						
Traditional pattern						
Model 1	1.00 (ref)	0.97 (0.79, 1.19)	0.98 (0.79, 1.23)	0.905	1.05 (0.81, 1.36)	0.730
Model 2	1.00 (ref)	0.96 (0.78, 1.18)	0.96 (0.76, 1.21)	0.742	1.02 (0.78, 1.32)	0.910
Modern pattern						
Model 1	1.00 (ref)	0.99 (0.80, 1.22)	1.05 (0.83, 1.32)	0.687	1.06 (0.81, 1.39)	0.680
Model 2	1.00 (ref)	0.98 (0.79, 1.21)	1.02 (0.81, 1.29)	0.877	1.02 (0.77, 1.35)	0.880
Western pattern						
Model 1	1.00 (ref)	1.04 (0.86, 1.26)	0.94 (0.75, 1.18)	0.725	0.99 (0.77, 1.27)	0.950
Model 2	1.00 (ref)	1.05 (0.87, 1.27)	0.96 (0.77, 1.21)	0.876	1.02 (0.79, 1.31)	0.910
CACS > 10 AU						
Traditional pattern						
Model 1	1.00 (ref)	1.07 (0.88, 1.31)	0.96 (0.76, 1.21)	0.694	0.96 (0.73, 1.25)	0.751
Model 2	1.00 (ref)	1.06 (0.87, 1.29)	0.93 (0.73, 1.18)	0.532	0.92 (0.70, 1.22)	0.570
Modern pattern						
Model 1	1.00 (ref)	1.07 (0.88, 1.31)	1.16 (0.92, 1.47)	0.200	1.19 (0.89, 1.58)	0.245
Model 2	1.00 (ref)	1.05 (0.85, 1.29)	1.10 (0.86, 1.40)	0.423	1.11 (0.82, 1.49)	0.501
Western pattern						
Model 1	1.00 (ref)	0.88 (0.75, 1.04)	0.91 (0.74, 1.12)	0.265	0.85 (0.65, 1.10)	0.216
Model 2	1.00 (ref)	0.89 (0.75, 1.06)	0.94 (0.76, 1.16)	0.413	0.87 (0.67, 1.14)	0.315

Model 1 adjusted for age, sex, center, year of screening, and daily log-energy intake.

Model 2 additionally adjusted for education level (university or higher, college graduate, high school or lower), physical activity (inactive, minimally active, health-enhancing), and smoking status (never, former, current)





## Summary of findings

Ischemic heart disease and cerebrovascular disease are responsible for 7.4 (13.2%) and 6.7 (11.9%) million deaths worldwide 2012.<sup>1</sup> In the United States, despite a decline since 1968, it still remains the leading cause of death, and accounted for 33.7% of all deaths in 2009.<sup>2, 3</sup> Likewise, the global prevalence of diabetes and metabolic syndrome is rapidly increasing with the number of diabetics projected to increase from 382 to 592 million between 2013 and 2035.

Diet plays an important role in shaping population health. Diet composition, analyzed as a cluster of 14 different dietary components, was associated with 26% of deaths and 14% of DALYS in the United States.<sup>4</sup> Dietary patterns acknowledges the complex interactions between nutrients and foods, estimates a larger cumulative effect compared to single nutrients, and may be easier to translate into effective interventions.<sup>5-7</sup> Dietary research have successfully been translated into intervention strategies such as the Mediterranean type diet and the Dietary Approaches to Stop Hypertension (DASH), however, these diets were developed in western populations, which typically consumes a diet higher in fat and lower in carbohydrate compared to Asians. The literature on dietary patterns among the various Asian countries and its role on health is more limited.<sup>8-11</sup>

This dissertation adds to the diet-disease evidence base by: 1) identifying and describing the major dietary patterns in a larger Korean cohort; 2) Evaluating the associations of Korean dietary patterns with the prevalence of diabetes and metabolic syndrome; and 3) Evaluating the association between Korean dietary patterns and the prevalence of subclinical atherosclerosis.

For the first aim, we used cross sectional design to identify and describe the major dietary patterns in 269,266 adult men and women who underwent a screening examination between January 2011 and December 2013 at the Kangbuk Samsung Total Healthcare Center in Seoul and Suwon, South Korea. Diet was assessed using a validated 103-item food frequency questionnaire. We used principal component analysis to derive three major dietary patterns, labelled as traditional Korean, modern Korean, and Western Korean dietary patterns that explained 20.7%, 11.4%, and 10.1%, of the total variation in daily dietary intakes. The modern and Western Korean patterns are likely a result of the ongoing nutrition transition in South Korea.

The Traditional Korean patterns had higher intakes of vegetables, mushrooms, potatoes, soya and other beans, fruits, oily and non-oily fish, shellfish, and seaweed. Modern Korean patterns had higher intakes of noodles, raw or salted fish, shellfish, red meat, processed meat, poultry, soda, and alcohol. Western Korean patterns had higher intakes of bread and cereals, milk and dairy products, snacks, and pizza, and lower intakes of alcohol, rice, and preserved vegetables. Participants with higher adherence to Modern compared to Traditional Korean patterns were more likely younger, male, have higher education, currently smoke, and be physically inactive. Participants with higher adherence to Western compared to Traditional Korean patterns were more likely younger, female, have higher education, and less likely to currently smoke, be physically active, or have any history of hypertension, diabetes, and dyslipidemia.

For the second aim, we evaluated the associations between the major Korean dietary patterns and the prevalence of diabetes and metabolic syndrome in the same cohort. However,

we only included 220,979 screening participants without any history of cardiovascular disease, cancer, diabetes, hypertension, and dyslipidemia. The crude prevalence of diabetes and metabolic syndrome was 1.4% and 8.3%, respectively. The adjusted odds ratio of diabetes comparing the 90<sup>th</sup> to the 10<sup>th</sup> percentile of dietary scores was 1.01 (95% CI 0.88, 1.16) for traditional, 1.32 (95% CI 1.13, 1.55) for modern, and 0.78 (95%CI 0.67, 0.91) for Western Korean dietary patterns. The adjusted odds ratio of metabolic syndrome comparing the 90<sup>th</sup> to the 10<sup>th</sup> percentile of dietary scores was 1.01 (95% CI 0.95, 1.07) for traditional, 1.76 (95% CI 1.64, 1.88) for modern, and 0.73 (95% CI 0.69, 0.78) for Western Korean dietary patterns. Compared to those without any metabolic syndrome criteria, the adjusted relative prevalent ratios of having one to two criteria for metabolic syndrome comparing the 90<sup>th</sup> to the 10<sup>th</sup> percentile of dietary scores were 1.02 (95%CI 0.99, 1.06) for traditional, 1.43 (95%CI 1.38, 1.48) for modern, and 0.85 (0.83, 0.88) for Western dietary patterns. The corresponding relative prevalent ratios of having three to five metabolic syndrome criteria comparing the 90<sup>th</sup> to the 10<sup>th</sup> percentile of dietary scores were 1.02 (95%CI 0.96, 1.09) for traditional, 2.14 (95%CI 2.00, 2.30) for modern, and 0.67 (0.63, 0.72) for Western dietary patterns.

We found no significant associations between the traditional Korean dietary pattern and the prevalence of diabetes or metabolic syndrome. Modern Korean patterns, characterized by higher intakes of meats and alcohol, were associated with higher odds of diabetes and metabolic syndrome. Higher adherence to Western Korean dietary patterns were associated with lower odds of diabetes and metabolic syndrome. Due to the younger age distribution of those with higher adherence to the Western Korean dietary pattern, we are uncertain on the

benefits of this Western Korean dietary pattern and suggest longer term studies to better evaluate them.

For the third aim, we evaluated the association between the major Korean dietary patterns and subclinical atherosclerosis. The study population consisted of adult men and women who had their coronary artery calcium score and diet measured during a screening examination between January 2011 and December 2013 at the Kangbuk Samsung Total Healthcare Center in Seoul and Suwon, South Korea. We included 27,028 screening participants who did not have any history of cardiovascular disease, cancer, diabetes, hypertension, and dyslipidemia.

