Association Between Vitamin D Status and Coronary Heart Disease Among Adults in Saudi Arabia: a Case-Control Study

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Association between vitamin D status and coronary heart disease among adults in Saudi Arabia: a case-control study

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Summary

Accumulating evidence suggests that vitamin D deficiency and insufficiency may play a role in the development of coronary heart disease (CHD) and associated risk factors. Saudi Arabia has witnessed a growing epidemic of CHD and associated risk factors during the last few decades for several reasons, including the rapid changes in lifestyle and urbanization. Furthermore, national studies have demonstrated that vitamin D deficiency is highly prevalent in Saudi Arabia. Thus, it is crucial to examine the function of vitamin D in the prevention of CHD in Saudi Arabia. Therefore, the aim of this study was to examine the association between vitamin D status and the risk of CHD among adults in Saudi Arabia. It also examined the association between vitamin D deficiency and cardio-metabolic risk factors, including obesity, diabetes, hypertension and hypercholesterolemia, among subjects with and without CHD in Saudi Arabia. In addition, the present study attempted to compare the levels of knowledge, attitudes and behaviours related to vitamin D between subjects with and without CHD. It also examined the association of vitamin D status with knowledge, attitudes and behaviours related to vitamin D among study subjects. A qualitative approach was used in this study to further understand of study subjects' knowledge about vitamin D and attitudes toward sun exposure. It also explored the social and cultural factors which may explain for the high prevalence of vitamin D deficiency in Saudi Arabia.

This mixed methods research involved both quantitative and qualitative approaches. For the quantitative research, a case-control study was conducted between May and October 2015. The study participants included 130 CHD cases and 195 controls who were recruited from three hospitals in the western region of Saudi Arabia. The King Abdullah Medical City (KAMC) and Tunsi private hospital were located in Makkah city, and King Abdul Aziz University Hospital (KAU) was located in Jeddah city. Face-to-face interviews were

conducted to collect data on participants' socio-demographic characteristics, family history of CHD, knowledge about vitamin D, attitudes toward sun exposure and vitamin D-related behaviours, including sun exposure behaviours, use of sun protection, intake of vitamin supplementation and consumption of foods rich in vitamin D. Furthermore, blood pressure measurements and anthropometric measurements were also taken. In addition, fasting blood samples were collected from study participants to measure serum levels of vitamin D, blood glucose and total cholesterol. This research project has also conducted qualitative in-depth interviews with 22 subjects who participated in the quantitative study. The qualitative study was conducted at the same hospitals and during the same data collection period. The interviews consisted of open-ended questions adapted from the existing literature.

The results of the case-control study demonstrated that vitamin D deficiency (serum 25(OH)D < 10 ng/mL) was significantly higher in CHD cases than in the controls (46% and 3%, respectively) ($p < 0.001$). It also showed that a relatively higher proportion of CHD cases had obesity (44% and 22%, respectively) and diabetes (35% and 14%, respectively) ($p < 0.001$) than controls. However, controls had significantly higher total serum cholesterol levels than CHD cases (13% and 5%, respectively) ($p < 0.001$). Moreover, the results indicated that vitamin D deficiency (serum 25(OH)D < 20 ng/mL) was significantly associated with increased risk of CHD (OR: 6.5, 95% CI: 2.7–15, $p < 0.001$) among adults in Saudi Arabia. When the associations between vitamin D status and cardio-metabolic risk factors were examined in subjects with and without CHD separately, the results showed that in subjects with CHD, vitamin D deficiency (serum 25(OH)D < 20 ng/mL) was significantly associated with an increased risk of diabetes (OR: 2.9, 95% CI: 1.02-8.5, $p=0.04$). However, no significant association was found between vitamin D deficiency and other cardio-metabolic risk factors (obesity, hypertension and hypercholesterolemia) in subjects with CHD. In contrast, in subjects without CHD, no significant associations were found between vitamin D deficiency (serum 25(OH)D < 20 ng/mL) and cardio-metabolic risk factors (diabetes, obesity, hypertension and hypercholesterolemia).

In relation to the comparison between subjects with and without CHD in terms of knowledge, attitudes and behaviours related to vitamin D, the results indicated that total knowledge score was higher in the control subjects than in the CHD subjects [2.5 (±1.8) and 1.6 (±2.2), respectively]. The CHD cases had better attitudes toward sun exposure than the control subjects, but the controls had better attitudes toward vitamin D than CHD cases ($p = 0.001$). In addition, the control subjects had a higher intake of multivitamin supplements compared to CHD cases (6.7% and 0.8%, respectively; $p = 0.010$). Similarly, the control subjects had a higher intake of butter ($p = 0.001$), oily fish ($p = 0.004$) and liver ($p = 0.003$) compared to the CHD cases; however, the CHD cases had a significantly higher intake of milk ($p = 0.001$). The results also demonstrated that vitamin D deficiency (serum 25(OH)D < 20 ng/mL) was significantly associated with low levels of knowledge about vitamin D (95% CI: 1.08–3.06, $P = 0.024$) as well as low intake of vitamin supplements including vitamin D, calcium, multivitamin and calcium supplements with vitamin D (95% CI: 2.12–8.92, $P < 0.001$).

The results of the qualitative study showed that the participants had reasonable levels of knowledge about vitamin D in some aspects, including the impact of vitamin D deficiency on bone health and exposure to sunlight as the key source of vitamin D. The participants also understood that the intake of vitamin D supplements is important to improve vitamin D status. There was a lack of adequate knowledge on food sources of vitamin D and the health effects of vitamin D deficiency, except for bone health. Although some participants had positive attitudes towards exposure to sunlight, it was restricted to the time of day, as they avoided hot temperatures during the middle of the day. Also, they only exposed their faces and hands to sunlight. In comparison, some participants had negative attitudes about exposure to sunlight and avoided sunlight. Also, participants identified a number of barriers that prevented them from receiving sufficient sunlight. These barriers included hot weather, changes in house designs and living in high-rise buildings, shortage of public areas, physical inactivity, and some religious principles such as wearing hijab. Finally, the study results identified some gender differences regarding adopting healthy behaviours to increase vitamin D status as female participants were more enthusiastic about carrying out behaviours that would improve their vitamin D status than male participants.

In conclusion, this research indicated an inverse association between vitamin D deficiency and increased risk of CHD among adults in Saudi Arabia. It also added some valuable insights on the knowledge, attitudes and behaviours related to vitamin D among adults in the country. These results emphasize the importance of addressing vitamin D deficiency in Saudi Arabia as a potential modifiable factor to reduce the incidence of CHD and associated risk factors in future generations. The results of this research may have important implications for the development of strategies to improve vitamin D status in the population living in Saudi Arabia and thereby help prevent the development of CHD.

Key words: vitamin D deficiency, coronary heart disease, diabetes, obesity, knowledge, attitudes, sun exposure, vitamin D supplements, Saudi Arabia, Middle East.

Statement of Originality

This thesis describes original research conducted by Najlaa Aljefree in the School of Medicine at Griffith University. This work has not previously been submitted for a degree in any university. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

Najlaa Aljefree

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To my parents and sisters, who provided love throughout my journey, thank you for your extraordinary love, support and sacrifice and for encouraging me to achieve what I have achieved.

To my friends, Rimante Ronto, Elham Nikbakht Nasrabadi, and Nasim Salehi, thank you for your smiles, small talk and laughs. These years would not have been the same without you.

Finally, to my husband and best friend, Hussein Alattas, thank you for everything and for being patient and supportive throughout my ups and downs.

Table of Content

List of Tables

List of Figures

List of Acronyms and Symbols

ACS	Acute coronary syndrome
AMI	Acute myocardial infarction
ATP III	Adult Treatment Panel III
BMI	Body Mass Index
CVD	Cardiovascular disease
CAD	Coronary artery disease
CADISS	Coronary Artery Disease in Saudis Study
CHD	Coronary heart disease
DBP	Diastolic blood pressure
EKG	Electrocardiogram
ENT	Ear, nose and throat clinics
FPG	Fasting plasma glucose
FAO	Food and Agriculture Organization
FFQ	Food frequency questionnaire
GCC	Gulf Cooperation Council
GHA	Gulf heart association
GRACE	Global Registry of Acute Cardiac Events
Gulf RACE	Gulf Registry of Acute Coronary Events
HC	Hypercholesterolemia
HDL	High-density lipoprotein
HPLC	High-Performance Liquid Chromatography
IOM	Institute of Medicine
IDF	International Diabetes Foundation
IOF	International Osteoporosis Foundation
IU	International Units
IHD	Ischemic heart disease
KAMC	King Abdullah Medical City
KAP	knowledge, attitudes, and practice
KAU	King Abdul Aziz University Hospital
LDL	Low-density lipoprotein
MENA	Middle East and North African

MI	Myocardial infarction
NHANES	National Health and Nutritional Examination Surveys
NCDs	Non-communicable diseases
NSTEMI	Non-ST segment elevation myocardial infarction
PTH	Parathyroid Hormone
RCT	Randomized controlled trials
RAAS	Renin-Angiotensin-Aldosterone System
SPACE	Saudi Project for Assessment of Coronary Events
SBP	Systolic blood pressure
STEMI	ST segment elevation myocardial infarction
TBF	Total body fat
TG	Triglycerides
UAE	United Arabic Emirates
UK	United Kingdom
USA	United States of America
UVA	Ultraviolet A
UVB	Ultraviolet B
VDRs	Vitamin D Receptors
WC	Waist circumference
WHI	Women Health Initiative study
WHO	World Health Organization
WHR	Waist-to-hip ratio
25(OH)D	25-hydroxyvitamin D
1, 25(OH) 2 D	1, 25 dihdroxyvitamin D

Publications, Presentations and Awards:

The candidate has produced five publications from the research project which are included in this thesis. The publications are co-authored with other researchers and include one systematic review of the literature and four original research papers. The contribution of the research candidate to each publication is outlined at the front of the relevant chapter.

Publications included in this thesis:

1- **Aljefree, N.,** & Ahmed, F. Prevalence of Cardiovascular Disease and Associated Risk Factors among Adult Population in the Gulf Region: A Systematic Review. *Advances in Public Health*, vol. 2015, Article ID 235101, 23 pages, 2015. doi:10.1155/2015/235101

2- **Aljefree N,** Lee P, Alsaqqaf JM, Ahmed F. Association between Vitamin D Status and Coronary Heart Disease among Adults in Saudi Arabia: A Case-Control Study. *Healthcare*, 2016: 77. doi:10.3390/healthcare4040077

3- **Aljefree N,** Lee P, Saqqaf J, Ahmed F. Association between Vitamin D Status and Cardio-Metabolic Risk Factors among Adults with and without Coronary Heart Disease in Saudi Arabia. *Journal of Diabetes and Metabolism*, 2016: 7(707):2. doi: 10.4172/2155-6156.1000707

4- **Aljefree, N,** Lee, P. & Ahmed, F. Knowledge and attitudes about vitamin D, and behaviors related to vitamin D in adults with and without coronary heart disease in Saudi Arabia. *BMC Public Health,* 2017: 17**,** 266. doi: 10.1186/s12889-017-4183-1

5- **Aljefree, N,** Lee, P. & Ahmed, F. Exploring knowledge and attitudes about vitamin D among adults in Saudi Arabia: a qualitative study. *Healthcare*, 2017 (Under review)

Relevant publication (with Griffith affiliation) not included in this thesis:

1- **Aljefree, N.,** & Ahmed, F. Association between dietary pattern and risk of cardiovascular disease among adults in the Middle East and North Africa region: a systematic review. *Food & Nutrition Research*, 2015: 59. doi: http://dx.doi.org/10.3402/fnr.v59.27486

Conference publications during my candidature:

1- **Aljefree N**, and Faruk A. Prevalence of Cardiovascular Disease and Associated Risk Factors among Adult Population in the Gulf Region: A Systematic Review. Accepted for the poster presentation. 10th Annual Gold Coast Health and Medical Research Conference, Gold Coast, Australia, 2014.

2- **Aljefree, N.,** & Ahmed, F. (2015). Association between dietary pattern and risk of cardiovascular disease among adults in the Middle East and North Africa region: a systematic review. Accepted for poster presentation. The Gold Coast Health and Medical Research Conference, Gold Coast, Australia, 2015.

3- **Aljefree, N.,** & Ahmed, F. (2015). Association between dietary pattern and risk of cardiovascular disease among adults in the Middle East and North Africa region: a systematic review. Medical, Medicine and Health Sciences (MMHS), Kuala Lumpur, Malaysia, 2015.

4- **Aljefree NM,** Lee P, Alsaqqaf JM, Ahmed F. (2016). Vitamin D status and coronary heart disease in Saudi Arabia. Accepted for poster presentation. PHAA 44th Annual conference & 20th Chronic Disease Network Conference, At Alice Spring/ Australia.

5- **Aljefree NM,** Lee P, Alsaqqaf JM, Ahmed F. (2016). Association between Vitamin D Status and Cardio-Metabolic Risk Factors among Adults with and without Coronary Heart Disease in Saudi Arabia. The Nutrition Society of Australia Annual Scientific Meeting, At Melbourne/ Australia.

6- **Aljefree NM,** Lee P, Alsaqqaf JM, Ahmed F. (2017). Vitamin D Status and Cardio-Metabolic Risk Factors in Saudi Arabia. 15th World Congress on Public Health, At Melbourne/ Australia.

<u>Awards and grants during my candidature:</u>

2012	Awarded King Abdul Aziz University for Nutrition and Dietetics scholarship
2012-2013	Awarded Griffith Award for Academic Excellence
2015	PhD Publication Incentive Scheme grants, Population and Social Health Research Program, Griffith Health Institute (round 1 - $500)
2015	PhD Publication Incentive Scheme grants, Population and Social Health Research Program, Griffith Health Institute (round 2 - $500)
2015	PhD researcher grant scheme, Population and Social Health Research Program, Griffith Health Institute ($3000)
2016	NSA Student Travel Grant

Chapter 1: Introduction

1.1 Background and rationale of the study

Cardiovascular disease (CVD) is one of the predominant causes of mortality and disability worldwide. Approximately 31% of the global deaths in 2012 were caused by CVD (WHO, 2016). According to World Health Organization (WHO) estimates, around 23.3 million CVD deaths will occur in 2030. The majority of these deaths will be due to coronary heart disease (CHD) (WHO, 2016). It is well documented that the main causes of death have changed significantly from malnutrition and infectious diseases to CVD and other non-communicable diseases during the past century (Motlagh, O'Donnell, & Yusuf, 2009). This shift is mostly due to changes in environment, urbanization, and lifestyle, including the high consumption of unhealthy food that is rich in calories and sugar, tobacco use, and physical inactivity (Ramahi, 2010).

The majority of CVD mortality is due to CHD (also known as ischemic heart disease or myocardial infarction) which potentially leads to heart attacks. The key problem that leads to the development of CHD is atherosclerosis. Atherosclerosis is the accumulation of cholesterol and fat inside the blood arteries, which causes difficulties in blood flow. Therefore, it can result in a heart attack if it blocks the blood vessels in the heart (Mendis, Puska, & Norrving, 2011). Several factors are known to contribute to the process of atherosclerosis, including obesity, elevated blood glucose, hypertension, elevated cholesterol levels, poor diet, physical inactivity, high tobacco consumption, and alcohol consumption. These factors are widely known as the most common risk factors, or “traditional” risk factors, for myocardial infarction (heart attack) globally (Yusuf, Reddy, Ôunpuu, & Anand, 2001).

Previous research has indicated that the rates of CHD have risen globally, but more specifically in developing countries. The death rates of ischemic heart disease (IHD) have been estimated to triple between 1990 and 2020 in the Middle East and North African countries (Yusuf et al., 2001). In Saudi Arabia, the Global Burden of Disease data demonstrated that CHD was the major cause of mortality in the years 1990, 2005, and 2010 (Memish et al., 2014). In addition, data from hospitals in Saudi Arabia indicated that CHD was the third major cause of hospital-based deaths (Kumosani, Alama, & Iyer, 2011). Moreover, CHD was found to be prevalent among 5.5% of the Saudi population (Al-Nozha, Arafah, et al., 2004). Furthermore, national studies within the country have reported a considerable prevalence of CHD risk factors among the population, with high rates of obesity (35.6%), hypertension (26%), diabetes (23.7%), and hypercholesterolemia (50%) (Al-Nozha, Abdullah, et al., 2007; Al-Nozha, Al-Maatouq, et al., 2004; Al-Nozha et al., 2005; Al-Nozha et al., 2008).

In recent years, vitamin D has been recognized in medical literature as an important micronutrient to human health, not only for its well-known function in bone health and the regulation of calcium and bone homeostasis, but also for the possible effect of vitamin D deficiency on health, including CHD, and several types of cancers (Geleijnse, 2011). Vitamin D is known as the sunshine vitamin because the exposure of human body to sunlight is the main source of this vitamin. There are also a few dietary sources of vitamin D including oily fish, egg yolks, and liver, as well as vitamin D dietary supplements. Despite the known benefits and sources of vitamin D, vitamin D deficiency and insufficiency are highly prevalent globally. The recent estimates indicate that vitamin D deficiency affects 20% to 25% of the total population in developed countries, including the USA, Europe, and Australia (Fields, Trivedi, Horton, & Mechanick, 2011). In Saudi Arabia, vitamin D deficiency is also an epidemic, even with the abundance of sunlight throughout the year (Ardawi, Sibiany, Bakhsh, Qari, & Maimani, 2012). In Saudi Arabia, majority of the studies that have measured vitamin D levels have shown a high prevalence of vitamin D deficiency among different population groups (Alfawaz, Tamim, Alharbi, Aljaser, & Tamimi, 2014; Ardawi et al., 2012; Elsammak, Al-Wossaibi, Al-Howeish, & Alsaeed, 2011; Ghannam, Hammami, Bakheet, & Khan, 1999; Naeem et al., 2011; Sadat-Ali, AlElq, Al-Turki, Al-Mulhim, & Al-Ali, 2009). A recent national-level survey also indicated a high level of vitamin D deficiency among males and females in Saudi Arabia (40% and 60%, respectively) (Tuffaha et al., 2015). Thus, vitamin D deficiency is now recognized as a serious public health problem in Saudi Arabia.

Recent data suggest that vitamin D deficiency can influence the cardiovascular system by activating the renin angiotensin aldosterone system (RAAS), which potentially leads to hypertension and left ventricular hypertrophy (Nitta, 2011). Likewise, vitamin D deficiency gives rise to parathyroid hormone (PTH), which in turn causes hypertension and increases the risk of myocardial contractility and thus, hypertrophy and fibrosis of the left ventricle can occur (Judd & Tangpricha, 2009; Nitta, 2011). Several epidemiological studies have reported an independent association between vitamin D deficiency and increased risk of CHD (Kim, Sabour, Sagar, Adams, & Whellan, 2008; Wang et al., 2008). Likewise, the association between vitamin D deficiency and CHD risk factors such as diabetes and hypertension has been shown in large observational studies globally (Lee, Gadi, Spertus, Tang, & O'Keefe, 2011; McGill, Stewart, Lithander, Strik, & Poppitt, 2008). Moreover, an inverse association between vitamin D levels and the risk of CHD was reported in a meta-analysis of 24 observational studies (Wang et al., 2012). Similarly, an association between vitamin D deficiency and cardiovascular mortality was reported in a meta-analysis of eight cohort studies (Schöttker et al., 2014). However, some observational studies have reported no association between vitamin D status and CHD risk factors such as hypertension and diabetes (Snijder et al., 2007; Alhumaidi, Adnan, & Dewish., 2013). Furthermore, a case-control study conducted in South India showed a significant association between high levels of vitamin D and the risk of CHD (Rajasree et al., 2001). To date, few randomized controlled trials (RCTs) have been conducted worldwide to evaluate the role of vitamin D supplementation in reducing CHD risk (LaCroix et al., 2009; Prince et al., 2008; Trivedi, Doll, & Khaw, 2003). Some showed no significance effect of vitamin D supplements on all cause of mortality including CVD mortality (LaCroix et al., 2009; Trivedi et al., 2003). However, other studies showed a slight effect of vitamin D supplements on CVD risk (Prince et al., 2008; Zittermann et al., 2009). Nevertheless, due to the small sample sizes of these studies, no firm conclusion on the role of vitamin D in CHD can be made. Furthermore, a recent large RCT published in 2016 reported no causal association between vitamin D and the risk of CHD; however, the results of this study were limited only to European ethnicity, not Arabic ethnicity (Manousaki, Mokry, Ross, Goltzman, & Richards, 2016). Thus, based on the existing literature, it is difficult to reach any firm conclusion regarding the relationship between vitamin D status and the risk of CHD, and therefore, further well-designed studies among different populations are warranted.

The studies that have examined the causes of vitamin D deficiency focused most on various biological factors. To date, little is known about the role of knowledge, attitudes and behaviours regarding vitamin D. Only one study has examined the knowledge and attitudes about vitamin D in Saudi Arabia; however, this study was conducted in college students, and it was difficult to generalize the results due to the small sample size and sex restriction (only eight females) (Christie & Mason, 2011).

Alongside the elevated rates of CHD and associated risk factors, Saudi Arabia is one of the countries with a high prevalence of vitamin D deficiency (40% among males and 60% among females) (Tuffaha et al., 2015). To our knowledge, no previous studies have been carried out that focused on the relationship between vitamin D status and the risk of CHD among Saudi adults. Even though this issue has been studied previously in populations of other countries, these findings are not generalizable to Saudis because Saudi Arabia has a unique culture and lifestyle which make it difficult to generalize results from other countries to Saudi population especially in case of diseases that can be affected by lifestyle such as CHD and vitamin D status. Moreover, the findings are somewhat inconsistent. Because vitamin D deficiency, CHD, and associated risk factors are vital issues in the Kingdom, it is important to investigate the relationship between these variables among Saudi adults in order to design appropriate interventions for prevention of CHD. Therefore, the aim of this study was to investigate the relationship between vitamin D status and the risk of CHD in Saudi Arabian adults. In addition, the study examined the knowledge and attitudes about, and behaviours toward, vitamin D in Saudi Arabia.

1.2 Research objectives

1- To investigate the associated socio-demographic characteristics with CHD.
2- To identify the cardio metabolic risk factors (obesity, diabetes, hypertension and hypercholesterolemia) and the life style behavioural risk factors (physical activity and smoking) for CHD.
3- To investigate vitamin D levels among subjects with and without CHD.
4- To examine the association between vitamin D status and CHD after controlling for potential confounding factors (objectives 1 and 2).
5- To examine an indirect association between vitamin D and CHD by investigating the association of vitamin D status and cardio metabolic risk factors (obesity, diabetes, hypertension and hypercholesterolemia).
6- To compare the knowledge, attitudes and behaviours toward vitamin D between subjects with and without CHD.

7- To examine the independent associations of vitamin D status with knowledge, attitudes, and behaviours related to vitamin D among study sample after controlling for potential confounders including CHD status.
8- To explore knowledge and attitudes toward vitamin D and the social and cultural factors that may contribute to the high prevalence of vitamin D deficiency in Saudi Arabia using qualitative approach.

1.3 Research questions

The primary research question that guides the current study is:

What is the relationship between vitamin D status and the risk of CHD among adults in Saudi Arabia?

Six subsequent-questions have been developed to answer the main research question:

1- Are there any differences in distributions of the sociodemographic characteristics, cardio-metabolic risk factors (obesity, diabetes, hypertension, and hypercholesterolemia), and lifestyle behavioural risk factors (smoking and physical activity) in subjects with and without CHD?

2- Are there any differences between subjects with and without CHD regarding serum vitamin D levels and the proportion of vitamin D deficiency?
3- Is there an independent association between vitamin D status and CHD after controlling for potential confounding effects of sociodemographic, cardio metabolic, and lifestyle risk factors?
4- What are the associations between vitamin D status and the common cardio metabolic risk factors (obesity, diabetes, hypertension, and hypercholesterolemia) among subjects with and without CHD?

5- Are there any differences in knowledge, attitudes, and behaviours regarding vitamin D between subjects with and without CHD? Is there any association between vitamin D status and knowledge, attitudes, and behaviours related to vitamin D among adults in Saudi Arabia?
6- What are the current levels of knowledge and attitudes about vitamin D among adults in Saudi Arabia? What are the social and cultural factors that affect people's knowledge and attitudes about vitamin D in Saudi Arabia?

1.4 Significance of the research

Saudi Arabia has experienced a massive improvement in socioeconomic conditions in the last few decades in several areas, including health and education. However, urbanization, the increased availability of food, and rapid changes in lifestyle have resulted in an increase in non-communicable diseases, such as CHD and associated risk factors (Almalki, Fitzgerald, & Clark, 2011). According to the Global Burden of Disease data, CHD was the leading cause of death in Saudi Arabia in 1990, 2005, and 2010 (Memish et al., 2014). Therefore, it is important to develop appropriate interventions to prevent CHD in the Saudi population.

Furthermore, recent literature has indicated that vitamin D deficiency is associated with various chronic diseases, such as CHD, and their risk factors (Kim et al., 2008; Wang et al., 2008). National studies in Saudi Arabia have reported low levels of vitamin D in both genders. Levels ranged from 8.4 to 11.6 ng/ml in males, and from 8 to 16.6 ng/ml in females (Ardawi et al., 2012; Elsammak et al., 2011; Naeem et al., 2011; Ardawi, Qari, Rouzi, Maimani, & Raddadi, 2011). However, as mentioned earlier, no studies have examined the association between vitamin D status and the risk of CHD in the Saudi population.

Given the high rates of CHD and associated risk factors in Saudi Arabia, along with the high prevalence of vitamin D deficiency in the country, there is a need for well-designed studies to examine the possible relationship between vitamin D status and the risk of CHD.

On the basis of the understanding of the vitamin D and CHD relationship, this study has the potential to recommend appropriate strategies for the control and prevention of CHD. Moreover, this study is expected to provide more in-depth evidence to address vitamin D deficiency in the country in order to develop specific health promotions and public health interventions.

1.5 Thesis structure and outline of chapters

The current thesis is structured to incorporate a series of published journal articles. The thesis consists of eight chapters including five manuscripts that have already been published or submitted in international peer-reviewed journals (four published and one under review).

Chapter one provides a brief background and rationale of the research. It also introduces the research questions and significance. Chapter two reports the current literature on CHD and vitamin D. Chapter two also includes manuscript 1, which systematically evaluates the current evidence on the prevalence of CHD and associated risk factors in the Gulf region, including Saudi Arabia. Chapter three illustrates the research methodology, including the research paradigm, research design, conceptual framework, data collection and analysis methods.

Chapter four includes manuscript 2, which reports the results of the association between vitamin D status and CHD among adults in Saudi Arabia. Chapter five includes manuscript 3, which presents the results about the association between vitamin D status and cardio-metabolic risk factors, including obesity, diabetes, hypertension, and hypercholesterolemia among subjects with and without CHD in Saudi Arabia. Chapter six presents manuscript 4, which includes the results regarding the knowledge and attitudes about vitamin D, and behaviours related to vitamin D in adults with and without coronary heart disease in Saudi Arabia using a quantitative approach. Chapter seven presents manuscript 5, which illustrates the results of the qualitative study on the knowledge and attitudes related to vitamin D in Saudi Arabia. Finally, chapter eight provides a general discussion on the findings of all four studies reported in chapters four, five, six, and seven. It also states the strengths and limitations of the research, future recommendations, implications of the research, and the conclusion. The thesis structure is outlined in Table 1.1 and Figure 1.1. Figure 1.2 shows a summary of the research questions and related papers.

Table 1.1: Thesis structure

Chapter	Section	Paper	Research questions
Chapter 1	Introduction	NA	NA
Chapter 2	Literature review	Manuscript 1	NA
Chapter 3	Methods	NA	NA
Chapter 4	Results	Manuscript 2	RQ1,2,3
Chapter 5	Results	Manuscript 3	RQ 4
Chapter 6	Results	Manuscript 4	RQ 5
Chapter 7	Results	Manuscript 5	RQ 6
Chapter 8	Discussion and conclusion	NA	NA

NA, not applicable; RQ, research question

Chapter 1: Introduction

Introduce a brief background of the research problem, research questions and significance of the research

Chapter 2: Literature review including manuscript 1

Present the current literature on CHD and vitamin D. Also, it present “Prevalence of Cardiovascular Disease and Associated Risk Factors among Adult Population in the Gulf Region: A Systematic Review”

Chapter 3: Methods

Provides the research methodology, including research paradigm, research design, conceptual framework, data collection and analysis methods

Chapter 4: Manuscript 2

Association between Vitamin D Status and Coronary Heart Disease among Adults in Saudi Arabia: A Case-Control Study

Chapter 5: Manuscript 3

Association between Vitamin D Status and Cardio-Metabolic Risk Factors among Adults with and without Coronary Heart Disease in Saudi Arabia

Chapter 6: Manuscript 4

Knowledge and attitudes about vitamin D, and behaviors related to vitamin D in adults with and without coronary heart disease in Saudi Arabia

Chapter 7: Manuscript 5

Exploring knowledge and attitudes about vitamin D among adults in Saudi Arabia: a qualitative study

Chapter 8: Discussion and conclusion

Provide the general discussion, strengths and limitations of the research, future recommendations, implications of the research, and conclusion.

Figure 1.1: Overview of thesis structure

RQ1: What are the distributions of the socio-demographic characteristics, cardio metabolic risk factors (obesity, diabetes, hypertension, and hypercholesterolemia), and lifestyle behavioural risk factors (smoking and physical activity) in subjects with and without CHD?

RQ2: Are there any differences between subjects with and without CHD regarding vitamin D serum levels and the proportion of vitamin D deficiency?

RQ3: Is there an independent association between vitamin D status and CHD after controlling for potential confounding effects of socio-demographic, cardio metabolic and lifestyle risk factors?

Chapter 4: Association between Vitamin D Status and Coronary Heart Disease among Adults in Saudi Arabia: A Case-Control Study **(manuscript 2)**

RQ4: What are the associations between vitamin D status and the common cardio metabolic risk factors (obesity, diabetes, hypertension, and hypercholesterolemia) among subjects with and without CHD?

Chapter 5: Association between Vitamin D Status and Cardio-Metabolic Risk Factors among Adults with and without Coronary Heart Disease in Saudi Arabia **(manuscript 3)**

RQ5: Are there any differences in knowledge, attitudes and behaviors regarding vitamin D between subjects with and without CHD? Is there any association of vitamin D status with knowledge, attitudes, and behaviours related to vitamin D among adults in Saudi Arabia?

Chapter 6: Knowledge and attitudes about vitamin D, and behaviors related to vitamin D in adults with and without coronary heart disease in Saudi Arabia **(manuscript 4)**

RQ6: What are the knowledge, attitudes, and behaviors about vitamin D among adults in Saudi Arabia? And what are the social and cultural factors that affect people's knowledge, attitudes, and behaviors about vitamin D in Saudi Arabia?

Chapter 7: Exploring knowledge and attitudes about vitamin D, and behaviors related to vitamin D among adults in Saudi Arabia: a qualitative study **(manuscript 5)**

Figure 1.2: A summary of the research questions of the thesis and related papers.

Chapter 2: Literature review

2.1 Introduction

This section provides an extensive review of literature related to coronary heart disease (CHD) and vitamin D. It is divided into six sub-sections. The first section gives a brief background of CVD, including definitions and aetiology. The second section provides background on Saudi Arabia. The third section includes manuscript 1, which describes the problem of CHD and associated risk factors in the Gulf region, including Saudi Arabia. In the fourth section, a brief background of vitamin D is provided. The fifth section discusses and summarizes the literature related to the association between vitamin D and CHD. Finally, the conclusion is provided.

2.2 Cardiovascular disease

2.2.1 Definitions and types

CVD is the principal cause of mortality and morbidity worldwide. The World Health Organization (WHO) has divided CVD into two main categories: CVDs due to atherosclerosis, and other CVDs (Mendis et al.,, 2011). CVDs resulting from atherosclerosis include CHD or ischaemic heart disease (heart attack) and cerebrovascular disease (stroke). Other forms of CVDs include rheumatic heart disease, congenital heart disease, cardiac arrhythmias and cardiomyopathies (Mendis et al., 2011). CHD, which is the central focus of this study, is also known as coronary artery disease (CAD). WHO defined it as the “narrowing of the blood vessels that supply the heart muscle” (WHO, 2016).

Atherosclerosis is a key vascular problem for the development of CVD. Atherosclerosis usually starts at an early age and slowly develops with an increase in age. When atherosclerosis occurs, the accumulation of cholesterol and fat inside the lumen of the blood arteries causes serious consequences when the blood vessels become smaller and the lumens become narrow due to this build-up. This makes it hard for blood to move through the blood vessels and results in the creation of blood clots, which cause blood movement to stop. If the blood clots interfere with the coronary artery, this can result in a heart attack, and if these clots affect the blood arteries in the brain, this can result in cerebrovascular disease (strokes) (Mendis et al., 2011; Ramahi, 2010).

The factors that promote the process of atherosclerosis have been categorized into two main groups: modifiable and non-modifiable risk factors. Modifiable risk factors include behavioural risk factors (smoking, physical inactivity and unhealthy food intake) and metabolic risk factors (hypertension, raised blood lipids, diabetes and obesity). Non-modifiable risk factors, such as age, gender, low socioeconomic status, and genetic factors, are those factors that individuals cannot change (Rawas, Yates, Windsor, & Clark, 2012).

2.2.2 The burden of CVD and associated risk factors

CVD is considered the key contributor to global death and is expected to increase in the future. The majority of CVD mortality is due to heart attacks and strokes. According to the WHO, the proportions of deaths from CHD and cerebrovascular disease (stroke) in males (46% and 34%) and females (38% and 37%) were much higher than those associated with other types of CVDs, such as rheumatic heart disease and inflammatory heart disease (Mendis et al., 2011). Additionally, the proportions of disability-adjusted life years (DALYs) associated with CHD and strokes in males (45% and 29%) and females (37% and 33%) were also higher than those associated with other CVDs (Mendis et al., 2011). The WHO also showed that in 2008, out of 17.3 million deaths, 7.3 and 6.2 million deaths were due to heart attacks (CHD) and strokes, respectively (WHO, 2016).

In developing countries, such as Middle East and North Africa (MENA) countries, the mortality rates of CHD and strokes are estimated to increase dramatically between 1990 and 2020 (Yusuf et al., 2001). The predicted rise in death rates from CHD (males, 174%; females, 146%) and strokes (males, 158%; females, 138%) among populations in the MENA region is greater than the estimated increase for developed countries during the same period (Yusuf et al., 2001).

Also, these countries are showing alarming rates of associated risk factors, which are greater than those in developed countries. A recent systematic review and meta-analysis examined the prevalence of several risk factors among Middle Eastern populations and showed that the overall prevalence of obesity, diabetes, hypertension and smoking was 24.5%, 10.5%, 21.7%, and 15.6%, respectively (Motlagh, O'Donnell, & Yusuf, 2009). Furthermore, the International Diabetes Foundation (IDF) has estimated that the diabetes rate will rise from 12.5% in 2011 to 14.3% by 2030 in the MENA region (Whiting, Guariguata, Weil, & Shaw, 2011). Also, according to the IDF, six countries in the MENA region were among the top-ten countries with the highest diabetes prevalence globally in 2011, and Saudi Arabia was one of these countries (Whiting et al., 2011). Also, the IDF expected a high prevalence of diabetes in these countries including Saudi Arabia in 2030 (Whiting et al., 2011).

2.3 Saudi Arabia

Saudi Arabia is the largest country in the Middle East region. It covers an area of 2.15 million km², and according to the last official census in 2010, it has a population of 27.1 million (Almalki et al., 2011). The proportion of Saudi citizens is 68.9% of the total population, including 50.2% males and 49.8% females. The majority of the population in Saudi Arabia is overwhelmingly young, with 67.1% of the residents under the age of 30 years and 37.2% under 15 years old. Meanwhile, only 5.2% of the population is over the age of 60 years. Saudi Arabia is witnessing a high birth rate (23.7/1000), an increased life expectancy (72.5 years in males and 74.7 years in females), and a declining death rate among infants and children, which is predicted to result in an increase in the total population to 39.8 million in 2025 and 54.7 million in 2050. More than 85% of the population lives in urban areas due to a the gradual shift from rural to urban living that has taken place in recent decades (Almalki et al., 2011).

Jeddah is the second largest city after the capital Riyadh. It lies on the coast of the Red Sea in the western region of Saudi Arabia between the latitudes of 21.25 and 21.45 north and the longitudes of 29.50 and 39.20 easts. Jeddah plays a very important role in the country's economic activities and imports, because it has a large sea port and is located close to the holy cities in Saudi Arabia (Makkah and Madinah) (Memish, Venkatesh, & Ahmed, 2003).

During the past 40 years, the Kingdom of Saudi Arabia has witnessed enormous improvement in socioeconomic development, with remarkable progress in several areas, including health, education, housing and the environment. The main source of wealth is from the industrial sector, which makes up about 51% of gross domestic product **(**GDP), mostly from oil and gas mining, followed by the service sector, which accounts for 43% of GDP and then the agriculture sector with 5%. The Kingdom of Saudi Arabia is the largest producer and exporter of oil in the world, and it has ambitious plans for making additional investments in oil refining, petrochemicals, phosphates and gas sectors, which might lead to more growth in the percentage of oil-derived export profits. This, in turn, has successfully affected Saudis by increasing their incomes, as the per-capita income was $8,140 in 2000 and reached $21, 312 in 2017. This has made Saudi Arabia the largest economic country in the Middle East (Almalki et al., 2011; WHO, 2017).

The economic improvement in Saudi Arabia has positively affected various sectors in the country, including the health care sector. In recent years, the overall burden of disease has been significantly reduced, with a large decline in deaths and disability from communicable diseases and an enormous decline in maternal deaths, combined with an increased life expectancy in Saudi Arabia. However, the rise in longevity, along with lifestyle changes, has led to changes in the patterns of disease, with a remarkable increase in non-communicable diseases (NCDs), in particular, CVD and diabetes (Almalki et al., 2011; WHO, 2017).

2.4 Prevalence of cardiovascular disease and associated risk factors among adult population in the gulf region: a systematic review (Manuscript 1)

2.4.1 Introduction

This section presents the prevalence data of CHD and associated risk factors in the Gulf region, including in Saudi Arabia. It includes a published systematic review that evaluates the available literature on the prevalence of CHD, strokes and associated risk factors, including diabetes, hypertension, obesity, dyslipidaemia, dietary habits, smoking and physical activity. This review included 62 studies that covered the prevalence data of CHD and risk factors between 1990 and 2014 of adults in the Gulf countries, including Saudi Arabia, Kuwait, Oman, Bahrain, Qatar, and the United Arab Emirates. The results of this systematic review highlighted the problem of CHD and associated risk factors in the Gulf region, especially Saudi Arabia. This paper also emphasises the need for urgent strategies to prevent and reduce the rates of CHD and associated risk factors in the region. Since 2014, few studies have been published on this topic in the context of Saudi Arabia (Al-Rubean et al., 2017; Ginawi et al., 2016; Kalaf et al., 2016).

This paper has been published as an original research paper in a peer-reviewed journal and has been designed and written according to the journal style including the reference style.

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Declaration:

I (the candidate) am the first and corresponding author of this paper. My contribution to the paper includes the development of the study design, review of literature, performed data search, article selection against inclusion and exclusion criteria, critical appraisal of included articles, quality assessment and writing of the manuscript for submission to the journal.

Signed: Date:

First author (corresponding): Najlaa Aljefree

Signed: Date:

Principal supervisor and co-author: Faruk Ahmed

2.4.2 Abstract

Background: CVD is a principal cause of mortality and disability globally.

Objective: To analyse the epidemiological data on CHD, strokes, and the associated risk factors among adult population in the Gulf countries.

Methods: A systematic review of published articles between 1990 and 2014 was conducted. *Results*: The analysis included 62 relevant studies. The prevalence of CHD was reported to be 5.5% in Saudi Arabia. The annual incidence of strokes ranged from 27.6 to 57 per 100 000 in the Gulf countries with ischaemic stroke being the most common subtype and hypertension and diabetes being the most common risk factors among stroke and ACS patients. The prevalence of overweight and obesity ranged from 31.2% to 43.3% and 22% to 34.1% in males and from 28% to 34.3% and 26.1% to 44% in females, respectively. In males, the prevalence of hypertension and diabetes ranged from 26.0% to 50.7% and 9.3% to 46.8%, respectively; in females these ranged from 20.9% to 57.2% and 6% to 53.2%, respectively. The prevalence of inactivity was from 24.3% to 93.9% and 56.7% to 98.1% in males and females, respectively. Relatively more males (13.4% to 37.4%) than females (0.5% to 20.7%) were current smokers. Available data indicate poor dietary habits with high consumption of snacks, fatty foods, sugar, and fast food.