The prevalence of CACS 1-10 AU and CACS>10 was 3.6% (n=985) and 4.6% (n=1,250), respectively. The adjusted CACS ratio comparing the third to the first tertile for the traditional, modern, and Western Korean patterns were 0.88 (95% CI 0.58, 1.34; P trend=0.539), 1.16 (95% CI 0.75, 1.80; P trend=0.483), and 0.86 (95%CI 0.59, 1.25; P trend=0.405), respectively. The adjusted CACS ratio comparing the 90<sup>th</sup> to the 10<sup>th</sup> percentile for the traditional, modern, and Western Korean patterns were 0.93 (95% CI 0.57, 1.50), 1.19 (95% CI 0.70, 2.05), and 0.84 (95%CI 0.54, 1.29), respectively. We failed to find any significant associations between traditional, modern, and Western dietary patterns, and the prevalence of subclinical atherosclerosis.

### Implications and future research

Our research suggest that there is three major dietary patterns in the Korean population. These dietary patterns may represent the different phases of the ongoing nutrition transition, urbanization and Westernization of the Korean society.

These results are unique as the three major dietary patterns may represent different phases of the ongoing nutrition transition in Korea. The traditional Korean dietary pattern is characterized by higher intakes of vegetables, fruits, fish, and soya and other bean products. We did not find any significant associations between higher adherence to this pattern with the prevalence of diabetes and metabolic syndrome. Higher adherence to traditional dietary patterns was associated with a small non-significant decrease in prevalent CAC ratio.

The modern Korean dietary pattern is characterized by higher intakes of noodles, raw or salted fish, shellfish, red meat, processed meat, poultry, soda, and alcohol. Those with higher adherence to this pattern had higher odds of prevalent diabetes and metabolic syndrome. Higher adherence to traditional dietary patterns was associated with a small non-significant increase in prevalent CAC ratio.

The Western Korean dietary pattern is characterized by higher intakes bread and cereals, milk and dairy products, snacks, and pizza, and lower intakes of alcohol, rice, and preserved vegetables. Those with higher adherence to this pattern had lower odds of prevalent diabetes and metabolic syndrome. Higher adherence to traditional dietary patterns was associated with a small non-significant decrease in prevalent CAC ratio.

Further nutritional epidemiological research is needed to better evaluate these diet-disease associations. First, further research is needed to investigate the associations of these dietary patterns with other cardiovascular disease risk such as systolic and diastolic blood pressure, serum glycated hemoglobin (HbA1c), insulin, and markers of dyslipidemia. Second, with further follow up of this cohort, longitudinal analysis could be used to investigate the role of diet over time. Third, using the results of this research, we will create a hypothesis driven dietary score formula. We will then evaluate the association of this dietary score with subclinical atherosclerosis. Additional randomized control trials should be performed to evaluate whether lower intakes of raw fish, salted fish, shellfish, red meat, processed meat, poultry, soda, and alcohol, with fruits, vegetables, and fish, would reduce subclinical atherosclerosis.

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- Nov 1999 – Jan 2001. Medical Officer in Pediatric Department, Selayang Hospital, Ministry of Health, Malaysia.
- Nov 1998 – Nov 1999. Medical Intern, Klang Hospital, Ministry of Health, Malaysia.
- Aug 1997 – Aug 1998. Medical Intern, M.S. Ramaiah, Medical Teaching Hospital, Bangalore, India
- Feb 1992 – Jul 1992. Research Assistant in an Occupational Health Research project on “Noise Pollution in Palm Oil Factories” , Department of Community Health, National University of Malaysia.

#### **4. PROFESSIONAL ACTIVITIES**

##### *4.1 Society membership*

- 2005 – Present. Member, International Epidemiological Association.
- 2006 – 2009. Secretary, College of Public Health Medicine, Academy of Medicine Malaysia.
- 2006 – Present. Member of the Academy of Medicine of Malaysia.
- 2002 – Present. Member of the Malaysian Medical Association, Malaysia.

##### *4.2 Participation in advisory panels and scientific committees*

- 2005- 2006. Member of the Governance Board for the Malaysian National Cancer Registry
- 2008 – 2009. Steering Committee Member, National Cancer Patient Registry (NCPR) - Colorectal Cancer.

## 5. EDITORIAL AND PEER REVIEW ACTIVITIES

- Referee for papers in the following journal:
  - Asia Pacific Journal Of Public Health
  - Journal Of University Malaya Medical Centre
  - The Malaysian Family Physician, The Journal Of The Academy Of Family Physicians Malaysia.

## 6. HONORS AND AWARDS

- 2013-2014. Alexander Langmuir Teaching Assistantship, Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health.
- 2012. Ellen B. Gold Fund for Epidemiology, Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health.
- 2008. Excellence Service Award, Faculty of Medicine, University of Malaya.
- 2007. Excellence Service Certificate. Faculty of Medicine, University of Malaya.
- 2006. Excellence Service Certificate. Faculty of Medicine, University of Malaya.
- 2006. Special Award for Excellence of Service. Malaysian Red Crescent Society.
- 2005. Certificate of Appreciation for Excellent Service Contribution in the Overseas Malaysian Humanitarian Assistance Mission 2004/2005. Deputy Prime Minister of Malaysia.
- 2004. Excellence Service Award. Hospital Kuala Lumpur, Ministry of Health Malaysia.
- 2004. 2nd Prize, Best Oral Presentation at the 1st Asia Pacific Conference on Public Health, 1-3rd October 2004, Kuala Lumpur, Malaysia.
- 2002. Best Oral Presentation at the 5th Scientific Meeting of the National Institutes of Health, Malaysia held on the 5th – 6th September 2002

## 7. PUBLICATIONS

### 7.1 Journal Articles (Peer-reviewed)

#### Pubmed Search: sanjay rampal or ("Rampal S" AND MALAYSIA)

\* Joint first authorship

1. Zhang Y, Chang Y, Ryu S, Cho J, Lee WY, Rhee EJ, Kwon MJ, Pastor-Barriuso R, **Rampal S**, Han WK, Shin H, Guallar E. Thyroid hormone levels and incident chronic kidney disease in euthyroid individuals: the Kangbuk Samsung Health Study. *Int J Epidemiol* 2014. Epub Jul 10. PMID: 25011453.
2. Law CW, **Rampal S**, Roslani AC, Mahadeva S. Development of A Risk Score to Stratify Symptomatic Adults Referred for Colonoscopy. *J Gastroenterol Hepatol*. 2014. Epub 2014 Jun 9. PMID: 24909623.
3. Chang Y, Kim BK, Yun KE, Cho J, Zhang Y, **Rampal S**, Zhao D, Jung HS, Choi Y, Ahn J, Lima JA, Shin H, Guallar E, Ryu S. Metabolically-healthy obesity and coronary artery calcification. *J Am Coll Cardiol*. 2014 Jun 24;63(24):2679-86. PMID: 24794119.
4. Zain SM, Mohamed R, Cooper DN, Razali R, **Rampal S**, Mahadeva S, Chan WK, Anwar A, Rosli NS, Mahfudz AS, Cheah PL, Basu RC, Mohamed Z. Genome-wide analysis of copy number variation identifies candidate gene loci associated with the progression of non-alcoholic fatty liver disease. *PLoS One* 2014;9(4):e95604. PMID: 24743702; PMCID: PMC3990722.
5. Zhang Y, Chang Y, Ryu S, Cho J, Lee WY, Rhee EJ, Kwon MJ, Pastor-Barriuso R, **Rampal S**, Han WK, Shin H, Guallar E. Thyroid hormones and mortality risk in euthyroid individuals: the Kangbuk Samsung Health Study. *J Clin Endocrinol Metab* 2014 Jul;99(7):2467-76. PMID: 24708095.
6. Jung HS, Chang Y, Yun KE, Kim CW, Choi ES, Kwon MJ, Cho J, Zhang Y, **Rampal S**, Zhao D, Kim HS, Shin H, Guallar E, Ryu S. Impact of body mass index, metabolic health, and weight change on incident diabetes in a Korean population. *Obesity* 2014. Epub Apr 4. PMID: 24706434.
7. **Rampal S**, Yang MH, Sung J, Son HJ, Choi YH, Lee JH, Kim YH, Chang DK, Rhee PL, Rhee JC, Guallar E, Cho J. Association between markers of glucose metabolism and risk of colorectal adenoma. *Gastroenterology* 2014;147(1):78-87. PMID: 24632359.
8. Apalasyam YD, **Rampal S**, Salim A, Moy FM, Bulgiba A, Mohamed Z. Association of ADIPOQ gene with obesity and adiponectin levels in Malaysian Malays. *Mol Biol Rep* 2014;41(5):2917-21. PMID: 24449366.
9. Yang MH, **Rampal S**, Sung J, Choi YH, Son HJ, Lee JH, Kim YH, Chang DK, Rhee PL, Rhee JC, Guallar E, Cho J. The prevalence of colorectal adenomas in asymptomatic Korean men and women. *Cancer Epidemiol Biomarkers Prev* 2014;23(3):499-507. PMID: 24443404.
10. Yang MH, Cho J, **Rampal S**, Choi EK, Choi YH, Lee JH, Kim YH, Chang DK, Rhee PL, Kim JJ, Guallar E, Rhee JC, Son HJ. The association between cecal insertion time and colorectal neoplasm detection. *BMC Gastroenterol* 2013;13(1):124. PMID: 23915303; PMCID: PMC3750659.

11. Tan HL, Zain SM, Mohamed R, **Rampal S**, Chin KF, Basu RC, Cheah PL, Mahadeva S, Mohamed Z. Association of glucokinase regulatory gene polymorphisms with risk and severity of non-alcoholic fatty liver disease: an interaction study with adiponutrin gene. *J Gastroenterol* 2014;49(6):1056-64. PMID: 23800943.
12. Yang MH, **Rampal S**, Sung J, Choi YH, Son HJ, Lee JH, Kim YH, Chang DK, Rhee PL, Kim JJ, Rhee JC, Chun HK, Guallar E, Cho J. The association of serum lipids with colorectal adenomas. *Am J Gastroenterol* 2013;108(5):833-41. PMID: 23545715.
13. Zain SM, Mohamed Z, Mahadeva S, **Rampal S**, Basu RC, Cheah PL, Salim A, Mohamed R. Susceptibility and gene interaction study of the angiotensin II type 1 receptor (AGTR1) gene polymorphisms with non-alcoholic fatty liver disease in a multi-ethnic population. *PLoS One*. 2013;8(3):e58538. PMID: 23484035; PMCID: PMC3590220.
14. Danaei G, Singh GM, Paciorek CJ, Lin JK, Cowan MJ, Finucane MM, Farzadfar F, Stevens GA, Riley LM, Lu Y, Rao M, Ezzati M; Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group. The global cardiovascular risk transition: associations of four metabolic risk factors with national income, urbanization, and Western diet in 1980 and 2008. *Circulation* 2013;127(14):1493-502, 1502e1-8. PMID: 23481623.
15. Choi YL, Sun JM, Cho J, **Rampal S**, Han J, Parasuraman B, Guallar E, Lee G, Lee J, Shim YM. EGFR mutation testing in patients with advanced non-small cell lung cancer: a comprehensive evaluation of real-world practice in an East Asian tertiary hospital. *PLoS One* 2013;8(2):e56011. PMID: 23468851; PMCID: PMC3585299.
16. Sun JM, **Rampal S**, Lee G, Lee J, Choi YL, Parasuraman B, Guallar E, Cho J, Shim YM. Real world impact of epidermal growth factor receptor mutation status on treatment patterns in patients with non-small cell lung cancer. *Lung Cancer* 2013 May;80(2):191-6. PMID: 23384673.
17. Zain SM, Mohamed Z, Mahadeva S, Cheah PL, **Rampal S**, Chin KF, Mahfudz AS, Basu RC, Tan HL, Mohamed R. Impact of leptin receptor gene variants on risk of non-alcoholic fatty liver disease and its interaction with adiponutrin gene. *J Gastroenterol Hepatol* 2013 May;28(5):873-9. PMID: 23278404.
18. Stevens GA, Singh GM, Lu Y, Danaei G, Lin JK, Finucane MM, Bahalim AN, McIntire RK, Gutierrez HR, Cowan M, Paciorek CJ, Farzadfar F, Riley L, Ezzati M; Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Body Mass Index). National, regional, and global trends in adult overweight and obesity prevalences. *Popul Health Metr* 2012;10(1):22. PMID: 23167948; PMCID: PMC3543235.
19. Thanapal MR, Tata MD, Tan AJ, Subramaniam T, Tong JM, Palayan K, **Rampal S**, Gurunathan R. Pre-emptive intraperitoneal local anaesthesia: an effective method in immediate post-operative pain management and metabolic stress response in laparoscopic appendicectomy, a randomized, double-blinded, placebo-controlled study. *ANZ J Surg* 2014 Jan-Feb;84(1-2):47-51. PMID: 23057502.
20. **Rampal S**, Mahadeva S, Guallar E, Bulgiba A, Mohamed R, Rahmat R, Arif MT, Rampal L. Ethnic differences in the prevalence of metabolic syndrome: results from a multi-ethnic population-based survey in Malaysia. *PLoS One* 2012;7(9):e46365. PMID: 23029497; PMCID: PMC3460855.

21. Apal Sammy YD, Ming MF, **Rampal S**, Bulgiba A, Mohamed Z. Association of melanocortin-4 receptor gene polymorphisms with obesity-related parameters in Malaysian Malays. *Ann Hum Biol* 2013 Jan;40(1):102-6. PMID: 22989167.
22. Apal Sammy YD, Ming MF, **Rampal S**, Bulgiba A, Mohamed Z. Genetic association of SNPs in the FTO gene and predisposition to obesity in Malaysian Malays. *Braz J Med Biol Res* 2012;45(12):1119-26. PMID: 22911346; PMCID: PMC3854209.
23. Abdullah NN, Aziz NA, **Rampal S**, Al-Sadat N. Mammography screening uptake among hospital personnel in Kuala Lumpur tertiary hospital. *Asian Pac J Cancer Prev* 2011;12(10):2643-7. PMID: 22320967.
24. Zain SM, Mohamed R, Mahadeva S, Cheah PL, **Rampal S**, Basu RC, Mohamed Z. A multi-ethnic study of a PNPLA3 gene variant and its association with disease severity in non-alcoholic fatty liver disease. *Hum Genet* 2012;131(7):1145-52. PMID: 22258181; PMCID: PMC3374090.
25. Apal Sammy YD, Ming MF, **Rampal S**, Bulgiba A, Mohamed Z. Gender-Dependent Association of a  $\beta$ 2-Adrenergic Gene Variant With Obesity Parameters in Malaysian Malays. *Asia Pac J Public Health*. Epub 2011 Dec 23. PMID:22199155.
26. Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ, Paciorek CJ, Lin JK, Farzadfar F, Khang YH, Stevens GA, Rao M, Ali MK, Riley LM, Robinson CA, Ezzati M; Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Blood Glucose). National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet* 2011;378(9785):31-40. PMID: 21705069.
27. Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, Singh GM, Gutierrez HR, Lu Y, Bahalim AN, Farzadfar F, Riley LM, Ezzati M; Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Body Mass Index). National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet* 2011;377(9765):557-67. PMID: 21295846.
28. Danaei G, Finucane MM, Lin JK, Singh GM, Paciorek CJ, Cowan MJ, Farzadfar F, Stevens GA, Lim SS, Riley LM, Ezzati M; Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Blood Pressure). National, regional, and global trends in systolic blood pressure since 1980: systematic analysis of health examination surveys and epidemiological studies with 786 country-years and 5.4 million participants. *Lancet* 2011;377(9765):568-77. PMID: 21295844.
29. Choong LP, Taib NA, **Rampal S**, Saad M, Bustam AZ, Yip CH. High tumour stage and margin clearance are still important prognostic factors for post-mastectomy locoregional recurrence in Malaysia. *Asian Pac J Cancer Prev* 2010;11(5):1409-16. PMID: 21198302.
30. Chong HY, Taib NA, **Rampal S**, Saad M, Bustam AZ, Yip CH. Treatment options for locally advanced breast cancer--experience in an Asian tertiary hospital. *Asian Pac J Cancer Prev* 2010;11(4):913-7. PMID: 21133600.