Conclusion: Effective preventative strategies and education programs are crucial in the Gulf region to reduce the risk of CVD mortality and morbidity in the coming years.

Key words: cardiovascular disease, strokes, obesity, diabetes, hypertension, Gulf Cooperation Council.

2.4.3 Introduction

Cardiovascular disease (CVD) is now recognized as the leading cause of death and disability worldwide [1]. The World Health Organization (WHO) estimated that in 2008, out of 17.3 million CVD deaths globally, heart attacks (myocardial infarction) and strokes were responsible for 7.3 and 6.2 million deaths, respectively [1]. According to the INTERHEART and INTERSTROKE studies, hypertension, diabetes, dyslipidaemia, obesity, smoking, physical activity, poor diet, and alcohol consumption are the most common risk factors for myocardial infarction (heart attack) and strokes worldwide [2, 3].

The Gulf Cooperation Council (GCC) is cooperation between Saudi Arabia, Bahrain, Oman, Qatar, the United Arab Emirates, and Kuwait. In 1981, the GCC was created to encourage investment and to adopt free trade between member states. This agreement also contributed to several fields including: education, culture, tourism, social opportunities, and health among the GCC members. The discovery of oil and other natural resources such as gas in the GCC countries including Saudi Arabia led to rapid development and economic growth [4]. Along with the rapid socioeconomic growth in the Gulf countries, there has been a change in lifestyle such as an increased consumption of poor quality foods and the adoption of a sedentary lifestyle [5], and as a consequence the rates of CVD and associated risk factors among the Gulf population have also increased; the rates sometimes exceed that of developed countries [5]. Furthermore, the number of deaths resulting from ischemic heart disease and hypertensive heart disease in the Middle East and North Africa region (including the GCC countries) was 294/100,000 and 115/100,000 respectively. Also, the number of disability-adjusted life years (DALYs) resulting from ischemic and hypertensive heart disease is 3702/100,000 and 1389/100,000, respectively, in the same region [6]. The WHO estimated the total number of non-communicable diseases resulting in death in the GCC states in 2008. CVD was estimated to account almost half of the deaths in Oman and Kuwait, 49% and 46%, respectively. The rate of CVD deaths was also high in Saudi Arabia, the UAE, Bahrain, and Qatar 42%, 38%, 32%, and 23%, respectively [7]. Although some systematic reviews on the prevalence of CVD and/or CVD risk factors in the Middle East region have been published [8, 9], these reviews were limited to either CVD risk factors only [8], or specific gender [9]. To our knowledge, this is the first systematic review that provides a comprehensive analysis on the prevalence of CHD, strokes, and associated risk factors in the Arabic Gulf countries. The aim of this paper was to review the epidemiology of CHD, strokes, and the related risk factors among the adult population in the GCC.

2.4.4 Methods

2.4.4.1 Data Sources: An extensive literature search was conducted on the prevalence of CHD and incidence of strokes and the burden of associated risk factors to identify articles or reports published between 1990 and 2014 using ProQuest Public Health, MEDLINE, PubMed, Google Scholar, and World Health Organization (WHO) website. A manual search of reference lists of original studies was searched. In addition, checking the review articles, contacting authors, the official website of the Gulf Heart Association were also searched http://www.gulfheart.org/ and the section labelled "GHA studies" was specifically scanned. The search terms used were shown in Figure 2.1.

2.4.4.2 Study Selection: A total of 7800 articles were identified in initial search. The titles and abstracts of all articles of potential interest were reviewed for inclusion and exclusion of studies. The criteria for selected studies aimed to include studies that indicated the prevalence of CHD and/or stroke and/or at least one of the associated risk factors: diabetes, hypertension, obesity, dyslipidaemia, dietary habits, smoking, and physical activity. All the included studies were required to only include individuals over 18. The CHD and stroke studies were not restricted by sample size due to the limited numbers of these studies in the GCC countries. However, all the included studies that examined the burden of the risk factors were restricted with a sample size that exceeded 500 except for diet studies. All selected studies were required to relate to at least one of the GCC populations. Only studies published in English and where full manuscripts were included. Studies were published in abstract form and those on congenital heart disease or other CVDs were excluded. A total of 190 full-text papers were identified and further reviewed. Finally, 62 articles including two articles by contacting authors directly were included in this review. Figure 2.2 summarizes the selection process of the reviewed studies.

2.4.4.3 Data Abstraction and Quality Assessment: Data extracted for each study included first author and publication year, sample size, demographic characteristics, the country of study, place of study, study objectives, year(s) of survey, response rate, study methods, the definition of CHD and/or stroke and/or associated risk factors, and the prevalence of CHD and/or stroke and/or associated risk factors. The quality of selected studies was assessed according to the Centre for Reviews and Dissemination guidelines [10]. Since there are few papers that addressed the study questions, no studies were excluded for their qualities. The quality assessment checklist of the included studies in the systematic review is shown in the far-right column of Tables 2.1 and 2.2.

2.4.4.4 Data Synthesis: A narrative synthesis was performed to identify the study questions. It included describing all the included papers, summarising the findings of the data extracted from each study, and exploring the relationships between the results of the different studies.

Cardiovascular disease

1- "Cardiovascular disease" OR "epidemiology of cardiovascular disease" OR "coronary heart disease" OR "epidemiology of coronary heart disease"

Strokes

2- "stroke" OR "epidemiology of stroke" OR "incidence of stroke"

Associated risk factors

3- "Cardiovascular risk factors" OR "coronary heart disease risk factors" OR "stroke risk factors" OR "diabetes mellitus" OR "epidemiology of diabetes mellitus" OR "NIDDM" OR "dyslipidaemia" OR "epidemiology of dyslipidaemia" OR "hypercholesterolemia" OR "high cholesterol" OR "smoking" OR "tobacco use" OR "epidemiology of smoking" OR "hypertension" OR "high blood pressure" OR "epidemiology of hypertension" OR "obesity" OR "overweight" OR "BMI" OR "epidemiology of obesity" OR "physical activity" OR "exercise" OR "epidemiology of physical activity" OR "Food consumption patterns" OR "eating habits" OR "dietary patterns" OR "food"

The Gulf region

4- "Gulf region" OR "Arab countries" OR "GCC" OR "Saudi Arabia" OR "Kuwait" OR "Oman "OR "Bahrain "OR "Qatar "OR "United Arab Emirates"
5- #1 AND #4
6- #2 AND #4
7- #3 AND #4
8- #1 AND #3 AND #4
9- #2 AND #3 AND #4

Figure 2.1: selected search terms

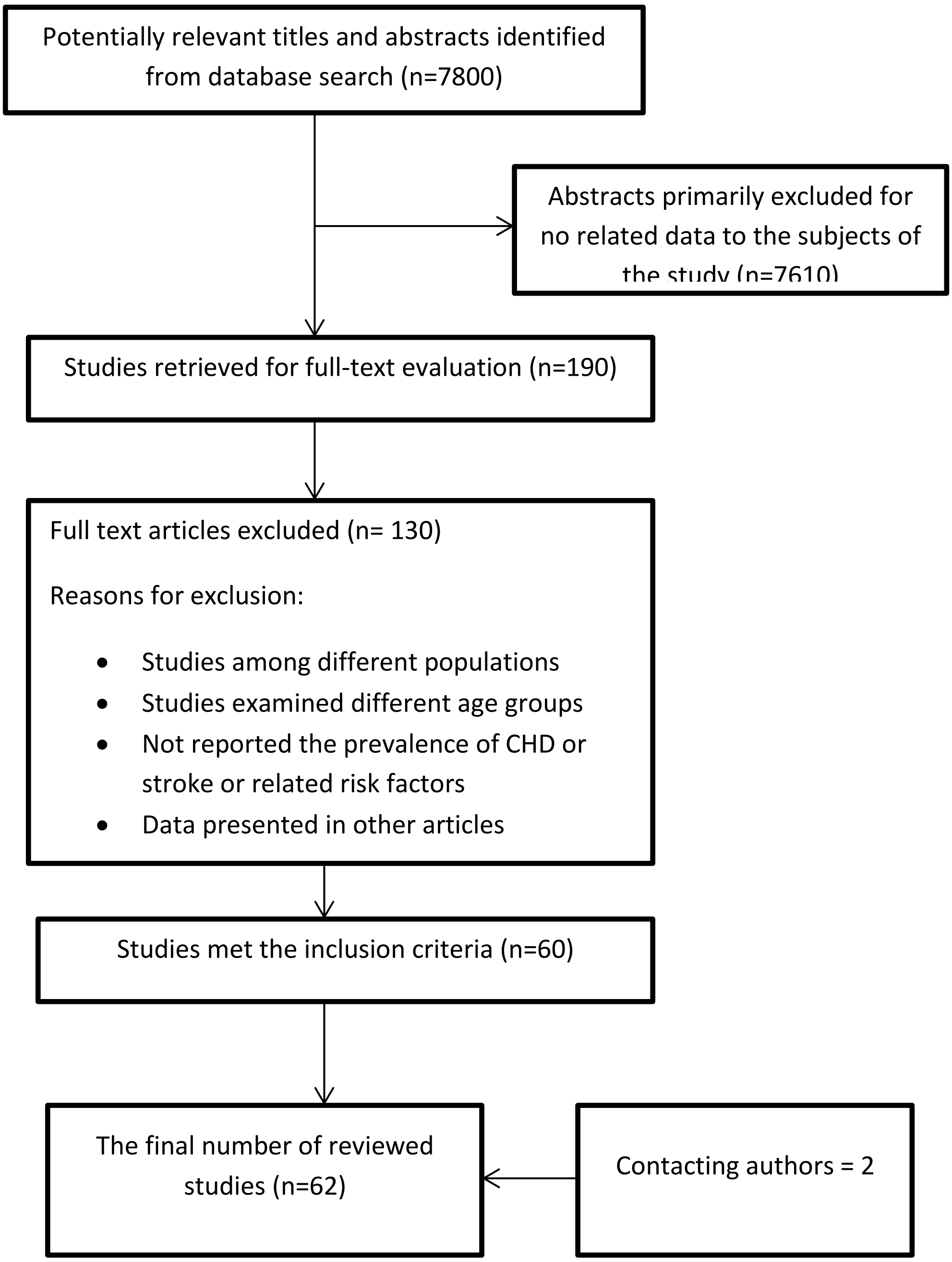

Figure 2.2: Study selection process

2.4.5 Results

Of the 62 articles that are reviewed in the present study, 13 were published in the 1990s, another 40 in the 2000s, and 9 in the last four years. Of the included studies, 4 reported data on CHD, 12 on stroke, and 46 on the prevalence of the associated risk factors. Further, of these 62 selected studies, 22 were carried out among Saudi, 8 in Bahraini, 10 in Kuwaiti, 5 in Omani, 6 in Qatari, and 8 in the UAE populations, and 3 were carried out in multiple GCC countries. Regarding the study design; 48 studies were cross-sectional, 7 were retrospective, and 7 were prospective observational studies. Seven studies looked at employees, 4 at university and college students, 8 at primary health care attendants, 14 at CHD and stroke patients, and 29 at the general population. The sample size in CHD and stroke studies ranged from 62 to 23,227 and in the burden of risk factors studies it ranged from 227 to 195,874. Response rates ranged from 59% to 99.8%. The summary of the included articles on CHD and strokes is shown in Table 1, whereas the summary of included articles on the burden of associated risk factors is shown in Table 2.

2.4.5.1 CHD and Strokes in the GCC Region:

Overall, there is a lack of information on CHD and strokes in Arabic Gulf countries. The only nationally representative study conducted in Saudi Arabia reported the crude prevalence of CHD of 5.5% among the Saudi population [11]. This survey reported a higher prevalence of CHD in males (6.6%) compared to females (4.4%) and in urban Saudis (6.2%) than rural Saudis (4.0%). Further, the prevalence of CHD increased with age from 3.9% in 30–39-year olds to 9.3% in the 60–70-year olds [11]. The Gulf Registry of Acute Coronary Events (Gulf RACE), a project of Gulf Heart Association aimed to describe the characteristics, in-hospital outcomes, and associated risk factors of the acute coronary syndrome patients (ACS) and recruited patients from 64 hospitals in Bahrain, Oman, Qatar, Kuwait, the UAE, and Yemen [12, 13]. The Gulf RACE study reported ACS was more prevalent in male (74%) than female (24%) patients [12]. It also reported a high prevalence of diabetes (40%), hypertension (49%), dyslipidaemia (32%), smoking (38%), and obesity (27%) among ACS patients in the five Gulf countries [13]. The highest rates of the risk factors were in Bahrain and Kuwait, except for smoking, which has the highest rates in the UAE and Kuwait [13].

The prevalence of CVD risk factors was higher in females than males, including diabetes (55% versus 36%), hypertension (70% versus 43%), and dyslipidaemia (44% versus 28%), respectively [12]. Significantly more males (47%) than females (5%) were current smokers [13]. Similarly, the Saudi Project for Assessment of Coronary Events (SPACE) registry reported the characteristics and prevalence of risk factors among ACS patients in Saudi Arabia [14]. The SPACE registry reported that ACS was more frequent in males (77%) than females (23%) [14]. Ischemic heart disease was present in 32% of the study population. The study also reported diabetes to be the most common risk factor for CHD (56%) followed by hypertension (48%), being a current smoker (39%), and hyperlipidaemia (31%) [14]. The available data on strokes and the associated risk factors in the GCC were derived mostly from retrospective hospital-based studies but no population-based studies. The data on strokes and associated risk factors was reported in 12 studies: 4 in Saudi Arabia [15–18], 1 in Bahrain [19], 3 in Kuwait [20–22], 3 in Qatar [23–25], and 1 from multiple GCC countries [26]. Five studies reported the incidence of stroke in Saudi Arabia, Kuwait, Qatar and Bahrain [15, 17, 19, 20, 25]. The incidence of stroke ranged from 27.6 per 100 000 in Kuwait to 57 per 100 000 in Bahrain [15, 17, 19, 20, 25]. Further, the most common type of stroke in the region was ischemic ranging from 69 to 90.1% [15, 17, 22, 25]. There was no data available on the incidence of strokes in Oman and the UAE. Only one study in Saudi Arabia reported on the number of stroke survivors as 186/100,000 [16]. Further, in the majority of stroke studies, the incidence of strokes was higher in males than females across all age groups and it increased with age [15, 17–20, 25], although there was still relatively high stroke incidence in younger age groups (≤45 years) in the GCC region [15, 17, 19, 23]. Across all stroke studies, hypertension (38.1–72.5%) was the most common risk factor, followed by diabetes (20–69.4%) for stroke patients [15, 17– 26]. Dyslipidaemia was reported in 4–61% of stroke patients [18–24, 26]. Smoking was reported in 1.6–40% of stroke patients in the GCC [15, 17–24, 26].

2.4.5.2 The Burden of the CHD and Stroke Risk Factors in the GCC Region:

The risk factors for CHD and stroke can be categorized into two groups: metabolic risk factors (obesity, hypertension, diabetes, and dyslipidaemia) and behavioural risk factors (diet, smoking, and physical activity). In this section, the burden of various risk factors among healthy population in the GCC states is described.

Overweight and Obesity: Prevalence of overweight and obesity has been reported in 13 studies: 4 in Saudi Arabia [28, 31, 32, 39], 2 in Bahrain [66, 68], 2 in Kuwait [54, 55], 2 in Oman [63, 65], 1 in Qatar [60], and 2 in the UAE [43, 46]. Based on the available national representative studies, the prevalence of overweight in males and females in the GCC region ranged from 28.8% to 42.4% and from 27.3% to 32.7%, respectively, while the prevalence of obesity in males ranged from 10.5% to 39.2% and in females ranged from 18.2% to 53%. The prevalence of overweight and obesity increased with age with the highest level in the middle age groups (30–39 and 40–49 years) [28, 31, 32, 39, 43, 46, 54, 55, 60, 63, 65, 66, 68]. The obesity rates in urban areas were higher than in rural areas [28, 31, 32, 63]. In general, the prevalence of overweight and obesity is remarkably high in the GCC states and Oman reported the lowest rates of obesity within the region.

Hypertension: The prevalence of hypertension was reported in 10 studies: 3 in Saudi Arabia [27, 33, 35], 1 in Bahrain [69], 2 in Oman [62, 65], 2 in Qatar [58, 60], and 2 in the UAE [43, 44]. The rate of hypertension in the GCC states ranged from 26% to 50.7% in males and from 20.9% to 31.7% in females [33, 35, 43, 44, 58, 62, 65, 69]. Across all studies, the prevalence of hypertension considerably increased with age with the highest rates in the 45–65 age groups. The prevalence of hypertension in Saudi Arabia was lower than Oman, Bahrain, and Qatar but close to the UAE. The lower rate of hypertension in Saudi Arabia may not be true reflection of the situation as the reported study was relatively old [35].

Diabetes Mellitus: The rates of diabetes mellitus in the GCC countries were addressed in 13 studies: 2 in Saudi Arabia [29, 31], 3 in Bahrain [67, 70, 72], 2 in Kuwait [51, 56], 2 in Oman [62, 65], 2 in Qatar [59, 60], and 2 in the UAE [43, 45]. The overall prevalence of diabetes ranged from 6% to 23.7% in the GCC. Three studies showed higher diabetes rates among females [31, 59, 67], while three studies indicated the opposite [29, 45, 56]. Four studies showed almost no difference in the prevalence of diabetes between genders [43, 51, 62, 65].The prevalence of diabetes rose proportionally with age and reached the highest rates in both sexes among those aged 55–64 years and over [29, 31, 43, 45, 51, 56, 59, 62, 65, 67]. It was also considerably higher among the urban population [29, 62]. Overall, the available data on the prevalence of diabetes in this region indicated that Saudi Arabia, Bahrain, and the UAE have the highest rates of diabetes compared to the other Gulf countries especially Kuwait, where the rates of diabetes were relatively lower; however this might be due to the underestimation of the actual prevalence in one Kuwaiti study as it excluded diabetic subjects on medication [56].

Dyslipidaemia: The prevalence of dyslipidaemia was reported in 7 studies: 3 in Saudi Arabia [27, 31, 37], 1 in Kuwait [53], 2 in Oman [62, 65], and 1 in the UAE [43]. There was no consistent definition of dyslipidaemia within the region. The majority of the dyslipidaemia studies reported the prevalence rate based on total cholesterol and triglycerides levels. Overall, dyslipidaemia levels were higher in males than females and increased with age gradually up to the age group of 50–59 when it became stable in some studies and slightly declined in others. The prevalence of hypercholesterolemia (HC) ranged from 17% to 54.9% in males and from 9% to 53.2% in females [27, 31, 37, 53, 62, 65]. There was no difference in HC between urban and rural residents [37, 62]. However, one study in Saudi Arabia showed higher rates of hypertriglyceridemia in the urban population (43.2%) than rural population (34.1%) [37]. Based on the available data on dyslipidaemia within the region, HC (≥5.2 mmol/L) was more prevalent in Saudi Arabia. The variation in definitions used in dyslipidaemia studies and the limited data in the GCC make it difficult to accurately compare between countries; however the levels of blood lipids appeared to be high in the Gulf region.

Diet: Six studies carried out in Saudi Arabia [40–42] and UAE [48–50] have determined the eating habits among adult population in these countries. The dietary patterns presented in these studies are mainly characterized by a high consumption of snacks, fatty food, salty food, and sugar. A study in Saudi Arabia reported that more than half of the study population was consuming a high amount of snacks and fatty and salty foods in daily basis [41]. Similarly, a high consumption of sugar and fast food was reported in the UAE [48, 49]. Further, a low consumption of fruits, vegetable, and cereals was reported in several studies [41, 49, 50]. One study showed a high intake of fruits, vegetables, and dates [42]. The findings from these surveys also demonstrated a high intake of total energy, fats, and protein [41, 48]. A Saudi survey showed a high proportion of total energy derived from fat and carbohydrates (38% versus 39%) and (46.1% versus 46.8%) in both males and females, respectively [41]. Some of the popular unhealthy food habits reported was not having breakfast, consuming less than two meals per day, and a high consumption of fast food meals [41, 49]. A number of studies have examined the association between some food items and CVD risk factors [40, 41, 49]. One study showed an inverse association between consumption of black tea and serum lipids [40], while another study reported a significant association of high intake of energy derived from fatty foods with BMI and hypertension in both genders [41]. Further, low consumption of cereals and fruits was found to be associated with obesity [49].

Smoking: The prevalence of smoking in the Gulf region was addressed in 9 studies: 3 in Saudi Arabia [27, 30, 38], 1 in Bahrain [71], 2 in Kuwait [52, 57], 1 in Oman [61], 1 in Qatar [60], and 1 in the UAE [43]. The rates of cigarette smoking in the GCC ranged from 13.4% to 37.4% in males and from 0.5% to 20.7% in females. Furthermore, the prevalence of smoking fluctuated from age group to age group. It was more common in males at younger ages (18–25 years); however some studies reported a high prevalence in the older age group (40–59 years). In females, the highest rates of smoking were in the older age group (40– 49 years) [30, 43, 52, 57, 61, 71]. One study in Saudi Arabia reported higher rates of cigarette smoking in urban than rural subjects [38]. Overall, the prevalence of smoking was higher in Saudi Arabia, Kuwait, the UAE, and Bahrain in comparison to Oman.

Physical Activity: The prevalence of physical activity in the GCC countries was presented in 7 studies: 2 in Saudi Arabia [34, 36], 1 in Bahrain [66], 1 in Kuwait [56], 1 in Oman [64], 1 in Qatar [60], and 1 in the UAE [47]. The prevalence of inactivity was found to be significantly higher among the younger population in the region, and across all age groups physical inactivity was higher in females than males. The rates of inactivity ranged from 24.3% to 93.9% in males and from 50% to 98.1% in females in the GCC [36, 47, 60, 64, 66]. In general, the rates of physical inactivity were considerably high in the GCC region especially Saudi Arabia.

Table 2.1: The characteristics and the main outcomes of the included studies on CHD and strokes in the GCC region.

[Reference] Country	Year(s) of survey	Total sample	Age, Range, mean	Sampling methods	Study design	Respons e Rate (%)	Diagnostic criteria	The main outcomes (CHD/Stroke/Associated risk factors/Mortality rates)	Quality assessment checklist (*)
CHD studies									
(Al-Nozha, Arafah, et al., 2004) Saudi Arabia	1995-2000	17293 M:47.3% F:52.04%	30-70	Two-stage stratified cluster	National cross-sectional survey	NR	WHO MONICA (monitoring trends and determinant in cardiovascular disease)	Overall prevalence: 5.5% M: 6.6% F: 4.4%	1-Y, 2-Y, 3-Y, 4-Y, 5-Y , 6-N, 7-NA
(AlHabib et al., 2009) Saudi Arabia	2005-2006	435 M:77% F: 23%	57.1	No sampling (all ACS patients included with no excluded patients)	Prospective study	NR	The Joint Committee of the European Society of Cardiology/American College of Cardiology (ACC)	Risk factors of ACS: DM 56%, HTN 48%, smoking 39%, hyperlipidaemia 31%	1-Y, 2-Y, 3-Y, 4-Y, 5-N, 6-Y, 7-NA
(El-Menyar et al., 2011) (Kuwait, Oman, Qatar, Bahrain, the UAE, and Yemen)	2007	6704 M & F= Not clear	56	No sampling (all ACS patients included with no excluded patients)	Prospective multi-national study	NR	The American College of Cardiology clinical data standards (ACC)/DM, hypertension, dyslipidaemia defined when patients known to have this risk factors & on treatment/regular smoking defined as 1 cigarette per day/non-smoker when stopped 12 months ago.	Overall prevalence: DM 40%, HTN 49%, dyslipidaemia 32%, smoking 38% In Oman: DM 37%, HTN, 53%, smoking 18%, dyslipidaemia 35%, obesity 22% In the UAE: DM 40%, HTN 50%, smoking 49%, dyslipidaemia 36%, obesity 20% In Qatar: DM 46%, HTN 49%, smoking 37%, dyslipidaemia 29%, obesity 23% In Bahrain: DM 51%, HTN 60%, smoking 32%, dyslipidaemia 45%, obesity 28% In Kuwait: DM 50%, HTN 56%, smoking 40%, dyslipidaemia 37%, obesity 37%	1-Y, 2-Y, 3-Y, 4-Y, 5-N, 6-Y, 7-NA
(El-Menyar et al., 2009) (Kuwait, Oman, Qatar, Bahrain, the UAE, and Yemen)	2007	8166 M:6183 F: 1983	M: 53 years F: 62 years	No sampling (all ACS patients included with no excluded patients)	Prospective multi-national study	NR	The American College of Cardiology clinical data standards (ACC)/DM, hypertension, dyslipidaemia defined when patients known to have this risk factors & on treatment/regular smoking defined as 1 cigarette per day/non-smoker when stopped 12 months ago.	Associated risk factors in men: DM 36%, HTN 43%, dyslipidaemia 28%, smoking 47% In women: DM 55%, HTN 70%, Dyslipidaemia 44%, smoking 5%	1-Y, 2-Y, 3-Y, 4-Y, 5-N, 6-N, 7-NA

Strokes studies									
(al Rajeh, Awada, Niazi, & Larbi, 1993) Saudi Arabia	1982-1992	500 M:342 F:158	M: 65.2 years F: 62.2 years	Non-random sampling (500 medical records of stroke patients)	Retrospective study	NR	NA	Incidence of stroke: 43.8 per 100,000 30-day mortality:12% Stroke types: ischemic strokes (76.2%) Risk factors: HTN 56%,DM 42% and smoking 6%	1-Y, 2-Y, 3-Y, 4-Not well described, 5-N, 6-N, 7-NA
(NUAMA, El-Sonbaty, Abdul-Baky, Marafie, & Al-Said, 1997) Kuwait	1989, 1992 and 1993	Not clear	60.6 years	Non-random (all patients with first-ever stroke, Patients with previous stroke were excluded	Prospective study	NR	WHO definition for diagnosing stroke/ HC defined as more than 5.78 mmol/l/ smoking as any current use of cigarette/ hypertension & DM were not clear	annual incidence: 27.6 per 100,000 The age-adjusted annual crude incidence: 145.6 per 100,000 30-day mortality: 10% Stroke types: Carotid-territory large infarction (46.5%), Risk factors: HTN 53%, DM 42%, HC 61%, smoking 23%	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-N, 7-NA
(Ashkanani, Hassan, & Lamdhade, 2012) Kuwait	2008	151 M: 96 F: 55	60.5 years	No-random (all ischemic stroke patients, there was an inclusion criteria)	Retrospective study	NR	Stroke defined according to WHO/stroke subtypes were defined according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria	Stroke types: Ischemic stroke (90.1%) Risk factors: DM 56.3%, dyslipidaemia 57%, HTN 68.9%, smoking 40%	1-Y, 2-Y, 3-Y, 4-N, 5-N, 6-Y, 7-NA
(Al-Shammri et al., 2003) Kuwait	1995- 1999	62 M:30 F: 32	64.1years	No random (all ischaemic stroke patients included)	Retrospective study	NR	Stroke defined according to WHO criteria	Risk factors: HTN 72.5%/ DM 69.4%, dyslipidaemia 30.6%, smoking 1.6% 30-day mortality: 12.9%	1-Y, 2-Y, 3-Y, 4-Y, 5-N, 6-N, 7-NA

(Akhtar et al., 2009) Qatar	2005- 2008	116 M: 85% F: 15%	53 years	Non-random (all patients diagnosed with PCS stroke, there was an inclusion criteria)	Prospective study	NR	Stroke defined according to Kidwell and Warach/DM as fasting blood glucose >140 mg/dl or in medication/ hypertension as >140/90 mm Hg or on medication/ dyslipidaemia as TC >5 mmol/l/ smokers as currently smokers or during the last 12 months/ obesity as BMI≥30	Risk factors: HTN 61%, DM 44%, obesity 66%, smoking 20%, dyslipidaemia 12% 30-day mortality rate: 10%	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-Partly, 7-NA
(Al-Rajeh et al., 1998) Saudi Arabia	1989-1990 and 1991-1993	488 M:314 F:174	All	Non-random (all Saudi patients with first stroke were included, there was excluded patients)	Prospective register	NR	The WHO multicentre Stroke Register/hypertension defined as BP>160/90 mm Hg/ DM defined as fasting blood sugar above 6.6 mmol/l	Incidence of stroke: 29.8 per 100,000 Age-adjustment incidence: 125.8 per 100 000 Stroke types: ischemic stroke 69% Risk factors: HTN 38.1%/ DM 37.1%/ smoking 19.3%,	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-N, 7-NA
(Qari, 2000) Saudi Arabia	1997- 2000	71 M: 55 F: 16	63 years	Non-random (all stroke patients included, no excluded patients)	Retrospective study	NR	NR	Stroke types: cerebral infarction 80% Risk factors: DM 27%, HTN 61%, smoking 28%, dyslipidaemia 4%/ Ischemic heart disease 8.5% 30-day mortality: 31%	1-Y, 2-Y, 3-Y, 4-Y, 5-N, 6-N, 7-NA
(Hamad et al., 2001) Qatar	1997	217 M: 72.4% F: 27.6%	57 years	Non-random (all stroke patients records were reviewed, only first-ever stroke cases were included)	Retrospective study	NR	Stroke defined according to the WHO criteria	Incidence of stroke: 41per 100,000 Stroke types: ischemic stroke (80%) Risk factors: HTN 63%/ DM 42%/ Ischemic heart disease 17% 30-day mortality rate:16%	1-Y, 2-Y, 3-Y, 4-Y, 5-N, 6-Y, 7-NA

(Al-Jishi & Mohan, 2000) Bahrain	1995	144 M & F = not clear	≥20	Non-random (all stroke cases were reviewed)	Retrospective study	NR	Stroke defined according to the WHO criteria	Incidence of stroke: 57 per 100,000 Stroke types: cerebral infarction 60% Risk factors: HTN 52%/ DM 20%/ dyslipidaemia 29%/ smoking 29%/ Ischemic heart disease 50%	1-Y, 2-Y, 3- Y, 4-N, 5-N, 6-N, 7-NA
(Deleu et al., 2006) Qatar	2001	303 M:72% F:28%	61.2 years	Non-random (the data of all stroke patients were reviewed, there was inclusion criteria)	Retrospective study	NR	Stroke: WHO criteria HTN:BP >140/90 mm Hg or on medication/ DM: past history or FPG (>7mmol/l) or on medication/ dyslipidaemia: TC >5.2 mmol/l or TG >2.0 mmol/l or HDL <0.9 mmol/l LDL >3.4 mmol/l/ BMI ≥30 kg/m²/ smokers: regular smoking within the last 5 years	Risk factors: HTN 69%/ DM 51%/ dyslipidaemia 57%/ obesity 30%/ smoking 26%/ CAD 23%	1-Y, 2-Y, 3-Y, 4-Y, 5-N, 6-Y, 7-NA
(Deleu et al., 2011) (Kuwait, Oman, Qatar and the UAE)	2006-2007	780 M:63.7% F: 36.3%	58.9 years	No sampling (all ischemic stroke patients were included, there was inclusion criteria)	Prospective registry	NR	HTN:BP >160/90 mm Hg or on medication/ DM: past history or elevated A1c or on medication/ dyslipidaemia: TC >5.2 mmol/l or TG >1.7 mmol/l or HDL >1.0 mmol/l LDL <3.4 mmol/l/ BMI ≥30 kg/m²/ smokers: regular smoking within the last 5 years	Risk factors: HTN 66.4%/ DM 55.3%/ current smokers 19.6%/ dyslipidaemia 30.1% 90-day mortality: 2.1%	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-Y, 7-NA
(Al Rajeh, Bademosi, et al., 1993) Saudi Arabia	1993	23,227 M:49.8% F:50.2%	NR	No sampling (all Saudi living in the Thugbah area were screened)	Community-based cross-sectional survey	NR	Stroke defined “sudden or rapid onset of focal or global brain dysfunction of vascular origin lasting for more than 24h or leading to death especially if diagnosed by physicians”	The overall prevalence of stroke survivors: 186 per 100 000	1-Y, 2-Y, 3-Y, 4-N, 5-Y, 6-N, 7-NA

M, male; F, female; U, urban; R, rural; DM, diabetes; IFG, impaired fasting glucose; HC, hypercholesterolemia; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; NR, not reported; ACS, acute coronary syndrome; BMI, body mass index; Y, yes; N, no; NA, not applicable. (*) the quality assessment checklist assessed according to the Centre for Reviews and Dissemination guidelines (CRD) for non-randomized studies: 1-Was the aim of the study stated clearly? / 2-Was the methodology stated? And was it appropriate? / 3-Were appropriate methods used for data collection and analysis? / 4-Was the data analysis sufficiently rigours? / 5-Were preventive steps taken to minimize bias? / 6-Were limitations of the study discussed? / 7-In systematic review, was search strategy adequate and appropriate?

Table 2.2: Characteristics and prevalence data of the included studies on the burden of CVD risk factors in the GCC region.

[Reference] Country	Year(s) of survey	Total sample	Age, mean, min to max	Sampling methods	Study design	Response rate (%)	Diagnostic criteria and/ or Dietary assessment methods	The main findings and prevalence data	Quality assessment checklist (*)
(Abalkhail, Shawky, Ghabrah, & Milaat, 2000) Saudi Arabia	1996-1997	1,649 M:1,175 F:474	≥40	random stratified sampling	cross-sectional study	76.6	HC: TC >6.2 mmol/l/ overweight BMI for men ≥27.2 women ≥26.9/ HTN: SBP ≥140 mm Hg or DBP ≥95 or on medication	Overweight 49.8%/ HTN 19.9%/ current smoking 18.8%, HC: overall 10.1% M: 10.3% F: 9.7%	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-N, 7-NA
(Al-Nuaim, Bamgboye, Al-Rubeaan, & Al-Mazrou, 1997) Saudi Arabia	1990-1993	10,651 M:50.8% F:49.2%	≥20	Multistage stratified cluster sampling	National epidemiological cross-sectional survey	69	Overweight and obesity defined according the WHO criteria	Overweight: Overall 31.2% M 33.1%, F 29.4%, U 33.6%, R 28.3% Obesity: Overall 22.1%, M 17.8%, F 26.6%, U 25.6%, R 17.6%	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-N, 7-NA
(Al-Nozha, Al-Maatouq, et al., 2004) Saudi Arabia	1995-2000	16917 M:8002 F:8804	30-70	Two-stage stratified cluster sampling	National epidemiological cross-sectional survey	98.2	DM was defined according to the WHO	DM: Overall 23.7%, M 26.2%, F 21.5%, U 25.5%, R 19.5% The prevalence of IFG overall 14.1% M 14.4%, F 13.9%	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-N, 7-NA
(Hashim, 2000) Saudi Arabia	1996	647 M:383 F:264	18-26	Random sampling	Cross-sectional study	91	Current smokers: currently smoking at least 1 cigarette per day	Current smoking overall29%, M 20%, F 9%	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-N, 7-NA
(Rahman Al-Nuaim, 1997) Saudi Arabia	1990-1993	2049 M:1033 F:1016	30-64	Multistage stratified cluster sampling	National Cross-sectional survey	92	DM: the random serum glucose according to the WHO criteria or self-reported/ HC: mild (5.2-6.2 mmol/l) sever (>6.2 mmol/l)/ HDL: <0.9 mmol/l/ BMI: WHO criteria	Overweight: M 38%, F 34% Obesity: M 23%, F 34% DM: M 16.4%, F 20% Smoking: M 21%, F 1% Moderate HC: M & F=21.5% Sever HC: M&F=9% LDL: M 6.6%, F 10.3% HDL: M 55%, F 47%	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-N, 7-NA

(Al-Nozha et al., 2005) Saudi Arabia	1995-2000	17,232 M:8215 F:9008	30-70	Two-stage stratified cluster sampling	National epidemiological cross-sectional survey	NR	Overweight and obesity defined according to the WHO	Overweight: Overall 36.9%, M 42.4%, F 31.8%, U 36.9%, R 36.9% Obesity: Overall 35.6%, M 26.4%, F 44% U 39.7%, R 27%	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-N, 7-NA
(Kalantan, Mohamed, Al-Taweel, & Abdul Ghani, 2001) Saudi Arabia	2001	1114 M:442 F:672	35-85	Cluster sampling	Cross-sectional study	NR	HTN: BP ≥140 mm Hg systolic and 90 mm Hg diastolic or self-reported with medication or both	HTN: Overall 30% M 33%, F 29%, U 29%, R 32%	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-N, 7-NA
(Al-Refaee & Al-Hazzaa, 2001) Saudi Arabia	1996	1333 M:100%	≥19	Random sampling	Cross-sectional study	75	Regular active: physically active for 30 or more minutes 2 or more days a week	Physically inactive 53%, irregularly active 27.5%, physically active on a regular bas 19%	1-Y, 2-Y, 3-,Y, 4-Y, 5-N, 6-N, 7-NA
(Al-Nozha, Abdullah, et al., 2007) Saudi Arabia	1995-2000	17,230 M: 47.7% F: 52.3%	30-70	Two-stage stratified cluster sampling	National epidemiological cross-sectional survey	NR	HTN: SBP ≥140 mm Hg or DBP ≥90 mm Hg	HTN: Overall 26.1% M 28.6%, F 23.9%, U 27.9%, R 22.4%	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-N, 7-NA
(Al-Nozha, Al-Hazzaa, et al., 2007) Saudi Arabia	1995-2000	17,395 M:8297 F:9098	30-70	Two-stage stratified cluster sampling	National epidemiological cross-sectional survey	NR	Physically active: 30 minutes or more of at least moderate-intensity activity for three or more times per week/Physical inactivity: participants who did not meet the physically active criteria	Physical inactivity: Overall 96.1% M 93.9%, F98.1%	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-Y, 7-NA
(Al-Nozha et al., 2008) Saudi Arabia	1995-2000	16.819 M:47.6% F: 52.4%	30-70	Two-stage stratified cluster sampling	National epidemiological cross-sectional survey	97	HC: TC ≥ 5.2 mmol/l / TG: ≥1.69 mmol/l	HC: Overall 54% M 54.9%, F 53.2%, U 53.4%, R 55.3% HG :Overall 40.3% M 47.6%, F 33.7%	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-Y, 7-NA

(Al-Haddad, Al-Habeeb, Abdelgadir, Al-Ghamdy, & Qureshi, 2003) Saudi Arabia	1999-2000	1752 M & F= not clear	35.5	Random sampling	Cross-sectional study	70	Current smokers: those who regularly or occasionally smoking on a daily, weekly or monthly basis/ non-smokers: those who never smoked.	<u>Current smokers</u> 52.3% U 55.9%, R 44.1%	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-Y, 7-NA
(Al-Baghli et al., 2008) Saudi Arabia	2004-2005	195,874 M: 99,946 F: 95,905	≥30	No random (All Saudis aged 30 and above and lived in the eastern region in SA were invited to participate in the screening programme)	Cross-sectional survey	99.1	Overweight and obesity defined according to the WHO	<u>Overweight:</u> overall 35.1% M 40.3%, F 29.7% <u>Obesity</u>: overall 43.8% M 36.1%, F 51.8%	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-Y, 7-NA
(Hakim et al., 2003) Saudi Arabia	1993-1998	F: 1764	30-70 years	Multistage stratified cluster sampling	CSS	NR	NR/ Structured questionnaire	• The consumption of black tea was 87.2% • Females who daily consumed > 6 cups of tea (>480 ml) were significantly more likely to have lower rates of dyslipidaemia including, high (TC) (OR= 0.63, 95% CI: 0.41-0.97), high TG (OR= 0.56, 95% CI: 0.35-0.86), high (LDL) (OR= 0.70, 95% CI: 0.45-1.07), and high (VLDL) (OR= 0.61, 95% CI: 0.39-0.93).	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-Y, 7-NA
(Abdel-Megeid, Abdelkarem, & El-Fetouh, 2011) Saudi Arabia	2008-2009	312 M:132 & F:180	21.1 years	Random selection	CSS	NR	BMI according to the National Institute of Health. HTN according to the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood	• The % of total energy from carbohydrates and fats was (38% vs. 39%) and (46.1% vs. 46.8%) in both M and F. • Unhealthy food habits were: high consumption of snacks (42.5%), a low consumption of vegetables	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-N, 7-NA