31. Tai ML, Goh KL, Mohd-Taib SH, **Rampal S**, Mahadeva S. Anthropometric, biochemical and clinical assessment of malnutrition in Malaysian patients with advanced cirrhosis. *Nutr J* 2010;9:27. PMID: 20576106; PMCID: PMC2909148.
32. Mahadeva S, Yadav H, **Rampal S**, Goh KL. Risk factors associated with dyspepsia in a rural Asian population and its impact on quality of life. *Am J Gastroenterol* 2010;105(4):904-12. PubMed PMID: 20179699.
33. Mahadeva S, Yadav H, **Rampal S**, Everett SM, Goh KL. Ethnic variation, epidemiological factors and quality of life impairment associated with dyspepsia in urban Malaysia. *Aliment Pharmacol Ther* 2010;31(10):1141-51. PMID: 20175766.
34. Sam IC, Abdul-Murad A, Karunakaran R, **Rampal S**, Chan YF, Nathan AM, Ariffin H. Clinical features of Malaysian children hospitalized with community-acquired seasonal influenza. *Int J Infect Dis* 2010;14 Suppl 3:e36-40. PMID: 20153233.
35. Yip CH, Taib NA, Choo WY, **Rampal S**, Thong MK, Teo SH. Clinical and pathologic differences between BRCA1-, BRCA2-, and non-BRCA-associated breast cancers in a multiracial developing country. *World J Surg.* 2009 Oct;33(10):2077-81. PMID: 19649760.
36. Sam IC, Wong LP, **Rampal S**, Leong YH, Pang CF, Tai YT, Tee HC, Kahar-Bador M. Maternal acceptance of human papillomavirus vaccine in Malaysia. *J Adolesc Health* 2009;44(6):610-2. PMID: 19465327.
37. **Rampal S**, Rampal L, Rahmat R, Zain AM, Yap YG, Mohamed M, Taha M. Variation in the prevalence, awareness, and control of diabetes in a multiethnic population: a nationwide population study in Malaysia. *Asia Pac J Public Health* 2010;22(2):194-202. PMID: 19443875.
38. Rampal L, **Rampal S**, Azhar MZ, Rahman AR. Prevalence, awareness, treatment and control of hypertension in Malaysia: a national study of 16,440 subjects. *Public Health* 2008;122(1):11-8. PMID: 17981310.
39. Rampal L, **Rampal S**, Khor GL, Zain AM, Ooyub SB, Rahmat RB, Ghani SN, Krishnan J. A national study on the prevalence of obesity among 16,127 Malaysians. *Asia Pac J Clin Nutr* 2007;16(3):561-6. PMID: 17704038.
40. Haniff J, Das A, Onn LT, Sun CW, Nordin NM, **Rampal S**, Bahrin S, Ganeslingam M, Kularatnam KI, Zaher ZM. Anemia in pregnancy in Malaysia: a cross-sectional survey. *Asia Pac J Clin Nutr* 2007;16(3):527-36. PMID: 17704035.
41. Lekhraj Rampal GR, Mohd Sidik S, **Rampal S**, Daniel Wong YJ, Chow PL, Liew JS, Shum YS. Prevalence of Overweight among Secondary School Students in Klang District, Selangor. *Malays J Nutr* 2007;13(1):1-8. PMID: 22692184.
42. Lim TO, Das A, **Rampal S**, Zaki M, Sahabudin RM, Rohan MJ, Isaacs S. Cross-cultural adaptation and validation of the English version of the International Index of Erectile Function (IIEF) for use in Malaysia. *Int J Impot Res* 2003;15(5):329-36. PMID: 14562133.

43. Rampal L, **Rampal S**, Azhar MZ, Sherina MS, Mohamad T, Ramlee R, et al. A national study on the prevalence and factors associated with smoking amongst Malaysians aged 18 years and above. *Malaysian Journal of Medicine and Health Sciences*. 2008;4(2):41-53.
44. Md Zain A, **Rampal S**, Rampal L. A case control study on risk factors associated with drug addiction amongst Malaysian males. *Malaysian Journal of Medicine and Health Sciences*. 2007;3(2):17-27.
45. Tan SS, Abu Hassan MR, Abdullah A, Ooi BP, **Rampal S**, Korompis T, et al. Treatment of hemodialysis (HD) patients with chronic hepatitis C (CHC) using an escalating dose regimen of pegylated interferon (PEGIFN) alfa-2B. *Hepatology*. 2007;46(4):279.
46. Rampal L, **Sanjay R**, Azhar MZ, Shafie O, Ramlee R, Sirajoon NAG. A population based national study on the prevalence of smoking among Malaysians aged 15 years and above. *Tobacco counters health*. 2006;4:113-21.
47. GR Lekhraj Rampal, **R Sanjay**, MZ Azhar, MS Sherina, D Ambigga, A Rahimah. A Population-based Study on the Prevalence and Factors Associated with Obesity in Selangor. *Malaysian Journal of Medicine and Health Sciences* 2006;2(2):89-97.
48. GR Lekhraj Rampal, **R Sanjay**, MZ Azhar, MH Kamil. A Community-based Study on the Prevalence and Factors Affecting Smoking in Terengganu State, Malaysia, 2004. *Malaysian Journal of Medicine and Health Sciences* 2006 ;2(2): 61-69
49. GR Lekhraj Rampal , M.Z. Azhar , **Sanjay R** . A Study on the Profile of 1016 Drug Addicts in Malaysia. *Malaysian J of Medicine and Health Sciences* 2005; 1 (2): 1-12.

## 7.2 *Books or monographs*

1. GCC Lim, **S Rampal**, Y Halimah (Eds). *Cancer Incidence in Peninsular Malaysia, 2003-2005*. National Cancer Registry. Kuala Lumpur 2008.
2. ARA Rahman, AS Kamarudin, A Das, G Kaur, MA Kamaluddin, NY Yew, S Gunavathy, **S Rampal**, S Sivashumugam, AFH Yusoff. 2008. *The Third National Health and Morbidity Survey (NHMS III) 2006, Hypertension and Hypercholesterolemia*. Institute for Public Health (IPH), Ministry of Health, Malaysia. ISBN: 978-983-3387-15-6

### 7.3 *Book chapters*

1. GRL Rampal, BH Choo, MZ Azhar, **Sanjay R**, NAG Sirajoon, O Shafie , R Ramlee, Ahmad Jesree. "Population based national study on the Prevalence of smoking among Malaysians aged 15 years and above." AK Varma(Ed). Tobacco Counters Health. New Delhi, Northern Book Centre 2006 , Vol. 4 pg. 113-121