							Pressure / Self-reported questionnaire (11 items)	(30%), a high consumption of fatty foods (36% in F; 44% in M), a high consumption of salty foods (36% in F; 43% in M), and a high consumption of sugar (41% in F; 38% in M). • A significant association between the high intakes of energy derived from fatty foods and BMI and HTN in both genders. • A significant association was found between the high consumption of salty foods and HTN. • A negative association was found between the consumption of vegetables, grains and beans and BMI and HTN in both genders.	
(Midhet, Al Mohaimeed, & Sharaf, 2010) Saudi Arabia	2009	2789 M: 1806 F: 981	30-70 years	Random selection	CSS	NR	NR/Questionnaire and 24-h recall	• The most popular food was kabsa (80% in M and 65% in F), fresh fruits (63% in M and 45% in F), vegetables (62% in M and 47% in F) and dates (45%) in both genders and soft drinks (21% in M and 25% in F).	1-Y, 2-Y, 3-Y, 4-Y, 5-N, 6-Y, 7-NA
(Hajat, Harrison, & Al Siksek, 2012) The UAE	2008-2010	50138 M: 43% F: 57%	18-75	No random (All UAE nationals residing aged 18 to 75 who were living in Abu Dhabi city were enrolled in the CVD screening program)	Cross-sectional national survey	Measured data (98.7-99.9), self-reported data (86.1-99.8)	Obesity and overweight: according to WHO/ DM: past history & on medication or HbA1c ≥ 6.5% or random glucose 11.1 mmol/l/ HTN: self-reported & on medication or SBP ≥ 140 mmHg or DBP ≥90 mmHg/ dyslipidaemia: self-reported on medication or LDL 4.1 mmol/l or HDL 1.0 mmol/l/ current smokers: 1 cigarette per day during the last 12 months or 1 water pipe per month during the last 3 months	Obesity: overall 35.4% M 31.6%, F 38.3% Overweight: overall 31.9% M 36.1%, F 28.8% Dyslipidaemia: overall 44.2% M 57.7%, F 33.9% HTN: overall 23.1% M 26%, F 20.9% Smoking: overall 11.6% M 25.8%, F 0.8% DM: overall 17.6% M 17.3%, F 17.9%	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-Y, 7-NA

(El-Shahat et al., 1999) The UAE	1997	3150 M:1516 F:1634	18-75	Stratified random sampling	Cross-sectional study	NR	HTN: SBP > 140 mmHg and/or DBP >90 mmHg and/or self-reported with medication	<u>HTN</u>: overall 31.6% M 47%, F 53%	1-Y, 2-Y, 3-Y, 4-N, 5-Y, 6-N, 7-NA
(Malik, Bakir, Saab, Roglic, & King, 2005) The UAE	1999-2000	5844 M:2499 F:3345	≥20	Stratified multistage cluster sampling	National epidemiological cross-sectional study	89	DM: fasting blood glucose ≥7.0 mmol/l or taking insulin or oral hypoglycaemic agents	<u>DM:</u>overall20% M 21.5%, F 19.2% <u>IFG:</u> overall 6.5% M 4.5%, F 8%	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-N, 7-NA
(Carter, Saadi, Reed, & Dunn, 2011) The UAE	2000-2001	535 F:100%	>19	Stratified random sampling	Cross-sectional survey	95	Overweight and obesity were defined according to WHO criteria	<u>Overweight</u> 27% <u>Obesity</u> 35%	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-Y, 7-NA
(Guthold, Ono, Strong, Chatterji, & Morabia, 2008) The UAE	2002-2003	1104 M: 72% F:28%	18-69	Multistage cluster random sample	Large cross-sectional survey	94.9	Physical inactivity: the person did not meet the following criteria: 3 or more days of various activity during the last week of at least 20 minutes per day or 5 or more days of moderate-intensity activity or walking during the last week of at least 30 minutes per day	<u>Physical inactivity</u> Overall 39.5% M 37.9%, F 56.7%	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-Y, 7-NA
(Al-Sarraj, Saadi, Volek, & Fernandez, 2010) The UAE	2010	227 M: 74 F: 153	18-50 years	Convenience sampling	CCS	NR	MetS according to ATP III/ 24-h recall	• A high intake of total energy, carbohydrate, fat and protein in M and F, (20971vs.17180 kjoules/day), (627.3 vs. 549.7 g/day), (207.5 vs. 150.1 g/day), and (175.5 vs. 151.5 g/day) respectively. • The mean intake of total sugar and fibre was high (224.4 vs. 202 g/day) and (44.4 vs. 33.3 g/day) respectively	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-Y, 7-NA

(Kerkadi, 2003) The UAE	2001-2002	F: 400	18-25 years	Convenience sampling	CSS	NR	BMI according to WHO/ self-administrated questionnaire	• The prevalence of overweight and obesity was 19.4% and 6.7% respectively. • food habits include: not having breakfast in 44.8% , fast food consumption once a day in 34.9%, having only 1 or 2 meals/day in 52.3% • A low consumption of cereals, vegetables and fruits by 54.4%, 51.5% and 49.5% respectively. A high intake of fat in 46.7% • A significant association between obesity and low consumption of cereals and fruits.	1-Y, 2-Y, 3-Y, 4-Y, 5-N, 6-N, 7-NA
(A. O. Musaiger & Abuirmeileh, 1998) The UAE	1993	2212 M: 1122 F: 1090	≥20	Random selection	CSS	NR	NA/ pre-tested structured questionnaire	• A low consumption of fruits, vegetables and milk in the study population. • Elderly adults (≥50) were more likely to consume fruits, vegetables, fish, milk and yoghurt than older adults. • Young adult females were more likely to consume fruits, vegetables and fish than young adult males.	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-N, 7-NA
(Abdella, Al Arouj, Al Nakhi, Al Assoussi, & Moussa, 1998) Kuwait	1995-1996	3003 M:1105 F:1898	≥20	Convenience sampling (all Kuwaiti +20 in the survey area invited to participate)	Cross-sectional study	NR	DM: according to the WHO diagnostic criteria for abnormal glucose tolerance	<u>DM</u>: overall 14.8% M 14.7%, F 14.8%	1-Y, 2-Y, 3-Y, 4-Y, 5-N, 6-N, 7-NA
(Memon et al., 2000) Kuwait	1996	3859 M:1798 F:2061	33.2	A three-stage stratified cluster sampling	Cross-sectional national study	96.5	Current smokers: if they were smoking at the time of the survey and had smoked more than 100 cigarette in their lifetime, former smokers: if they had smoked more than 100 cigarette in their life but no longer smoking, never smokers: when they had never smoked or smoked less than 100	<u>The prevalence of smoking:</u> Overall 17% M 34.4%, F 1.9%	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-Y, 7-NA

							cigarettes in their life		
(F. Ahmed, C. Waslien, M. Al-Sumaie, & P. Prakash, 2012) Kuwait	1998-2009	32,811 M:15,110 F:17,701	20-69	**convenience sampling (**Kuwaitis in health examination for Gov. & Hajj health check-ups & PHCCs)	National cross-sectional survey	NR	HC: moderate (5.2-6.22 TC mmol/l) sever (>6.23 TC mmol/l)	HC prevalence increased from 1998-1999 (M 35%; F 31%) until 2006-2007 (M 56%; F 53.6%), then declined in 2008-2009 (M 33.7%; F 30.6%)	1-Y, 2-Y, 3-Y, 4-Y, 5-N, 6-Y, 7-NA
(Al Rashdan & Al Nesef, 2010) Kuwait	2006	2280 M:918 F:1362	20-65	Systematic random sampling	National cross-sectional survey	77.6	Overweight and obesity were defined according to the WHO criteria	Combined overweight & obesity: 80.4% Obesity: M 39.2%, F 53%	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-N,7-NA
(F. Ahmed, C. Waslien, M. A. Al-Sumaie, & P. Prakash, 2012) Kuwait	1998-2009	38,611 M: 17,491 F: 21,120	20-69	convenience sampling (Kuwaitis in health examination for Gov. & Hajj health check-ups & PHCCs)	National cross-sectional survey	NR	Overweight and obesity defined according to the WHO criteria	Obesity increased from 1998-1999 (M 22.8%; F 28.4%) until 2008-2009 (M 34.1%; F 43%) Overweight increased from 1998-1999 (M 36.5%; F 33.4%) until 2008-2009 (M 43.3%; F 34.3%)	1-Y, 2-Y, 3-Y, 4-Y, 5-N, 6-Y, 7-NA
(Ahmed, Waslien, Al-Sumaie, Prakash, & Allafi, 2013) Kuwait	2002-2009	6356 M: 2745 F: 3611	20-69	convenience sampling (Kuwaitis in health examination for Gov. & Hajj health check-ups & PHCCs)	National cross-sectional survey	NR	diabetes defined according to the WHO criteria	IFG decreased from 2002-2009 by (M: 7.4%, F: 6.8%) and DM decreased in the same period by (M 9.8%, F 8.9%) The prevalence in 2008-2009: IFG (M 6%, F 5.3%) DM (M 9.3%, F 6%) Physical activity (M 42.1%, F 19.2%)	1-Y, 2-Y, 3-Y, 4-Y, 5-N, 6-Y, 7-NA
(Mohammed, Newman, & Tayeh, 2006) Kuwait	2006	761 M: 261 F: 500	M: 21 years F: 20.8 years	Random sampling	Cross-sectional study	84.5	Water-pipe smokers: a person who smoked sheesha and had smoked sheesha for at least one month, people who had not smoked sheesha were classified as sheesha non-smokers	Water-pipe smoking: M 24.6%, F 5.5% Cigarette smoking: M 38.8%, F 7.9%	1-Y, 2-Y, 3-Y, 4-Y, 5-N, 6-N, 7-NA

(A Bener, Al-Suwaidi, Al-Jaber, Al-Marri, & Elbagi, 2004) Qatar	2003	1208 M:508 F:700	25-65	A multistage stratified cluster sampling	Cross-sectional study	80.5	BP according to the WHO criteria	HTN: 32.1% M 32.6%, F 31.7%	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-N, 7-NA
(Abdulbari Bener et al., 2009) Qatar	2007-2008	1117 M:571 F:546	>20	A multistage stratified cluster sampling	Cross-sectional study	77.9	DM was defined according to the WHO expert group	DM: 16.7% M 15.2%, F 18.1%	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-Y, 7-NA
(A. O. Musaiger, Al-Khalaf, F. A., & Shahbeek, N. E. , 1994) Qatar	1992	603 F:100%	18-67	Convenient sampling	Cross-sectional survey	NR	Obesity & overweight: according to the WHO definition/ self-reported of past history of DM and HTN	HTN: 12.3%, DM: 12.9% Smoking: 3.2%, overweight: 30%, obesity: 33.6%, regular exercise: 16%	1-Y, 2- partly, 3- not entirely appropriate, 4-Y, 5-N, 6-N, 7-NA
(AA Al Riyami & Afifi, 2004) Oman	2000	7011 M:50% F:50%	≥20	A multistage stratified probability-sampling	Cross-sectional national survey	83-91.5	Current smokers: people who were smoking at the time of the survey and had smoked more than 100 cigarette in their life/ former smokers: if they had smoked more than 100 cigarette in their life but no longer smoking/ never smokers: if they had never smoked or had smoked less than 100 cigarette in their life	Current smoking: 7% M 13.4%, F 0.5% Former smokers: 2.3% Never smokers: 90.7%	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-N, 7-NA
(Al-Moosa, Allin, Jemiai, Al-Lawati, & Mossialos, 2006) Oman	2000	7179 M: 50% F: 50%	≥20	A multistage stratified probability-sampling design	Cross-sectional national survey	96	The WHO criteria for glucose intolerance, HC and HTN	DM: overall11.6% M 11.8%, F 11.3%, U 17.7%, R 10.5% HTN: overall 21.5% M 32.5%, F 22.7%, U 26.4%, R 20.2% HC: overall 50.6% M 50.8%, F 50.4%, U 50%, R 50.7%	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-Y, 7-NA

(Al-Lawati & Jousilahti, 2004) Oman	1991 and 2000	5086 M:2128 F:2958 6400 M:3069 F:3331	≥20	Convenient sampling A multistage stratified probability-sampling design	Cross-sectional surveys	92 91	overweight and obesity were defined according to the WHO criteria	Overweight: in 1991 (M 28.8%, F 29.5%) in 2000 (M 32.1%, F 27.3%) Obesity: in 1991 (M 10.5%, F 25.1%) in 2000 (M 16.7%, 23.8%)	1-Y, 2-Y, 3-Y, 4-Y, 5-N, 6-N, 7-NA 1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-N, 7-NA
(Al-Lawati & Jousilahti, 2008) Oman	2001	1421 M:49% F:51%	≥20	A probabilistic random sampling	Community based cross-sectional study	75.5	DM: FPG ≥5.6 mmol/l or 2hG ≥11.1 mmol/l or on medication/ HTN: SBP ≥130 mm Hg and/or DBP ≥85 mm Hg or on medication/ TC: ≥5.2 mmol/l/ TG: ≥1.69 mmol/l/ HDL: <1.03 mmol/l or on medication for dyslipidaemia/ current smokers: people who smoking at the time of the survey/ physical activity at leisure time and/or at work	HTN (M 24.7%, F 13.8%) DM (M 12.9%, F 11.9%) HC (M 34.5%, F 34.5%) TG (M 24.4%, F 13%) HDL (M 75.9%, F 71.6%) Inactivity (M 24.3%, F 69.3%) Smoking (M 9.6%, F 0)	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-Y, 7-NA
(Asya Al Riyami et al., 2012) Oman	2008	40,179 M: 52% F: 48%	≥18	A multistage stratified cluster sampling design	Community-based national cross-sectional survey	93.5	The WHO criteria for diagnosis HTN, HC, BMI and DM were used	Overweight: overall 29.5% M 31.2%, F 28% Obesity: overall 24.1% M 22%, F 26.1% HTN: overall 40.3% M 50.7%, F 31% DM: overall 12.3% M 12.4%, F 12.1% HC: overall 33.6% M 33.1%, F 33.9% HDL: overall 35.2% M 26.3%, F 42.7% LDL: overall 32% M 33%, F 31.2% TG: overall 18% M 21.6%, F 14.9%	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-Y, 7-NA

(Al-Mahroos & Al-Roomi, 2001) Bahrain	1995-1996	2013 M:1168 F:845	40-69	Stratified sampling design	Cross-sectional national survey	70	Overweight and obesity: WHO criteria. Physical activity was assessed by walking and cycling information: walkkm= 5 × walkwk (walking/day in average week) + walkkm (walking in weekend). Cyclekm= 5 × cyclewk (cycling/day in average week) + cyclewe (cycling in weekend).	age-adjusted prevalence of overweight: M 39.9%, F 32.7% age-adjusted prevalence of Obesity: M 25.3%, F 33.2% Physical activity: 21% of men and 6% of women aged 50-59 walked 1-3 km per day, 68% of men & 93% of women aged 50-59 walked less than 1 km per day	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-N, 7-NA
(A. O. MUSAIGER & AL-MANNAI, 2002) Bahrain	2002	514 M:298 F:216	30-79	Probability cluster sampling design	Cross-sectional community-based survey	NR	DM was defined by self-reported past history of diabetes	DM: 9% M 41.3%, F 58.7%	1-Y, 2-Y, 3-not entirely appropriate, 4-Y, 5-N, 6-Y, 7-NA
(A. Musaiger & Al-Mannai, 2001) Bahrain	2001	514 M:298 F:216	30-79	Probability cluster sampling design	Cross-sectional community-based survey	NR	Overweight and obesity were defined according to the WHO criteria	Overweight: Overall 31% M 35.2%, F 31% Obesity: Overall 48.7% M 21.2%, F 48.7%	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-N, 7-NA
(Al-Mahroos, Al-Roomi, & McKeigue, 2000) Bahrain	1995-1996	2090 M:1192 F:834	40-69	Stratified sampling design	Cross-sectional national survey	62	HTN: SBP ≥160 mmHg, DBP ≥95 mmHg or on antihypertensive	HTN: M: 21% in 40-49 years, 29% in 50-59 years F: 33% in 50-59 years, 43% in 60-69 years	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-N, 7-NA
(Al-Mahroos & McKeigue, 1998) Bahrain	1995-1996	2029 M & F= not clear	40-69	Stratified sampling design	Cross-sectional national epidemiological	59-70	DM was defined according to WHO criteria	DM: M: 23% in 40-49 years, 29% in 50-59 years F: 36% in age groups 50-59 and 37% 60-69 years	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-N, 7-NA
(Hamadeh & Musaiger, 2000) Bahrain	2000	516 M:299 F:217	30-79	Random cluster-sampling design	Cross-sectional study	NR	Current smokers: a person smoking at least 1 cigarette per day regularly/ ex-smokers: person who gave up smoking at least 6 months previously/ non-smoker: person who had never smoked regularly	Overall cigarette smoking: (M 27.1%, F3.2%) Overall sheesha smoking: (M 5%, F 17.5%) Overall total smoking: M 32.1%, F 20.7%	1-Y, 2-Y, 3-Y, 4-Y, 5-Y, 6-N, 7-NA

(Al Zurba & Al Garf, 1996) **Bahrain**	1996	498 M: 174 F: 324	≥20	Random selection from health care centres attendances	Cross-sectional study	86.9	DM was defined according to WHO criteria OR if the person had a previous history of DM	The prevalence of known diabetes subjects: M: 18.4%/ F: 16.7% The prevalence of unknown diabetes: M: 8%/ F: 8.3% The overall prevalence of diabetes: 25.5% M: 26.4%/ F: 25%	1-Y, 2-Y, 3-Y, 4-Y, 5-N, 6-Y, 7-NA

M, male; F, female; U, urban; R, rural; DM, diabetes; IFG, impaired fasting glucose; HC, hypercholesterolemia; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; NR, not reported; ACS, acute coronary syndrome; BMI, body mass index; Y, yes; N, no; NA, not applicable.

(*) the quality assessment checklist assessed according to the Centre for Reviews and Dissemination guidelines (CRD) for non-randomized studies: 1-Was the aim of the study stated clearly? / 2-Was the methodology stated? And was it appropriate? / 3-Were appropriate methods used for data collection and analysis? / 4-Was the data analysis sufficiently rigours? / 5-Were preventive steps taken to minimize bias? / 6-Were limitations of the study discussed? / 7-In systematic review, was search strategy adequate and appropriate?

2.4.6 Discussion

This review revealed that, in the GCC region, there is a lack of information on the prevalence of CHD with only exception in Saudi Arabia where one national survey reported 5.5% prevalence of CHD [11], which is lower than the prevalence rate reported in Egypt 8.3% [73], while it is higher than in India (3%), China (2%), and Europe (5%) [74, 75]. However, it is important to note that the Saudi report is relatively old and may not reflect the current situation. The rates of ACS and associated risk factors appeared to be very similar in Saudi Arabia (SPACE report) and other Gulf states (Gulf RACE report) except for diabetes, which is more prevalent in Saudi Arabia. However, the SPACE registry results came from phase 1 (pilot study) and thus based on smaller sample size compared to that of Gulf RACE [13, 14].

In contrast to other ACS registries around the world, the prevalence rates of diabetes and current smoking are higher in the Gulf region, while a higher prevalence of hypertension and dyslipidaemia is observed in the Euro heart of the acute coronary syndrome survey and Canadian ACS registry [13,14, 76, 77]. The rates of diabetes are ranged from 23.3% to 25.1% in the Euro heart survey, Canadian ACS registry, and the Global Registry of Acute Cardiac Events (GRACE) [76, 77], while the prevalence of diabetes is much higher among the ACS patients in the Gulf States especially in Saudi Arabia (56%) [13, 14]. One possible explanation for this high rate of diabetes could be due the high prevalence of obesity and physical inactivity in the GCC region, especially in Saudi Arabia. Furthermore, the mean age of presentation in the SPACE and Gulf RACE cohort is about ten years younger than that reported in the Euro heart survey and the GRACE cohort [13, 14, 78, 79]. This might be due to the high rates of uncontrolled risk factors in the Gulf region as well as the high percentage of younger populations in these countries.

The crude annual incidence of stroke in the Gulf countries was generally lower than the reported incidence in some Arabic countries, for example, Libya (63/100,000) [80] and Northern Palestine (51.4/100,000) [81]. The incidence is even much lower than that which is observed in some of the developed countries such as Scotland (280/100,000) [82] and the East Coast of Australia (206/100,000) [83]. The low rates of strokes in the GCC countries could be explained by the relatively younger age of patients in these countries. Further, the majority of stroke studies in the region had no record on the number of patients who died before reaching hospital, thus underestimating the actual incidence rate.

Several studies in the Gulf States have reported a high incidence of stroke at a younger age. Of the stroke patients, 9.8% to 25% were less than 45 years old [17, 23, 25]. The higher proportion of undiagnosed hypertension and diabetes might be a reason for younger stroke patients. One study in Saudi Arabia showed that only half of the hypertensive stroke patients were actually on medication [17]. Further, lack of awareness about stroke in the Gulf countries might have led to an increase in the incidence of strokes as well as the rates of associated risk factors [84].

When looking at the burden of risk factors among healthy subjects in the GCC region, the prevalence of obesity in adult females is one of the highest amongst females worldwide. This review found that almost half of the females in Kuwait and Bahrain and around 35% of females in Saudi Arabia, the UAE, and Qatar were obese. The overall prevalence of overweight and obesity in the GCC is higher than that which was reported in other Middle Eastern countries such as Lebanon and Turkey [85, 86].The prevalence was even higher than in many developed countries such as the USA and in developing countries such as India [87, 88].The food customs in the Gulf region, such as weddings and religious events, might be an important contributory factor for such a high rate of obesity as they serve food that is rich in fat, usually “Kabsa,” which includes meat (from sheep or small camel) with rice. Even socialising with friends and family is usually around eating meals and snacks.

Likewise, more than half of the GCC population are physically inactive, with only a small proportion of people being active on a regular basis. Furthermore, the rate of inactivity appeared to be remarkably higher in Saudi Arabia than in other Gulf countries. The reviewed studies also indicated that males are more likely to be physically active than females, a finding similar to that was reported in Turkey and Pakistan [47].The unique social, cultural, and environmental factors of the GCC states, such as hot climate, lack of outdoor facilities, the limited number of health clubs, high cost of attending such clubs especially for females, high level of employment of domestic helpers, and the high dependency on automobiles are blamed on the increased levels of physical inactivity in both genders but more noticeably in females. Also, females have more social barriers that make it difficult for them to exercise outside the home without a family member [5, 89].

In the Gulf region, males start smoking cigarettes at an early age (before 18 years), while females generally start after 30s. Cigarette smoking by younger and unmarried females is viewed as culturally unacceptable and can potentially destroy their reputation. However, the case is different when smoking sheesha (water-pipe) as Arabic societies in general accepts sheesha smoking by females irrespective of their age and/or social status.

Hypertension and diabetes are the two major risk factors associated with CHD and stroke patients in all studies in the Gulf region; this might be related to the high rates of undiagnosed hypertensive and diabetic patients within the region. In Saudi Arabia, about 70% of the hypertensive people were unaware of their disease [35]. A similar situation was reported in Oman, the UAE, and Bahrain [44, 65, 69]. Likewise, a large number of diabetic subjects in Saudi Arabia (28%) and the UAE (41%) were unaware of their disease [29, 45].

The high rates of uncontrolled diseases such as hypertension and diabetes could be a reason for the relatively young age of CHD and stroke patients in the Gulf region.

The prevalence of dyslipidaemia in general is high in the GCC countries. The available national surveys indicated that half the Saudi population have high level of total cholesterol and almost half of the males and one-third of Saudi females have high level of hypertriglyceridemia [37]. The rates of HC in Saudi Arabia are similar to that reported in USA (53.2%) [90]. Dyslipidaemia is a major risk factor for CHD and plays a central role in the development of atherosclerosis. The high rates of dyslipidaemia in the GCC countries may be due to the high prevalence of physical inactivity, obesity, and diabetes among the Gulf populations. Also, as mentioned before, food customs and the consumption of high fatty foods might be contributing factors.

This review has a number of limitations. First, there was a lack of recent nationally representative reports in the GCC countries, and thus it is difficult to compare the data between GCC countries. Second, there was significant heterogeneity between studies with respect to definitions of the risk factors, design, and population characteristics. Third, only a few studies reported stroke incidence and the majority of them were hospital-based studies with an absence of data on Oman and the UAE. Fourth, there were only a few studies focusing on hypertension, dyslipidaemia, and physical activity. Moreover, the number of included studies relating to the prevalence of risk factors in Qatar and Bahrain were also relatively low. However, the strength of this review was that the literature search was conducted on multiple databases including personal contact of the authors to capture all relevant documents.

2.4.7 Conclusion

The present review revealed lower incidence of strokes in the GCC countries than in developed countries and that those affected were younger than in some developing and developed countries. Although there was lack of nationally representative data on the prevalence of CHD in the region, high prevalence of key risk factors was observed. Further, the patterns of risk factors were very similar between the Gulf countries; this may be due to the similarity in culture, religion, cuisine, lifestyle, and environmental factors between these countries. With the rapid urbanization in the Gulf region and the relatively young population, the prevalence of CHD and strokes is expected to increase in the next few decades, which in turn will raise the rate of CVD mortality and morbidity in the region. Well-designed population based nationally representative surveys focusing on CVD and its associated risk factors are crucial in the Gulf States. Furthermore, there is a need to increase the awareness of the high prevalence of CVD and associated risk factors among the public along with education programs on nutrition and healthier lifestyles including increase in physical activity levels in both men and women. In addition, there is also a need for preventative strategies, especially for type 2 diabetes, to be used in the region and the cooperation in management strategies, especially in obesity and diabetes is also crucial across the region. Moreover, addressing some of the cultural and social barriers that were mentioned previously is also important for reducing the risk of CVD and related risk factors among the GCC population.

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2.5 Vitamin D: Background

2.5.1 The definition and metabolism of vitamin D

Vitamin D "is a generic name for a group of fat-soluble steroids of which the two major forms are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol)" (Geleijnse, 2011). Vitamin D is important for bone mineralization and is responsible for the regulation of calcium and phosphate homeostasis in combination with the Parathyroid hormone (PTH) (McGreevy & Williams, 2011). More recently, an increasing amount of evidence has indicated that vitamin D deficiency is associated with multiple sclerosis, diabetes, some types of cancers, asthma and CVD (Judd & Tangpricha, 2009; Nitta, 2011). Vitamin D is widely known as the "sunlight vitamin" as almost 80-90% of vitamin D is produced in the body in cells beneath the skin when a person is exposed to sunlight, whereas the other 10-20% is acquired through dietary sources (Mithal et al., 2009). Vitamin D can be acquired through a limited number of dietary sources, which include: liver, butter, oily fish, egg yolks, vitamin D fortified milk and margarine, and dietary supplements (Geleijnse, 2011).

It is crucial that both forms of vitamin D, vitamin D3 (cholecalciferol), which is the form of vitamin D after sun exposure, and vitamin D2 (ergocalciferol) or D3, which are the forms obtained through dietary sources, to go through two hydroxylation reactions to become active inside the human body (Mithal et al., 2009). The activation occurs first when the two forms of vitamin D, D2 and D3, are imparted to the liver and are converted into 25-hydroxyvitamin D, or 25(OH)D, which is the significant form of vitamin D. The 25(OH)D is then transported to the kidney and goes through another hydroxylation to produce the 1, 25 dihdroxyvitamin D (1, 25(OH)2D) by using the enzyme of 1α-hydro-xylase (1α-OHase) under the influence of PTH. The 1, 25(OH)2D is the hormonal and biological active form of vitamin D, also known as calcitriol (Figure 2.3) (Judd & Tangpricha, 2009; Nitta, 2011).

Serum 25(OH)D is regarded as a significant biomarker that reflects the total vitamin D obtained through sunlight exposure and dietary intake (Judd & Tangpricha, 2009). Hence, the best way in which to determine the vitamin D status is to measure serum 25(OH)D, rather than 1, 25 (OH)2D, for several reasons, including: its longer circulation (half-life of up to three weeks), which means it is more stable; its higher concentration in the circulation; and the fact that the production of 1, 25 (OH)2D is mainly regulated by PTH, which also regulates the levels of serum calcium. This means that levels of serum 1, 25 (OH)D may be increased in cases of vitamin D deficiency to retain normal calcium levels (Judd & Tangpricha, 2009).

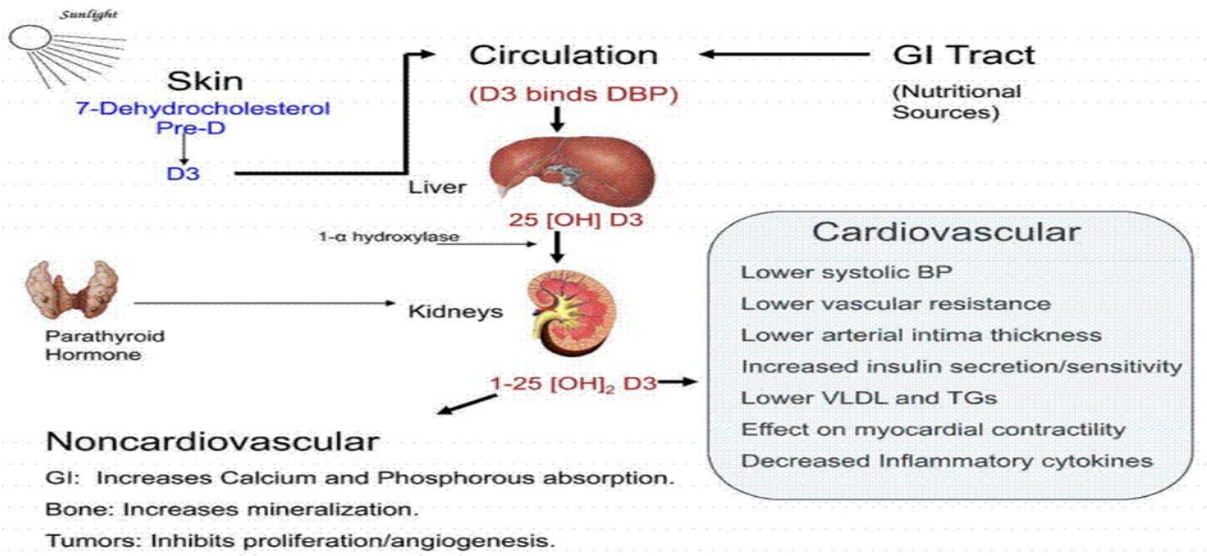

Figure 2.3: Vitamin D synthesis, activation and effects. Adapted from (Vacek, 2010).

2.5.2 Vitamin D deficiency

No international agreement exists to define the optimum levels of serum 25 (OH)D. The International Osteoporosis Foundation (IOF) guideline currently defines vitamin D deficiency and insufficiency as serum 25 (OH)D levels less than 25 nmol/l (≤10 ng/ml) and 50 nmol/l (20ng/mL), respectively (Dawson-Hughes et al., 2010). These data were mainly based on randomized control trials (RCTs) for bone health because a limited number of randomized interventions have investigated the association between vitamin D and chronic diseases, such as CHD and cancer. Hence, the deficient level of vitamin D, according to the studies examining vitamin D in bone health, is the level at which the production of PTH increases, as high levels of PTH can lead to bone loss and fractures (Ross, Taylor, Yaktine, & Del Valle, 2011). However, most experts have defined vitamin D deficiency as serum 25 (OH)D levels less than 20ng/mL (50 nmol/l) (Geleijnse, 2011; Holick, 2007; Shils & Shike, 2006). Table 2.3 shows the distribution of vitamin D status regarding serum 25(OH)D concentrations.

Table 2.3: The classification of vitamin D status regarding to serum 25(OH)D concentrations.

25(OH)D vitamin D concentrations	**25(OH) vitamin D status**
<10 ng/ml	Severely deficient
10 to <20 ng/ml	Deficient
20 to <30 ng/ml	Insufficient
≥30 ng/ml	Adequate
≥100 ng/ml	Possible toxicity

25(OH) vitamin D: 25-hydroxy vitamin D; 1 ng/ml = 2.5 nmol/l. Table adapted from (Shils & Shike, 2006)

2.5.3 Recommendation for vitamin D intake

The Institute of Medicine (IOM) recently provided guidelines for vitamin D intake in 2010. As mentioned earlier, these guidelines are based on bone health interventions and do not address the amount of vitamin D essential for the prevention of chronic diseases such as CVD, because insufficient evidence exists to determine the role of vitamin D in preventing chronic disease. The current recommended dietary allowance for vitamin D is 400-600 international units (IU) for adults 18-70 years old and 800 IU for adults 70 years and older. These recommendations are considered conservative and are related to bone health but no other health effects (Ross et al., 2011).

2.5.4 Risk factors for vitamin D deficiency

Risk factors for vitamin D deficiency include older age, pigmented skin, air pollution, the use of sunscreen, smoking, obesity, exclusive breastfeeding, northern latitudes and specific types of clothing and cultural practices (Holick, 2007). Table 2.4 summarizes the main risk factors for vitamin D deficiency.

Table 2.4: Causes of vitamin D deficiency (Holick, 2007).

Causes	Effects
Reduced skin synthesis	
Sunscreen use: absorption of UVB radiation by sunscreen	Reduced vitamin D3 synthesis: SPF 8 by 92.5%, SPF 15 by 99%
Skin pigment: absorption of UVB radiation by melanin	Reduced vitamin D3 synthesis by as much as 99%
Aging: reduction of 7-dehydrocholesterol in the skin	Reduced vitamin D3 synthesis by 75% in 70 years old
Season, latitude and time of day	Above 35 degrees north latitude, little or no vitamin D3 can be produced from November to February
Institutionalized and home-bound	Reduced vitamin D3 synthesis because of reducing sun exposure
Patients with skin grafts for burns: marked reduction of 7-dehydrocholesterol in the skin	Decrease the amount of vitamin D3 the skin can produce
Decrease bioavailability	
Malabsorption: reduction in fat absorption resulting from cystic fibrosis, celiac disease, Whipple's disease, Crohn's disease, bypass surgery, medications that reduce cholesterol absorption	Impairs the body's ability to absorb vitamin D
Obesity: sequestration of vitamin D in body fat	Reduces availability of vitamin D
Increased catabolism	
Anticonvulsants, glucocorticoids, HAART (AIDS treatments), and antirejection medications	Activates the destruction of 25(OH)D and 1,25-dihydroxyvitamin D to inactive calcitroic acid

Breastfeeding	
Poor vitamin D content in human milk	Increases infant risk of vitamin D deficiency when breast milk is sole source of nutrition
Decreased synthesis of 25(OH)D	
Liver failure: mild-moderate dysfunction	Causes malabsorption of vitamin D, but with possible production of 25(OH)D
Dysfunction of 90% or more	Inability to make sufficient 25(OH)D
Increased urinary loss of 25(OH)D	
Nephrotic syndrome: loss of 25(OH)D bound to vitamin D-binding protein in urine	Results in substantial loss of 25(OH)D to urine
Decreased synthesis of 1,25-dihydroxyvitamin D	
Chronic kidney disease: stages 2 and 3	Causes decreased phosphorus and serum levels of 1,25-dihydroxyvitamin D
Stages 4 and 5	Causes hypocalcaemia, secondary hyperparathyroidism and renal bone disease

2.5.5 The global epidemiology of vitamin D deficiency

The prevalence of vitamin D deficiency is becoming a global epidemic. In the United States (US), according to the National Health and Nutrition Examination Survey (NHANES III), vitamin D deficiency was present in 25-50% of adults (Looker, Dawson-Hughes, Calvo, Gunter, & Sahyoun, 2002). In Europe, a study showed that mean serum levels of 25 (OH)D were from 20-30 nmol/l and 40-50 nmol/l among older adults in Southern and Northern Europe, respectively (Van der Wielen et al., 1995). A survey among Italian postmenopausal women indicated that almost 30% had serum 25 (OH)D lower than 25 nmol/l (Bettica, Bevilacqua, Vago, & Norbiato, 1999). Similar results have been reported among adolescents in Greece (Lapatsanis et al., 2005).

It is difficult to compare the prevalence of vitamin D deficiency among different populations because a variety of definitions and assays have been used to determine vitamin

D deficiency (Mithal et al., 2009). Despite the fact that various definitions have been used, the Middle Eastern and Asian regions have shown the highest rates of vitamin D deficiency in both genders for several reasons, including wearing clothing that covers the entire body, lifestyles that do not allow people to spend a lot of time in the sun, and air pollution as well as hot climates, which make sun exposure undesirable (Mithal et al., 2009).

Within the Asian region, vitamin D deficiency (<50 nmol/l) in North India was prevalent among 96% of neonates, 84% of pregnant women and 91% of school-aged girls (Mithal et al., 2009). Likewise, almost 89% of female school students in North China had serum 25(OH)D levels less than 50 nmol/l, and 48% of old males had less than 25 nmol/l of 25(OH)D (Foo, Zhang, Zhu, Greenfield, & Fraser, 2005; Yan et al., 2000). In the Middle East region, 35% of the elderly in Israel were reported to have vitamin D deficiency (<25 nmol/l), whereas in Jordan, Lebanon and Iran, approximately 60%-65% of the population were affected (Mithal et al., 2009). A study among women in the UAE showed severe levels of vitamin D deficiency (≤10 ng/ml) (Fields, Trivedi, Horton, & Mechanick, 2011). Limited studies have been carried out to investigate the reasons behind the low levels of vitamin D in the Middle East, especially among women. Available studies suggested that it may be due to some cultural and religious practices that limit sun exposure, the low intake of dietary vitamin D and the high burden of obesity (Fields et al., 2011; Mithal et al., 2009).

2.5.6 The prevalence of vitamin D deficiency in Saudi Arabia

In Saudi Arabia, the vitamin D status of the population would be expected to be at adequate levels due to the presence of plentiful sunlight throughout the year as well as the availability of fortified food products with vitamin D (Ardawi et al., 2012). However, studies in Saudi Arabia have indicated that vitamin D deficiency is common among adults of both genders. A study was conducted in the early 1980s among a group of Saudi university students aged 18-26 years, and a group of elderly people with a mean age of 62 years

(Sedrani, Elidrissy, & El Arabi, 1983). This study reported low mean serum vitamin D levels in both the elderly (3.6 ng/ml) and university students (males 8.4 ng/ml; females 11.5 ng/ml). However, it was significantly lower among the elderly subjects in comparison with the younger university students, and it was also significantly higher in female students than male students (Sedrani et al., 1983). Similarly, a study among females with a mean age of 35 years showed that almost half of the study subjects suffered from vitamin D deficiency (≤20 nmol/l) (Ghannam et al., 1999). More recently, a study was carried out on males and females separately during the period of 2008 to 2009, and it showed a higher mean serum vitamin D level in females (41.54nmol/l) than in males (29 nmol/l); however, both were deficient (Ardawi et al, 2011; Ardawi et al., 2012). Another study reported no significant difference between males and females in their mean serum vitamin D levels (10 .1 ng/ml and 9.9 ng/ml, respectively), although both groups were severely deficient (Elsammak et al., 2011).

On the other hand, some recent studies indicated that vitamin D deficiency is more prevalent among females than among males. A study that Naeem et al. (2011) conducted showed that only 32% of the study subjects had adequate vitamin D levels (≥30 ng/ml). Also, the mean serum vitamin D levels were higher among males (32 ng/ml) than among females (23 ng/ml) (Naeem et al., 2011). Alfawaz et al. (2014) indicated that females had a significantly higher prevalence of vitamin D deficiency (<50 nmol/l) than males (78% vs. 72%, respectively). Another study reported relatively higher levels of vitamin D among the Saudi population, as almost half of the study subjects had adequate vitamin D levels (≥72 nmol/l) (Alsuwaida et al., 2013). Furthermore, the prevalence of vitamin D deficiency (<50 nmol/l) was significantly higher in females (34.8%) than in males (13.4%) (Alsuwaida et al., 2013). Similarly, a study conducted among only Saudi females indicated that 79% had vitamin D deficiency (<25 nmol/l) (Al-Mogbel, 2012). Furthermore, The Saudi Health Interview Survey (SHIS), which is a nationally representative survey, conducted in 2013 among Saudis 15 years old and above reported a prevalence of vitamin D deficiency (<28 ng/ml) of about 40.6% and 62.6% among males and females, respectively (Tuffaha et al., 2015). In summary, vitamin D deficiency is common among Saudi adults, especially in females.

2.5.7 Knowledge and attitudes in relation to vitamin D

As mentioned previously, a high prevalence of vitamin D deficiency has been reported worldwide. The lack of knowledge about the health benefits of vitamin D and its sources may be the reason behind the high burden of vitamin D insufficiency/deficiency. A limited number of studies have investigated the existing knowledge and attitudes regarding vitamin D among different populations and age groups. A cross-sectional survey in the United Kingdom (UK) examined the level of awareness of vitamin D deficiency among people considered to be at high risk, such as individuals with darker skin and people who cover their entire bodies as part of their cultures and religions (Alemu & Varnam, 2012). This study indicated low levels of knowledge and awareness of this vitamin; almost one-quarter of the study subjects had never heard about the vitamin, especially older people, and half of the study subjects were unaware of vitamin D deficiency symptoms. The study also showed that during the last year before the study, 34% of the study subjects exposed only their faces and hands to sunlight (Alemu & Varnam, 2012). Likewise, a number of studies in China, Australia, Netherlands, Saudi Arabia and Kuwait have reported low levels of knowledge and awareness about vitamin D among these populations and have shown how this might affect their behaviours in relation to vitamin D. Kung and Lee (2006) indicated low levels of knowledge of vitamin D and its sources in middle-aged and elderly Chinese women. The study also showed negative attitudes and behaviours toward sunlight among subjects who had good knowledge of vitamin D and who knew that sunlight is the main source of this vitamin. Of these subjects, 76% spent less than one hour in the sun weekly, and 75% used sunscreen products (Kung & Lee, 2006). A study of older people living in residential homes in Netherlands showed that 38% of the study subjects knew about vitamin D (Oudshoorn et al., 2011). Also, the study demonstrated that people who had good knowledge of vitamin D had higher adequate vitamin D levels (Oudshoorn et al., 2011).

In Queensland, Australia, the number of people who agreed that using sun protection could reduce vitamin D levels increased during the period between 2006 and 2009 (Janda, Kimlin, Whiteman, Aitken, & Neale, 2007; Youl, Janda, & Kimlin, 2009). According to these studies, the sun protection practice in Australia has been reduced due to the disagreement between public health messages related to the importance of sun exposure for producing sufficient vitamin D, and the importance of sun protection for reducing the risk of skin cancer. A more recent survey examined the knowledge of and attitudes among Queensland office workers toward vitamin D, and how these affect their sun protection behaviour (Vu, van der Pols, Whiteman, Kimlin, & Neale, 2010). The survey indicated a low level of accurate knowledge about vitamin D and only 69% of the study subjects knew about vitamin D. Of the people who had knowledge of vitamin D, only half of them knew about its health benefits in maintaining bone health. The study also indicated that there was confusion about how to preserve adequate levels of vitamin D, through safe sun exposure and sun protection behaviours (Vu et al., 2010).

In the Arabic Gulf countries, studies have shown that limited knowledge exists in relation to vitamin D among these populations (Al Bathi, Al Zayed, Qenai, Makboul, & El-Shazly, 2012; Christie & Mason, 2011). A study investigated the knowledge, attitudes and practices related to vitamin D among subjects who suffered from vitamin D deficiency in Kuwait; they showed low rates of knowledge and negative attitudes towards vitamin D. It also found that almost one-quarter of the study subjects were unaware of their condition (Al Bathi et al., 2012). A qualitative study among female college students in Saudi Arabia also showed a lack of knowledge about vitamin D sources and its health benefits (Christie & Mason, 2011). In fact, the study subjects were unaware of any of the other health benefits of vitamin D rather than the fact that it is essential for bone health. Some of the barriers identified in the study for poor sun exposure practices among Saudi females included the hot climate, cultural factors (covering clothes and wearing a burka) and the lack of outdoor activities. Although this was the first study in Saudi Arabia to examine people's knowledge of and attitudes towards vitamin D, the study findings may not be representative of the entire population due to the small sample size and sex restriction (eight females), as well as the qualitative nature of the study (Christie & Mason, 2011). In summary, relatively few global studies have assessed the existing knowledge and attitudes towards vitamin D and have explored in-depth vitamin D related behaviours, such as sun exposure, outdoor activities and the use of sunscreen and their association with vitamin D status.

2.6 Vitamin D and Coronary heart disease

2.6.1 The mechanism by which vitamin D defends against CHD

During the past few decades, accumulating evidence has suggested that vitamin D may play a crucial role in different parts of the human body, including the bones and the kidneys. For example, animals and clinical studies have shown that vitamin D is important in regulating metabolism in the heart and blood vessels. However, the exact mechanism by which vitamin D defends against CHD is not fully clear, as limited information is obtainable from clinical trials. Nevertheless, the proposed mechanism includes the role of the active form of vitamin D (1, 25 (OH)2D) in regulating the PTH and the renin-angiotensin-aldosterone system (RAAS), and in the down regulation of inflammation as well as the wide distribution of vitamin D receptors (VDRs) in the human body (Figure 2.4) (Nemerovski et al., 2009; Nitta, 2011).

Vitamin D receptors (VDRs) are present in almost all tissues of the human body, such as colonic cells, cardiac myocytes and endothelial cells. This distribution of VDRs plays a crucial role in cardiac physiology. The effect of the absence of VDRs on CVD was observed first in animal studies (Nemerovski et al., 2009). In the animal studies, genetic modification was conducted so that the animals would have no VDRs; hence, they had heart failure and left ventricular hypertrophy. These results were consistent with the evidence observed in patients with end-stage renal disease (Manson, 2010). In patients with end-stage renal disease, the levels of 25 (OH)D fail to convert to 1, 25 (OH)2D; thus, the levels of 1, 25 (OH)2D become deficient, and as a result, the levels of PTH increase. As a consequence, the elevated levels of PTH lead to an increase in blood pressure and cardiac contractility, which develop myocardial dysfunction and arterial hypertension (Nemerovski et al., 2009; Nitta, 2011). Hence, vitamin D also has a direct role in regulating PTH (Nemerovski et al., 2009; Nitta, 2011).

Moreover, vitamin D has indirect effects on cardiac function by negatively regulating the RAAS. The activation of the RAAS plays a significant role in changing and controlling blood pressure, as it leads to the reabsorption of water and sodium as well as peripheral arterial vasoconstriction, thus raising the blood pressure. Data from clinical and animal studies have indicated that the active form of vitamin D, 1, 25 (OH)2D can reduce renal renin secretion through VDR receptors (Artaza et al., 2011). Vitamin D deficiency has also been linked to excess inflammation, which is an important factor that affects the process of atherosclerosis plaque and erosion formation. 1, 25 (OH)2D via VDRs in the vascular walls and immune cells plays a direct role in the down regulation of inflammation through activating the anti-inflammatory cytokines (IL-10) and the suppression of inflammatory cytokines (IL-6, IL-12, and TNF-α) (Artaza et al., 2011; Nemerovski et al., 2009).

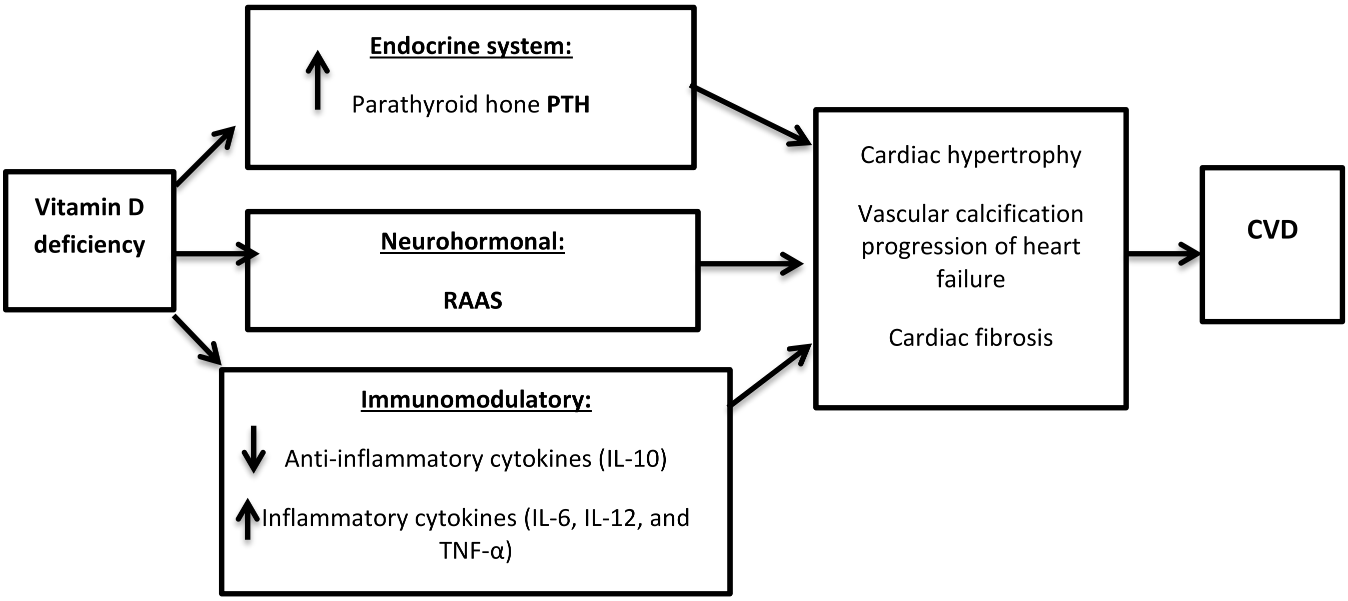

Figure 2.4: CVD pathophysiology of vitamin D deficiency. Adapted from (Nemerovski et al., 2009).

2.6.2 Studies on vitamin D and risk of CHD

Vitamin D is known for its important function in bone metabolism; however, it has also been recently connected to different diseases, including CHD and associated risk factors. Observational and epidemiological studies have indicated a potential role for vitamin D in reducing the risk of CHD. In this section, the available observational and intervention studies that have reported on the association of vitamin D with CHD and the associated risk factors are summarized.

2.6.2.1 Cross-sectional studies:

Some cross-sectional studies in the 1980s and 1990s have reported an association between vitamin D, as an environmental factor, and the risk of CHD. A number of studies have indicated an inverse association between exposure to sunlight and the occurrence of CHD. Countries that are located at higher latitudes and that receive less sunlight have been reported as having higher rates of ischemic heart disease (IHD) (Douglas & Rawles, 1999; Zittermann, Schleithoff, & Koerfer, 2005). A study examined the association of seasonal variation with the occurrence and mortality of acute myocardial infarction (AMI) in the US between 1994 and 1996 (Spencer, Goldberg, Becker, & Gore, 1998). The authors reported that the occurrence of AMIs and hospital death from AMIs peaked in the winter and decreased during the summer. No clear explanation for this seasonal pattern related to AMI was provided in this study. However, the authors suggested that the low levels of vitamin D during the winter may be a potential explanation for these results (Spencer et al., 1998). Similarly, another study suggested that the high mortality rate of CHD in North-West England, Northern Ireland and Scotland was due to the high latitude and the dominant climate in this area, which is characterised as cloudy with low amounts of sunlight (Grimes, Hindle, & Dyer, 1996). Furthermore, the seasonality of the incidence and mortality of CHD in Scotland was examined between 1962 and 1971, and the study found that there was seasonal variation, with rates peaking during the winter season; however, the authors provided no clear explanation for these results (Douglas, Dunnigan, Allan, & Rawles, 1995).

The NHANES survey in the US during the periods of 1988-1994 and 2000-2004 also reported the association between vitamin D status and CVD risk. From 1988-1994, the findings of NHANES indicated that subjects with self-reported CVD had a higher prevalence of 25(OH)D deficiency compared to those without CVD (29.3% vs. 21.4%) (Kendrick, Targher, Smits, & Chonchol, 2009). It was also reported that subjects with 25(OH)D deficiency had a higher prevalence of angina, heart failure, and MI compared to subjects with adequate levels [OR: 1.20 (95% CI: 1.01, 1.36)] after the controlling of confounders (Kendrick et al., 2009). Likewise, the NHANES survey in 2000-2004 reported an increase in the burden of CHD, heart failure and strokes with vitamin D deficiency (Kim, Sabour, Sagar, Adams, & Whellan, 2008). CHD risk factors, including diabetes, obesity, hypertension and high triglyceride levels, have also been associated with lower serum levels of vitamin D in the NHANES (1988-1994) (Martins et al., 2007). However, a study showed no significant association between serum 25(OH)D and systolic or diastolic blood pressure in older adults in the Netherlands (Snijder et al., 2007). This study had some limitations that might have affected the findings. For example, the majority of the study subjects had adequate levels of vitamin D, and the authors acknowledged that this could potentially be the reason for their findings, as 25(OH)D might affect blood pressure at only insufficient and deficient levels. Furthermore, this study used a single blood pressure measurement, which can lead to some inaccuracy in the assessment of blood pressure (Snijder et al., 2007). Similarly, another study indicated no significant association between serum levels of vitamin D and metabolic syndrome in overweight and obese adults, but it was significantly correlated with body max index (BMI) and type 2 diabetes (McGill et al., 2008).

Another study examined the prevalence of vitamin D deficiency and related characteristics in patients with MI who enrolled in a prospective MI registry during the year of 2008 (Lee et al., 2011). In this study, almost 75% of the patients were classified as vitamin D deficient (≤20 ng/ml), and another 21% had insufficient vitamin D status (<30->20 ng/ml). In addition, vitamin D deficiency was found to be associated with diabetes, inactivity and higher BMI among MI patients (Lee et al., 2011). Anderson et al. (2010) analysed a large number of medical record databases (41,504) prospectively to determine the correlation of serum levels of vitamin D with CVD and the associated risk factors. They reported a significant association of vitamin D deficiency with hypertension, diabetes, hyperlipidaemia, peripheral vascular disease, CHD, MI, heart failure and stroke among people who attended health care centres. In this study, about 64% of the study participants had vitamin D deficiency (≤30 ng/ml) (Anderson et al., 2010).

In Malaysia, low serum levels of vitamin D were found to be significantly associated with obesity [(OR (95%CI) 2.57 (1.51, 4.39)] and metabolic syndrome [(OR (95%CI) 1.73 (1.02, 2.92)] in adults (Moy & Bulgiba, 2011). Serum 25(OH)D levels were also inversely correlated with metabolic syndrome in a population in England (Hyppönen, Boucher, Berry, & Power, 2008). Similarly, vitamin D deficiency was also associated with metabolic syndrome and high triglyceride levels among young European adults in Iceland, Ireland and Spain (Muldowney et al., 2011). Another study conducted among adults in Germany also reported a significant correlation between low vitamin D levels and obesity and inactivity levels (Hintzpeter, Mensink, Thierfelder, Müller, & Scheidt-Nave, 2007). In Qatar, a Gulf country, a retrospective study reported a three times higher risk of MI among Qatari males with lower serum levels of 25(OH)D compared to those with adequate vitamin D status (El-Menyar et al., 2012).

A cross-sectional study in Germany also reported a link between vitamin D deficiency and myocardial dysfunction (Pilz, Marz, et al., 2008). This study showed an association of vitamin D deficiency with mortality due to heart failure [HR (95%CI) 2.84 (1.20-6.74)] and mortality due to sudden cardiac death [HR (95%CI) 5.05 (2.13-11.97)] (Pilz, Marz, et al., 2008). Similarly, all-cause mortality was examined by using a quartile of serum 25(OH)D levels in the NHANES (1988-1994), and the study showed that in the general population, the lowest vitamin D level quartile was independently correlated with all-cause mortality [(95%CI) 1.28 (1.11-1.48)] (Melamed, Michos, Post, & Astor, 2008). Also, death rates due to CVD were higher in the lowest quartile of serum 25(OH)D levels; however, these findings are not statistically significant (Melamed et al., 2008).

2.6.2.2 Cohort and case-control studies:

A number of studies have examined the relationship between vitamin D status and the incidence and outcomes of CHD among subjects who were free of the disease at baseline. Using a food frequency questionnaire, one prospective cohort study examined the dietary intake of vitamin D and calcium and the use of supplements and CHD mortality among 34,486 postmenopausal women without CHD at baseline in Iowa (Bostick et al., 1999). This study showed, after eight years of follow-up, that no significant associations existed between CHD death and the dietary intake of vitamin D and vitamin D supplements; however, a significant association was determined between dietary calcium intake and supplemental calcium and CHD death (Bostick et al., 1999). More recently, the Framingham Offspring cohort study specified that, after 5.4 years of follow-up, low levels of vitamin D were associated with an increased risk of CVD in subjects with no history of the disease (Wang et al., 2008). It reported a hazard ratio of 1.80 (95% CI, 1.05-3.08) for developing a CVD event for subjects with severe vitamin D deficiency (25(OH)D <10 ng/ml) when compared with subjects with higher levels of serum vitamin D (Wang et al., 2008). Furthermore, the Health Professionals study showed that, after 10 years of follow-up, men with no history of CVD and with deficient levels of serum vitamin D (≤15 ng/ml) were more likely [RR 2.09 (95% CI, 1.24-3.54)] to have a higher risk for MI than those with higher levels of vitamin D (≥30 ng/ml) (Giovannucci, Liu, Hollis, & Rimm, 2008).

In a community-based case-control study in Auckland, New Zealand, an inverse association was observed between vitamin D deficiency and MI (Scragg, Jackson, Holdaway, Lim, & Beaglehole, 1990). Conversely, a case-control study in South India examined the association between serum 25(OH)D and ischemic heart disease (IHD), and it showed that serum levels of 25(OH)D were significantly higher in IHD patients compared to the controls (Rajasree et al., 2001). In fact, serum vitamin D was at toxic levels (≥222.5 nmol/l, ≥89 ng/ml) among IHD patients in this study (Rajasree et al., 2001). On the contrary, another case-control study in India that was conducted at the same time (1999-2001), reported an independent association between severe vitamin D deficiency (<10 ng/ml) and the increased risk of MI [(OR (95%CI) 4.5 (2.2–9.2)] (Roy et al., 2015).

The relationship of plasma levels of 25(OH)D with the prevalence of hypertension and other risk factors has also been examined in some studies. The Health Professionals

Follow-up Study and the Nurses' Health Study cohorts reported that, after four years of follow-up, the serum levels of 25(OH)D were inversely associated with hypertension, and the relative risk for the incidence of hypertension among men and women with vitamin D deficiency (<15ng/ml) was 6.13 (95% CI, 1.00-37.8) and 2.67 (95% CI, 1.05-6.79), respectively, when compared with the subjects with higher levels of 25(OH)D (≥30ng/ml) (Forman et al., 2007). Likewise, a nested case-control study among women who were free of hypertension at baseline also demonstrated the protective role of vitamin D against hypertension (Forman, Curhan, & Taylor, 2008). Women with vitamin D deficiencies (<30ng/ml) had an odds ratio of 1.47 (95% CI, 1.10-1.97) in contrast with women who had optimal levels (Forman et al., 2008). A case-control study in Saudi Arabia reported no association between vitamin D status and diabetes, and they also reported a high prevalence of vitamin D deficiency (<20ng/ml) in both diabetic patients (76.6%) and non-diabetic patients (58%). They also, concluded that vitamin D deficiency was prevalent in the study subjects regardless of the presence of diabetes (Alhumaidi et al., 2013). Furthermore, the authors indicated that the presence of some medical conditions, such as hypothyroidism and euthyroid multinodular goitre, in the control group may have contributed to the high prevalence of vitamin D deficiency in the non-diabetic group (Alhumaidi et al., 2013). Thus, future studies should be carefully designed particularly using the appropriate criteria for selection and exclusion while comparing cases and controls or controlling for potential confounders.

Some prospective cohort studies have also examined the relationship between mortality rates and serum levels of 25(OH)D. Dobnig et al. (2008) reported that, after 7.7 years of follow-up, the hazard ratios for coronary angiography patients in the lower quartile of 25(OH)D were higher for all-cause mortality [HR 1.53 (95% CI, 1.17-2.01)] and CVD mortality [HR 1.82 (95% CI, 1.29-2.58)] compared with patients in the highest quartile

(Dobnig et al., 2008). Moreover, among the same group of patients, low plasma levels of 25(OH)D were significantly and independently associated with fatal strokes [OR 0.58 (95% CI, 0.43-0.78)] (Pilz, Dobnig, et al., 2008).

2.6.2.3 Randomized controlled trials studies (RCTs):

The early RCTs of vitamin D supplementation have mainly concentrated on the effect of vitamin D in reducing blood pressure. A study among elderly in China showed no significant effect of vitamin D3 and calcium in reducing hypertension (Pan, Wang, Li, Kao, & Yeh, 1992). Similar results have been reported in the UK (Scragg, Khaw, & Murphy, 1995). A randomized trial among 18 subjects with hypertension in Germany found a significant decrease in hypertension among subjects who were exposed to UVB for six weeks (three times per week) when compared with the subjects who were exposed to UVA (Krause, Bühring, Hopfenmüller, Holick, & Sharma, 1998). This study also reported an increase (162%) in the serum levels of 25(OH)D and a decrease (15%) in the serum levels of PTH among the group exposed to UVB, which can synthesize vitamin D (Krause et al., 1998). Similarly, an RCT with vitamin D3 and calcium supplementation conducted among elderly German women for eight weeks reported an effective 9% reduction in systolic blood pressure (Pfeifer, Begerow, Minne, Nachtigall, & Hansen, 2001a).

However, some other recent RCTs have failed to show any effect of vitamin D on reducing blood pressure. For example, the Women Health Initiative study (WHI) is a large randomized trial among 36,282 postmenopausal women in the US examining the combined effect of calcium and vitamin D supplementation on hypertension in postmenopausal women (Margolis et al., 2008). This study did not show any significant difference in hypertension level between the treatment group (calcium 1 g/day and vitamin D 400 IU/day) and the control group after seven years of follow up (Margolis et al., 2008).

A recently published trial showed a slight but significant increase in systolic blood pressure rather than a decrease between two groups of overweight and obese subjects who were randomized to high doses of vitamin D (20,000 IU/week) and (40,000 IU/week) for one year when compared with the placebo group (Jorde, Sneve, Torjesen, & Figenschau, 2010). However, a meta-analysis recently published has pooled ten trials on vitamin D supplementation and hypertension, and it has reported no significant effect of vitamin D supplementation on systolic or diastolic blood pressure (Pittas et al., 2010).

Furthermore, few RCTs have been conducted to examine the role of vitamin D supplementation in reducing CVD risk. A large RCT among postmenopausal women in the US (WHI) reported, after seven years of follow-up, no significant effect of combined supplementation with vitamin D and calcium on all causes of mortality (LaCroix et al., 2009). Likewise, an RCT in the UK among elderly subjects receiving vitamin D supplementation (100,000 IU/ four months) for five years showed no significant difference between the vitamin D group and the control group for all cause of mortality, CVD death and cancer death (Trivedi et al., 2003). Similarly, a multicentre randomized trial among elderly women with vitamin D insufficiency in France showed no difference in the occurrence of CVD events between the vitamin D and calcium group (800 IU and 1000mg respectively) and placebo group after one year (Brazier et al., 2005). An intervention trial was conducted among type 2 diabetes subjects who were randomized into two groups receiving either a high dose of vitamin D supplementation (40,000 IU/week) or a placebo (Jorde & Figenschau, 2009). This study found no significant changes in glucose metabolism between the two groups after six months; however, a significant increase in serum 25(OH)D, along with a significant decrease in serum PTH, was noticed in the vitamin D supplemented group compared to the control group (Jorde & Figenschau, 2009).

Conversely, some interventions have shown a slight effect of vitamin D supplementation on CVD risk. A small RCT was conducted among Australian elderly women (n=302) who received either both vitamin D (1000 IU/day) and calcium (1000 mg/day) or calcium only for one year (Prince et al., 2008). This study showed a slightly lower incidence of ischemic heart disease (CHD) in the vitamin D and calcium group than in those who received only calcium (1.3% and 2%, respectively) (Prince et al., 2008). However, no difference was found in the rate of stroke between the two groups (Prince et al., 2008). Similar results were reported in another intervention study among 200 overweight and obese subjects who were participating in a weight-reduction program in Germany (Zittermann et al., 2009). The study examined the effect of vitamin D supplementation (83 mg/day) on weight loss and CVD risk factors. After one year, no effect on weight loss was demonstrated; however, serum levels of 25 (OH)D increased, whereas serum levels of triglycerides decreased in the vitamin D supplementation group compared to the placebo group (-13.5% and +3%, respectively). Nevertheless, the study showed that LDL cholesterol levels increased more in the vitamin D group than in the placebo group (+5.4% and -2.5% respectively) (Zittermann et al., 2009). A large RCT called the "Mendelian Randomization Study" was conducted in 2015 as well. This study used genetic variants to examine the effect of vitamin D deficiency on CHD. The results reported no association between vitamin D deficiency and CHD. However, the results of this study are generalizable only to European populations and only among generally healthy adults (Manousaki et al., 2016).

2.7 Conclusion

In conclusion, the majority of published observational studies have demonstrated a significant inverse association between vitamin D deficiency and the risk of CHD (Anderson et al., 2010; Dobnig et al., 2008; El-Menyar et al., 2012; Forman et al., 2008; Forman et al., 2007; Giovannucci et al., 2008; Hintzpeter et al., 2007; Hyppönen et al., 2008; Kendrick et al., 2009; Kim et al., 2008; Lee et al., 2011; Martins et al., 2007; Melamed et al., 2008; Moy & Bulgiba, 2011; Muldowney et al., 2011; Pilz, Dobnig, et al., 2008; Pilz, Marz, et al., 2008; Scragg et al., 1990; Wang et al., 2008). However, some studies have reported no association between vitamin D deficiency and hypertension (Snijder et al., 2007), as well as metabolic syndrome (McGill et al., 2008). Also, one case-control study in Saudi Arabia examining the association between vitamin D and diabetes reported a high prevalence of vitamin D deficiency in both diabetic and non-diabetic groups (Alhumaidi et al., 2013). In addition, another case-control study showed a significant association between toxic levels of vitamin D (≥89 ng/ml) and IHD (Rajasree et al., 2001).

Furthermore, the observational studies are prone to selection and information bias as well as residual confounding, which may play a major role in these conflicting results through unknown confounders or the inaccurate measurement of these confounding factors (Geleijnse, 2011). For example, some cross-sectional studies did not examine and control for factors that might affect vitamin D levels, such as the dietary intake of food rich in vitamin D, physical activity levels and outdoor activity, and some socioeconomic factors, such as type of job; thus, their results might be weak (Geleijnse, 2011; Moy & Bulgiba, 2011). In addition, in some countries and ethnic groups including Saudi Arabia, observational studies regarding the association between vitamin D and CHD are absent. Therefore, the association between vitamin D status and CHD still remains unclear and there is a need for further well designed observational studies in different populations, which is crucial before considering any interventions.

Chapter 3: Research Methodology

3.1 Introduction

The previous chapter provided the background on CHD and vitamin D and reviewed the literature on the relationship between vitamin D status and the risk of CHD. It also identified the gaps in this field and described the rationale of the study. This chapter provides a description of the methods used in this study. A summary of the research approach undertaken to address the research questions is provided. Also, the research questions and conceptual framework are explained. Moreover, the study design, research participants, sample size calculation, data collection methods, ethical consideration, data analysis and rigour are presented.

3.2 Research paradigm

The selection of a research paradigm subsequently determines the study design and methodology applied to address the key research questions. Within the social sciences, two main paradigms or philosophical stances have been advanced, namely positivism and constructivism (Feilzer, 2010). Positivism is commonly applied in the area of social research and is described as a 'natural science' (Newman, 2003). This approach was founded on the concept that one stable social reality exists. This implies that one single truth can be revealed and forms the basis on which quantitative research methods have been established (Creswell & Clark, 2007). Conversely, constructivism was built on the premise that a multitude of realities exist, thus advocating for a subjective world view and the application of qualitative research methods (Feilzer, 2010). A mixed method research design has been employed by some researchers to combine quantitative and qualitative data collection methods. As a result, another paradigm has gained prominence to have the capacity to integrate a wide variety of research approaches. It is known as the paradigm of pragmatism (Feilzer, 2010).

The pragmatic paradigm advocates that both individual and collective realities exist, and it seeks to resolve practical challenges and examine real day-to-day experiences (Creswell & Clark, 2007; Feilzer, 2010). The adoption of a more versatile approach, as opposed to the binary stances of positivism and constructivism, has facilitated researchers to progress towards the application of a range of suitable methods or skills, as required (Creswell & Clark, 2007). The pragmatic research paradigm has acquired widespread recognition and is now commonly used in the social sciences field. A more enhanced and refined appreciation of the research topic can be gained through this analytical process, where it can be examined from multiple viewpoints (Creswell & Clark, 2007; Feilzer, 2010).

The pragmatic paradigm was selected in the present study, as it facilitates the exploration of more in-depth knowledge of the topic being examined (Creswell & Clark, 2007; Sandelowski, 2000). Multiple data sources can be validated, and evidence-based conclusions can be drawn by applying powerful techniques such as the triangulation method, which involves a comprehensive verification of the findings. Also, qualitative and quantitative methods can be combined to address some of the limitations associated with each approach (Creswell & Clark, 2007). In the present study, quantitative methods were applied to examine if there is a relationship between vitamin D and CHD. It also sought to establish a relationship between vitamin D status and knowledge, attitudes and behaviours related to vitamin D. A comprehensive analysis of the influence of knowledge, attitudes and behaviours on vitamin D deficiency, along with identifying the obstacles to managing this issue was undertaken, using qualitative research methods.

3.3 Study design

A case-control hospital-based study design was employed to examine the association between vitamin D status and the risk of CHD among adults in Saudi Arabia. In the hierarchy of research study designs, experimental design is the leading method for establishing the association and causality between a risk factor and a disease ahead of observational designs including cross-sectional, case-control and cohort (Bowling, 2009). However, experimental design is expensive and time consuming, which makes it impossible to apply in the present study. A case-control design was chosen because it has some advantages over alternative observational study designs such as cross-sectional and cohort: It is fairly inexpensive, may provide relatively quick findings and is easier and more suitable for studying complicated diseases with multiple risk factors, such as CHD (Bowling, 2009). In addition, case-control studies require smaller sample sizes in order to establish an association between the risk factor and the disease in comparison with alternative observational study designs. Furthermore, previous observational studies regarding the association between vitamin D status and CHD were mainly cross-sectional studies, with a limited number of well-designed case-control studies (Rajasree et al., 2001; Scragg et al., 1990). For all of the above-mentioned reasons, the case-control study design was considered the most suitable to achieve the study objectives.

3.4 Conceptual framework

Through searching the literature, some gaps regarding CHD and vitamin D status in Saudi Arabia were identified. While some international studies have pointed out the positive association between vitamin D deficiency and CHD (Kim et al., 2008; Wang et al., 2008), findings have been inconclusive (Rajasree et al., 2001; Scragg et al., 1990). Moreover, to date, no previous studies have focused on the relationship between vitamin D status and CHD among Saudi adults. In addition, international studies have demonstrated that vitamin D deficiency plays a role in CHD cardio-metabolic risk factors, including diabetes, hypertension, obesity and hypercholesterolemia (Anderson et al., 2010; Margolis et al., 2008; Martins et al., 2007; McGill et al., 2008; Pfeifer, Begerow, Minne, Nachtigall, & Hansen, 2001b). In Saudi Arabia, only one study has examined the association between vitamin D and diabetes (AlhumaidiL et al., 2013).

The framework shown in Figure 3.1 reflects the hypothesized relationships among the above-mentioned variables and CHD in this study. The main research question to be answered in this study is whether vitamin D status is associated with increased risk of CHD among adults in Saudi Arabia. In the current study, the blue arrows in Figure 3.1 show all possible socio-demographic, cardio-metabolic and behavioural risk factors that may be associated with CHD. Therefore, we need to take into account these factors to assess the association between vitamin D status and the risk of CHD.

After that, the association between vitamin D status and CHD (the question marks) was examined among the study subjects after controlling for potential confounding factors. Next, there is a possibility that vitamin D status is associated with cardio-metabolic risk factors among the study sample. Hence, the red arrow indicates the association between cardio-metabolic risk factors and vitamin D status to examine the indirect association between vitamin D and CHD.

Previous research has shown how knowledge, attitudes and behaviours related to vitamin D, such as sun exposure and the use of vitamin D supplementation, might affect vitamin D status in different populations (Al Bathi et al., 2012; Alemu & Varnam, 2012; Kung & Lee, 2006). However, in the context of Saudi Arabia, only one study has explored these concepts. This study was undertaken among college students, and due to its small sample size and gender restriction (8 females) as well as the qualitative nature of the study, it has been difficult to generalize the results to the general population (Christie & Mason, 2011). Thus, the literature has illustrated the effect of knowledge, attitudes and behaviours on serum vitamin D levels in some countries and ethnic groups. In Figure 3.1, the black arrows refer to the association of vitamin D status with participants' knowledge, attitudes and behaviours related to vitamin D. Hence, the black arrows indicate the possible association between knowledge, attitudes and behaviours related to vitamin D and vitamin D status among adults in Saudi Arabia. Furthermore, qualitative data was collected to enable deeper exploration and further understanding regarding the effects of knowledge, attitudes, and behaviours related to vitamin D among adults in Saudi Arabia.

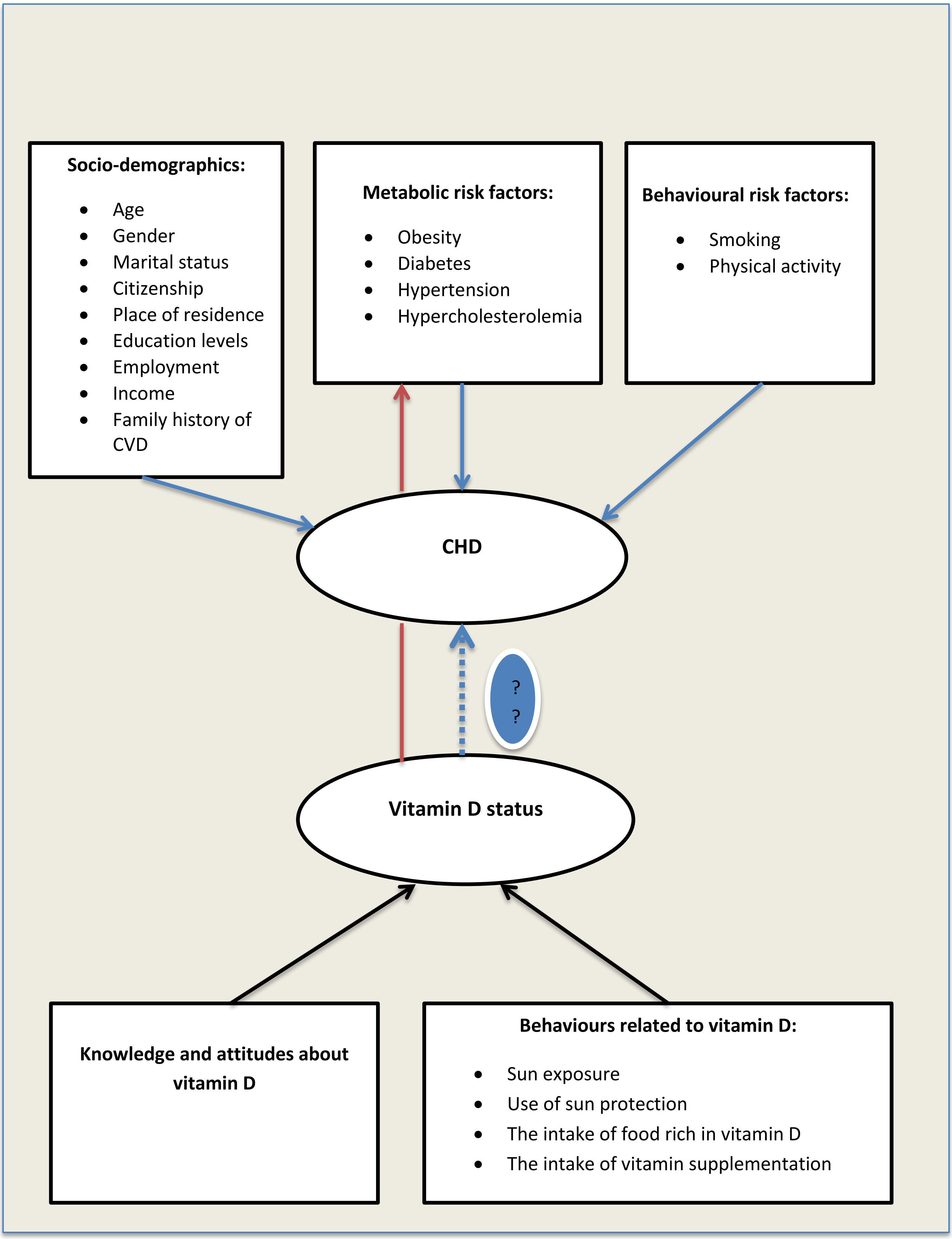

Figure 3.1: Operational framework of the study

3.5 Study population

3.5.1 Research setting

The case and control subjects were recruited from three hospitals in the cities of Jeddah and Makkah, in the Western region of Saudi Arabia. Data collection was undertaken in the period between May and October 2015. It was conducted during the summer season, when average daily sunlight lasts for 9 hours in Jeddah and Makkah cities. Case subjects were collected from King Abdullah Medical City (KAMC) in Makkah (130 subjects). KAMC provides a good site for recruiting cases with CHD for two reasons: First, it has a cardiac centre which is one of the largest cardiac surgical facilities in the Western region. Second, the KAMC hospital receives CVD patients who are referrals from several areas in the Western region of the Kingdom. Control subjects were recruited from ophthalmology clinics at King Abdul Aziz University Hospital (KAU) in Jeddah (42 subjects) and from family medicine clinics and ear, nose and throat (ENT) clinics at Tunsi private hospital in Makkah (153 subjects). It is noteworthy to mention some difficulties that surrounded the selection of the study subjects. The data collection was conducted during Muslims' pilgrimage time in Makkah. Since the KAMC hospital is located in Makkah and close to the pilgrims' place, the outpatient clinics of KAMC were closed in order to deliver health services for pilgrims alone; hence, control subjects were recruited from two different hospitals in Makkah and Jeddah.

3.5.2 Cases' definition and selection

CHD cases were identified as subjects who were diagnosed with CHD after performing any of the following clinical tests: electrocardiogram (EKG), stress testing, echocardiography and coronary angiography. CHD cases were either first incident with an acute event or had been diagnosed previously with myocardial infarction, clinical artery disease or chronic stable angina. The approach to patient (cases) recruitment involved a physician (cardiologist) and the researcher selecting CHD patients from the cardiac centre or emergency department at the hospital based on the definitions and inclusion and exclusion criteria. Then, the researcher explained to the potential cases the nature of the study and invited them to participate in the research.

3.5.3 Controls' definition and selection

The controls were subjects who had no history of CVD and were matched in age (within 0–5 years) and gender with the cases. They were selected by physicians and the researcher from among subjects who were visited the outpatient clinics (ophthalmology, family medicine and ear, nose and throat clinics) at the hospitals during the same data collection period.

3.5.4 Inclusion and exclusion criteria for study subjects

<u>The inclusion criteria for the current study subjects include:</u>

- being a native Saudi or resident in Saudi Arabia for at least five years, and
- being an adult 18 years or older.

<u>The exclusion criteria include:</u>

- subjects who had medical conditions that could affect vitamin D metabolism including metabolic bone disorders such as osteomalacia and osteoporosis. Medical conditions also include liver disease, kidney disease, active malignant disease, tumour-induced osteomalacia, hyperparathyroidism, granulomatous disease, tuberculosis, lymphomas and hyperthyroidism. Furthermore, subjects with malabsorption resulting from celiac disease, Crohn's disease, cystic fibrosis, Whipple's disease and bypass surgery were also excluded (Holick, 2007).