### 7.4 *Published Abstracts*

1. Rahman AR, Kamarudin AS, Ngau Y, **Rampal S**, Kaur G, Kamaluddin A, et al. Prevalence, awareness; treatment and control in Malaysia; 1996-2006: A nationwide survey. *Journal of Hypertension*. 2008;26:S251-S251.
2. B P Ooi, M Z Faizal, M Radzi, C H Ching, I Ahmad, K K Kiew, K L Chin, **S Rampal**. Optimizing and Increasing Erythropoietin Dose Significantly Reduces Pack Cell Transfusion Requirement During Treatment of Chronic Hepatitis C with Pegylated Interferon Among Hemodialysis Patients. *Malaysian Journal of Malaysia* 2008;63(Suppl B):42
3. B P Ooi, M Z Faizal, M Radzi, C H Ching, I Ahmad, K K Kiew, K L Chin, **S Rampal**. Effect of Increasing Erythropoietin Doses on Hemoglobin Levels During Treatment of Chronic Hepatitis C with Pegylated Interferon Among Hemodialysis Patients. *Malaysian Journal of Malaysia* 2008;63(Suppl B):43
4. M L S Tai, M Sanjiv, H Siti, **S Rampal**, K L Goh. Short Term Naso-Gastric Feeding in Hospitalised Patients with Advanced Cirrhosis: Preliminary Data from a Randomised Trial. *Malaysian Journal of Malaysia* 2008;63(Suppl B):57
5. Noor Rizawati M, Noran Naqiah, Mas Ayu S, **Sanjay R**. The prevalence of Home fall among the elderly in Masjid Tanah Province , Melaka. *Malaysia Journal of Community Health* 2008; 14(1): 59-60
6. Tan SS, Abu Hassan MR, Abdullah A, Ooi BP, **Rampal S**, Korompis T, Merican MI. Treatment of hemodialysis (HD) patients with chronic hepatitis C (CHC) using an escalating dose regimen of pegylated interferon (PEGIFN) alfa-2B. *Hepatology* 2007; 46(4): 279

7. Rose Nani Mudin, Noran Naqiah Hairi, **Sanjay Rampal**. "Does Secondhand Tobacco Smoke Exposure During Pregnancy Increase the Risk of Low Birth Weight?". *Malaysian Journal of Public Health Medicine* 2007;7(S2):18.
8. **Sanjay Rampal**, Lekhraj Rampal, Choo BH, Mafauzy Mohamed, Loong YY. Prevalence, awareness, treatment and control of Diabetes in Malaysia, 2004. *Malaysian Journal of Public Health Medicine* 2007;7(S2):19.
9. **Sanjay Rampal**, Azhar Md Zain, GR Lekhraj Rampal. Risk Factors Associated with Drug Dependence in Malaysian Males. *Malaysian Journal of Public Health Medicine* 2007;7(S2):23.
10. Lekhraj Rampal, **Sanjay Rampal**, Azhar Md Zain, Ramlee Rahmat, MS Sherina, AR Hejar, Aziz Alsafi Ismail. Novel Methods of Risk Identification, Stratification and Behavioral Intervention for HIV/AIDS and CVD Prevention. *Malaysian Journal of Public Health Medicine* 2007;7(S2):28.
11. M Parameswaran, **S Rampal**, K Shanggar, Khaidir, PH Tun, K Siti Hajar, K Nohidayu, MP Hazwani, A Nor HAFizah, A Razack, N Dublin. Diagnostic Properties of the Malay Overactive Bladder (OABV8) for use in the Malaysian Population. *Malaysian Journal of Public Health Medicine* 2007;7(S2):39.
12. Saimy Ismail, **Sanjay Rampal**, Hoe VCW. Post Tsunami Lhokseumawe, Aceh: A Situational Analysis. *Malaysian Journal of Public Health Medicine* 2007;7(S2):11.
13. Norli Abdul Jabbar, Nor Aini Mohd Noor, **Sanjay Rampal**. Analysis of dengue death cases in Selangor, Malaysia, 1<sup>st</sup> January 2007 to 1<sup>st</sup> April 2007. *Malaysian Journal of Public Health Medicine* 2007;7(S2):3.
14. Norli Abdul Jabbar, B Venugopalan, **Sanjay Rampal**. Influenza outbreak in the national service centre in Paya Indah camp, Kuala Langat, Selangor. *Malaysian Journal of Public Health Medicine* 2007;7(S2):8.
15. Mohd Aminuddin MY, Mas Ayu Said, Noorah M Salleh, **Sanjay Rampal**, Noran Naqiah Hairi. Factors associated with relapse of drug addiction among males in Selangor Darul Ehsan. *Malaysian Journal of Public Health Medicine* 2007;7(S2):29.
16. Gerard Lim CC, **Sanjay R**, Haniff J, Halimah Y, Lim TO, Ng KH, Ibrahim , Purushothaman V. National Cancer Registry of Malaysia: Where do we go from here?. *JUMMEC* 2006;S1: 26-27.
17. Goh PP, **Rampal S LR**, Choong YF. National Cataract Surgery Registry 2002-2003 - Predictors For Poor Visual Outcome. *American Journal of Ophthalmology* 2006;139(4): S4
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## 7.5 *Proceedings*

1. Rampal S, Rampal L, Md Zain A, Mohamed M, Mohamad Taha A. Differences in the prevalence of diabetes mellitus in urban and rural Malaysia: a problem of urbanization. Recent Trends in Diabetes, Obesity, and Metabolic Syndrome. Organized by JAMA and NUHS. pg 23.
2. Chong WP, Yap WF, S Rampal, Azman W. Short and long term clinical outcome of female patients with STEMI. Annual Scientific Meeting National Heart Association of Malaysia. 2008.
3. Hoe VCW, Ng CW, Maznah D, Sanjay R, Moy FM, Choo WY, S Noor Ghani, Noorlaili AZ, Roshidi I. 2008. Public health policies and the indigenous people of Malaysia. Proceedings of The International Conference on Indigenous People (ICIP). pg 14.
4. Maznah D, Ng CW, Moy FM, Sanjay R, Hoe VCW, S. Noorlaili. 2008. Breast Cancer Awareness And B.S.E. Practice Among Females Of Pahang, Malaysia. The 40th Asia Pacific Academic Consortium For Public Health Conference, 7-9 Nov 2008, Kuala Lumpur. Pg 118
5. Jabar N A, Rampal S, Roshidi Ismail, Ahmad Fauzi Md Sharif. 2008. Validation of Malay version of Activities of Daily Vision Scale (ADVA-M) in UMMC, Malaysia. The 40th Asia Pacific Academic Consortium for Public Health Conference, 7-9 Nov 2008, Kuala Lumpur. Pg 132
6. Moy FM, Sanjay R, Hoe VCW, Ng CW, Maznah D. 2008. Obesity among the elderly in rural Pahang in Malaysia, 2008. Recent Trends in Diabetes, Obesity, and Metabolic Syndrome. Organized by JAMA and NUHS. pg 26.
7. Chong HY, Rampal S, Saad M, Bustam AZ, taib NA, Yip CH. Outcome of locally advanced breast cancer in UMMC - Is primary surgery a better option? Malaysian Oncological Society Annual Scientific Meeting Sabah 2008. Page 48
8. Samsudin S, Rampal S, Taib NA, Yip CH. Institutional inclusion criteria for sentinel lymph node biopsy for breast cancer: a study of two cohorts for predictors of node negativity. Malaysian Oncological Society Annual Scientific Meeting Sabah 2008. Page 46
9. Lekhraj Rampal, Sanjay Rampal, Mohd Azhar, Mohamad Taha, Sherina Mohd Sidik. Prevalence and factors associated with Metabolic Syndrome in Malaysia. Fourth Malaysian Conference & Exhibition

on Healthy Ageing - Metabolic Disorders: An Integrated Approach to Healthy Living. 28-30 March 2008,