3.6 Sample size

In order to achieve the study aim, two groups were selected; CHD cases and control group who were subjects without CHD.

The formula used to calculate the sample size is: $N = \frac{Z^2 \times P \times (1-P)}{m^2}$

N= Sample size in the case group

Z= 1.96 for a 95%CI

P= (5.5%) the prevalence of CHD in Saudi population (Al-Nozha, Arafah, et al., 2004).

m= desired margin of error (5%)

$$N = \frac{(1.96)^2 \times 0.055 \times (1-0.055)}{(0.05)^2} = 80 \text{ cases}$$

We added 50% in case of non-response and increased by another 30% for enhance the quality of the observational study design and the generalizability of the results.

(80 × 0.80) + 80 = 144 cases (for the patient group)

In order to increase variability in the control group and reduce potential selection bias in the selection of control group, this study used a ratio of 1:1.5 for cases and controls. Therefore, the sample size was 144 for cases and 216 for controls.

3.7 Data collection methods

3.7.1 Quantitative data

3.7.1.1 Medical records:

Data regarding the presence of health problems listed in the exclusion criteria were determined by checking the participants' medical records.

3.7.1.2 Survey:

All cases and controls were interviewed in person by the researcher using a structured questionnaire. The survey tool included two main questionnaires:

1- The first questionnaire was used to collect information on participants' socio-demographic characteristics including age, gender, marital status, citizenship, place of residence, education level, employment and monthly income. It was also used to collect information regarding family history of CVD and behavioural risk factors including tobacco consumption and levels of physical activity.

2- The second questionnaire consisted of three sections and was adapted from a number of questionnaires that were identified in the literature (Alemu & Varnam, 2012; Kung & Lee, 2006; Vu et al., 2010). Section one collected data regarding participants' knowledge about vitamin D. Section two collected data with regard to participants' attitudes toward vitamin D and sun exposure. Finally, section three assessed participants' behaviours in relation to vitamin D, including sun exposure habits, use of sun protection, use of supplementation and intake of food rich in vitamin D. The information sheet and informed consents for this study in Arabic and English are provided in Appendix 1 and 2, respectively. The survey used in this study is provided in Appendix 3.

3.7.1.3 Anthropometric and blood pressure measurements:

Anthropometric measurements including weight and height were taken after interviewing the participants to determine their body mass index (BMI). The participants' blood pressure was also measured after the interview. The participants sat in an upright position for 5 minutes then blood pressure was measured twice using standard equipment. The average reading was recorded.

3.7.1.4 Biochemical measurements:

A single blood sample (10 mL) was collected from both cases and controls via venepuncture to assess their serum 25(OH)D, fasting glucose and total cholesterol levels. The blood samples were centrifuged, and then the separated serum was kept frozen at – 80 °C until laboratory analysis began. Serum vitamin D levels were assessed using chemiluminescence microparticle immunoassay (CMIA) on the Architect system (Abbott) (Wiesbaden, Germany), which is a convenient and accurate method to assess the concentration of 25(OH)D. The intra-assay coefficient of variation was 2.7%, and the inter-assay coefficient of variation was 4.6%. A biochemical analyser (Thermo Fisher Scientific, Espoo, Finland) was used to measure fasting blood glucose and total cholesterol. The laboratories are certified by the Saudi Ministry of Health and are placed in the same hospitals where the study was conducted.

3.7.2 Qualitative data

In-depth interviews were conducted to explore knowledge about vitamin D and attitudes regarding sun exposure. They also explored social and cultural factors that might affect vitamin D deficiency in Saudi Arabia. A convenience sample of 22 participants was selected by consulting with study subjects during data collection in the quantitative study phase and asking them whether they were willing to participate in qualitative interviews. Furthermore, the qualitative interview participants were selected from both cases and controls. An in-depth face-to-face interview was chosen because it is better to discuss cultural and religious issues individually rather than in a group. Also, it might be difficult to have groups including both genders due to some cultural traditions; thus, a face-to-face interview was considered the most appropriate method for collecting qualitative data in this study. The interview was semi-structured with prepared open-ended questions that were adapted from the literature and covered the above-mentioned factors. The interviews were conducted in

Arabic by the researcher in the same hospitals, and they were fully transcribed. The information sheet and informed consents for qualitative study in Arabic and English are provided in Appendix 4 and 5, respectively. The open-ended questions for qualitative interviews are provided in Appendix 6.

3.8 Variables and measurements

Table 3.1 illustrates the measurements of all variables in this study, including CHD (dependent variable), vitamin D status (independent variable), socio-demographics, CHD risk factors, knowledge and attitudes about vitamin D, and vitamin D-related behaviours. The following section provides the definitions of all variables in the current study:

- Coronary heart disease (CHD) is also known as coronary artery disease (CAD). It is defined by the WHO as the 'narrowing of the blood vessels that supply the heart muscle' (WHO, 2016). In this study, CHD refers to patients with clinical artery disease, myocardial infarction and chronic stable angina.
- Vitamin D deficiency was defined as a serum concentration of 25(OH)D less than 10 ng/ml, while those with a concentration between 10 and <19.9 ng/ml were defined as having insufficient vitamin D levels. A serum vitamin D concentration of 20 ng/ml and above was considered adequate vitamin D status (Gallagher et al., 2010). In the present study, vitamin D deficiency and insufficiency were combined in some cases for analysis purposes; hence, vitamin D deficiency was also defined as a serum concentration of 25(OH)D less than 20 ng/ml
- Hypertension was defined in this study according to the WHO criteria as a mean BP ≥ 140 mmHg for systolic (SBP) and/or ≥ 90 mmHg for diastolic

blood pressure (DBP), or if the subject was on antihypertensive drugs (Shils & Shike, 2006).

- Type 2 diabetes was defined according to the WHO standards of diagnosis of glucose intolerance when fasting plasma glucose (FPG) is ≥ 7.0 mmoI/L (126 mg/dL), or a random value at or above 11.1 mmol/L (200mg/dL), or when the subjects was taking medications for diabetes (Shils & Shike, 2006).
- Hypercholesterolemia was defined according to the Adult Treatment Panel III (ATP III) guidelines as high total cholesterol (HC) ≥ 240 mg/dL (Shils & Shike, 2006).
- Overweight and obesity was defined according to the WHO. Subjects were overweight when their BMI was 25 – 29.9 kg/m^2, and subjects were obese when their BMI was ≥ 30 kg m^2 (Shils & Shike, 2006).
- Smoking was assessed by asking the study participants about their smoking habits during the year prior to the study. A current smoker was defined in this study as a person who smokes at least one cigarette per day. A previous smoker is a person who used to smoke but quit. A non-smoker is a person who has never smoked at all (Wells, Broad, & Jackson, 2004).
- Water-pipe smoking was assessed by asking the study participants. Water-pipe smokers were defined as subjects who smoked at least one water-pipe per week at the time of the interview (Shaikh, Vijayaraghavan, Sulaiman, Kazi, & Shafi, 2008).
- Physical activity was self-reported and classified into the following categories: high activity or exercise, such as jogging or swimming for 20 minutes or more three days or more per week, which causes sweating or hard breathing; moderate activity, such as walking reasonable distances, light work and usual

day-to-day activities but no exercise; and sedentary activity, such as staying at home most of the time or doing little walking outside (Ardawi et al., 2012; Wells et al., 2004).

- Family history of CVD was defined as having any first-degree relatives with CVD diagnosed before the age of 55 years (Wells et al., 2004).
- Knowledge of vitamin D in this study refers to the level of understanding of vitamin D and vitamin D deficiency (Kung & Lee, 2006).
- Attitudes of vitamin D refer to feelings towards vitamin D deficiency, supplementations and sun exposure (Kung & Lee, 2006).

Table 3.1 The measurements of study variables.

Study variables	Measure characterization
CHD (dependent variable)	The medical records
Vitamin D (independent variable)	A single blood test
Socio-demographics	
Age	20-29 years, 30-39 years 40-49 years, 50-59 years 60-65 years, >65 years
Gender	male, female
Marital status	Single, married, divorced, widowed
Citizenship	Yes I have Saudi citizenship No
Education levels	No formal education Up to primary level Secondary level high school Bachelor or diploma degree master or PhD degree
Employment status	Employed full time Employed part time Unemployed Student Self-employed Retired House wife
Monthly income	<5000 SR 5000-10,000 SR 10,001-15,000 SR 15,001 SR-25,000SR 25,001SR-35,000SR ≥35,001SR

Family history of CVD	yes for the presence of first-degree relatives with CVD history no for no history of CVD
CHD risk factors	
Hypertension	The participants sat in an upright sitting position for 5 minutes then blood pressure was measured twice using standard equipment. Average reading was recorded.
Type 2 diabetes	A single blood test
Dyslipidaemia	A single blood test
Overweight and obesity	The measurement of height (meters) and weight (kilograms) in light clothing then BMI was calculated by divided weight in kilograms by height in meters squared.
Cigarettes smoking	current smoker, previous smoker non-smoker
Water-pipe smoking	Yes, no
physical activity	high, moderate sedentary
Knowledge, attitude and vitamin D related behaviours	Questions related to knowledge, attitudes and vitamin D related behaviours including sun exposure habits, use of sun protection, the intake of food rich in vitamin D, and the use of vitamin supplementations were selected from previous validated surveys (Alemu & Varnam, 2012; Kung & Lee, 2006; Vu et al., 2010).

3.9 Project management and research procedure

The first step in conducting this research was gaining ethical approvals from Griffith University and the included hospitals. Thereafter, the researcher started selecting case and control subjects. The researcher and the cardiologist initially identified potential study cases from the cardiology and emergency departments in the KAMC hospital. Furthermore, physicians and the researcher identified matched controls from the outpatient clinics in the KAU and Tunsi private hospital. The researcher met with the potential study subjects to ensure their eligibility to participate in the study and whether they could perform all the study activities, including blood draws and anthropometric measurements. The purpose of the study was explained to the study participants, and the researcher also made sure that all study subjects provided written informed consent before participating in the study. All participants were informed that participation was voluntary; there was no coercion. Also, all participants were encouraged to ask any questions, and they were free to withdraw from the study at any time.

In the next step, the study participants were interviewed by the researcher using a structured questionnaire to collect data regarding the socio-demographics, behavioural risk factors and knowledge, attitude and vitamin D-related behaviours. After completion of the questionnaires, nurses collected each participant's height and weight information using a standard scale and measured the blood pressure using standard equipment provided by the hospital. After the anthropometric and blood pressure measurements were taken, a single blood sample was collected from each study subject and frozen to assess serum levels of 25(OH)D, fasting glucose and total cholesterol. The data regarding exclusion criteria was checked from medical records. Information regarding exclusion criteria and diagnosis of cases was reported on the screening sheet, which is provided in Appendix 7. Similarly, results from blood tests and anthropometric and blood pressure measurements were reported on the data collection sheet, which is provided in Appendix 8.

In this study, the researcher worked together with physicians and nurses in the included hospitals. The researcher sought the required ethical approval and obtained informed consent from all study participants. The researcher also collaborated with physicians to recruit cases and controls and invite them to participate in the study. In addition, the researcher met the potential study subjects, explained the purpose of the study and ensured the study was conducted according to the study protocol. The researcher also interviewed the study subjects using the structured questionnaire and ensured the confidentially of participants by keeping the data and questionnaires in a secure place. Furthermore, physicians helped in recruiting the study subjects and checking the medical records. Nurses collected blood samples, height and weight measurements and blood pressure measurements. Laboratory staff ran the tests on the blood samples.

3.10 Ethical considerations

The researcher sought ethical approval for this study from the Griffith University Human Research Ethics Committee (GU Ref No: MED/59/14/HREC). Furthermore, ethical approval was also sought from the KAMC Institutional Review Board (IRB No: 15-194) and the KAU Research Ethics Committee (Reference No ll8-15). Participation in the study was voluntary. Written informed consent was obtained from all participants in both quantitative and qualitative studies. If some participants were illiterate, family members were required to sign for them. No subject was allowed to participate in the study until the informed consent was read and signed. The confidentially of participants was assured by using unidentifiable codes, and the data was stored in a secure place to which only the research coordinator had access. In addition, anonymity was guaranteed as all patients' names and personal information were kept enclosed.

3.11 Data analysis

3.11.1 Quantitative data analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) Version 22. In the first step, univariate analysis was used to measure the socio-demographic characteristics and serum vitamin D levels of the study participants. Participants (subjects with and without CHD) were classified into three groups depending on serum vitamin D levels: (1) deficient (< 10 ng/ml); (2) insufficient (10 to < 19.9 ng/ml); and

(3) adequate (≥20 ng/ml) (Gallagher et al., 2010). Serum vitamin D levels were dichotomized into new responses: 0 = Adequate vitamin D status (≥ 20 ng/ml), 1 = Vitamin D deficiency (< 20 ng/ml). Results were presented as proportions or percentages of observations.

In the second step, bivariate analyses (Chi-square tests) were used to examine associations between categorical variables. The analyses were conducted to compare the case-control groups in relation to serum vitamin D levels. The proportions of patients with vitamin D deficiency were compared by case-control groups (subjects with and without CHD). The analyses attempted to answer the following question: *'Are there any differences between subjects with and without CHD regarding serum vitamin D levels and the proportion of vitamin D deficiency?'*

Pearson Chi-square tests were used for comparisons between subjects with and without CHD in relation to socio-demographic characteristics (age, gender, marital status, citizenship, place of residence, education level, employment, income and family history of CHD), behavioural risk factors (smoking and physical activity) and cardio-metabolic risk factors (obesity, diabetes, hypertension, and hypercholesterolemia). The analyses attempted to answer the following question: *'What are the distributions of the socio-demographic characteristics, cardio-metabolic risk factors (obesity, diabetes, hypertension, and hypercholesterolemia) and lifestyle behavioural risk factors (smoking and physical activity) in subjects with and without CHD?'*

Multivariate logistic regression analyses were performed to examine the association between vitamin D status (independent variables) and the risk of CHD (dependent variables). Both variables were transformed into binary variables (Reference category coded as 0). All significant variables were included in the multivariate logistic regression analysis as confounding variables. As a result, the association between vitamin D status and the risk of

CHD among adults in Saudi Arabia was adjusted for potential confounding factors including socio-demographics, BMI, fasting glucose, total cholesterol, exercise, smoking, intake of vitamin D supplements, intake of calcium supplements with vitamin D, use of sunscreen, and time spent in sun exposure. The analyses attempted to answer the following question: '*Is there an independent association between vitamin D status and CHD after controlling for potential confounding effects of socio-demographic, cardio-metabolic, and lifestyle risk factors?'*. Further details about this analysis are provided in Chapter 4, (Section 4.4.5).

Moreover, multivariate logistic regression models was also performed to examine the association between vitamin D status and the cardio-metabolic risk factors (obesity, diabetes, hypertension, and hypercholesterolemia) in subjects with CHD and subjects without CHD. Different combinations of significant variables such as socio-demographics, the use of vitamin supplementation, behavioural risk factors, sun exposure habits and use of sunscreen were entered into the multivariate regression as confounding variables. The analyses attempted to answer the following question: '*Are there associations between vitamin D status and the common cardio-metabolic risk factors (obesity, diabetes, hypertension, and hypercholesterolemia) among subjects with and without CHD?'* Further details about this analysis are provided in Chapter 5, (Section 5.4.3).

Pearson Chi-square tests were also used for comparisons between subjects with and without CHD regarding knowledge, attitudes, and behaviours related to vitamin D. The analyses attempted to answer the following question: '*Are there any differences in knowledge, attitudes and behaviours regarding vitamin D between subjects with and without CHD?'* In addition, three multivariate regression models were used to examine the independent associations between vitamin D status and knowledge, attitudes and vitamin D-related behaviours. In this particular analysis, cases and controls were combined due to small sample size, and the multivariate regressions were adjusted for age, gender and CHD. The analyses attempted to answer the following question: *'Is there any association between vitamin D status and knowledge, attitudes and behaviours related to vitamin D among adults in Saudi Arabia?'* Further details about this analysis are provided in Chapter 6, (Section 6.4.4).

3.11.2 Qualitative data analysis

The qualitative (in-depth interview) data was transcribed into text and sorted according to participants and data. Thematic analysis was used for data analysis to identify key themes in regard to vitamin D deficiency that were developed from issues mentioned by study subjects. Further details about this analysis are provided in Chapter 7, (Section 7.4.3).

3.12 Rigour (validity and reliability of the study)

It is vital for the researcher to consider the rigour of methodology for data collection in order to ensure the quality of the research. Rigour in general is related to the reliability and validity of the data and reducing the risk of bias (Bowling, 2009). Validity in research refers to the accuracy of a measurement and whether it measures the true value of what it aims to measure. Reliability is the reproducibility of the results of a measurement and the stability of a measurement over time (Bowling, 2009). In regard to the key variables in this study, CHD and vitamin D, the researcher and physicians ensured that the confirmation of CHD diagnosis for all cases followed standard procedures and cross-checked for accuracy, even if the cases were diagnosed by different specialists. In addition, to ensure the consistency and precision of 25-hydroxyvitamin D (25OH-D) measurement, the same assay method was used for all cases and controls. Also, information regarding the two measures of the coefficient of variability (CV), the inter-assay CV and the intra-assay CV, for (25OH-D) was collected. Moreover, height and weight measurements used to calculate BMI and the measurement of blood pressure were conducted by trained nurses using standard calibrated equipment from the same hospitals to ensure the accuracy of the data and the consistency of the measurements.

The other independent variables such as socio-demographics, behavioural risk factors and knowledge, attitudes and behaviours regarding vitamin D were measured using validated questionnaires from previous studies (Alemu & Varnam, 2012; Kung & Lee, 2006; Laviolle et al., 2005; Vu et al., 2010). After developing the final questionnaire for the current study from the existing literature and modifying it according to the study objectives, consultations with experts were undertaken to gain some feedback regarding the final questionnaire and whether it reflected the objectives of the study. Furthermore, a pilot test was carried out to assess and evaluate the content of the questionnaire and overall design, as well as language clarity, then revised and finalised. Moreover, in order to achieve reliability in the current research, the researcher was responsible to conduct all interviews to ensure the quality and consistent delivery of the questionnaire survey.

3.13 Conclusion

This chapter explained the methods used in this research. In the beginning, the mixed methods research paradigm (pragmatic) was determined to be a suitable paradigm for this research. Furthermore, the study design and conceptual framework were explained. Also, data collection methods and data analysis were provided. The next four chapters (chapters 4, 5, 6, and 7) provide the research results and findings which are presented as journal articles and submitted to international peer-reviewed journals.

Chapter 4: Association between Vitamin D Status and Coronary Heart Disease among Adults in Saudi Arabia: A Case-Control Study (Manuscript 2)

4.1 Introduction

The current literature demonstrates a high burden of CHD among adults in Saudi Arabia (Al-Nozha et al., 2004). Data from the Global Burden of Disease shows that CHD was the leading cause of death in 1990, 2005 and 2010 in Saudi Arabia (Memish et al., 2014). Vitamin D deficiency is also reported to be highly prevalent in Saudi Arabia (Tuffaha et al., 2015; Ardawi et al., 2012; Elsammak et al., 2011). Recent evidence suggests that low levels of vitamin D may be associated with increased risk of CHD (Schöttker et al., 2014; Lee et al., 2011). In Saudi Arabia, no previous studies have been carried out that focused on the relationship between vitamin D status and the risk of CHD among the adult population. In this chapter, the association between vitamin D status and CHD was examined among adults in Saudi Arabia. Data was collected from a case-control study that was conducted in the cities of Jeddah and Makkah in the western region of Saudi Arabia. The results revealed that vitamin D deficiency was significantly more common in CHD cases than in the controls. The results also demonstrated that subjects with vitamin D deficiency (serum 25(OH)D < 20 ng/mL) were 6.5 times more likely to suffer from CHD than the subjects with an adequate vitamin D status. These results underline the importance of maintaining adequate levels of vitamin D in Saudi Arabia as a factor that could be modified to reduce the incidence of CHD. In the next chapter, the association between vitamin D deficiency and cardio-metabolic risk factors (including obesity, diabetes, hypertension and hypercholesterolemia) was examined among subjects with and without CHD in Saudi Arabia.

This paper has been published as an original research paper in a peer-reviewed journal and has been designed and written according to the journal style including the reference style.

The bibliographic details of the paper are as follows:

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Declaration:

I (the candidate) am the first and corresponding author of this paper. My contribution to the paper includes the development of the study design, completed the human research ethics application, conducted data collection, performed data analysis, and writing of the manuscript for submission to the journal.

Signed: Date:

First author (corresponding): Najlaa Aljefree

Signed: Date:

Principal supervisor and co-author: Faruk Ahmed

4.2 Abstract

Recent evidence has pointed out an association between vitamin D deficiency and coronary heart disease (CHD). Due to the growing epidemic of CHD and vitamin D deficiency in Saudi Arabia, exploring the role of vitamin D in the prevention of CHD is crucial. The aim of this study was to examine the association between vitamin D status and CHD in Saudi Arabian adults. This case-control study included 130 CHD cases and 195 age-sex matched controls. Study subjects were recruited from three hospitals in the western region of Saudi Arabia. Study participants were interviewed face-to-face to collect data on their socio-demographic characteristics and family history of CHD. Fasting blood samples were collected, and serum levels of vitamin D, glucose, and total cholesterol were measured. Body weight, height, and blood pressure measurements were also recorded. Severe vitamin D deficiency (25(OH)D < 10 ng/mL) was much more prevalent in CHD cases than in controls (46% and 3%, respectively). The results of multivariate logistic regression showed that vitamin D deficiency (25(OH)D < 20 ng/mL) was associated with CHD, with an odds ratio of 6.5 (95% CI: 2.7–15, $p < 0.001$). The current study revealed that vitamin D deficiency is independently associated with CHD, suggesting an important predictor of CHD among Saudi adults.

Keywords: cardiovascular disease; vitamin D deficiency; diabetes; obesity; Saudi Arabia; Middle East

4.3 Introduction

Cardiovascular disease (CVD) is one of the most common causes of death and disability globally. The Gulf region, including Saudi Arabia, is facing a massive burden of CVD and associated risk factors [1]. Data from hospitals have indicated that CVDs are the leading cause of hospital admissions in Saudi Arabia, and coronary heart disease (CHD) is the third most prominent cause of hospital-based mortality in the country, after traffic accidents and senility [2]. In Saudi Arabia, CHD was found to be prevalent among 5.5% of the population [3]. Furthermore, national-level studies have reported a significant burden of CHD risk factors among the Saudi population, including obesity, diabetes, and hypercholesterolemia [4–7]. However, besides known relationships between traditional risk factors (such as obesity, diabetes, and hypertension) and CHD, other important factors, including poor dietary habits and deficiency of micronutrients such as vitamin D, have recently been found to be associated with the burden of CHD and other chronic diseases [8].

Evidence to date suggest that vitamin D deficiency may negatively affect the cardiovascular system by activating the renin-angiotensin-aldosterone system, which leads to the development of hypertension and left ventricular hypertrophy [9,10]. In addition, low levels of vitamin D can result in an increase in parathyroid hormone (PTH), which causes an increase in blood pressure as well as myocardial contractility. This in turn may lead to hypertrophy and fibrosis of the left ventricle and vascular medial smooth muscles [9,10]. Large epidemiological studies such as the National Health and Nutritional Examination Surveys (NHANES) and the Framingham Offspring cohort have shown that low levels of vitamin D were independently associated with a higher risk of myocardial infarction, heart failure, and stroke [11,12]. Furthermore, a meta-analysis of 24 studies reported an inverse association between vitamin D deficiency and risk of CVD [13]. Likewise, a recent meta-analysis of eight prospective cohort studies showed that serum levels of vitamin D in the lowest quintile were significantly associated with increased all-cause mortality including cardiovascular mortality [14]. However, the previous studies included in the meta-analysis were largely from European countries and the United States; hence, they may not be culturally or ethnically appropriate for the Saudi population. In the Middle Eastern countries, few studies have focused on the association between vitamin D status and the risk of CVD

[15,16]. To our knowledge, no previous studies among Saudi adults have been carried out that focused on the relationship between vitamin D status and the risk of CHD. In Saudi Arabia, vitamin D deficiency is highly prevalent, even though there is plentiful sunlight throughout the year [17–23]. Several studies have reported low levels of vitamin D ranging from 8.4 to 11.6 ng/mL and from 8 to 16.6 ng/mL in males and females, respectively [17,18,22–24]. Because both CHD and vitamin D deficiency are significant problems in the Saudi population, there is a need to examine whether vitamin D deficiency is independently associated with CHD in this population and thereby generate evidence for developing appropriate interventions. Therefore, the present study was designed to examine the association between vitamin D status and CHD among adults in Saudi Arabia.

4.4 Materials and Methods

4.4.1 Study Design and Population

A case-control study design was applied to examine the association between vitamin D status and CHD among adults living in the two largest cities in Saudi Arabia, Jeddah and Makkah, which are both located in the Western region of the country. Study participants were recruited from three hospitals; King Abdullah Medical City (KAMC) and Tunsi private hospital in Makkah and King Abdul Aziz University Hospital (KAU) in Jeddah. Data collection was conducted in the summer between May and October 2015, when the average temperature reached 37 ◦C and the average daily sunlight was 9 hours in coastal cities such as Jeddah and Makkah. The sample size consisted of 130 CHD cases and 195 controls with a ratio of 1:1.5. The study protocol was approved by the Griffith University Human Research Ethics Committee (GU Ref No: MED/59/14/HREC), Research Ethics Committee in KAU (Reference No ll8-15), and Institutional Review Board in KAMC (IRB No: 15-194). All CHD cases (n = 130) were recruited from KAMC hospital in Makkah, which provided a good site for recruiting potential subjects for the current study because it has a large cardiac surgical facility and because a large majority of the cardiovascular patients in this hospital have been referred from different areas in the western region of the Kingdom. Cases were recruited from subjects who were admitted to KAMC hospital during the research period and were either first incident with an acute event or have been diagnosed earlier with clinical artery disease, myocardial infarction, or chronic stable angina and met the selection criteria. Controls were recruited from two hospitals, KAU in Jeddah (42 participants) and Tunsi private hospital in Makkah (153 participants). Controls were matched in age (within 0–5 years) and gender and had no history of CVD. They were recruited from ophthalmology clinics in KAU hospital and from family medicine clinics and nose and throat (ENT) clinics in Tunsi hospital. All potential study subjects (152 cases and 236 controls) in the hospitals were approached to participate in the study during the time of data collection. Nine cases and 35 controls were excluded because they did not meet the eligibility criteria. Written informed consent was obtained from eligible subjects before their participation in the study. Of the eligible study subjects, 13 cases and 6 controls refused to participate in the study. Figure 4.1 shows the subjects' recruitment process and reasons for refusal to participate in the study.

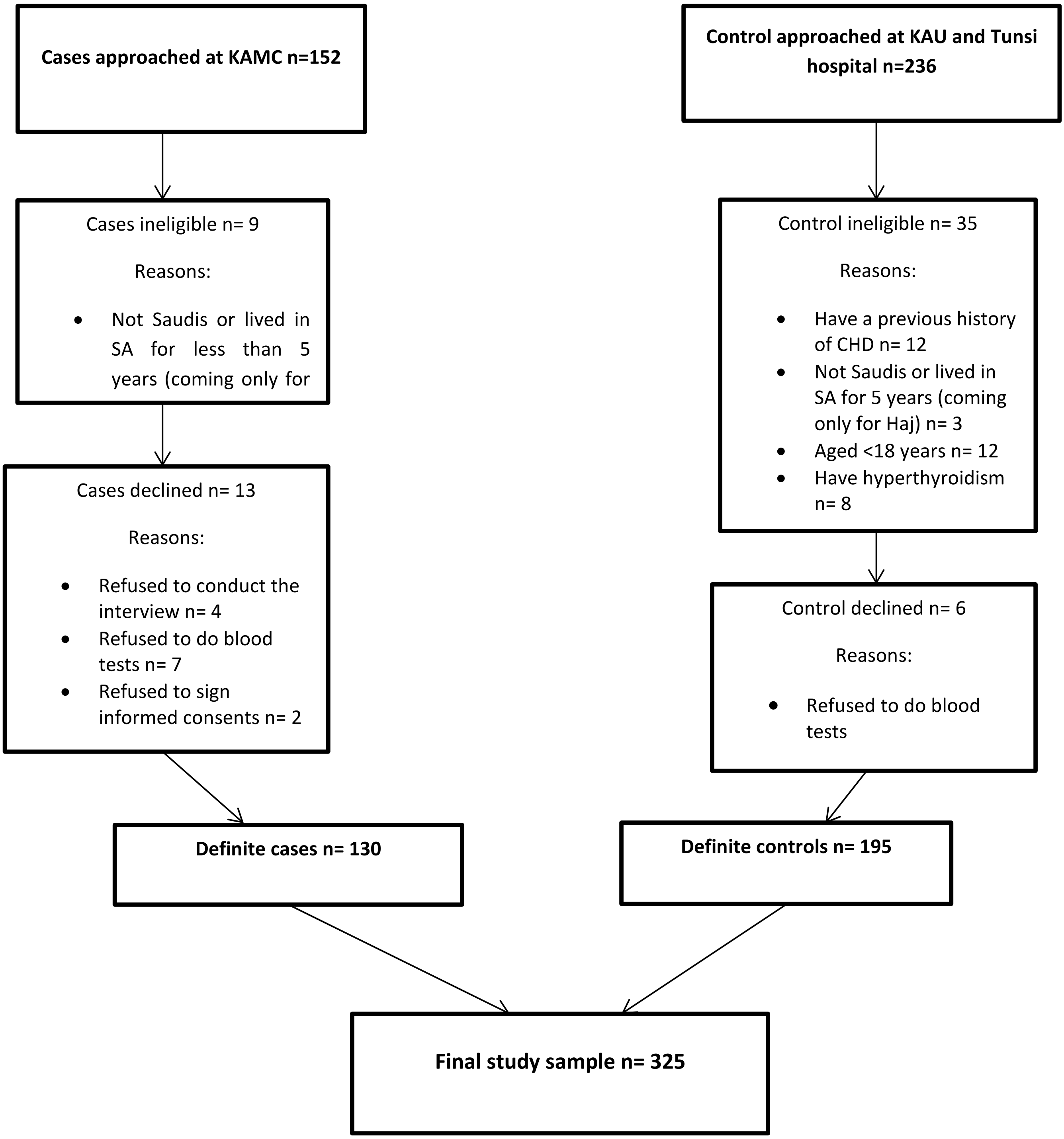

Figure 4.1: The subjects' recruitment process and reasons for refusal to participate in the study.

4.4.2 Inclusion and Exclusion Criteria

Inclusion criteria for both cases and controls included being a native Saudi or resident in Saudi Arabia for at least five years and being an adult of 18 years or older. Exclusion criteria included having a medical condition that could affect vitamin D metabolism, including metabolic bone disorders such as osteoporosis. Subjects were also excluded if they had liver disease, kidney disease, hyperparathyroidism, granulomatous disease, tuberculosis, lymphomas or hyperthyroidism. Furthermore, subjects with malabsorption resulting from celiac disease, Crohn's disease, and bypass surgery were also excluded [25].

4.4.3 Data Collection

Face-to-face interviews were conducted with all participants using a structured questionnaire. Data were collected on participants' sociodemographic characteristics, such as age, gender, marital status, education level, nationality, and monthly income. In addition, information was collected regarding family history of CVD and behavioral risk factors, for instance, cigarette smoking, water-pipe smoking, and levels of physical activity. Subjects who smoked at least one cigarette per day were considered current smokers. Subjects who had never smoked were considered non-smokers. A previous smoker was a person who had previously smoked but had quit [26]. Water-pipe smokers were subjects who smoked at least one water-pipe per week at the time of the interview [27]. Physical activity was self-reported and classified as moderate activity, such as jogging, walking, or swimming; vigorous activity that causes sweating or hard breathing, such as heavy lifting, aerobics, or fast bicycling; and sedentary, such as staying at home most of the time or doing a little walking outside [26]. The participants were also asked to report the use of dietary supplements, including both dose and duration, for vitamin D and calcium supplements with vitamin D. Similarly, the participants also asked to report sun exposure during weekdays and weekend (times spent outdoor) and the use of sunscreen. Measurement of height (centimeters) and weight (kilograms) in light clothing were taken using a standard scale after the participants were interviewed. Then, body mass index (BMI) was calculated by dividing the weight in kilograms by height in meters squared. Overweight and obesity were defined according to the World Health Organization (WHO) definition. The subjects were considered overweight when BMI was 25.0–29.9 kg/m², and the subjects were defined as obese when BMI was ≥30 kg/m² [28]. The participants were asked to sit for 5 minutes before their blood pressure was measured using standard equipment. Hypertension was defined according to the WHO criteria as a blood pressure ≥140 mmHg for systolic blood pressure (SBP) and/or ≥90 mmHg for diastolic blood pressure (DBP) [28].

4.4.4 Biochemical Measurements

A hematological technician collected 10 milliliters of venous blood from each case and control (325 subjects), using a disposable syringe to assess their serum levels of 25(OH)D, fasting glucose, and total cholesterol. The blood samples were centrifuged at 2000 rpm for 15 minutes, and then serum was separated. All serum samples were kept frozen at −80 °C until further lab analysis. Serum levels of 25(OH)D were measured by chemiluminescence microparticle immunoassay (CMIA) on the Architect system (Abbott) (Wiesbaden, Germany). The intra- and inter-assay coefficients of variation (CVs) were 2.7% and 4.6%, respectively. Fasting glucose and total cholesterol were measured using biochemical analyzer (Thermo Fisher Scientific, Espoo, Finland). The laboratories are located at the same hospitals where the study was undertaken and are certified by the Saudi Ministry of Health. Vitamin D deficiency and insufficiency were defined as serum concentrations of 25(OH)D < 10 ng/mL, and 10 to <19.9 ng/mL, respectively. A serum concentration of 25(OH)D ≥ 20 ng/mL was considered to be an adequate vitamin D level [29]. In the current study, vitamin D deficiency and insufficiency were combined for analysis purposes due to the small sample size; therefore, vitamin D deficiency was defined as having serum concentration of 25(OH)D < 20 ng/mL. Diabetes was defined according to the WHO standard of diagnosis of glucose intolerance when fasting plasma glucose (FPG) was ≥126 mg/dL [28]. High total cholesterol (HC) was defined according to the Adult Treatment Panel III (ATP III) guidelines as HC ≥ 240 mg/dL [28].

4.4.5 Statistical Analysis

Statistical analyses were performed using Statistical Package for Social Science (SPSS) version 22 (IBM SPSS Software, Chicago, IL, USA). A chi-square test was used to assess the association between each independent variable (including vitamin D status) and the outcome status (CHD). For the purpose of regression analyses, the distribution of SBP, DBP, fasting glucose, and total cholesterol were divided onto equal thirds (tertiles). Multivariate logistic regression models were conducted to examine the relationship between vitamin D status and CHD. Vitamin D status was categorized into two groups; vitamin D deficiency was defined as serum 25(OH)D < 20 ng/mL, where vitamin D deficiency and insufficiency were combined together to increase the statistical precision due to the small sample size, and adequate vitamin D status was defined as serum 25(OH)D ≥ 20 ng/mL. The multivariate logistic regression analysis was carried out using different models. The first model was a crude model with no adjustment for confounders. The second model was created by including only socio-demographic variables, such as age, gender, education, employment, citizenship, place of residence, marital status and family monthly income. The final model was created by adding other potential confounders such as BMI, fasting blood glucose, total cholesterol, smoking, exercise, use of vitamin D supplements, use of calcium supplements with vitamin D, time spends for sun exposure and the use of sunscreen. As there were very few subjects in either group of the study sample who smoked a water-pipe, we combined cigarette smoking and water-pipe smoking for the logistic regression. Likewise, due to the low number of subjects in either group who practiced vigorous exercise, moderate and vigorous exercise was combined for the logistic regression. $p < 0.05$ was considered statistically significant.

4.5 Results

The socio-demographic characteristics of the CHD cases and controls are shown in Table 1. Almost 65% of cases had first incident with an acute event at the time of data collection and 35% of cases were previously diagnosed with CHD. As expected, there were no significant differences in the distribution of age and gender categories between case and control groups. Eighty-one percent of the cases and 63% of the controls were Saudis. The majority of the cases and controls were married (70% and 72%, respectively) and had low to medium family monthly income (72% and 69%, respectively). Relatively more participants in the control group were highly educated ($p < 0.001$) and doing a paid job ($p < 0.001$) than the participants in CHD cases. Nearly 85% of the participants in the control group were non-smokers, and 59% of participants with CHD were non-smokers ($p < 0.001$). However, practicing moderate exercise ($p = 0.007$) was more common in CHD cases than in controls (Table 4.1).

The clinical characteristics of the CHD cases and controls are shown in Table 2. Vitamin D deficiency ($p < 0.001$) was significantly higher in CHD cases than in the controls; 46% of the participants in the CHD group were vitamin D deficient (serum 25(OH)D < 10 ng/mL), whereas the rate of deficiency was only 3% in the control group. On the other hand, 61% of the controls had adequate vitamin D levels (serum 25(OH)D ≥ 20 ng/mL) compared to 24% of the CHD cases (Table 2). A significantly higher proportion of the participants in the CHD cases were obese (44% and 22%, respectively) and had higher fasting blood glucose levels (FPG ≥ 126 mg/dL) (35% and 14%, respectively) than those in the control group ($p < 0.001$). A relatively higher proportion of participants in the control group had higher total serum cholesterol levels (≥240 mg/dL) (13% and 5%, respectively) than in the CHD group ($p < 0.001$). There was no significant difference in the distribution of SBP levels between the two groups (Table 4.2).

The results of the multivariate logistic regression are shown in Table 3. Vitamin D deficiency (serum 25(OH)D < 20 ng/mL) was significantly associated with increased odds of CHD ($p < 0.001$). After adjustment for age, gender, education, employment, citizenship, place of residence, marital status, family income, BMI, blood glucose, total cholesterol, smoking, exercise, and use of vitamin D supplements, calcium supplements with vitamin D, sun exposure, and the use of sunscreen, subjects with vitamin D deficiency (serum 25(OH)D < 20 ng/mL) were 6.5 times more likely to suffer from CHD compared to those with adequate vitamin D levels (serum 25(OH)D ≥ 20 ng/mL) (OR: 6.5, 95% CI: 2.7–15, $p < 0.001$) (Table 4.3).

Table 4.1: Comparison of socio-demographic, family history of CVD, and lifestyle behaviors variables in cases and controls

Variables	Cases (n= 130) %	Control (n= 195) %	P-value
Age (years)			
<49	25.4	30.3	
≥ 49	74.6	69.7	0.340
Gender			
Male	63.1	63.1	
Female	36.9	36.9	> 0.05
Marital status			
Single	5.4	17.4	
Married	70.0	71.8	**<0.001**
Divorced	24.6	10.8	
Citizenship			
Saudis	80.8	62.6	
Non-Saudis	19.2	37.4	**<0.001**
Place of residence			
Rural	12.3	1.0	
Urban	85.4	98.5	
Semi-rural	2.3	0.5	**<0.001**
Education			
Up to primary levels	51.6	14.3	
High School & bachelor or diploma degree	24.6	34.9	
Master or PhD degree	23.8	50.8	**<0.001**
Employment			
Employed (Full time, Part time, self-employed)	32.3	81.5	
Unemployed (Student, Retired, House wife)	67.7	18.5	**<0.001**
Family income (SR/monthly)*			
< 5000	71.5	69.5	
5000-15000	10.0	18.9	
15000- ≥ 25000	18.51	11.6	**0.036**
Smoke cigarettes			
Current < 20 cigarettes/day	15.4	10.3	
Previous smoker	25.4	5.1	
Non-smoker	59.2	84.6	**<0.001**
Water pipe smoker			
Yes	3.1	9.7	
No	96.9	90.3	**0.022**
Moderate exercise			
Never & rarely	33.8	44.6	
1-2 times/week	16.9	23.6	
More than 3-4 times/week	49.2	31.8	**0.007**
Vigorous exercise			
Never & rarely	97.7	96.4	
1-2 times/week	0.8	0.0	
More than 3-4 times/week	1.5	3.6	0.259
Family history of CVD			
Yes	40.8	41.5	
No	59.2	58.5	.890

*P-value based on X^2 -test; *Saudi Riyal (1SR= .37 AUD*

Table 4.2: Comparison of clinical characteristics in cases and controls

Variables	Cases (n= 130) %	Control (n= 195) %	P-value
BMI			
Normal weight < 25 kg/m²	30.8	32.8	
Overweight 25 – 29.9 kg/m²	25.4	45.1	
Obese ≥ 30 kg/m²	43.8	22.1	**<0.001**
SBP			
< 140 mmHg	86.2	87.7	
≥ 140 mmHg	13.8	12.3	0.685
DBP			
< 90 mmHg	95.4	94.4	
≥ 90 mmHg	4.6	5.6	0.684
Fasting glucose			
FPG is < 126 mg/ dL	64.6	86.2	
FPG is ≥ 126 mg/ dL	35.4	13.8	**<0.001**
Total Cholesterol			
< 240 mg/dL	94.6	86.7	
≥ 240 mg/dL	5.4	13.3	**0.020**
Vitamin D			
Adequate ≥ 20 ng/mL	23.8	61	
Insufficient 10 to <19.9 ng/mL	30	35.9	
Deficiency < 10 ng/mL	46.2	3.1	**<0.001**

P-value based on X² -test; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose.

Table 4.3: Odd ratios (95% confidence interval) for CHD among subjects with Vitamin D deficiency in adults in Saudi Arabia.

	Crude OR[1] (95% CI)	Adjusted OR[2] (95% CI)	Adjusted OR[3] (95% CI)
Two-category models			
Adequate (≥ 20 ng/mL)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Deficient (<20 ng/mL)	5 (3.04-8.20) **<0.001**	7.88 (3.79-16.3) **<0.001**	6.56 (2.91-14.7) **<0.001**
Three-category models			
Adequate (≥ 20 ng/mL)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Insufficient (10 to < 19.9 ng/mL)	2.13 (1.22-3.73) **<0.007**	2.79 (1.24-6.31) **<0.013**	2.22 (.87-5.64) **<0.093**
Deficient (< 10 ng/mL)	38.3 (15.1-97) **<0.001**	103.2 (26.3-404) **<0.001**	131 (25.8-670) **<0.001**

[1] Multivariate Logistic Regression model with no adjustment

[2] Multivariate Logistic Regression model after adjustment for age, gender, education, employment, citizenship, place of residence, marital status, family income

[3] The final model after additional adjustment for smoking, exercise, BMI, blood glucose, total cholesterol, vitamin D supplements and calcium supplements with vitamin D

4.6 Discussion

The findings of the present study revealed that the subjects with vitamin D deficiency, when defined as serum 25(OH)D < 20 ng/mL, were 6.5 times more likely to suffer from CHD than the subjects with adequate vitamin D status (serum 25(OH)D ≥ 20 ng/mL). Several studies conducted in developed countries have also demonstrated similar results [30,31]. For example, an inverse association between vitamin D deficiency and myocardial infarction (MI) was reported among adults in New Zealand [32]. In the United States, an NHANES study stated that the participants with vitamin D deficiency had a higher prevalence of angina and MI compared to that in the participants with adequate levels of vitamin D (OR: 1.20 (95% CI: 1.01, 1.36) [33]. In a Gulf country, Qatar, a study indicated that males with vitamin D deficiency had a three times higher risk of MI than males with an adequate vitamin D levels [16]. More recently, a study among an Indian population showed 4.5 times higher risk of MI among subjects with vitamin D deficiency (<10 ng/mL) [34]. It is important to note that different studies across the globe have used different criteria for defining vitamin D deficiency, and the reason for this is that the accurate cut-off value for defining vitamin D deficiency remains controversial. There is disagreement surrounding serum PTH, which is inversely associated with low levels of vitamin D. Some studies have suggested that the production of PTH escalates when serum levels of 25(OH)D are less than 10 ng/mL, which leads to bone loss and fractures [35]. However, other studies have indicated that levels of serum 25(OH)D ranging from 18 ng/mL to 30 ng/mL lead to increased PTH levels and cause bone loss [29]. Nevertheless, regardless of the definition used to assess the association between vitamin D status and CHD, a large majority of the studies showed an inverse association similar to what was found in the present study.

The protective role of vitamin D against CHD could be explained by the wide distribution of vitamin D receptors (VDRs) in the vascular walls, which plays a crucial role in cardiac physiology [36]. Animal studies have shown a direct effect of the absence of VDRs on cardiac function. These studies, which genetically modified the animals to have no vitamin D receptors or no 1, 25 (OH)2D, indicated that they developed left ventricular hypertrophy and heart failure [36]. The results of animal studies were corroborated by the findings observed in patients with end-stage renal disease (ESRD) [37]. Human ESRD studies provided one of the first pieces of evidence that supported the role of vitamin D deficiency in the development of CHD. Due to damage in the kidneys, ESRD patients failed to convert 25 (OH)D into 1, 25 (OH)2D, which in turns leads to increased levels of PTH. The high level of PTH causes elevated blood pressure and cardiac contractility, which contributes to myocardial dysfunction, arterial hypertension, and heart failure [9,36,37].

The current research revealed 61% prevalence of adequate vitamin D levels ($\geq$20 ng/mL) among the healthy subjects (controls), which appears to be consistent with previous studies within Saudi Arabia. Naeem et al. showed that the mean vitamin D levels were 32 ng/mL and 23 ng/mL among Saudi males and females, respectively [20]. Likewise, Alsuwaida et al. stated that 50% of study participants had adequate vitamin D levels $\geq$ 30 ng/mL [38]. A national survey conducted in Saudi Arabia in 2013 among Saudis from both genders aged 15 years and above reported that vitamin D deficiency (<28 ng/mL) was prevalent among 40.6% of males and 62.6% of females [39].

This study has several strengths. It was not restricted to a specific gender, as it examined both males and females. Furthermore, it has demonstrated the association between vitamin D deficiency and CHD after controlling for a wide range of socio-demographic factors and behavioral confounding factors such as using vitamin D supplements, time spent outdoor for sun exposure, and the use of sunscreen. In addition, data related to CHD risk factors were measured at the same hospitals but not self-reported, which added more value to the results. Finally, this study indicated an independent association of vitamin D deficiency with CHD, which has never been explored before in Saudi Arabia.

However, this research has a number of limitations. First, the research used a case-control design, which can only draw inferences about the association between the exposure and outcome variables but not deduce the casual relationship. Second, the measurements of serum vitamin D concentration were not done before the diagnosis of cases. However, a case-control study provides stronger evidence than a cross-sectional design. Third, recall bias might be an issue in this study, as both cases and controls were asked to remember information, including their smoking history. Fourth, case and control subjects were recruited from different hospitals, which might have introduced some selection bias. It is noteworthy that the data collection was conducted during Haj season (Muslim pilgrimage), and the KAMC hospital closed the outpatient's clinics to the public except for pilgrims in order to deliver health services to them. Thus, it was not possible to recruit control subjects from KAMC hospital in Makkah, from where the cases were recruited. Consequently, the control subjects were recruited from other hospitals located in Makkah and Jeddah. However, these hospitals were situated within a distance of only 70 km, and both were in the western region of the Kingdom. Further, any differences in socio-demographic characteristics between cases and controls were taken into account in the final regression model in order to minimize the effect of selection bias. Fifth, a single measurement of vitamin D status was another limitation as 25 (OH)D has a half-life of up to three weeks and it only reflects the current status [10]; thus, multiple measurements would have been the best reflection of the average of vitamin D status. Finally, the duration of time since diagnosis with CHD for cases who were previously diagnosed was not collected; however, only one-third of cases were diagnosed with CHD earlier.

4.7 Conclusions

The current study revealed an inverse association between vitamin D status and CHD among adults in Saudi Arabia after adjusting for potential confounding factors. Findings of the present study have important implications for future strategies for CHD prevention by improving vitamin D status among adults in Saudi Arabia.

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Chapter 5: Association between Vitamin D Status and Cardio-Metabolic Risk Factors among Adults with and without Coronary Heart Disease in Saudi Arabia (Manuscript 3)

5.1 Introduction

The prevalence of cardio-metabolic risk factors is very high in Saudi Arabia (Al-Nozha, Abdullah, et al., 2007; Al-Nozha et al., 2008). As indicated in our systematic review in chapter 2 (Aljefree & Ahmed, 2015), almost half of all the adults in Saudi Arabia had elevated cholesterol levels, and half of all females were obese. Also, nearly a quarter of the adult population had diabetes and elevated blood pressure. Several studies have illustrated that vitamin D deficiency may be associated with increases of cardio-metabolic risk factors such as diabetes and hypertension (Lee et al., 2011; Martins et al., 2007). Thus, in this chapter, the association between vitamin D deficiency and cardio-metabolic risk factors, including obesity, diabetes, hypertension and hypercholesterolemia, was examined separately among subjects with and without CHD in Saudi Arabia.

As a result of using data collected from a case-control study, this study indicated that in subjects with CHD, vitamin D deficiency (serum 25(OH)D < 20 ng/mL) was significantly associated with an increased risk of diabetes. However, no significant association was found between vitamin D deficiency and other cardio-metabolic risk factors (obesity, hypertension and hypercholesterolemia) in subjects with CHD. On the other hand, no significant associations were found between vitamin D deficiency and various cardio-metabolic risk factors in subjects without CHD, as our results indicated that diabetes is significantly associated with vitamin D deficiency among subjects with CHD, but not with controls. This suggests that diabetes could be considered confounding when the association between vitamin D status and CHD is examined. Therefore, it is noteworthy to mention that it has been adjusted for diabetes when the association between vitamin D status and CHD was examined in the previous chapter. The results of this chapter are important because they enable the development of appropriate interventions that target the improvement of vitamin D status in Saudi Arabia in order to reduce the incidence of CHD and associated risk factors. In the next chapter, further investigation of knowledge, attitudes and behaviours related to vitamin D among study subjects was undertaken.

This paper has been published as an original research paper in a peer-reviewed journal and has been designed and written according to the journal style including the reference style.

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Declaration:

I (the candidate) am the first and corresponding author of this paper. My contribution to the paper includes the development of the study design, completed the human research ethics application, conducted data collection, performed data analysis, and writing of the manuscript for submission to the journal.

Signed: Date:

First author (corresponding): Najlaa Aljefree

Signed: Date:

Principal supervisor and co-author: Faruk Ahmed

5.2 Abstract

Objective: Recent literature has suggested an association between low serum vitamin D levels and the burden of cardio-metabolic risk factors (obesity, diabetes, hypertension, and hypercholesterolemia). In the context of the high prevalence of vitamin D deficiency and cardio-metabolic risk factors in Saudi Arabia, this study was designed to examine the association between vitamin D deficiency and cardio-metabolic risk factors among adults with coronary heart disease (CHD) and without CHD in Saudi Arabia.

Methods: A total of 130 CHD subjects and 195 subjects without CHD were recruited from three hospitals in the western region of the Kingdom. Fasting blood samples were collected from each subject to measure serum levels of vitamin D, glucose, and total cholesterol. Anthropometric and blood pressure were also measured.

Results: Subjects with CHD had a higher prevalence of diabetes (35.4% and 14%, respectively) and obesity (44% and 22%, respectively) compared with subjects without CHD. However, subjects without CHD had a higher prevalence of cholesterol (13.3% and 5.4%, respectively) and overweight (45% and 24.4%, respectively) than subjects with CHD. The results indicated that vitamin D deficiency [serum 25(OH)D < 20 ng/mL] was associated with increased risk of diabetes in CHD subjects (OR: 2.9, 95% CI: 1.02-8.5, $p = 0.04$), while there was no association observed in subjects without CHD (OR:1.4, 95% CI: 0.5-3.8, $p = .616$). No significant associations were found between vitamin D deficiency and other cardio-metabolic risk factors including obesity, hypertension, and hypercholesterolemia, in either group.

Conclusion: The present study reveals that vitamin D deficiency was associated with a higher risk of diabetes only in subjects with CHD, but not in subjects without CHD.

However, this differential association between vitamin D deficiency and other cardio-metabolic risk factors was not observed. Further studies are needed to confirm these findings.

Keywords: Vitamin D deficiency; Coronary heart disease; Diabetes; Obesity; Saudi Arabia; Hypertension; Middle East; Hypercholesterolemia

5.3 Introduction

Vitamin D deficiency or insufficiency is widespread across the globe and it is currently recognized as a re-emerging public health problem [1]. International research has indicated that the prevalence of vitamin D deficiency ranges from 25% to 50% of the total adults in the United States [2]. Similar prevalence rates have also been reported in Europe [3,4]. However, the highest rates of vitamin D deficiency have been reported in sunny regions such as Asia and the Middle East [5]. Although vitamin D has widely been known for its significant role in bone health, inadequate levels of vitamin D have recently been linked to chronic diseases such as cardiovascular disease [6]. In addition, a number of studies have also shown an association between low levels of serum vitamin D and an increased risk of cardio-metabolic risk factors such as diabetes and obesity [6-9]. Both clinical and animal studies have indicated the role of vitamin D in regulating cardiac metabolism and reducing the risk of other cardio-metabolic risk factors such as hypertension and high blood lipids [10]. These studies have also suggested some possible mechanisms including the significant role of vitamin D in regulating the parathyroid hormone and the reninangiotensin-aldosterone system, which in turn changes the blood pressure by reabsorption of water and sodium, hence raising the blood pressure [10,11]. In the Gulf region and Saudi Arabia in particular, the prevalence of cardio-metabolic risk factors has been increasing, mostly because of changing lifestyle along with socio-economic transformations [12]. Several studies among Saudi adults have shown high rates of cardio-metabolic risk factors including obesity (35.6%), hypertension (26.1%), diabetes (23.7%), and hypercholesterolemia (50%) [13-17]. Furthermore, according to the International Diabetes Federation (IDF), Saudi Arabia is one of the countries with the highest number of estimated diabetic subjects in the world [18]. In addition, a high prevalence of coronary heart disease (CHD) has been reported in the Saudi population (5.5%) [19]. Data from hospitals in Saudi Arabia have also showed that CHD is the third leading cause of hospital-based death in the kingdom [20]. Figure 5.1 reflects the hypothesized relationships among study variables. Recently, we have demonstrated an association between vitamin D deficiency and CHD among Saudi adults [21]. Since various cardio-metabolic risk factors are the major drivers for the development of CHD, it is important to explore whether each of the common cardio-metabolic risk factors is independently associated with vitamin D status in the Saudi population.

Despite genetic predisposition and other factors, such as urbanization and changing lifestyle, that can influence the high prevalence of cardio-metabolic risk factors in Saudi Arabia, evidence has shown that changes in dietary patterns and deficiencies in micronutrients such as vitamin D might also be contributing to this phenomenon [22,23]. However, there are limited studies in Saudi Arabia that have examined the association between vitamin D status and cardio-metabolic risk factors including diabetes and obesity among healthy adults [24,25]. Considering the growing epidemic of cardio-metabolic risk factors as well as vitamin D deficiency among the Saudi population, there is a need for further studies to evaluate the association between vitamin D status as a potential modifiable risk factor and the cardio-metabolic risks in order to develop an appropriate intervention for targeting risk factors that are associated with CHD. Moreover, vitamin D function may differ between subjects with CHD and subjects without CHD. No previous studies have examined whether the association of vitamin D deficiency with cardio-metabolic risk factors vary between subjects with CHD and subjects without CHD. Therefore, this study attempts to evaluate the association between vitamin D status and cardio-metabolic risk factors including obesity, diabetes, hypertension and hypercholesterolemia among subjects with CHD and subjects without CHD in Saudi Arabia.

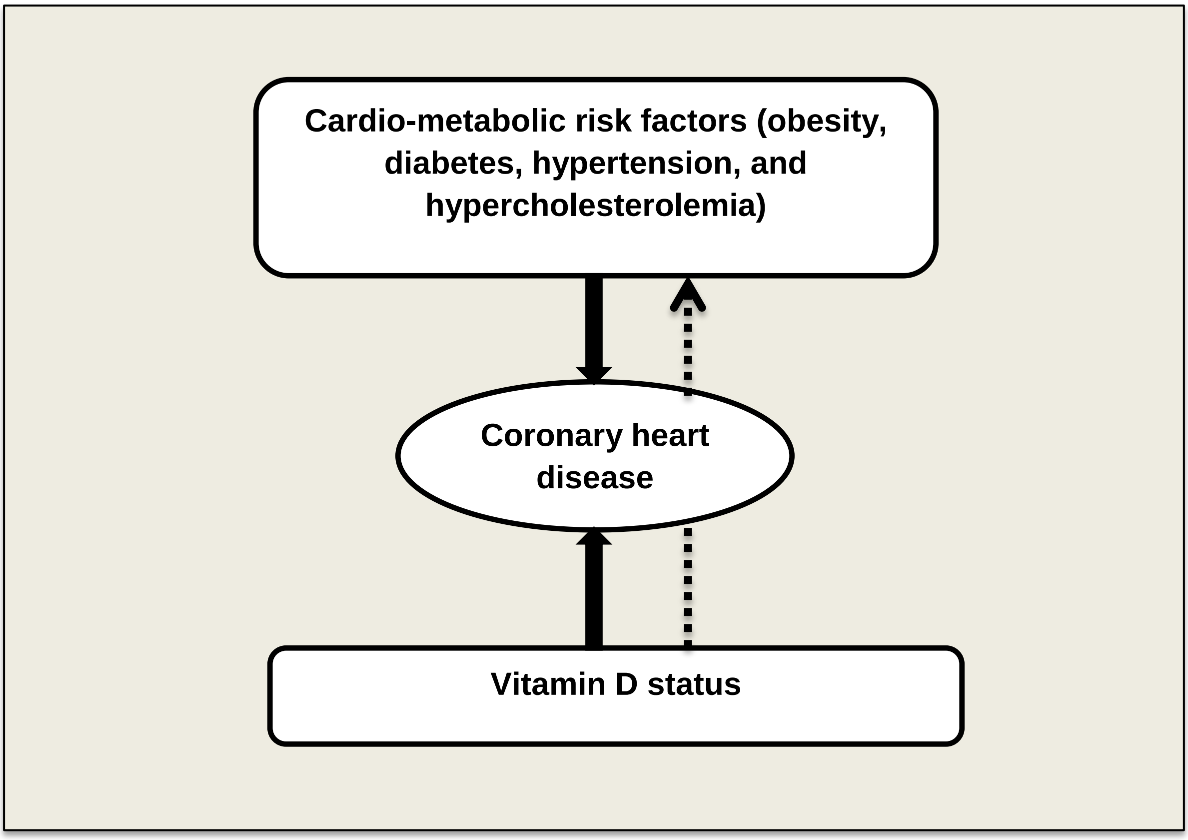


Figure 5.1: Associations between study variables

5.4 Methods

5.4.1 Study population

Data collection took place between May and October 2015 during summertime in the two large cities in the western region of Saudi Arabia, Jeddah, and Makkah. The study participants included were adults from both genders. A total of 130 CHD patients were recruited from the cardiology department in King Abdullah Medical City (KAMC) in Makkah and 153 subjects with no CHD were recruited from family medicine clinics and nose and throat (ENT) clinics in Tunsi private hospital in Makkah. An additional 42 subjects with no CHD were recruited from ophthalmology clinics in King Abdul Aziz University (KAU) hospital in Jeddah. Ethical approval has been sought from Griffith University Human Research Ethics Committee (GU Ref No: MED/59/14/HREC), the Institutional Review Board in KAMC (IRB No: 15-194), and the Research Ethics Committee in KAU (Reference No ll8-15). All included subjects were Saudis or residents in KSA for at least five years. Subjects with medical conditions that may potentially affect vitamin D metabolism such as osteoporosis, liver disease, kidney disease, hyperthyroidism and hyperparathyroidism were excluded. Data collection An interviewer-administered questionnaire was used for collecting data after written informed consent was obtained from all participants. Sociodemographic factors such as age, gender, nationality, marital status, level of education, and family income levels were collected. Furthermore, data regarding the family history of cardiovascular disease (CVD) and behavioral risk factors were also collected. Behavioral risk factors collected in the survey included cigarette smoking, water-pipe smoking, and levels of physical activity. A current smoker was defined as a subject who was smoking at least one cigarette per day on a regular basis [26]. A non-smoker was defined as a subject who had never smoked. A person who had previously smoked but had quit was considered a previous smoker [26]. A person who smoked from a water-pipe at least once per week at the time of the interview was considered a water-pipe smoker [27]. Physical activity was classified into the following: moderate activity (such as jogging, walking or swimming), vigorous activity (such as heavy lifting, aerobics or fast bicycling), and sedentary (such as staying at home most of the time or doing a little walking outside) [26]. Information related to the use of vitamin D dietary supplements and calcium supplements with vitamin D were also collected, including both dosage and duration. Likewise, information on sun exposure and time spent outdoors during weekdays and weekends as well as the use of sunscreen were also collected. Blood pressure, height (meters), and weight (kilograms) were measured after interviewing the study subjects using the hospital's standard equipment. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared. Obesity was defined as when participants' BMI was ≥30 kg/m², and a patient was considered overweight when his/her BMI was 25–29.9 kg/m² [28]. Hypertension was defined as BP ≥140 mmHg for systolic blood pressure (SBP) and/ or ≥90 mmHg for diastolic blood pressure (DBP) [28].

5.4.2 Biochemical measurements

To measure serum levels of 25(OH)D, total cholesterol and glucose, 10 mL fasting blood samples were taken from all participants via venipuncture. The serum samples were centrifuged at 2000 rpm for 15 minutes before separation occurred. After that, the blood samples were kept frozen at -80°C for additional lab analyses. The chemiluminescence microparticle immunoassay (CMIA) on the Architect system (Abbott) was used to measure serum levels of 25(OH)D, whereas cholesterol and glucose levels were measured using Thermo Fisher Scientific (Espoo, Finland). Vitamin D deficiency was defined as having a serum level of 25(OH)D less than 10 ng/mL, insufficient vitamin D level as 25(OH)D 10 to < 19.9 ng/mL, and an adequate vitamin D level was defined as having serum of 25(OH)D ≥ 20 ng/mL [29]. Due to the small sample size we combined vitamin D deficiency and insufficiency for analysis purposes; thus vitamin D deficiency was defined in the current study as having serum of 25(OH)D < 20 ng/mL. High total cholesterol (HC) was defined according to the Adult Treatment Panel III (ATP III) as HC ≥ 240 mg/dL [28]. Diabetes was defined according to the World Health Organization (WHO) definition as fasting plasma glucose (FPG) at ≥ 126 mg/ dL [28].

5.4.3 Statistical analysis

Statistical Package for Social Science (SPSS) version 22 was used to perform the statistical analyses. A series of chi-square tests were used to compare the sociodemographic, family history of CVD, and lifestyle behavior variables for both groups according to vitamin D status [deficient as serum 25(OH)D < 20 ng/mL, and adequate as serum 25(OH)D ≥ 20 ng/mL]. Also, dependent variables (obesity, diabetes, total cholesterol, and hypertension) were tested for all socio-demographic and lifestyle characteristics using chi-square tests or Fisher's exact tests as appropriate to identify the possible confounders (data not showed). Results were reported as % (N) for categorical variables.

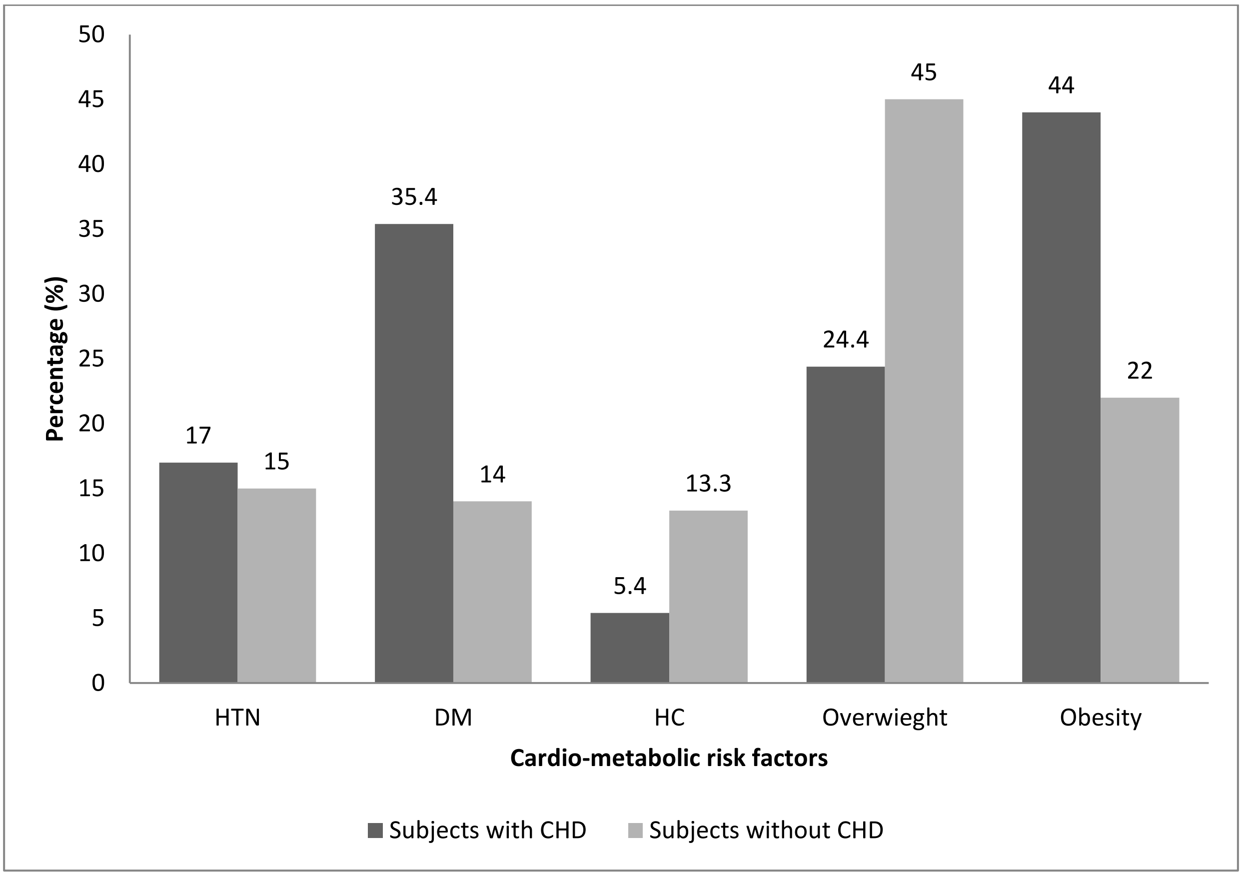
Multivariate logistic regression models were conducted to examine the associations between vitamin D status and cardio-metabolic risk factors, including obesity, diabetes, hypertension, and hypercholesterolemia in subjects with CHD and subjects without CHD. Different logistic regression models with adjustments for potential confounders were performed to identify the association of each dependent variable and vitamin D status. First, the crude model with no adjustment was applied for each dependent variable. Various combinations of significant independent variables, including socio-demographic, lifestyle behaviors, sun exposure, the use of sunscreen, and the use of vitamin supplementation, were entered into the second model to predict the outcome variables. Furthermore, among the study participants, there were a few subjects who smoked a water-pipe and practiced vigorous exercise; hence, cigarette smoking and water-pipe smoking were combined for the logistic regression, and moderate and vigorous exercise was also combined. Moreover, overweight and obese subjects (defined as 25-29.9 and ≥ 30 kg/m^2, respectively) were also combined in order to apply binary regression. The multivariate logistic regression results were reported including odds ratios (OR) with 95% confidence intervals (CI) for risk estimates. A p value < 0.05 was considered statistically significant.

5.5 Results

Table 5.1 depicts the distribution of the socio-demographic characteristics, family history of CVD, and lifestyle behaviors variables of the study participants with and without CHD by vitamin D status. In the CHD patient, there was significant difference in employment status between the subjects with vitamin D deficiency and subjects with adequate vitamin D status. A significantly higher proportion of subjects in the vitamin D deficiency group were employed at the time of the survey compared with the subjects with adequate vitamin D status. In subjects without CHD, there were significant differences in age, gender, citizenship, and family income between the subjects with vitamin D deficiency and subjects with adequate vitamin D status. A significantly higher proportion of subjects in the vitamin D deficiency group were older in age, male, Saudis, with low-medium family income compared with the subjects with adequate vitamin D status. Figure 5.2 shows the prevalence of cardio-metabolic risk factors among subjects with CHD and subjects without CHD. The prevalence of diabetes and obesity were significantly higher in subjects with CHD compared with subjects without CHD, (35.4% and 14%, $p = < 0.001$, for diabetes, respectively, and 44% and 22%, $p = < 0.001$, for obesity, respectively). In contrast, the prevalence of high cholesterol levels and overweight were significantly higher in subjects without CHD compared with subjects with CHD (13.3% and 5.4%, $p = 0.02$, for high cholesterol levels, respectively, and 45% and 24.4%, $p = < 0.001$, for overweight, respectively). There was no significant difference in the prevalence of hypertension between the groups (Figure 5.2).

Table 5.2 depicts the results of multivariate logistic regression analyses for both subjects with CHD and subjects without CHD groups. In subjects without CHD, there was no significant association observed between vitamin D deficiency and obesity, diabetes, hypertension, and hypercholesterolemia. In subjects with CHD, vitamin D deficiency [serum 25(OH)D < 20 ng/mL] was significantly associated with an increased risk of diabetes (p =

0.04). After adjustment for age, gender, BMI, family history of CVD, vitamin D supplements, calcium supplements with vitamin D, sun exposure, and the use of sunscreen, the CHD patients with vitamin D deficiency [serum 25(OH)D < 20 ng/mL] were 2.9 times more likely to suffer from diabetes compared to those with adequate vitamin D levels (OR: 2.9, 95% CI: 1.02-8.5, p = 0.04). In subjects with CHD, no significant associations were observed between vitamin D deficiency and other cardio-metabolic risk factors, including obesity, hypertension and hypercholesterolemia (Table 5.2).



HTN, hypertension; DM, diabetes; HC, hypercholesterolemia

Figure 5.2: Cardio-metabolic risk factors among subjects with CHD and subjects without CHD

Table 5.1: Socio-demographic, family history of CVD, and lifestyle behaviors variables according to vitamin D status in subjects with CHD and subjects without CHD

Variables	**Subjects with CHD N= 130**			**Subjects without CHD N= 195**		
	Deficient (< 20 ng/ml) **% (N)**	**Adequate** (≥ 20 ng/ml) **% (N)**	**P-value**	**Deficient (< 20 ng/ml) % (N)**	**Adequate (≥ 20 ng/ml) % (N)**	**P-value**
Age (years)						
<49	28.3 (28)	16.1 (5)	.175	19.7 (15)	37 (44)	**.011**
≥ 49	71.7 (71)	83.9 (26)		80.3 (61)	63 (75)	
Gender						
Male	67.7 (67)	48.4 (15)	**.052**	52.6 (40)	69.7 (83)	**.016**
Female	32.3 (32)	51.6 (16)		47.4 (36)	30.3 (36)	
Marital status						
Single	6.1 (6)	3.2 (1)		22.4 (17)	14.3 (17)	
Married	72.2 (72)	61.3 (19)	.253	63.2 (48)	77.3 (92)	.099
Divorced	21.2 (21)	35.5 (11)		14.5 (11)	8.4 (10)	
Citizenship						
Saudis	81.8 (81)	77.4 (24)		77.6 (59)	52.9 (63)	
Non-Saudis	18.2 (18)	22.6 (7)	.588	22.4 (17)	47.1 (56)	**.001**
Place of residence						
Rural	11.1 (11)	58.1 (18)		1.3 (1)	0.8 (1)	
Urban	85.9 (85)	38.7 (12)	.433	97.4 (74)	99.2 (118)	.431
Semi-rural	3 (3)	3.2 (1)		1.3 (1)	0 (0)	
Education						
Up to primary	49.5 (49)	41.1 (39)		9.2 (7)	17.6 (21)	
levels	49.5 (49)	48.8 (105)		82.9 (63)	78.2 (93)	
High School &			.489			.169
bachelor or diploma	1 (1)	46.2 (6)		7.9 (6)	4.2 (5)	
Master or PhD						
Employment						
Employed (Full time, Part time, self-employed)	36.4 (36)	19.4 (6)		76.3 (58)	84.9 (101)	
Unemployed (Student, Retired, House wife)	63.6 (63)	80.6 (25)	**.007**	23.7 (18)	15.1 (18)	.133
Family income						
(SR/monthly)*	40.4 (40)	51.6 (16)		18.4 (14)	50.4 (60)	
< 5000	41.4 (41)	29 (9)	.439	66.4 (52)	35.3 (42)	**.001**
5000-15000	18.2 (18)	19.4 (6)		13.2 (10)	14.3 (17)	
≥ 15000						
Smoking						
Current smoker	20.2 (20)	9.7 (3)		27.6 (21)	15.1 (18)	
Previous smoker	28.3 (28)	16.1 (5)	.083	2.6 (2)	6.7 (8)	.061
Non-smoker	51.5 (51)	74.2 (23)		69.7 (53)	78.2 (93)	
Exercise						
Never & rarely	33.3 (33)	35.5 (11)		44.7 (34)	42 (50)	
1-2 times/week	17.2 (17)	16.1 (5)	.974	26.3 (20)	21.8 (26)	.551
More than 3-4 times/week	49.5 (49)	48.4 (15)		28.9 (22)	36.1 (43)	
Family history of CVD						
Yes	42.4 (42)	35.5 (11)	.493	50 (38)	36.1 (43)	**.055**
No	57.6 (57)	64.5 (20)		50 (38)	63.9 (76)	

*P-value based on X^2 -test; *Saudi Riyal (1SR= .37 AUD)*

Table 5.2: Results of Multivariate Logistic Regression Analysis for subjects with CHD and subjects with-out CHD

Variables	Subjects with CHD N= 130		Subjects without CHD N= 195	
	Crude OR (95% CI)	**Adjusted OR (95% CI)**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**
Obesity				
Adequate (≥ 20 ng/ml)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Deficient (< 20 ng/ml)	(1.6, 0.6-3.7)[1]	(2, 0.7-6)[2]	(1.3, 0.7-2.4)[1]	(1.9, 0.9-3.8)[6]
Diabetes				
Adequate (≥ 20 ng/ml)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Deficient (< 20 ng/ml)	(0.4, 0.17-1.1)[1]	(2.9, 1.02-8.5)[3]*	(1.3, 0.5-2.9)[1]	(1.4, 0.5-3.8)[7]
Hypertension				
Adequate (≥ 20 ng/ml)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Deficient (< 20 ng/ml)	(0.8, 0.2-2.2)[1]	(0.7, 0.2-2.2)[4]	(0.79, 0.3-1.8)[1]	(0.6, 0.2-1.8)[8]
Hypercholesterolemia				
Adequate (≥ 20 ng/ml)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Deficient (< 20 ng/ml)	(0.77, 0.14-4.1)[1]	(0.8, 0.04-1.6)[5]	(1.1, 0.5-2.7)[1]	(0.6, 0.2-2.3)[9]

[1] Logistic Regression model with no adjustment

[2] Multivariate Logistic Regression model after adjustment for age, gender, smoking, exercise, vitamin D supplements, calcium supplements with vitamin D, sun exposure, and the use of sun screen.

[3] Multivariate Logistic Regression model after adjustment for age, gender, BMI, vitamin D supplements, calcium supplements with vitamin D, sun exposure, and the use of sun screen.

[4] Multivariate Logistic Regression model after adjustment for age, gender, BMI, vitamin D supplements, calcium supplements with vitamin D, sun exposure, and the use of sun screen.

[5] Multivariate Logistic Regression model after adjustment for age, gender, BMI, family history of CVD, vitamin D supplements, calcium supplements with vitamin D, sun exposure, and the use of sun screen.

[6] Multivariate Logistic Regression model after adjustment for age, gender, citizenship, vitamin D supplements, calcium supplements with vitamin D, sun exposure, and the use of sun screen.

[7] Multivariate Logistic Regression model after adjustment for age, gender, BMI, vitamin D supplements, calcium supplements with vitamin D, sun exposure, and the use of sun screen.

[8] Multivariate Logistic Regression model after adjustment for age, gender, BMI, exercise, family history of CVD, vitamin D supplements, calcium supplements with vitamin D, sun exposure, and the use of sun screen.

[9] Multivariate Logistic Regression model after adjustment for age, gender, BMI, education, smoking, vitamin D supplements, calcium supplements with vitamin D, sun exposure, and the use of sun screen.

* < 0.05

5.6 Discussion

Several earlier studies have reported the relation of vitamin D status with various cardio-metabolic risk factors in different population groups [9, 30, 31]. However, there is an important unanswered question which is whether the association between vitamin D deficiency and cardio-metabolic risk factors is partially due to their interrelationships with CHD? To move this field forward, there is a need for well-designed studies with an aim to systematically explore these associations. Therefore, the present study endeavored to compare the association of vitamin D status and cardio-metabolic risk factors in subjects with and without CHD. To our knowledge, this is the first study that revealed a differential association between vitamin D deficiency and cardio-metabolic risk factors in Saudi adults with and without CHD.

Diabetes is a significant risk factor for developing CVD. Our results demonstrated that vitamin D deficiency, defined by using a cut-off of serum 25(OH)D $\leq$ 20 ng/mL was significantly associated with increased risk of diabetes only in subjects with CHD. The association remained significant even after controlling for potential confounders. On the contrary, one case-control study in Saudi Arabia reported no association between vitamin D status and diabetes [24]. The authors concluded that vitamin D deficiency was highly prevalent in their study subjects regardless of the presence of diabetes. They further explained that due to not applying strict exclusion criteria, the subjects in the control group had medical conditions such as hypothyroidism and euthyroid multinodular goiter that affect vitamin D metabolism, and thereby led to high prevalence of vitamin D deficiency in the non-diabetic subjects [24]. However, in the Mini-Finland Health Survey, a significant inverse association between serum vitamin D level and the incidence of diabetes was found after a 17-year follow-up [32]. Several other studies also reported similar results [9, 33]. Furthermore, a number of studies reported an association between vitamin D deficiency and impaired glucose metabolism. For example, in a study of healthy, non-diabetic postmenopausal females, vitamin D deficiency (< 12.5 ng/mL) was associated with fasting serum glucose [34]. The possible mechanism for the effect of vitamin D deficiency on diabetes is not fully understood; however, previous studies suggested that vitamin D deficiency may contribute to insulin resistance. Low levels of serum vitamin D may also contribute to insulin secretion through its direct effect on the β-cell function [35]. Moreover, vitamin D deficiency could be an indirect risk factor for CHD as it may produce serious consequences such as immunosuppressive effect and inflammatory markers [36].

On the other hand, we did not find any association between diabetes and vitamin D deficiency among subjects without CHD. One of the possible explanations for this finding is that vitamin D deficiency might influence the β-cell functions or exacerbate insulin resistance in diabetic subjects only among those with CHD. However, with the current data set we are unable to confirm this postulation. Another possible reason for these findings could be due to the higher prevalence and severity of vitamin D deficiency [serum 25(OH)D < 20 ng/mL] among subjects with CHD (76.2%) than subjects without CHD (39%). Further, the prevalence of severe vitamin D deficiency [serum 25(OH)D < 10 ng/mL] was also more common in subjects with CHD (46.2%) compared to the subjects without CHD (3.1%) (Data not showed).

Obesity is one of the well-established risk factors for CVD and it is considered to be a significant health problem in both developed and developing nations. Numerous studies have indicated that low levels of serum vitamin D were inversely associated with different assessing indicators of obesity, including BMI, body weight, and waist circumference (WC). In the United States, the NHANES (1988-1994) reported a significant association between obesity and lower serum levels of vitamin D [33]. Similar results have been reported in other developed countries [30, 37, 38]. The availability of vitamin D from both sources, sun exposure and dietary intake, is reduced in obese subjects because of confinement in adipose tissues, which provide the possible explanation for the relationship between vitamin D deficiency and obesity [39]. In Saudi Arabia, one study has examined the association between vitamin D status and obesity among both adolescent and adults [25]; however, they reported an association between vitamin D deficiency and obesity in adolescents but not adults [25]. The current research findings showed no association between high BMI and serum vitamin D levels among subjects with and without CHD. In the present study, BMI was used as an indicator of obesity, which is not an ideal tool to measure body fat; thus, further studies are needed to examine the association between vitamin D status and obesity using more appropriate indicators, such as total body fat (TBF), waist-to-hip ratio (WHR), and WC [40].