10. Cheah HS, Cha K, S Rampal. Delayed appendectomy and risks of perforation. 16<sup>th</sup> Asian Congress of Surgery, Beijing , China. October 2007.
11. Kaulsay R, Rampal S, Puriviappan P. Effectiveness of desloratadine in improving quality of life in patients with persistent allergic rhinitis. 26th Congress of the European Academy of Allergology and Clinical Immunology. 9-13 June 2007.
12. Cha K, Cheah HS, Koh PS, Rampal S. Gastric adenocarcinoma: One and three year survival rates after gastric surgery. Annual Scientific Meeting of the College of Surgeons, Academy of Medicine of Malaysia. June 2007.
13. Nurillyanee AS, Cha K, S Rampal. Prevalence of diverticulosis in Malaysia. A cross sectional study of One Thousand Colonoscopy Results in University Malaya Medical Center. Annual Scientific Meeting of the College of Surgeon-Academy of Medicine of Malaysia. June 2007.
14. Chong WP, Lau CY, S Rampal, Wu CS, Lean PL, Haizal HK, Azman W. Routine, Delayed elective coronary angiography after STEMI does not improve clinical outcome. Annual Scientific Meeting National Heart Association of Malaysia 2007.
15. Wu CS, Chong WP, Lau CY, S Rampal, Haizal HK, Azman W. Short term clinical outcome and predictive factors of failed reperfusion in STEMI patients treated with streptokinase: a single centre experience. Annual Scientific Meeting National Heart Association of Malaysia. 2007.
16. S Rampal, Noran NMH, Mas AS, Victor HCWA, Awang BAM, Noormah D, Rugayah B, Atiya AS. 2006. Clinical Epidemiology - An alternative approach to clinical research. 40th Malaysia-Singapore Congress of Medicine. 2006. pg 64.
17. S Rampal, A Das, J Haniff, TO Lim, GCC Lim. Six month and one year survival rates of common cancers in Malaysia. The XVIIth International Epidemiology Association (IEA) World Congress of Epidemiology (WCE 2005). 2005. Pg 335..
18. GR Lekhraj Rampal, S Rampal, MZ Azhar, O Shafii, R Ramlee, NAG Sirajoon, AA Ismail. 2005. Prevalence of Hypertension in Malaysia, 2004. The XVIIth International Epidemiology Association (IEA) World Congress of Epidemiology (WCE 2005). 2005. Pg 367

## 8. TEACHING

### 8.1 Advisees

1. Atheel R Badir. Master of Public Health, University of Malaya, 2008-2009.
  2. Mohamad Rodi bin Isa. Master of Public Health, University of Malaya, 2008-2009.
  3. Zuhair Abdelfatah Abdelhai. Master of Public Health, University of Malaya, 2008-2009.
  4. Samsiah Awang. Master of Public Health, University of Malaya, 2008-2009.
  5. Rafdzah Binti Ahmad Zaki. Master of Public Health, University of Malaya, 2007-2008
  6. Norazwana bt Nik Mohd Salleh. Master of Public Health, University of Malaya, 2007-2008
  7. Tukur Ismail. Master of Public Health, University of Malaya, 2007-2008.
  8. Vijayan a/I Kannan. Master of Public Health, University of Malaya, 2007-2008.
  9. Noraliza Zabari. Master of Public Health, University of Malaya, 2007-2008.
  10. Khalid Mohamed Adam Tahir. Master of Public Health, University of Malaya, 2006-2007.
  11. Osman Adam Osman Ali. Master of Public Health, University of Malaya, 2006-2007.
  12. Asnida Binti Anjang Rahman. Master of Public Health, University of Malaya, 2006-2007.
  13. Heitham Mohammed Ibrahim Awadallah. Master of Public Health, University of Malaya, 2006-2007.
  14. Umar Yagoub Mohammad. Master of Public Health, University of Malaya, 2005-2006.
  15. Tariq Mohd Al Sabahi. Master of Public Health, University of Malaya, 2005-2006.
  16. Suzaida binti Abdul Wahab. Master of Public Health, University of Malaya, 2005-2006.
- Master of Public Health - 4 year program**
17. Harishah Talib. Master of Public Health, University of Malaya, 2008.
  18. Norli binti Abdul Jabbar. Master of Public Health, University of Malaya, 2008.
  19. Sharmini Selvarajah a/p R Selvarajah. Master of Public Health, University of Malaya, 2010.
  20. Siti Rohana bt. Saad. Master of Public Health, University of Malaya, 2009.
  21. Dr Ariza Zainudin. Master of Public Health, University of Malaya, 2009.

22. Dr Maslinor binti Ismail. Master of Public Health, University of Malaya, 2009.
23. Dr Nik Nairan binti Abdullah. Master of Public Health, University of Malaya, 2009.
24. Dr Sunita bt. Abdul Rahman. Master of Public Health, University of Malaya, 2009.
25. Dr. Rohana binti Johan. Master of Public Health, University of Malaya, 2009.
26. Dr. Shahril Azian bin Masrom. Master of Public Health, University of Malaya, 2009.
27. Dr. Rafidah binti Abd. Latif. Master of Public Health, University of Malaya, 2009.



8.2 *Classroom instructions*

- Public Health Surveillance (340.770), Teaching assistant at Johns Hopkins Bloomberg School of Public Health, 2013/2014, 5 credit hours
- Professional Epidemiology Methods 2 (340.769), Teaching assistant at Johns Hopkins Bloomberg School of Public Health, 2013/2014, 4 credit hours
- Observational Epidemiology (340.608), Teaching assistant at Johns Hopkins Bloomberg School of Public Health, 2013/2014, 4 credit hours
- Principles of Epidemiology (340.601), Teaching assistant at Johns Hopkins Bloomberg School of Public Health, 2013/2014, 5 credit hours
- Design and Conduct of Clinical Trials (Epidemiology 340.613.11), Teaching assistant at Graduate Summer Institute of Epidemiology and Biostatistics, Johns Hopkins Bloomberg School of Public Health, 2013/2014, 2 credit hours
- Professional Epidemiology Methods 2 (340.764), Teaching assistant at Johns Hopkins Bloomberg School of Public Health, 2012/2013, 4 credit hours
- Principles of Epidemiology (340.601), Teaching assistant at Johns Hopkins Bloomberg School of Public Health, 2012/2013 Summer session, 5 credit hours
- Professional Epidemiology Methods 2 (340.764), Teaching assistant at Johns Hopkins Bloomberg School of Public Health, 2011/2012, 4 credit hours
- Epidemiologic Methods 2 (340.752), Teaching assistant at Johns Hopkins Bloomberg School of Public Health, 2011/2012, 5 credit hours
- Principles of Epidemiology (340.601), Teaching assistant at Johns Hopkins Bloomberg School of Public Health, 2011/2012, 5 credit hours
- Epidemiologic Methods For Planning And Evaluating Health Services (340.638.11) , Teaching assistant at Johns Hopkins Bloomberg School of Public Health, Graduate Summer Institute of Epidemiology and Biostatistics, 2011, 2 credit hours
- Principles of Epidemiology (340.601), Teaching assistant at Johns Hopkins Bloomberg School of Public Health, 2011/2012 Summer session, 5 credit hours
- Principles of Epidemiology (340.601), Teaching assistant at Johns Hopkins Bloomberg School of Public Health, 2010/2011, 5 credit hours

- Critical Readings And Special Topics In Epidemiology, Postgraduate class at University of Malaya, 2008/2009, 42 hours
- Principles Of Biostatistics, Postgraduate class at University of Malaya, 2008/2009, 12 hours
- Introduction To Meta-Analysis, Postgraduate class at University of Malaya, 2008/2009, 30 hours
- Research Methodology, Postgraduate class at University of Malaya, 2008/2009, 21 hours
- Foundation Of Biostatistics, Postgraduate class at University of Malaya, 2007/2008, 38 hours
- Non-Ionising Radiation In Medicine, Postgraduate class at University of Malaya, 2007/2008, 3 hours
- Statistical Computing With SPSS, Postgraduate class at University of Malaya, 2007/2008, 8 hours
- Biostatistics, 2007/2008, Postgraduate class at University of Malaya, 8 hours
- Systematic Review And Meta-Analysis, Postgraduate class at University of Malaya, 2007/2008, 18 hours
- Survival Analysis, Postgraduate class at University of Malaya, 2007/2008, 10 hours
- Computer Applications To Public Health, Postgraduate class at University of Malaya, 2007/2008, 2 hours
- Mph Yr 2 Research Proposal Development For Epidemiological Studies, Postgraduate class at University of Malaya, 2007/2008, 30 hours
- Mph Yr 1 Research Methods, Postgraduate class at University of Malaya, 2007/2008, 2 hours
- Biostatistics For Master Of Clinical Oncology, Postgraduate class at University of Malaya, 2006/2007, 22 hours
- Foundation Of Biostatistics, Postgraduate class at University of Malaya, 2006/2007, 32.5 hours
- Mph Yr 1 Research Methods, Postgraduate class at University of Malaya, 2006/2007, 1.5 hours
- Biostatistics, Postgraduate class at University of Malaya, 2006/2007, 12 hours