The present study also showed no significant association between vitamin D deficiency and hypertension in both groups, and a similar finding was reported for the Dutch population [41]. On the other hand, other studies found an inverse association between vitamin D status and hypertension [9, 31, 33]. However, a recently published meta-analysis has shown no significant effect of vitamin D supplementation on SBP and DBP [42]. Furthermore, results of this study showed no significant association between vitamin D deficiency and hypercholesterolemia in both groups, which is consistent with previous research [43]. It was noticed that few studies worldwide have focused on the association between vitamin D status and blood lipids in general, especially high cholesterol levels, even though they are the major risk factors for CHD [44]. Some studies reported significant association between low serum vitamin D levels and high triglycerides [33, 45, 46], but not with hypercholesterolemia. The possible explanation for our results is that all subjects in the current study were hospital-based patients, thus if they have been clinically diagnosed with hypertension and hypercholesterolemia, they would be on medication for those conditions; hence, the prevalence of hypertension and hypercholesterolemia in our sample is lower than the actual prevalence, thus could not detect any associations of vitamin D status with hypertension and hypercholesterolemia. In Saudi Arabia and the Gulf region, no previous studies have examined the association of vitamin D deficiency with hypertension and hypercholesterolemia.

A few randomized controlled trials (RCTs) have evaluated the effect of vitamin D supplementation on the reduction of cardio-metabolic risk. They reported no significant difference in glucose metabolism [47], hypertension levels [48], and/or weight loss between vitamin D supplementation groups and control groups [46].

This study has a number of limitations. The research design is one limitation as it cannot deduce the cause-effect relationship. Recall bias could be another limitation because study participants were asked to remember some information, including their smoking history. Also, a single measurement of serum vitamin D levels was considered a limitation since multiple measurements reflect the average vitamin D status. The present study also has a number of strengths. The measurements of cardio-metabolic risk factors were done in the same hospitals and were not self-reported, which increased internal validity. In addition, adjusting for a varied range of socio-demographic and behavioral confounding factors, such as using vitamin D supplements, level of sun exposure, and the use of sunscreen, to demonstrate the association between low vitamin D serum levels and cardio-metabolic risk factors increased the validity of the study results.

5.7 Conclusion

In conclusion, the current study revealed that risk of diabetes was independently associated with vitamin D deficiency only among subjects with CHD and not subjects without CHD. Furthermore, no significant associations were detected between vitamin D deficiency and other cardio-metabolic risk factors, including obesity, hypertension, and hypercholesterolemia, in both groups. Further studies with larger sample sizes are needed to confirm these results.

5.8 References

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Chapter 6: Knowledge and attitudes about vitamin D, and behaviors related to vitamin D in adults with and without coronary heart disease in Saudi Arabia (Manuscript 4)

6.1 Introduction

Vitamin D deficiency is highly prevalent in Saudi Arabia as shown by national studies (Tuffaha et al., 2015; Ardawi et al., 2012). As our results indicated in chapters 4 and 5, vitamin D deficiency is associated with increased risk of CHD among adults in Saudi Arabia; further investigation was then undertaken to study the current situation of vitamin D in Saudi Arabia. Hence, this chapter aimed to compare the knowledge, attitudes and behaviours towards vitamin D between subjects with and without CHD. It also examined the independent associations of vitamin D status with knowledge, attitudes, and behaviours related to vitamin D among the study sample irrespective of CHD status. The results revealed that the control subjects were more knowledgeable about vitamin D than the CHD cases. However, the cases with CHD had better attitudes toward sun exposure than the controls had. Also, the control subjects had a significantly higher intake of multivitamin supplements, butter, oily fish and liver compared to the CHD cases, while the CHD cases had a significantly higher intake of milk. The results illustrated that vitamin D deficiency (serum 25(OH)D < 20 ng/mL) was significantly associated with low levels of knowledge about vitamin D as well as with low intake of vitamin supplements after controlling for potential confounders including CHD status. These results are important as they highlight significant information that may reduce vitamin D deficiency in the Kingdom. In the next chapter, a qualitative approach was used to further understand the study subjects' knowledge about vitamin D and their attitudes toward sun exposure.

This paper has been published as an original research paper in a peer-reviewed journal and has been designed and written according to the journal style including the reference style.

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Declaration:

I (the candidate) am the first and corresponding author of this paper. My contribution to the paper includes the development of the study design, completed the human research ethics application, conducted data collection, performed data analysis, and writing of the manuscript for submission to the journal.

Signed: Date:

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6.2 Abstract

Background: Vitamin D deficiency is prevailing in Saudi Arabia. Recent national data indicated an inverse association between vitamin D status and coronary heart disease (CHD), which increases concerns about vitamin D deficiency as a serious public health problem. Therefore, the current study aimed to investigate whether knowledge, attitudes and behaviors related to vitamin D contribute to the prevalence of vitamin D deficiency among adults with and without CHD in Saudi Arabia.

Methods: This case-control study consisted of 130 CHD cases and 195 matched controls. The study subjects were recruited from three hospitals in Saudi Arabia. Structured interviews were completed to collect data on participants' socio-demographics, knowledge about vitamin D, attitudes toward sun exposure, and behaviors related to vitamin D. Also, serum vitamin D levels were measured.

Results: Severe vitamin D deficiency [serum 25(OH)D < 10 ng/mL] was more prevalent in the CHD cases than in the controls (46% and 3%, respectively). The total knowledge score was higher in the controls than in the cases [2.5 (±1.8) and 1.6 (±2.2), respectively]. The cases had better attitudes toward sun exposure compared to the controls (p = 0.001); however, the controls had better attitudes toward vitamin D compared to the cases (p = 0.001). The controls had a higher consumption of multivitamin supplements than the cases (6.7% and 0.8%, respectively; p = 0.010). Similarly, the controls had a higher consumption of butter (p = 0.001), oily fish (p = 0.004), and liver (p = 0.003) than the cases; however, the cases had a significantly higher intake of milk (p = 0.001). A multivariate logistic regression showed that vitamin D deficiency [25(OH)D < 20 ng/mL] was associated with low levels of knowledge about vitamin D, with an odds ratio of 1.82 (95% CI: 1.08-3.06, P=0.024).

Vitamin D deficiency was also associated with low intake of vitamin supplements, with an odds ratio of 4.35 (95% CI: 2.12-8.92, $P<0.001$).

Conclusion: The present study revealed that low levels of knowledge about vitamin D and low consumption of vitamin supplementation, including vitamin D, calcium, multivitamin, and calcium supplements with vitamin D, may have contributed to the higher prevalence of vitamin D deficiency among the CHD cases than among the controls. Further studies using a qualitative approach are crucial to explore the underlying reasons for unfavorable attitudes toward sun exposure that may contribute to the high burden of vitamin D deficiency in the country.

Key words: Vitamin D deficiency, knowledge, attitudes, sun exposure, vitamin D supplements, Saudi Arabia

6.3 Introduction

Recent evidence has indicated that vitamin D deficiency and insufficiency are becoming global epidemics [1]. Studies conducted in Western countries have shown that vitamin D deficiency was present in 20% -25% of the total population [2, 3, 4]. In the Middle East region, approximately 60%–65% of the population was affected [1]. Vitamin D deficiency also has a significant presence in Saudi Arabia, even though there is plentiful sunlight throughout the year. The majority of studies that have measured vitamin D levels in Saudi Arabia have indicated a high prevalence of vitamin D deficiency among different population groups [5, 6, 7, 8, 9, 10]. A recent national survey showed that almost 40% of males and 60% of females in Saudi Arabia had vitamin D deficiency [11].

Aside from the classical role of vitamin D in bone health and the regulation of calcium and bone homeostasis, several large observational studies worldwide have shown an association between vitamin D deficiency and the risk of coronary heart disease (CHD) and associated risk factors such as hypertension and diabetes [12, 13, 14, 15, 16]. Furthermore, recent meta-analyses of observational studies also reported significant associations of vitamin D deficiency with cardiovascular disease (CVD) mortality [17], and the increased risk of CVD [18]. Thus, the existing literature of observational studies indicated an association between vitamin D deficiency and the risk of CHD. Nevertheless, to date only a few randomized controlled trials (RCTs) have been conducted to examine the effect of vitamin D supplementation on reducing the risk of CHD [19, 20, 21]. However, these studies have failed to demonstrate any causal relationship between vitamin D status and the risk of CHD [19, 20, 21]. These studies are flawed with small sample size. Moreover, Mendelian randomization study on the role of vitamin D in CHD illustrated that there is no association between vitamin D deficiency and the risk of CHD [22]. However, this result is only generalizable in European ethnicity but not in Middle Eastern populations. While the casual relationship between vitamin D deficiency and the risk of CHD cannot be determined based on limited number of studies, yet vast literature consistently demonstrated an association between vitamin D deficiency and the risk of CHD.

Exposure to sunlight is the main source of vitamin D, and there are also a few dietary sources of vitamin D, including oily fish and egg yolks, as well as vitamin D dietary supplements [23]. Although the biological factors that reduce serum vitamin D levels are known, the effects of cultural and lifestyle behaviors, as well as knowledge and attitudes about vitamin D, need further investigation. Relatively few studies have assessed knowledge and attitudes in relation to vitamin D worldwide [24, 25, 26, 27]. Only one study in Saudi Arabia has examined the knowledge and attitudes about vitamin D [28]; however, the study had limitations such as it was conducted only among college students and with a small sample size and sex restriction (only eight females were involved) [28].

Furthermore, in Saudi Arabia, we have demonstrated the association between vitamin D deficiency [25(OH)D < 20 ng/mL] and the presence of CHD among adults [OR: 6.5, 95% CI: 2.7–15, p = < 0.001] [29]. We have also found an association between vitamin D deficiency [25(OH)D < 20 ng/mL] and diabetes among subjects with CHD [OR: 2.9, 95% CI: 1.02–8.5, p = 0.04] in Saudi Arabia [30]. Taking into consideration the high rates of CHD and associated risk factors such as obesity, diabetes, hypertension, and hypercholesterolemia in Saudi Arabia [31, 32, 33, 34], as well as the high prevalence of vitamin D deficiency in the country [6, 9], there is a need to effectively address these problems. Thus, it is essential to investigate whether knowledge and attitudes regarding vitamin D may play a role in establishing healthy/unhealthy behaviors that contribute to the difference in vitamin D status between CHD patients and subjects without CHD in Saudi Arabia. Therefore, this research aimed to (1) report the prevalence of vitamin D deficiency in subjects with and without CHD, (2) compare the levels of knowledge and attitudes about vitamin D between the two groups, (3) investigate and compare vitamin D-related behaviors in both groups, and (4) to examine the associations of vitamin D status with knowledge, attitudes, and behaviors about vitamin D. This information is expected to provide evidence for developing appropriate health promotions and educational interventions for the general population, thereby increasing knowledge and understanding about the importance of vitamin D and potentially reducing the risk of CHD in Saudi Arabia.

6.4 Methods

6.4.1 Study population

This case-control study has been described in detail elsewhere [29]. In brief, the current study was conducted in the summertime between May and October 2015 in the cities of Jeddah and Makkah, Saudi Arabia. All included participants were adults of both genders, either Saudis or people who had been residents of Saudi Arabia for at least five years. A total of 152 cases and 236 controls were approached, but 9 cases and 35 controls were ineligible as they did not meet the inclusion criteria. Of the remaining eligible subjects, 13 cases and 6 controls declined to participate in this study. Finally, 130 subjects with CHD (the cases) and 195 subjects without CHD (the controls) were took part in this study. The cases were recruited from the cardiology department at King Abdullah Medical City (KAMC), and the controls were recruited from family medicine clinics and nose and throat clinics at Tunsi private hospital (153 subjects), and ophthalmology clinics at King Abdulaziz University (KAU) hospital (42 subjects). Study participants with medical conditions that may influence vitamin D metabolism, including kidney disease, osteoporosis, liver disease, hyperparathyroidism, and hyperthyroidism, were excluded. All eligible subjects signed written informed consent forms before participating in the study.

Ethical approval was obtained from the Griffith University Human Research Ethics Committee (GU Ref No: MED/59/14/HREC), the Institutional Review Board at KAMC (IRB No: 15-194), and the Research Ethics Committee at KAU (Reference No ll8-15).

6.4.2 Data collection

All study participants were interviewed in person using a structured questionnaire. Data were collected in relation to participants' socio-demographic, such as age, gender, marital status, education level, place of residence in Saudi Arabia, nationality, employment, and monthly income. Likewise, data related to behavioral risk factors such as cigarette smoking, water-pipe smoking, and physical activities were also collected during interviews. The definition of a current smoker was a participant who smoked at least one cigarette per day, whereas a previous smoker was defined as a participant who had previously smoked but had quit. A water-pipe smoker was defined as a participant who smoked at least one water-pipe per week at the time of data collection. The practicing exercise was categorized into moderate exercise, such as jogging or walking; vigorous exercise, such as aerobics or bicycling; and sedentary behaviors, such as doing only a little bit of walking outside the home. The structured questionnaire also included three additional sections to collect information on knowledge, and attitudes about, and behaviors toward, vitamin D in Saudi Arabia. Sections one and two gathered data on knowledge and attitudes about vitamin D and sun exposure, and section three gathered data on participants' behaviors in relation to vitamin D, including sun exposure habits (time spent outdoors during weekdays and weekends, and parts of the body that get exposure to the sun) and use of sun protection. Section three in the questionnaire also asked participants to report the amount and duration of using supplementation, including vitamin D, calcium, multivitamins, and calcium supplements with vitamin D. Questions related to the frequency of intake of some food items rich in vitamin D, such as milk, butter, eggs, oily fish (salmon, tuna, sardines), and liver were also included. Questions related to knowledge and attitudes about, and behaviors toward, vitamin D were adapted from a number of validated questionnaires [24, 25, 26] (questions in Additional file 1).

6.4.3 Biochemical measurements

Blood samples (10 ml) were collected from all study subjects via venipuncture to assess their serum levels of 25(OH)D using chemiluminescence microparticle immunoassay (CMIA) on the Architect system (Abbott). The blood samples were centrifuged at 2000 rpm for 15 minutes then the serum was separated and was kept frozen at - 80°C while waiting for additional laboratory analyses. All laboratories are certified by the Saudi Ministry of Health and located in the same hospitals where the study took place. The definition of vitamin D deficiency and insufficiency were as serum concentrations of 25(OH)D < 10 ng/mL and 10 to < 19.9 ng/mL, respectively, while adequate vitamin D serum level was defined as 25(OH)D ≥ 20 ng/mL [35].

6.4.4 Statistical analysis

Statistical analyses were accomplished using the Statistical Package for Social Science (SPSS) Version 22. Categorical variables were reported as numbers and percentages. Since there were few subjects in each group who smoked a water-pipe and few subjects were practicing vigorous exercise, cigarette smoking and water-pipe smoking were combined, and moderate exercise was also combined with vigorous exercise as one category. Normality tests were completed for all variables. A chi-square test was used to compare vitamin D status [deficient as serum 25(OH)D < 10 ng/mL, insufficient as serum 25(OH)D 10 to 19.9 ng/mL, and adequate as serum 25(OH)D ≥ 20 ng/mL] between subjects with CHD and subjects without CHD. Likewise, chi-square tests were used to compare knowledge about vitamin D, attitudes toward vitamin D and sun exposure, and vitamin D-related behaviors including sun exposure, the use of sun protection, the use of supplementation, and the intake of food rich in vitamin D between subjects with CHD and subjects without CHD.

The scoring system for knowledge about vitamin D was as follows: study subjects were asked about their knowledge related to vitamin D during the interview by the researcher (NA). Participants who were considered to have a high knowledge level of vitamin D were those who chose the right answers for questions 1, 3, 4, and 5 out of five questions on vitamin D knowledge and were scored according to the total correct answers. Conversely, participants who chose the wrong answers to all of those questions were considered to have a low knowledge level. Similarly, we also calculated the total scores for attitudes (four questions) and behaviors (questions about sun exposure and using of sun protection, the intake of supplements, and the consumption of food rich in vitamin D, respectively) (questions in supplementary materials). After that, we regrouped them using the median of the study sample as a cut-off point to determine the levels of knowledge, attitudes, and three categories of behaviors in order to conduct the multivariate logistic regression.

A Mann-Whitney U test was carried out to compare the difference in total knowledge score between the cases with CHD and the controls. Moreover, a Mann-Whitney U test was also conducted in order to compare the difference in the consumption of food items rich in vitamin D between the two groups, as all food items were not normally distributed. Finally, three multivariate logistic regression models were conducted to examine if there independent associations of vitamin D status with knowledge, attitudes, and vitamin D related behaviors. Because of the small sample size, we combined case and control subjects and controlled for age, gender, and CHD status. In consideration of strong collinearity between CHD and education, employment, citizenship, and marital status identified in our previous studies involving the same sample, these sociodemographic variables were not included in the models. Moreover, because of the small sample size, we combined vitamin D deficiency and insufficiency together to increase the statistical precision; hence, vitamin D deficiency and adequate vitamin D status were defined as [serum 25(OH)D < 20 ng/mL and ≥20 ng/mL, respectively] for the purpose of multivariate logistic regression analysis. A p value < 0.05 was considered statistically significant.

6.5 Results

The socio-demographic characteristics of study subjects are shown in Table 6.1. The majority of the cases with CHD and the controls without CHD had similar gender distribution (63% males and 37% females) and were married. In comparison with the controls, a greater proportion of the CHD subjects were 49 years and older (74.6% and 69.7%, respectively), living in rural areas (12.3% and 1%, respectively), and Saudi citizens (81% and 63%, respectively). However, the controls without CHD were more educated, more employed (either full time, part time, or self-employed), and more frequent smokers than the cases with CHD.

6.5.1 Prevalence of vitamin D deficiency

Figure 6.1 shows vitamin D status in subjects with and without CHD. There was a significant difference between the two groups with respect to vitamin D status ($p = < 0.001$). Over 46% of the CHD cases were classified as having a vitamin D deficiency [serum 25(OH)D < 10 ng/mL], whereas only 3% of the controls had a vitamin D deficiency. Likewise, the majority of the control subjects had adequate vitamin D levels [serum 25(OH)D ≥ 20 ng/mL] in contrast to the CHD cases (61% and 24%, respectively).

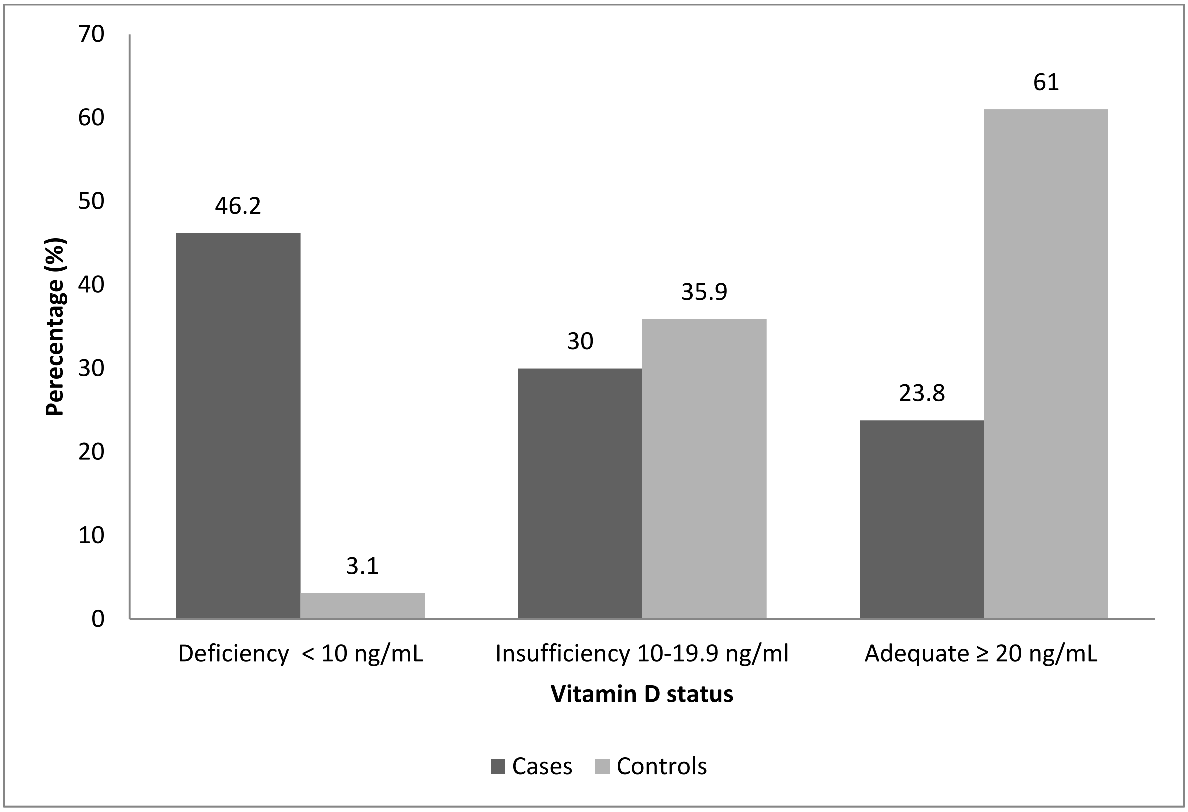

Figure 6.1: Vitamin D status among case and control subjects.

6.5.2 Knowledge about vitamin D

Table 6.2 illustrates knowledge about vitamin D between the cases with CHD and the controls without CHD. There was a significant difference between the groups related to knowledge about vitamin D. Almost 70% of the controls have heard or learned about vitamin

D compared to only 40% of the CHD cases (p = 0.001). Doctors and friends/relatives were the main source of information about vitamin D in both groups. Also, half of the controls knew that vitamin D is important for bone health, compared to 31% of the cases (p = 0.003). Similarly, half of the controls knew that exposure to sunlight is the main source of vitamin D, compared to only 29% of the cases (p = 0.001). In addition, a quarter of the controls admitted that oily fish is a good food source for vitamin D, compared to only 10% of the cases (p = 0.001). Similarly, 10% of the controls and 4% of the cases admitted that milk is a good food source for vitamin D. The total knowledge score was higher in the controls than in the cases [2.5 (±1.8) and 1.6 (±2.2), respectively].

6.5.3 Attitudes toward vitamin D

Table 6.3 illustrates attitudes toward vitamin D stratified by case and control groups. The controls had better attitudes about vitamin D as more than 80% of the controls responded yes to the question of whether vitamin D was important to health, in compared to only 46% of the cases (p = 0.001). However, the cases with CHD had better attitudes toward sun exposure as 48% of the cases reported that they like to be exposed to sunlight all the time, compared with only 18% of the controls. At the same time, 18% of the controls stated that they avoid sunlight, compared with 11% of the cases (p = 0.001). In addition, more cases than controls agreed with the statement, “I’m concerned that my current vitamin D level might be too low” (65% and 51%, respectively) (p = 0.001). All of the cases and the majority of the controls (92%) did not use a parasol to shade themselves from sunlight (p = 0.001).

6.5.4 Vitamin D-related behaviors

Table 6.4 illustrates vitamin D-related behaviors stratified by case and control groups. Regarding sun exposure behaviors, the majority of subjects in the case and control groups worked indoors (81% and 97%, respectively) (p = 0.001). A high proportion of controls were exposed to sunlight for less than 30 minutes per day (64.6% and 44.6%, respectively) (p =

0.001). Also, more cases than controls had sufficient sun exposure (30-60 minutes or more per day) during weekdays (37.7% and 25.2%, respectively) (p = 0.001). Likewise, more cases than controls were sufficiently exposed to sunlight (less than 30 minutes and 30-60 minutes per day or more) during weekends (64.6% and 51.3%, respectively) (p = 0.001). However, 49% of the controls and 35% of the cases do not spend time outdoors exposed to sunlight at all during weekends (p = 0.001). The majority of cases and controls only exposed their faces and hands to sunlight (73% and 80%, respectively); however, a larger proportion of the cases exposed both arms to the sunlight compare to the controls (18% and 5%, respectively) (p = 0.001). In addition, 20% of the controls reported using sun protection 1-4 times per week and more than five times per week, compared with only 0.8% of the cases (p = 0.001). The results also showed that more controls than cases were consuming multivitamin supplements (6.7% and 0.8%, respectively) (p = 0.010). There were no significant differences between the case and control groups regarding the consumption of vitamin D supplements, calcium supplements, and calcium supplements with vitamin D (all p values > 0.05).

Moreover, the consumption of food items that are rich in vitamin D was also compared between the two study groups. Table 6.5 presents the difference in the intake of some food items that are rich in vitamin D between the cases and controls. Drinking milk was more common among the cases than the controls as 54% of the cases were drinking milk regularly (3-6 times a week, or once a day or more), compared with only 36% of the controls (p = 0.002). However, eating butter (p = 0.001), oily fish (p = 0.034), and liver (p = 0.001) was more common among the controls than the cases. Approximately 12% of the controls had a high consumption of butter, compared with only 3.9% of the cases (p = 0.001). In addition, 25.6% of the controls had a high consumption of oily fish, compared with 15.4% of the cases (p = 0.034). Furthermore, 9.2% of the controls had a high consumption of liver, compared with 6.9% of the cases (p = 0.001). There was no significant difference in the consumption of eggs between the two groups (p > 0.05). Similarly, the cases had a significantly higher intake of milk (*p* = 0.001) than the controls. Conversely, the controls had a higher consumption of butter (*p* = 0.001), oily fish (*p* = 0.004), and liver (*p* = 0.003).

6.5.5 Associations of vitamin D status with knowledge, attitudes, and behaviors about vitamin D

We conducted the multivariate logistic regression analysis to examine the independent associations of vitamin D status with knowledge, attitudes, and behaviors about vitamin D in the study subjects after controlling for potential confounders including CHD. Table 6.6 illustrates the results of the multivariate logistic regression modelling (Model 1 - Model 3). Low levels of knowledge about vitamin D was significantly associated with vitamin D deficiency [25(OH)D < 20 ng/mL] (*P*=0.024). After adjustment for age, gender, and CHD, subjects with lower levels of knowledge about vitamin D were 1.82 times more likely to suffer from vitamin D deficiency compared to those with higher levels of knowledge about vitamin D (OR: 1.82, 95% CI: 1.08-3.06). Furthermore, low intake of vitamin supplements, including vitamin D supplements, calcium supplements, multivitamin supplements, and calcium supplements with vitamin D, was significantly associated with vitamin D deficiency (*P*<0.000). After adjustment for age, gender, and CHD, subjects with lower intake of vitamin supplements were 4.35 times more likely to suffer from vitamin D deficiency compared to those with higher intake of vitamin supplements (OR: 4.35, 95% CI: 2.12-8.92). No significant associations were detected between vitamin D deficiency and attitudes about vitamin D, behaviors regarding sun exposure and using sun protection, and the consumption of food rich in vitamin D.

Table 6.1 Socio-demographic characteristics and lifestyle behaviors variables among case and control subjects

Variables	Cases (n= 130)		Controls (n= 195)	
	N	%	N	%
Age (years)				
< 49	33	25.4	59	30.3
≥ 49	97	74.6	136	69.7
Gender				
Male	82	63	123	63
Female	48	37	72	37
Marital status				
Single	7	5.4	34	17.4
Married	91	70	140	71.8
Divorced	32	24.6	21	10.8
Citizenship				
Saudis	105	80.8	122	62.6
Non-Saudis	25	19.2	73	37.4
Place of residence				
Rural	16	12.3	2	1
Urban	111	85.4	192	98.5
Semi-rural	3	2.3	1	0.5
Education				
Up to primary levels	67	51.6	28	14.4
High School & bachelor or diploma degree	61	46.9	156	80
Master or PhD degree	2	1.5	11	5.6
Employment				
Employed (Full time, Part time, self-employed)	42	32.3	159	81.5
Unemployed (Student, Retired, House wife)	88	67.7	36	18.5
Family income (SR/monthly)*				
< 5000	56	43.1	74	37.9
5000-15000	50	38.5	94	48.2
15000- ≥ 25000	24	18.5	27	13.8
Smoking				
Current < 20 cigarettes/day	23	17.7	39	20
Previous smoker	33	25.4	10	5.1
Non-smoker	74	56.9	146	74.9
Exercise				
Never & rarely	44	33.8	84	43.1
1-2 times/week	22	16.9	46	23.6
More than 3-4 times/week	64	49.2	65	33.3

**Saudi Riyal (1SR= .37 AUD*

Table 6.2 knowledge regarding vitamin D stratified by case and control groups

Variables	Cases (n= 130)		Controls (n= 195)		P-value*
	N	%	N	%	
Have you ever heard/learnt about vitamin D?					
Yes	53	40.8	136	69.7	**.001**
No	77	59.2	59	30.3	
Where have you heard or learnt about vitamin D?					
Newspaper/Magazine	1	0.8	4	2.1	**.001**
TV	2	1.5	8	4.1	
Doctor	28	21.5	42	21.5	
Friends/Relatives	16	12.3	45	23.1	
School/university	3	2.3	22	11.3	
Internet	3	2.3	7	3.6	
Other health professionals (dietician)	0	0	10	5.1	
I don't know	77	59.2	57	29.2	
Vitamin D helps which of the following health effects?					
Prevention of kidney disease	0	0	2	1	**.003**
Healthy bones	41	31.5	99	50.8	
Prevention of cancer	3	2.3	2	1	
I don't know	86	66.2	92	47.2	
Where do you think the body gets vitamin D from?					
Diet	7	5.4	18	9.2	**.001**
Sun exposure	38	29.2	98	50.8	
Supplements	3	2.3	5	2.6	
I don't know	82	63.1	74	37.9	
What type of food is a good source of vitamin D?					
Vegetables & fruits	3	2.3	28	14.4	**.001**
Milk	5	3.8	19	9.7	
Fatty fish (salmon, sardines)	14	10.8	49	25.1	
Olive oil					
Eggs	0	0	3	1.5	
I don't know	8	6.2	14	7.2	
	100	76.9	82	42.1	
Knowledge total score†	1.6 (± 2.2)		2.5 (± 1.8)		**.001**

**P-value based on X^2 -test*

† Numbers refer to mean and standard deviation for each group, P-value based on Mann-Whitney U test

Table 6.3 Attitudes toward vitamin D stratified by case and control groups

Variables	Cases (n= 130)		Controls (n= 195)		P-value*
	N	%	N	%	
Do you think vitamin D is important for your health?					
Yes	61	46.9	159	81.5	**.001**
No	2	1.5	17	8.7	
I don't know	67	51.5	19	9.7	
How do you feel about sun exposure?					
I like to expose to sunlight all the time	62	47.7	34	17.4	**.001**
I like to expose to sunlight sometimes	47	36.2	101	51.8	
I rarely expose to sunlight	6	4.6	26	13.3	
I avoid expose to sunlight	15	11.5	34	17.4	
Do you often use a parasol to shade from the sun?					
Yes	0	0	15	7.7	**.001**
No	130	100	180	92.3	
How much do you agree or disagree with the following statement: "I'm concerned that my current vitamin D level might be too low"					
Disagree	10	7.7	41	21	**.003**
Neither agree or disagree	35	26.9	53	27.2	
Agree	85	65.4	101	51.8	

**P-value based on X^2 -test*

Table 6.4 Vitamin D related behaviors stratified by case and control groups

Variables	Cases (n= 130)		Controls (n= 195)		P-value*
	N	**%**	**N**	**%**	
Sun exposure and using of sun protection					
Do you work mainly:					
Indoor	106	81.5	191	97.9	**.001**
Outdoor	24	18.5	4	2.1	
How much time do you often spend outdoors per day on weekdays?					
Not at all	23	17.7	20	10.3	**.001**
<30 min	58	44.6	126	64.6	
30-60 min	27	20.8	45	23.1	
>60 min	22	16.9	4	2.1	
How much time do you often spend outdoors per days on weekends?					
Not at all	46	35.4	95	48.7	**.001**
<30 min	48	36.9	46	23.6	
30-60 min	19	14.6	47	24.1	
>60 min	17	13.1	7	3.6	
Which parts of your body get exposed to the sun?					
Face	0	0	0	0	**.001**
Hand	12	9.2	29	14.9	
Face & hand	95	73.1	156	80	
Both arms	23	17.7	10	5.1	
Both legs	0	0	0	0	
Completely covered	0	0	0	0	
How often do you wear sunscreen while outdoors in the sun?					
Never	129	99.2	156	80	**.001**
1-4 times/week	0	0	23	11.8	
>5 times/week	1	0.8	16	8.2	
The use of supplementation					
Do you take vitamin D supplements					
Yes	18	13.8	21	10.8	.403
No	122	86.2	174	89.2	
Do you take calcium supplements?					
Yes	4	3.1	9	4.6	.488
No	126	96.9	186	95.4	
Do you take multivitamin supplements?					
Yes	1	0.8	13	6.7	**.010**
No	129	99.2	182	93.3	
Do you take calcium supplements with vitamin D?					
Yes					
No	1	0.8	5	2.6	.239
	129	99.2	190	97.4	

The intake of food rich in vitamin D					
How often do you drink milk?					
Never					
1-2 times/week	33	25.4	82	42.1	**.002**
3-6 times/week	27	20.8	43	22.1	
≥ once/day	27	20.8	37	19	
	43	33.1	33	16.9	
How often do you eat butter?					
Never					
1-2 times/week	113	86.9	132	67.7	**.001**
3-6 times/week	12	9.2	40	20.5	
≥ once/day	4	3.1	20	10.3	
	1	0.8	3	1.5	
How often do you eat eggs?					
Never	21	16.2	32	16.4	.998
1-2 times/week	95	73.1	142	72.8	
3-6 times/week	14	10.8	21	10.8	
≥ once/day	0	0	0	0	
How often do you eat oily fish (salmon, tuna, sardine)?					
Never					
1-2 times/week	66	50.8	72	36.9	**.034**
3-6 times/week	44	33.8	73	37.4	
≥ once/day	14	10.8	41	21	
	6	4.6	9	4.6	
How often do you eat liver?					
Never	106	81.5	125	64.1	**.001**
1-2 times/week	15	11.5	52	26.7	
3-6 times/week	7	5.4	18	9.2	
≥ once/day	2	1.5	0	0	

**P-value based on* X^2 *-test*

Table 6.5 Differences in intake of food items that rich in vitamin D between cases and controls

Food items	**Cases**		**Controls**		**Mann-Whitney U**	**Z-value**	**P-value***
	Median	**Range**	**Median**	**Range**			
Milk	0.50	0-3	0.28	0-3	9700.5	-3.701	**.001**
Butter	0	0-1	0	0-2	10157.0	-4.018	**.001**
Eggs	0.28	0-1	0.28	0-1	12205.5	-0.581	.561
Oily fish	0	0-1	0.14	0-2	10399.0	-2.877	**.004**
Liver	0	0-1	0	0-0.79	10700.5	-2.978	**.003**

**P-value based on Mann-Whitney U test*

Table 6.6 Results of Multivariate Logistic Regression Analysis

	Adjusted OR* (95% CI)	P-value
Model 1: Knowledge about vitamin D		
High knowledge levels	1.00 (referent)	
Low knowledge levels	1.82 (1.08-3.06)	**0.024**
Model 2: Attitudes toward vitamin D		
Good attitude	1.00 (referent)	
unfavorable attitude	0.96 (0.58-1.59)	0.899
Model 3: Vitamin D related behaviors		
Sun exposure and using of sun protection		
High score	1.00 (referent)	
Low score	1.54 (0.87-2.71)	0.132
Intake of vitamin supplements		
High intake	1.00 (referent)	
Low intake	4.35 (2.12-8.92)	**<.000**
Consumption of food rich in vitamin D		
High intake	1.00 (referent)	
Low intake	0.87 (0.53-1.4)	0.612

* Multivariate Logistic Regression model after adjustment for age, gender, and CHD

6.6 Discussion

The current study revealed a number of important findings. First, the cases with CHD had a higher prevalence of vitamin D deficiency compared with the controls. Second, knowledge of various aspects of vitamin D was lower among the CHD cases than the controls. Third, the cases with CHD had a better attitudes toward sun exposure compared with the controls; however, the controls had better attitudes toward vitamin D compared to the cases. Fourth, a higher proportion of the CHD cases were sufficiently exposed to sunlight during weekdays and weekends. Almost three-quarters of the subjects in both groups were only exposing their faces and hands to sunlight. Fifth, the controls had a higher intake of multivitamin supplements and a higher consumption of butter, oily fish, and liver compared with the CHD cases, while milk intake was higher among the CHD cases than the controls. Finally, after controlling for potential confounding factors, low levels of knowledge about vitamin D and the low intake of vitamin supplements were significantly associated with vitamin D deficiency.

The study findings demonstrated that vitamin D deficiency was significantly more prevalent in the CHD cases than the controls. Previous studies have reported similar results [36, 37]. Based on these findings, the present study attempted to answer an important question, which are whether the higher prevalence of vitamin D deficiency in the CHD cases compared with the controls is due to differences in knowledge, attitudes, and vitamin D-related behaviors in both groups?. To the best of our knowledge, this is the first study that has compared the knowledge and attitudes about, and behaviors toward, vitamin D between subjects with and without CHD. It is also the first study to examine the associations between vitamin D status and knowledge, attitudes, and behaviors about vitamin D in Saudi Arabia.

The traditional knowledge, attitudes, and practice (KAP) survey theory suggests a direct linear relationship between knowledge, attitudes, and behaviors, which is, according to several studies, very simple and not true [38]. This is because people's behaviors have a multifactorial nature and depend on many factors such as socio-cultural and environmental factors, not just knowledge and attitudes [38]. Thus, our study showed inconsistent findings between knowledge, attitudes, and behaviors in both groups.

The present study showed that the controls had higher levels of knowledge about vitamin D compared with the CHD cases. The total score of knowledge about vitamin D was higher in the controls than in the cases, including understanding the importance of vitamin D in disease prevention and knowledge of sources of vitamin D, such as sun exposure and certain foods. This difference in knowledge between the cases and controls may be due to the fact that the control subjects were more educated than the cases. These results are consistent with the multivariate logistic regression results that showed a significant association between low levels of knowledge about vitamin D and vitamin D deficiency in our sample after controlling for CHD. A study among older adults in Netherlands has reported similar results as the higher levels of knowledge about vitamin D were associated with higher vitamin D serum levels [27].

Overall, the present study showed a lack of knowledge about vitamin D in both groups, but more specifically in the CHD cases. Approximately one-third of the controls and two-thirds of the cases have never heard or learned about vitamin D. In addition, of those who reported that they have heard about vitamin D, 38% of the controls and 63% of the cases reported that they did not know any of the vitamin D sources, including the role of sun exposure in production of vitamin D. Moreover, there was a confusion about dietary sources of vitamin D among those who reported diet as a source of vitamin D as only a few subjects knew some of the richest sources of dietary vitamin D, such as milk (4% of the cases and 10% of the controls) and fatty fish (11% of the cases and 25% of the controls). Evidence to date has also indicated low levels of knowledge about vitamin D among different populations. A study conducted in the UK showed that approximately one-third of the study participants had never heard about vitamin D, especially older participants [24]. Likewise, low levels of knowledge about vitamin D have been reported in Chinese women [25]. Similarly, a survey in the Netherlands revealed that only 38% of survey participants had heard about vitamin D [27]. Relatively better knowledge about vitamin D has been reported in Australia. A survey conducted in Queensland showed that 69% of the participants knew about vitamin D, and almost 50% of them knew its role in protecting bone health [26]. In Kuwait, a Gulf country, a cross-sectional survey indicated low levels of knowledge about vitamin D among the Kuwaiti population [39].