- Mph Yr 2 Research Proposal Development For Epidemiological Studies, Postgraduate class at University of Malaya, 2006/2007, 8.5 hours
- Introduction To Stata, Postgraduate class at University of Malaya, 2006/2007, 6 hours
- Introduction To Stata, Postgraduate class at University of Malaya, 2006/2007, 3 hours
- Systematic Review And Meta-Analysis, Postgraduate class at University of Malaya, 2006/2007, 12 hours
- International Classification Of Diseases, MBBS teaching at University of Malaya, 2008/2009(1), 3 hours
- Epidemiology Of Specific Diseases, MBBS teaching at University of Malaya, 2008/2009(1), 2 hours
- DPHS/SPM module on Epidemiology & Statistics, MBBS teaching at University of Malaya, 2008/2009(1), 16 hours
- DPHS/SPM module on Epidemiology & Statistics, MBBS teaching at University of Malaya, 2007/2008(1), 23 hours
- Community Residence Program, MBBS teaching at University of Malaya, 2007/2008(2), 2 hours
- Community Residence Program, MBBS teaching at University of Malaya, 2007/2008(2), 224 hours
- Nursing Research & Statistics, MBBS teaching at University of Malaya, 2007/2008(1), 4 hours
- DPHS/SPM module on Epidemiology & Statistics, MBBS teaching at University of Malaya, 2006/2007(2), 23 hours
- Nursing Research & Statistics, MBBS teaching at University of Malaya, 2006/2007(1), 2 hours
- Community Residence Program, MBBS teaching at University of Malaya, 2006/2007 (2), 2 hours
- Community Residence Program, MBBS teaching at University of Malaya, 2006/2007 (2), 224 hours
- Introduction course In Biostatistics, MBBS teaching at University of Malaya, 2006/2007(2), 14 hours

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- Community Residence Program, MBBS teaching at University of Malaya, 2005/2006(2), 224 hours
- Community Residence Program, MBBS teaching at University of Malaya, 2005/2006(2), 2 hours
- Oncology Nursing Sciences, MBBS teaching at University of Malaya, 2008/2009(1), 2 hours

**9. RESEARCH PROJECT PARTICIPATION:**

1. Influence of lifetime occupation on muscle strength and functional ability. Principle Investigator (PI). Project Grant of RM 51,700 from 2008-2009.
2. Assessment of children and families affected by HIV/AIDS. Co-Investigator. UNICEF Grant of RM 200,000 from 2008-2008.
3. The Effect of Testosterone Therapy in Aging Men with Low Serum Testosterone Levels , Co-Investigator. Project Grant of RM 300,000 from 2008 - 2009.
4. Prevention of Chronic Diseases at worksite. Co-Investigator. Project Grant of RM 50,000 from 2007-2009
5. National Health Morbidity Survey III. Questionnaire Development Group, Co investigator and biostatistician in the Hypertension and Hypercholesterolemia group, Project Grant by Ministry of Health Malaysia from 2005 – 2008.
6. Novel methods of risk identification, stratification and behavioral intervention for HIV/AIDS and CVD prevention. Co-Investigator. Project Grant from Ministry of Science, Technology and Innovation (MOSTI-IRPA) from 2004 - 2009.

## **10. ACADEMIC SERVICE**

### *10.1 Faculty of Medicine, University of Malaya*

- 2007-2009. Head of Epidemiology and Biostatistics Unit at the Department of Social and Preventive Medicine
- 2009-present. Faculty member, Julius Center University Malaya (Centre for Clinical Epidemiology and Evidence Based Medicine)
- Community Residency Programme Coordinator. MBBS Phase III CRP Coordinator - 2008 & 2009.
- Academic Adviser at First Degree Level. MBBS Phase II. 10 students. 2006/2007.

## 11. CONFERENCES AND PRESENTATIONS

1. 1st Asia Pacific Conference on Health Policy and Planning in an Era of Emerging Technologies and Cancer. Organizing Committee. 17-18 Nov-08. Organized by the College of Public Health Medicine, Academy of Medicine of Malaysia and Ministry of Health Malaysia.
2. 5th National Public Health Pre Conference Workshop. Invited Speaker on Regression Analysis. 12-Nov-08. Organized by the Malaysian Society of Public Health Physicians and Ministry of Health Malaysia.
3. 41st APACPH Annual Conference - Global Public Health Challenges. Organizing Committee . 7-9 Nov 2008. Organized by the Faculty of Medicine, University of Malaya.
4. Systematic Review and Meta analysis. Organizer and Presented on Searching and Retrieving Literature, Critical Appraisal, Introduction To Meta Analysis. 22-24 Oct 2008. Organized by the SPM department, Faculty of Medicine, University of Malaya.
5. National Seminar on Health Technology Assessment. Organizing Committee. 9-10 Oct 2008. Organized by the HTA Section, Medical Development Division, Ministry of Health Malaysia and MaHTAS and College of Public Health Medicine, Academy of Medicine of Malaysia.
6. Recent Trends in Diabetes, Obesity, and Metabolic Syndrome. Poster on Differences In The Prevalence Of Diabetes Mellitus In Urban And Rural Malaysia: A Problem Of Urbanization. 1-2 Aug 2008. Organized by the Journal of the American Medical Association (JAMA) and the National University Health System, Singapore.
7. 42nd Malaysia-Singapore Congress of Medicine, Pre Congress Workshop. Invited Speaker on Introduction To Critical Appraisal, Statistics For Clinicians - An Overview and Rapid Critical Appraisal. 31 Jul 2008. Organized by Academy of Medicine of Malaysia.
8. Good Clinical Practice Workshop. Invited Speaker on Investigator's Responsibility, Study Coordinator, Essential Documents, Archiving. 17 Jul 2008. Organized by Clinical Research Centre Hospital Sultanah Aminah, Johor Bharu.
9. Stata Workshop. Invited Speaker on Inferential Analysis And Analyzing Data. 10-11 Jul 2008. Organized by Institute of Health System Research, Ministry of Health Malaysia.
10. MERDU SPSS analysis workshop. Invited Speaker on Analyzing Clinical Research Data & Introduction to Diagnostic Testing. 25 Jun 2008. Organized by MERDU, Faculty of Medicine, University of Malaya.

11. Good Clinical Practice Workshop. Invited Speaker on Clinical Trial Design, Protocol Development, Investigator's Responsibility, IP, Essential Documents And Archiving. 24-26 Jun 2008. Organized by Clinical Investigative Centre, University Malaya Medical Centre.
12. Good Clinical Practice Workshop. Invited Speaker on Investigator's Responsibility, SC, Essential Documents, Archiving. 26 May 2008. Organized by the Clinical Research Center, Sarawak General Hospital.
13. Asia Europe Clinical Epidemiology and Evidence-Based Medicine Programme - Practice of Evidence Based Medicine. Organizing Committee and Tutor. 14-16 Apr 2008. Organized by the University of Malaya and Centre of Evidence Based Medicine, University of Oxford.
14. 2nd National Pediatric Research Conference. Invited Speaker on Study Design: A Clinician's Perspective. 28 Mar 08. Organized by the College of Pediatrics, Academy of Medicine of Malaysia.
15. Biostatistics for Clinicians. Invited Speaker on One Way ANOVA. 26-Mar-08. Organized by the Clinical Investigation Centre (CIC), University Malaya Medical Centre.
16. Course on Survival Analysis in medical research. Sole Faculty. 14-15 Feb 2008. Organized by the Department of Social and Preventive Medicine, Faculty of Medicine, University of Malaya.
17. Biostatistics for Clinicians. Invited Speaker on Probability Distributions and One Way ANOVA. 30 Jan 2008. Organized by CIC, University Malaya Medical Centre.
18. Research Methods: Introductory Course. Invited Speaker on Sampling Techniques & Sample Size Estimation, Descriptive Statistics And Good Clinical Practice. 15-17 Jan 2008. Organized by the Health Research Development Unit, Faculty of Medicine, University of Malaya.
19. Systematic Review Workshop. Invited Speaker on Meta Analysis. 13 Dec 2007. Organized by the Institute of Health Systems Research, Ministry of Health Malaysia.
20. Good Clinical Practice Workshop. Invited Speaker on Clinical Trial Design, Protocol Development, Investigator's Responsibility, IP, Essential Documents And Archiving. 11-12 Dec 2007. Organized by the CIC, University Malaya Medical Centre.
21. How To Do A Clinical Trial On Your Own. Invited Speaker on Clinical Trials In UMMC. 5 Dec 2007. Organized by the CIC, University Malaya Medical Centre.
22. Asia Europe Clinical Epidemiology and Evidence-Based Medicine Programme, "Advance Diagnostic Research: Theory and Practice". Organizing Committee and Facilitator. 20-22 Nov



2007. Organized by the Julius Centre, University Medical Centre Utrecht, the Netherlands and Faculty of Medicine, University of Malaya.
23. National Heart Institute Research Day 3 Aug 2007. Invited Judge for Scientific presentations. Organized by the National Heart Institute of Malaysia.
24. Good Clinical Practice Workshop. Invited Speaker on Clinical Trial Design, Protocol Development, Investigator's Responsibility, IP, Essential Documents and Archiving. 23 May 2007. Organized by the Universiti Putra Malaysia.
25. Good Clinical Practice Workshop. Invited Speaker on Clinical Trial Design, Protocol Development, Investigator's Responsibility, IP, Essential Documents And Archiving. 3-5 May 2007. Organized by the CIC, University Malaya Medical Centre.
26. 2<sup>nd</sup> Asia Pacific Conference on Public Health. Secretary of the Main Organizing and Scientific Committee. 2 – 5 May 2007. Organized by the College of Public Health Medicine, Academy of Medicine of Malaysia, Universiti Putra Malaysia and Ministry of Health Malaysia.
27. Choosing the Correct Study Design. Invited Speaker on Diagnostic Research, Prevalence Studies and Interventional Studies. 16 Mar 2007. Organized by the Academy of Family Physician Malaysia.
28. SPSS Hands-On Workshop. Invited Speaker on Categorical Data Analyses, Regression and Correlation. 6-8 Mar 2007. The Nursing Research Steering Group of University Malaya Medical Centre.
29. Malaysian National Cancer Registry Report Writing Expert Meeting. Facilitator. 2 – 4 Mar 2007. Organized by the National Cancer Registry of Malaysia.
30. Research Methodology and Biostatistics Workshop. Invited Speaker on Descriptive Statistics, Correlation & Linear Regression, Logistic Regression, Analysis Of Diagnostic Research. 9-12 Jan 2007. Organized by the Malaysian Society of Anesthesiologists and Ministry of Health Malaysia.
31. Regional Evidence-based Medicine Workshop: Clinical Epidemiology as a Tool for Evidence-based Practice. Organizing Committee and Facilitator. 11-14 Dec 2006. Organized by the Ministry of Health Malaysia, University of Malaya and Julius Centre, University Medical Centre Utrecht, Netherlands.
32. Foundations of Research Methods. Invited Speaker on Experimental Study, Study Population, Sampling, Sample Size Estimation, Overview Of Statistical Methods & Introduction to SPSS. 22-24 Nov 2006. Organized by the Malaysian Armed Forces Hospital, Lumut.

33. Pre Conference Workshop for the 9th NIH Scientific Meeting: Towards better health: GRIPP. Invited Speaker on Analyzing Data With Stata: An Introduction. 18 Sep 2006. Organized by the Ministry of Health Malaysia.
34. Research Methods: Introductory Course. Invited Speaker on Overview Of Statistical Methods, Sampling Techniques & Sample Size Estimation, Data Management & Processing, Good Clinical Practice. 13-15 Sep 2006. Organized by the Health Research Development Unit, Faculty of Medicine, University of Malaya.
35. The IEA-EEF European Congress of Epidemiology 2006: Epidemiology and Health Care Practice. Participant. 28 Jun – 1 Jul 2006. Organized by the International Epidemiology Association-European Epidemiology Federation (IEA-EEF).
36. Annual Scientific Meeting College of Surgeons, Academy of Malaysia (AMM). Invited Speaker on Retrospective Studies - Do's and Don'ts. 23-25 Jun 2006.
37. Malaysian National Cancer Registry Expert Panel Review and Coding Meeting. Facilitator. 9-11 Jun 2006. Organized by the National Cancer Registry of Malaysia.
38. Systematic Review for Evidence Based CPG Development. Facilitator. 27-29 Mar 2006. Organized by the Ministry of Health Malaysia.
39. Foundations of Research Methods Workshop in Melaka. Invited Speaker on Introduction To Data Management Using SPSS, Sample Size Calculation, Analysis Of Diagnostic Research , Correlation And Linear Regression and Introduction to Survival Analysis. 6-9 Mar 2006. Organized by Hospital Melaka, Ministry of Health Malaysia.
40. Research Methods and Biostatistics Introductory course. Invited Speaker on Analysis Of Diagnostic Test Accuracy And Agreement. 16 Feb 2006. Organized by the Association of Clinical Registries Malaysia.
41. Malaysian National Cancer Registry Report Writing Workshop. Organizing Committee and Facilitator. 16-17 Dec 2005. National Cancer Registry.
42. Foundations of Research Methods Workshop. Invited Speaker on Study Population, Sampling & Sample Size Estimation, Introduction To SPSS, Descriptive Analysis, Analyzing Data Using SPSS 15-17 Dec 2005. Organized by the Malaysian Armed Forces Hospital, Lumut.
43. Evidence-based Medicine Workshop: Clinical Epidemiology as a Tool for Evidence-Based Practice. Organizing Committee and Tutor. 25-27 Nov 2005. Organized by the Ministry of Health, University of Malaya, University Medical Centre Utrecht, Netherlands.

44. Research Methods Workshop. Invited Speaker on Study Population and Sample Size Calculation, Descriptive Analysis And Inferential Analysis. 15-16 Aug 2005. Organized by the Ophthalmology Services of the Ministry of Health Malaysia.
45. Malaysian National Cancer Registry Expert Panel Review and Coding Meeting. Invited Speaker on Review Of Cancer Classification And Coding . 28-31 Jul 2005. Organized by the National Cancer Registry of Malaysia.
46. Research Method Course. Invited Speaker on Descriptive Statistics. 27 Jul 2005. Organized by the Health Research Development Unit, Faculty of Medicine, University of Malaya.
47. 4th National Public Health Conference. Participant. 15 – 17 Mar 2005. Organized by the Malaysian Society of Public Health Physicians and Ministry of Health Malaysia.
48. Clinical Trial Methods and Good Clinical Practice(GCP) workshop. Invited Speaker on Study Population and Sample Size Calculation, Blinding, Randomization, Descriptive Analysis and Analysis Of Clinical Trial Data. 21-25 Feb 2005. Organized by the Clinical Epidemiology Unit of Aga Khan University and INCLEN (International Clinical Epidemiology Network) Trust International.

## **12. CONTRIBUTION TO SOCIETY:**

1. Mar – Apr 2005. Volunteered For The Malaysian Red Crescent Society Tsunami Humanitarian Mission To Aceh, Indonesia.
2. Oct – Nov 2005. Represented University Malaya Medical Centre / Malaysian Red Crescent Society In The Malaysian Humanitarian Medical Relief Mission For Earthquake Survivors In Pakistan.
3. Mar 2005 - Present Member of the Emergency Medical Response Unit, Malaysian Red Crescent Society.