With respect to attitudes toward vitamin D and sun exposure, almost half of the cases responded “I do not know” to whether vitamin D was important for health, compared to 80% of the controls responding “yes” to the importance of vitamin D for general health. This might be partly due to the higher level of knowledge among the control subjects. However, results showed that the CHD cases had better attitudes toward sun exposure than the controls as a large majority of the CHD cases said, “I like to expose all the time and/or sometimes to sunlight”, whereas a higher proportion of the controls said “I avoid exposure to or rarely expose myself to sunlight”. Similarly, only half of the controls and 65% of the cases were concerned about their current vitamin D status. These results indicated three important points. First, the controls had better attitudes toward vitamin D than the cases. Second, the cases had better attitudes toward sun exposure than the controls, even though they were less knowledgeable about vitamin D. Third, in general, our study sample had an unfavourable attitude toward vitamin D and sun exposure, with a lack of awareness about the importance of vitamin D and exposure to sunlight. Negative attitudes toward sun exposure have been reported among Arabic Gulf populations [39]. Previous studies have also reported negative attitudes toward sun exposure, even among subjects who were considered knowledgeable about vitamin D [25]. This is similar to our findings, as the current study highlighted contradictory results between knowledge about vitamin D and attitudes toward sun exposure. The control subjects had higher levels of knowledge about sun exposure as the main source of vitamin D; however, one-third of the controls had negative attitudes toward sun exposure and stated that they avoided or rarely exposed themselves to sunlight, which may suggest that being knowledgeable about vitamin D does not necessary influence attitudes toward exposure to sunlight as the major source of vitamin D. Furthermore, one possible explanation for cases having better attitudes toward sun exposure than the controls might be due to the interrelationship between attitudes and other variables, such as beliefs [38]. This means cases might answer what they think it is correct or healthy, as the majority of patients are trying to act healthier after being affected by a disease.

Regarding vitamin D-related behaviors, findings related to exposure to sunlight in our study showed that even though a higher percentage of the CHD cases were sufficiently exposed to sunlight, a large percentage of the subjects in each group were not exposed to sunlight during weekdays (17.7% of the cases and 10.3% of the controls) and weekends (35.4% of the cases and 48.7% of the controls). Additionally, more than three-quarters of the participants in both groups only exposed their faces and hands to sunlight, which indicates that very small parts of their bodies were exposed to sunlight for a limited time during the day; hence, our results showed poor sun exposure behaviors among the study subjects, which explain why we did not find a significant association between vitamin D status, and sun exposure behavior in our study. Moreover, the reason the controls had lower levels of exposure to sunlight during weekdays might be due to the higher rate of employment among the controls compared to the CHD cases, which means the controls had longer hours of working at indoor offices and thus, less sun exposure during weekdays.

The current results also indicated limited consumption of vitamin D supplements and multivitamin supplements by the study subjects in general. Higher consumption of vitamin D supplements has been reported in different populations [40]. The use of vitamin D supplements has a significant effect on vitamin D serum levels, especially among those who were rarely exposed to sunlight. The study results showed that the controls had a higher consumption of multivitamin supplements than the cases, which might have affected their vitamin D status. This result is consistent with the results of the multivariate logistic regression as it reported a significant association between vitamin D deficiency and the low intakes of vitamin supplements, including vitamin D supplements, calcium supplements, multivitamin supplements, and calcium supplements with vitamin D.

The consumption of foods rich in vitamin D including butter, oily fish, and liver was significantly higher in the controls than in the cases, except for milk. Overall, consumption of milk was relatively low in our sample, as 42% of the controls and a quarter of the cases reported never drinking milk on a weekly basis. The Ministry of Health in Saudi Arabia fortified fresh milk, powdered milk, and buttermilk with vitamin D in order to reduce the high burden of vitamin D deficiency [41]. Previous studies have also reported low milk consumption in the Saudi population [42]. Furthermore, the consumption of oily fish was low in our sample, especially among the CHD cases, even though Jeddah and Makkah are located on the coast. The poor consumption of butter, fish, and liver among the cases might be due to changes in their dietary patterns after being affected by CHD. Furthermore, results of the regression analysis did not show a significant association between vitamin D deficiency and the low consumption of food rich in vitamin D in our study sample, which may be due to the fact that only 10–20% of vitamin D in human bodies is obtained from food sources [23].

The current study has several limitations. First, the study sample was small. However, the cases and controls were selected from three different hospitals in the two main cities in the western region of the kingdom; hence, it is expected that the results of the study are likely to be generalizable to Saudis living in the western region. Second, the current study did not investigate the reasons for avoiding sunlight and for the poor consumption of vitamin D supplements and/or foods rich in vitamin D among study subjects. Moreover, courtesy bias might be a weakness of this survey as participants may want to give answers that they believe the researcher want to hear. For example, a large number of cases (65%) answered they are concerned about their vitamin D status, even though about two-third of them never heard or learnt about vitamin D. On the other hand, there are limited studies of knowledge and attitudes about, and behaviors toward, vitamin D in Saudi Arabia and the Middle East region. The strength of this study was that no previous studies have compared knowledge and attitudes about, and behaviors toward vitamin D between subjects with and without CHD as well as examined the associations between vitamin D status and knowledge, attitudes, and behaviors about vitamin D in Saudi Arabia.

6.7 Conclusions

In conclusion, the present study showed that vitamin D deficiency was highly prevalent in subjects with CHD than in the controls. Knowledge about vitamin D was higher among the controls, and they had a higher intake of multivitamin supplements and a higher consumption of butter, oily fish, and liver, while the CHD cases had a higher intake of milk and were sufficiently exposed to sunlight during weekdays and weekends. Our findings, thus, suggest that low levels of knowledge about vitamin D and the low consumption of vitamin supplementations, including vitamin D, calcium, multivitamin, and calcium supplements with vitamin D, may have contributed to the high prevalence of vitamin D deficiency among the CHD cases. Although knowledge, attitudes, and behaviors may not be strongly associated with each other in this study, the results have provided valuable information for prevention of vitamin D deficiency, which may contribute to future interventions of CHD. Moreover, additional studies using qualitative approaches are essential to explore the underlying reasons for unfavorable attitudes toward sun exposure and behaviors that might have contributed to the high burden of vitamin D deficiency in Saudi Arabia.

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Chapter 7: Exploring knowledge and attitudes about vitamin D among adults in Saudi Arabia: a qualitative study (Manuscript 5)

7.1 Introduction

Available evidence from Saudi Arabia indicates that vitamin D deficiency is an epidemic in the country (Ardawi et al., 2012; Elsammak et al., 2011; Tuffaha et al., 2015).As we demonstrated, there is an association between vitamin D deficiency and increased risk of CHD among adults in Saudi Arabia; as a result, it is important to further explore the reasons behind the high prevalence of vitamin D deficiency in the Kingdom. There is a shortage of studies that investigate the cultural and lifestyle behaviours that affect vitamin D status globally, particularly in the Middle East region. Therefore, this chapter is aimed at exploring knowledge of and attitudes toward vitamin D using a qualitative approach. The social and cultural factors that may have resulted in the high prevalence of vitamin D deficiency in Saudi Arabia is also explored. The results showed that there are reasonable levels of knowledge, in some aspects, about vitamin D, including sun exposure as the main source of vitamin D and the effect of vitamin D on bone health. Also, some participants had positive attitudes about exposure to sunlight, but they were avoiding the strong heat in the middle of the day. The majority of study participants indicated that they only exposed their faces and hands to sunlight, while others completely avoided sunlight. Furthermore, participants identified important barriers that prevented them from getting sufficient sunlight. The results also illustrated gender differences regarding the adoption of healthy actions to increase vitamin D status. These results added valuable information that is useful to the development of interventions to address vitamin D deficiency in Saudi Arabia.

This paper has been published as an original research paper in a peer-reviewed journal and has been designed and written according to the journal style including the reference style.

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Declaration:

I (the candidate) am the first and corresponding author of this paper. My contribution to the paper includes the development of the study design, completed the human research ethics application, conducted data collection, performed data analysis, and writing of the manuscript for submission to the journal.

Signed: Date:

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7.2 Abstract

Vitamin D deficiency is widespread in Saudi Arabia. The aim of this study was to explore participants' knowledge about vitamin D and attitudes toward sun exposure. The study also aimed to explore the social and cultural factors that might potentially contribute to vitamin D deficiency in Saudi Arabia. Face-to-face interviews were carried out in the cities of Jeddah and Makkah between May and October 2015. The interview questions were semi-structured, and the data was analyzed using thematic analysis. Study participants showed a reasonable level of knowledge in different areas about vitamin D; including the effect of vitamin D deficiency on bone health and exposure to sunlight as the main source of vitamin D. Participants were also knowledgeable about vitamin D supplements as another source of this vitamin. Nevertheless, there was a shortage of knowledge in relation to dietary sources of vitamin D. In respect to attitudes toward sun exposure, some participants had positive attitudes toward sunlight and were willing to expose themselves to sunlight, but it was restricted to the early morning or late afternoon to avoid the heat. These participants who liked exposure to sunlight were largely exposing only their faces and hands to sunlight. Other participants had negative attitudes toward sun exposure and were avoiding sunlight. Moreover, the study participants identified several barriers to sun exposure, including hot climate, living in high-rise buildings, limited public areas allowing outdoor activities, lifestyle issues such as physical inactivity, and some religious concerns such as wearing hijab. The study results also demonstrate that females were more enthusiastic to take actions to improve their vitamin D status in comparison with males. Recommendations for health education interventions that increase awareness about vitamin D sources, especially food sources, are made. Also, educational interventions should focus on increasing awareness about the sufficient time of the day and duration for sun exposure to improve vitamin D status and the importance of the intake of vitamin D supplements as an affordable source to

improve vitamin D status. Increasing males' awareness of the benefits of vitamin D is important to encourage them to adopt behaviors to improve vitamin D.

Key words: Vitamin D deficiency; Knowledge; Attitudes; qualitative; Sun exposure; Vitamin D supplements; Saudi Arabia

7.3 Introduction

Vitamin D deficiency is highly prevalent in sunny countries such as Saudi Arabia. Previous studies within the country indicated a high rate of vitamin D deficiency among both males and females [1, 2]. A recent national survey reported high rates of vitamin D deficiency: 40% in males and 60% in females in Saudi Arabia [3]. Vitamin D deficiency has historically been known to increase the risk of some musculoskeletal disorders, such as osteoporosis [4]. Further, several studies have shown an association between vitamin D deficiency and other major chronic diseases such as cancer, diabetes, and cardiovascular disease (CVD), worldwide [5-7]. Recently, we reported an independent association between vitamin D deficiency [25(OH)D < 20 ng/mL] and coronary heart disease (CHD) among adults in Saudi Arabia [OR: 6.5, 95% CI: 2.7-15] (p = < 0.001) [8], as well as an association between vitamin D deficiency and diabetes among adults with CHD in the Kingdom [OR: 2.9, 95% CI: 1.02-8.5] (p = 0.04) [9]. These findings suggest that prevention of vitamin D deficiency is vital to reducing the risk of CHD and its associated risk factors in Saudi Arabia.

Several studies have focused on the biological factors that cause vitamin D deficiency around the world; however, few studies have examined the effects of cultural and lifestyle behaviors and knowledge and beliefs that influence vitamin D status [10-12]. Recently, we conducted a study using a quantitative approach to examine knowledge and attitudes about, and behaviors toward, vitamin D in subjects with and without CHD in Saudi Arabia [13]. The results showed that low levels of knowledge about vitamin D and low consumption of vitamin supplements, including multivitamins and vitamin D supplements, were associated with vitamin D deficiency [13]. Hence, the present study was designed to better understand the underlying reasons for the differences in knowledge about vitamin D as well as to explore in more depth behaviors related to vitamin D in Saudi Arabia. The present study also identified the cultural and social factors that might influence vitamin D related knowledge and attitudes in Saudi Arabia. The findings of this study provide additional information that can be useful for developing targeted health promotion and educational interventions concerning vitamin D deficiency in Saudi Arabia. Therefore, the aims of this qualitative study were to 1) explore participants' knowledge and their sources of information about vitamin D, 2) explore participants' attitudes regarding sun exposure, and 3) explore the social and cultural factors that might potentially contribute to vitamin D deficiency in Saudi Arabia.

7.4 Methods

7.4.1 Study design

In-depth interviews were conducted between May and October 2015 in three hospitals located in the western region of Saudi Arabia (in the cities of Jeddah and Makkah). The in-depth, face-to-face interview method was chosen because some cultural issues are sensitive and thus are better discussed individually rather than in groups. Moreover, due to cultural traditions, it might be difficult to have a group that included both genders, so this method was considered the most appropriate way to collect data in this setting. The interviews were semi-structured, with prepared open-ended questions that were adapted from the literature [11, 14, 15]. In this study, the interview questions have been modified to suit the Saudi population (questions in additional file 1).

7.4.2 Recruitment of study subjects

Participants were selected through consultation with the study subjects of the quantitative study of this research project during the data collection [8]. They were asked whether they were willing to participate in the qualitative interviews. The interviews were conducted by the researcher (NA) and took place in the three hospitals where the quantitative study was undertaken: King Abdullah Medical City (KAMC), King Abdulaziz University (KAU), and Tunsi private hospital. The interviews were recorded and then fully transcribed. Ethical approval was obtained from the Griffith University Human Research Ethics Committee (GU Ref No: MED/59/14/HREC), the KAMC Institutional Review Board (IRB No: 15-194), and the KAU Research Ethics Committee (Reference No ll8-15). Study subjects confirmed their agreement to participate in the interviews by signing informed consent forms.

7.4.3 Data analysis

All interviews were fully transcribed by the researcher (NA) after listening to the voice recordings several times. Thematic analysis was used to analyze the data by manually identifying codes and themes. The coding process and theme development was accomplished by the first two authors. NA conducted the initial coding and grouped similar codes together. PL checked all the coding and modified several codes and extracted the common themes based on issues raised by the study participants, while confirming all contextual information with NA during the interviews. NA and PL also discussed and verified all the developed themes.

7.5 Results:

A total of 22 participants took part in the in-depth face to face interviews. The saturation of the data were determined at this point as no more new issues were raised by the last one or two participants. The study participants comprised 11 males and 11 females. The majority of study participants were 49 years and above, married, living in urban areas, Saudis, employees and well educated. The socio-demographic characteristics of study participants are shown in Table 7.1. Each interview lasted approximately 25 to 35 minutes. During the data analysis, four broad themes were revealed: 1) knowledge and information sources about vitamin D, 2) attitudes regarding exposure to sunlight, 3) reasons preventing people from getting sufficient sun exposure, and 4) gender differences regarding taking actions against vitamin D deficiency.

Table 7.1 Socio-demographic characteristics of study participants

Variables	Number	%
Group		
Cases	10	54.5
Controls	12	45.5
Age (years)		
< 49	4	18
≥ 49	18	82
Gender		
Male	11	50
Female	11	50
Marital status		
Single	1	5
Married	17	77
Divorced	4	18
Citizenship		
Saudis	17	77
Non-Saudis	5	23
Place of residence		
Rural	0	0
Urban	21	95.5
Semi-rural	1	4.5
Education		
Up to primary levels	3	14
High School & bachelor or diploma degree	15	68
Master or PhD degree	4	18
Employment		
Employed (Full time, Part time, self-employed)	15	68
Unemployed (Student, Retired, House wife)	7	32
Family income (SR/monthly)*		
< 5000	6	27
5000-15000	9	41
15000- ≥ 25000	7	32

**Saudi Riyal 1SR= .37 AUD*

7.5.1 Knowledge and information sources about vitamin D

7.5.1.1 General understanding of vitamin D deficiency

In the beginning, participants were asked to simply describe what they knew about vitamin D. The purpose of this question was to clarify whether the participants had sufficient knowledge about vitamin D and whether this information was valid. In response to this question, several study participants stated: *"Vitamin D is important for bone health; exposure to sunlight is the main source of vitamin D."*

In addition, some participants mentioned vitamin D supplements as another source of vitamin D besides sun exposure. A few participants also pointed out food rich in vitamin D as a source of vitamin D.

"*I think taking vitamin D supplements is vital to increase vitamin D levels.*" Participant #22, Male.

"*The consumption of food rich in vitamin D and vitamin D supplements would help prevent vitamin D deficiency.*" Participant #4, Female.

A few participants had unclear information about the intake of food rich in vitamin D and vitamin D supplements. One male participant suggested that eating a variety of food might help to improve his vitamin D status. He stated:

"*The intake of different types of fruit and vegetables prevents vitamin D deficiency."*Participant #16, Male.

Likewise, another female participant believed that taking vitamin D supplements alone is not efficient to improve vitamin D status. She stated:

"*We should not depend on supplements and pills to fill our need for vitamin D; we should take vitamin D from its natural sources."* Participant #7, Female.

A few participants named other health benefits related to vitamin D: improving eyesight and depression.

"I know that vitamin D deficiency may cause depression" Participant #1, Female, and

"I know that vitamin D is very important to bone health and eyesight." Participant #1, Male.

However, three participants stated they did not know anything about vitamin D.

7.5.1.2 Source of information about vitamin D

Study participants were also asked to clarify their source of information about vitamin D. They identified the following sources of information about vitamin D: doctors, media, family and friends, and college/universities.

Information from doctors:

Many participants had learned about vitamin D through private visits to doctors. Most of them said they did a blood test and found that they were vitamin D deficient. Also, most of them said that doctors advised them to get exposure to sunlight regularly and to take vitamin D supplements:

"*After I gave birth to my daughter, the doctor asked me to do a blood test. I was vitamin D deficient and he advised me to take vitamin D supplements.*" Participant #1, Female.

"*I learned about the risk of vitamin D deficiency from my doctor. After that, I started searching and reading about vitamin D to gain more information.*" Participant #4, Female.

Moreover, some participants said that they had learned about vitamin D when they were accompanying parents or wives while visiting doctors.

"*When I was going with my father to the doctor, I heard about the importance of vitamin D.*" Participant #10, Male.

Information from the media:

The media was also a source of information about vitamin D, as the participants mentioned television, the internet, newspapers, and magazines as their sources of information as follows:

"*I have heard about vitamin D via television programs.*" Participants #8 and 19, Males.

"*I knew about vitamin D through reading newspapers and the internet.*" Participants #18 and 22, Males.

Information from family and friends or learned at college/universities:

A number of participants reported hearing about vitamin D from their family or friends or through learning at colleges and universities. Also, there was one female participant who mentioned the she got her information about vitamin D by attending a large health educational workshop. She stated that:

"I heard about vitamin D while attending a workshop that aimed to educate women about their health in Jeddah. In the workshop they said Saudi Arabia has a high prevalence of vitamin D deficiency and Saudi women should take vitamin D supplements." Participant #9, Female.

7.5.2 Participants' attitudes about exposure to sunlight

7.5.2.1 Feelings about sun exposure

Participants were asked to state how they feel about exposure to sunlight. The purpose of this question was to know whether the participants liked or disliked exposing themselves to sunlight, which is the key source of vitamin D. Some participants expressed positive attitudes toward sun exposure, such as:

"I like to expose myself to sunlight and never tried to avoid it." Participants #9 and 12, Females.

Although many participants stated that they like sun exposure, they had a preference for sun exposure under certain various conditions. For example, in consideration of high temperature and potentially harmful UV rays in midday, many participants mentioned:

"I prefer to expose myself to sunlight only during late afternoon." Participant #10, Male.

"I like to expose myself to sunlight sometimes, but I tend to avoid the strong, hot sunlight." Participants #3, 4, and 20, Females.

Due to some cultural concerns, a few female participants stated that an appropriate place was required for them to uncover their bodies in order to have sufficient sun exposure. They stated:

"I like to expose myself to sunlight but I cannot go out, I only expose myself at home via windows." Participant #11.

"I want to expose myself to sunlight and like sun exposure, but only in an appropriate place where I can take my hijab off." Participant #2.

However, some other participants had negative attitudes toward sun exposure, such as:

"*I do not like sunlight. I rarely get exposed to sun."* Participants #21, Female; and #8, 15 and 19 Males.

"I avoid sunlight because it is too hot; I usually go out for a walk at night." Participant #13, Male.

7.5.2.2 Preferable time and duration of sun exposure for people who do not mind exposure to sunlight

Exposure to sunlight is a key determinant that affects vitamin D status. The effectiveness of sun exposure depends on different elements, including the season, the time of the day, duration of exposure, and body parts that are exposed to sunlight. Some participants mentioned that they do not expose themselves to sunlight during the summer because of the strong heat that might reach 50° Celsius, especially in the western region cities, such as Jeddah and Makkah.

"I usually go out at night but not during the day especially in summer." Participant #4, Female.

Moreover, many participants said they prefer the time of the early morning (between 6 am and 10 am) or late afternoon to expose themselves to sunlight, as we mentioned previously, to avoid harmful UV rays during the midday:

"I expose myself to sunlight usually during the early morning between 6 am and 7am for less than half an hour." Participant #1, Female.

Further, these participants, however, said that they only exposed their face and hands to sunlight and for approximately 10 to 30 minutes. The following quotes illustrate this:

"I only expose my face and hands." Participant #10, Male, and #9 Female.

"*I expose myself to sunlight during the early morning for less than 15 minutes. Only my face and hands are exposed to sunlight, as I wear the traditional thawb when I go to work every day."* Participant #18, Male.

Other female participants stated that they prefer the late afternoon (between 4 pm and 6 pm) to expose themselves to sunlight, as it is a suitable time for them to go to the gym. They also stated that more parts of their body, such as legs and arms, were exposed to sunlight and their exposure to sunlight tended to be for a longer time.

"I expose myself to sunlight when I go to the gym almost three times per week. Usually I expose my legs, arms, and face to sunlight." Participant # 2.

On the other hand, only one male participant indicated a higher level of sun exposure due to his work duties as he works outside for several hours daily. He stated:

"I expose myself for 2-3 hours every day, as I work outdoors." Participant # 22.

7.5.3 Reasons discouraging people from getting sufficient sun exposure

7.5.3.1 Hot weather all year round

Hot weather, including summer heat, and high humidity, was one of the main barriers highlighted by study participants that prevented them from getting adequate sun exposure. Saudi Arabia in general has a desert climate which is hot almost all throughout the year and mild in winter.

"*In my opinion, the main reason for vitamin D deficiency is the high temperature and hot weather."* Participant # 22, Male.

"*The hot weather in Saudi Arabia is one cause of vitamin D deficiency"* Participants #13 and 17 Males.

"I believe the hot climate in the country is behind vitamin D deficiency." Participant #9, Female.

7.5.3.2 Avoiding sun exposure due to specific health conditions

Some participants mentioned health conditions, such as headache and dizziness, as the main reasons hindering them from getting enough sun exposure. The following quotes indicate that:

"Sun exposure makes me feel dizzy" and *"I avoid sunlight; it causes me a headache."* Participants #13 and 21, Males.

Another male participant added:

"I have a sun allergy. I cannot expose myself to sunlight." Participant # 15.

Similarly, another male participant mentioned sunlight's effect of causing darker skin as a reason stopping him from exposing himself to sunlight.

"I avoid sunlight; I do not want to have darker skin." Participant # 19.

7.5.3.3 House designs: limited access to an open area with sufficient sunlight

Many participants reported that house designs were hindering them from getting adequate sun exposure. They mainly admitted that living in units without private balconies was stopping people, especially females, from receiving sunlight. For example, one female stated:

"*When I go to my family's house, I walk freely on their private terrace and expose myself to sunlight; however, I cannot do this at my home because I live in a small unit."* Participant # 3, Female.

Furthermore, some participants showed a good understanding of the difference between the current and past house architecture in Saudi Arabia. They argued that in the past, houses of most Saudi families had inner spaces that allowed sun rays to enter the house, allowing people to get sufficient sun exposure. In addition, the inside spaces were designed to protect the privacy of the family, as it is an important aspect of Saudi culture. However, the modern design of houses in the country includes completely covered houses or units in high-rise buildings, which clearly does not have this important feature. The following quotes illustrate this:

"*Old houses were designed to have uncovered spaces inside the house that allowed sunlight into the house, but now we live in completely covered high-rise buildings."* Participant #2, Female.

"House designs in Saudi Arabia are different from the past. We used to have indoor spaces that allowed sunlight to enter the house while remaining private." Participant #8, Male.

7.5.3.4 Limited public areas enabling outdoor activities

Many participants believed that the shortage of outdoor public areas, such as public parks and walking trails, is the main reason for their limited sunlight exposure. Some female participants emphasized that it is as a key problem, especially for females in the Kingdom. They stated:

"We have a limited number of public parks with different facilities. Most entertainment places are indoors and covered because of the hot weather." Participant # 3.

"*I prefer to join a gym that has an open private area that allows me to be exposed to sunlight."* Participant 251 # 12.

Likewise, only one male participant pointed out the same issue for young males. He stated: *"There are no outdoor areas for young males to gather that encourage them to expose themselves to sunlight, so they usually go to indoor entertainment centers because of the hot weather*." Participant # 6.

7.5.3.5 Lifestyle issues, especially physical inactivity in Saudi Arabia

Some participants believed that the lifestyle of Saudis might be the reason for the high prevalence of vitamin D deficiency in the country. They pointed out some issues related to having an indoor lifestyle and the lack of physical activity as a barrier to achieving adequate vitamin D serum levels. For example, some male participants said:

"*Not practicing exercise, including walking or jogging, is the main reason for vitamin D deficiency."* Participants # 7 and 15.

Similarly, some participants drew attention to the high dependency on cars for traveling around the city. They stated:

"We do not walk in the street. We usually use cars to go shopping or to work. It might be the reason." Participants #20 and 21, Females.

7.5.3.6 Cultural and religious concerns

Many participants of both genders believed that wearing hijab might be a factor related to the prevalence of vitamin D deficiency among females in Saudi Arabia. Since the majority of Saudi females wear black abayas as hijab to cover themselves, participants also stated that the color of the hijab plays a big role in preventing absorption of sufficient sunlight. The following quotes from two female participants clarify this:

"*Wearing abayas might be a reason for vitamin D deficiency among females in Saudi Arabia.*" Participants # 4 and 12 Females.

"Because we wear black abayas to cover our bodies outside our homes, we may not be exposed to the sun's rays during the day." Participant # 1, Female.

Some also believed that wearing hijab can be a big issue but only for females who do not have a proper private place at home that helps them to get sufficient sun exposure.

"Wearing hijab might be the reason for vitamin D deficiency among females, especially those who do not have a private balcony or backyard to help get exposure to sunlight; most families live like this in our units." Participants #12, Female, and #6, Male.

"Hijab might be a reason for vitamin D deficiency among Saudi females; however, if they want to prevent themselves from being vitamin D deficient, then it is not an excuse." Participant #14, Female.

Nevertheless, other female participants mentioned that they still had a problem with getting exposure to sunlight in a culturally appropriate way even though they have some private uncovered places in their homes. They described the issue as being due to the fact that in

Saudi culture and as being a Muslim, women should be hidden from males' view; thus, they must avoid getting seen by their neighbors, which makes it difficult for them to get sun exposure.

"Even though I have a private balcony, the neighbors could see me, so I have to be careful." Participant # 1, Female.

There were mixed perspectives with regard to the effect of wearing hijab. Another group of participants had a totally different opinion. They believed that wearing hijab cannot be a cause of vitamin D deficiency and pointed out other factors, which according to them, are the main reasons for vitamin D deficiency in the country. The following quotes describe their point of view:

"In the past, women were wearing hijab, yet they had fewer bone problems." Participant #2, Female.

"I do not believe hijab can cause vitamin D deficiency, as women can go out at any time. It's the hot weather that stops them." Participant #8, Male.

7.5.4 Gender differences regarding taking actions against vitamin D deficiency

Many female participants, who were vitamin D deficient, were keen to take actions to improve their vitamin D status. They admitted that doctors had advised them and suggested some methods to increase vitamin D status. These actions and methods included practicing activities to help increase sun exposure, the ingestion of vitamin D supplements, and the consumption of food rich in vitamin D. Some females' quotes illustrate this:

"After I gave birth to my little girl, I was exposing myself and my baby to sunlight to gain vitamin D. I also was taking vitamin D supplements, as I found that I was vitamin D deficient." Participant #1, Female.

"I was taking vitamin D supplements as the doctor asked me to do after I was diagnosed with vitamin D deficiency. Currently, I go to the gym three times a week to expose myself to sunlight and drink fortified milk. I also repeat the blood test every six months." Participant #2, Female.

"I was diagnosed with vitamin D deficiency and currently take vitamin D supplements, as I only expose myself to sunlight through windows at my home." Participant #4, Female.

On the other hand, only a few male participants said they did the blood test and measured serum vitamin D levels after the doctor advised them. One male stated that since he was told that he was vitamin D deficient, he did not take any actions to improve his vitamin D status, but he plans to take some supplements to improve his vitamin D status.

"Even though I work outdoors every day and expose myself to sunlight for long hours, I am vitamin D deficient and planning to take vitamin D supplements in the future." Participant #22, Male.

The rest of the male participants did not do the blood test for vitamin D even though doctors had advised some of them to do it. Also, some of them said they were taking multivitamin supplements and drinking milk. They believed this was enough to get sufficient vitamin D levels. For example, one participant stated:

"I take the required amount of vitamin D through drinking fortified milk with vitamin D and taking multivitamin supplements." Participant #13, Male.

7.6 Discussion:

In the present study, we used a qualitative approach to explore knowledge and attitudes about vitamin D among adults in Saudi Arabia. We also explored social and cultural factors that might potentially contribute to vitamin D deficiency problems in the country. This study has revealed the following key findings: 1) Study participants showed a reasonable level of knowledge about vitamin D in areas related to the effect of vitamin D deficiency on bone health. Participants also had a general understanding of the importance of sun exposure as the main source of vitamin D and of the consumption of vitamin D supplements as an affordable source of this vitamin. However, there was limited knowledge regarding food rich in vitamin D. 2) The participants had mixed feelings toward sun exposure. Some of them had positive attitudes toward sun exposure and were willing to expose themselves to sunlight; however, it was based on some conditions, such as avoiding the high temperature during the middle of the day. Also, some participants expressed negative attitudes toward sun exposure and even avoided sunlight. 3) Participants who did not mind sun exposure were mostly exposing only their faces and hands to sunlight. 4) Several barriers for sun exposure identified by the participants are included hot weather, house designs and living in high-rise buildings, and limited public areas allowing outdoor activities that encourage exposure to sunlight. 5) Lifestyle issues such as physical inactivity and some cultural and religious concerns such as wearing hijab are also factors impeding Saudi people from accessing sufficient sunlight. 6) Female participants were more enthusiastic to take actions to improve their vitamin D status in comparison with male participants.

The present study indicated that participants generally recognized the importance of exposure to sunlight and the intake of vitamin D supplements as good sources of vitamin D. It is noted that the study participants might have limited knowledge about the food sources of vitamin D, as very few participants mentioned milk and cheese as possible sources of vitamin D. Also, some participants thought eating a variety of fruits and vegetables would protect people against vitamin D deficiency, which reflects that some of the participants had received confusing information about this vitamin. The majority of study participants pointed out the effect of vitamin D on bone health. Participants were also aware of the major sources of vitamin D, including exposure to sunlight and the intake of vitamin D supplements. Although food sources of vitamin D were not commonly recognized among the participants, only 10-20% of vitamin D in human bodies is obtained through food sources [16]. Moreover, participants indicated their sources of information regarding vitamin D, including doctors, media, and college/universities. Hence, these are identified as valid channels to introduce and provide information about vitamin D and the importance of vitamin D to the general population. Several studies indicated associations between vitamin D deficiency and several chronic diseases, such as CHD and diabetes [7-9, 17]. The results of the present study will be useful for developing vitamin D prevention strategies that consider more relevant communication channels and target specific aspects of vitamin D deficiency.

The study results indicated that some participants had positive attitudes toward sun exposure, while others had the opposite attitudes and were avoiding sunlight. Negative attitudes toward exposure to sunlight were also reported among different populations, such as China and Australia [11, 15]. Exposure to sunlight is a key determinant that affects vitamin D status. The effectiveness of sun exposure depends on different elements, including the season, the time of the day, duration of exposure, and body parts that are exposed to sunlight. In the current study, the constant hot temperature in the country was the main factor affecting study participants' attitudes and behaviors toward sun exposure, as many participants reported that they avoid the strong heat, and it can cause them some health problems, such as allergic reactions and dizziness. The summer season can last for a long period, from March to November, in Saudi Arabia, and in the western region, in particular, it lasts almost all year round; thus, the majority of the participants considered hot climate as a key barrier to sunlight exposure in Saudi Arabia. Furthermore, besides the hot temperature, Saudi Arabia has unique cultural and religious principles of women wearing hijab to cover themselves. Also, for Saudi males, the traditional clothes have the same features of covering the body parts, but the only difference is in the color (males wear white thawbs, and females wear black abayas). Wearing clothes that cover most of the skin can affect the synthesis of vitamin D, as the skin is not exposed to UVB rays [18]. Thus, the cultural and religious practices, as well as the hot climate in the Kingdom, are considered to have a strong impact on receiving sufficient sun exposure among the population. Moreover, our results suggest that participants may not be completely aware of the amount of sun exposure body parts need to achieve sufficient vitamin D status. Most of the participants who did not mind sun exposure were exposing only their faces and hands to sunlight, and they considered themselves as people who like exposure to sunlight and probably believe it is sufficient. In Saudi Arabia, people usually have darker skin by nature, which affects vitamin D synthesis. The amount of melanin in the skin absorbs UVB which, as result, reduces vitamin D synthesis by slowing the conversion of 7-dehydrocholesterol to vitamin D3 in the skin [18]. Hence, people with darker skin have less efficient vitamin D production in the skin compared to people with lighter skin [18]. This, in fact, makes it more important for Saudi people to expose more parts of the body for a longer time to achieve sufficient vitamin D. The available evidence on sun exposure suggests spending 15 minutes exposed to sunlight without using sunscreen in order to get the beneficial effect of sunlight and avoid the damaging effects at the same time [19]. However, as we indicated previously, because Saudi people have darker skin and mostly wear clothes that cover their skin, they probably need one hour or more of sun exposure to produce the required amount of vitamin D. More research is needed to determine the required length of time of sun exposure to produce a sufficient amount of vitamin D in people with darker skin who cover their skin.

Our results also showed that living in modern buildings (such as high-rise buildings) due to the changes in house designs in the country is a reason preventing many people from getting exposed to sunlight, especially women. As mentioned previously, many female participants were living in units in high-rise buildings with no open areas, which make it difficult for them to expose themselves to sunlight. These results are consistent with a study conducted in Saudi Arabia that reported that the majority of women with vitamin D deficiency were living in units or small houses in crowded suburbs that do not get enough sunlight [20]. Similarly, a study conducted in Australia showed that living in high-rise buildings was linked to the high prevalence of vitamin D deficiency among migrants [21]. Also, some lifestyles factors, such as using cars for transportation and rarely walking outside as well as physical inactivity, lead to reduced opportunities for sunlight exposure. This also has a significant impact on public health in respect to the amount of physical activity required to prevent chronic disease such as obesity and CHD.

The present study indicated that female participants were keener to take some actions to improve their vitamin D status than the male participants after they were diagnosed with vitamin D deficiency. Many female participants started consuming vitamin D supplements after consulting with their doctors, while only two males reported consuming multivitamin supplements. Females also intended to expose themselves to sunlight to increase their serum vitamin D levels. Several studies have shown gender differences in health-related behaviors, indicating that women are more health conscious than men [22, 23]. A study in the USA reported that women aged 17 to 44 years were visiting physicians twice as much as men of the same age. Also, women were 50% more likely to obtain prescription medicine and use that medicine than males of the same age [24].

Based on our findings, there is a need for health education to increase the awareness about the importance of vitamin D and its health effects rather than focusing on only bone health. Furthermore, increasing awareness about the required duration of sun exposure, time of the day, and body parts that need sun exposure is very important in order for people to have sufficient sun exposure. In addition, increasing the general population’s awareness about the food sources of vitamin D and what fortified food is available should also be emphasized to prevent vitamin D deficiency. In Saudi Arabia, milk is fortified with vitamin D, including buttermilk, powder milk and fresh milk [25]. Also, some kinds of cheese and breakfast cereals are also fortified with vitamin D [25]. Moreover, there is a need to increase the availability of suitable places for outdoor activities such as walking and exercising for both genders and to provide private places for women only to allow them to uncover themselves and get the required sun exposure in a cultural appropriate manner. These places, such as gyms and health centers, should be available at affordable prices. Because of the hot climate in the country, along with the cultural and religious behaviors of wearing hijab, increasing the awareness of the benefits of vitamin D supplements is very vital to reduce the high prevalence of vitamin D deficiency.

This study has a number of strengths. The interviews were conducted in the Arabic language, allowing direct communication with the study participants to gain direct insight into the issues embedded in a complex social and cultural context. In addition, the researcher who conducted the interviews (NA) is from the same ethnic group as the study participants and understands their culture and traditions, which helped participants to feel more trust and to speak up easily to share their experiences. Moreover, most existing studies addressing issues related to vitamin D deficiency used quantitative approaches. There is a shortage of qualitative Knowledge, attitudes, and practice (KAP) studies that explore social and cultural factors that influence vitamin D deficiency in Saudi Arabia. This study has added further evidence to explore the underlying issues related to vitamin D deficiency in the Kingdom. The study also has some limitations. Since the interviews were conducted while patients were visiting the hospitals, some patients were in a rush to leave to go back to work or to get their kids from school. In addition, due to the qualitative nature of this study, the results are not generalizable. Furthermore, as the participation in the study was based on the subject's willingness to participate in the interview thus; it might introduce bias as subjects who agreed to be part of the interview might have better understanding of health knowledge than those who chose to not participate in the interview.

7.7 Conclusion

The current study revealed a number of significant findings that will provide health planners with an overview of the attitudes regarding exposure to sunlight among adults in Saudi Arabia and the barriers to adopting behaviours related to vitamin D. It also exemplifies the level of knowledge about different aspects of vitamin D in the country. Health education and promotion programs in the country should focus on the sources of vitamin D, including sun exposure, vitamin supplementation, and food sources, and should clarify the available food fortified with vitamin D in the Kingdom. They also need to increase the awareness about the long-term effect of vitamin D deficiency and its correlation with chronic disease. Health education programs should also highlight the importance of the consumption of vitamin D supplements as an affordable way to improve vitamin D status and should indicate the required amount of time of sunlight exposure in order to have sufficient vitamin D status. Moreover, health promotion efforts should also target males to increase their awareness of the importance of vitamin D and encourage them to adopt vitamin D related behaviors that would be beneficial in improving vitamin D status. Government sector may take an important role in providing suitable areas for outdoor activities and sun exposure for both genders that would be culturally acceptable.

7.8 References

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Chapter 8: General Discussion and Conclusion

8.1 Introduction

Chapter’s four to seven have included separate discussion sections that explained the research findings in comparison with the existing national, regional, and international literature. The previous chapters also provided the strengths and limitation of each study. This final chapter summarises the key findings from each of the four preceding chapters and provides a general discussion of the study findings. It also discusses the strengths and limitations, as well as the implications, of the research and recommendations for future research.

Available evidence in Saudi Arabia indicated a high burden of vitamin D deficiency among the population (Tuffaha et al., 2015). Also, as shown in the systematic review in chapter 2, the prevalence of CHD and the associated risk factors are very high in Saudi Arabia. Recent international evidence suggests that low levels of serum vitamin D may be associated with an increased risk of CHD (Lee et al., 2011; Roy et al., 2015). In Saudi Arabia, no previous studies have been carried out that focused on the relationship between vitamin D status and the risk of CHD among the adult population. Thus, this research project aimed to examine the association between vitamin D status and the risk of CHD among adults in Saudi Arabia. It also sought to investigate the knowledge, attitudes, and behaviours related to vitamin D among the study population, which added more insight to the reasons behind high levels of vitamin D deficiency in Saudi Arabia. To meet the overall aim of this thesis, six research questions were answered in four peer-reviewed papers and presented in chapters four through seven. The analysis was conducted according to the research framework that was presented in chapter 3. First, we examined the association between vitamin D status and CHD after controlling for potential confounding factors. After that, the association between cardio-metabolic risk factors, including diabetes, obesity, hypertension and hypercholesterolemia, and vitamin D status was examined to investigate the indirect association between vitamin D status and CHD. After demonstrating the association between vitamin D deficiency and the risk of CHD among adults in Saudi Arabia, and due to the high prevalence of vitamin D deficiency in Saudi Arabia, which makes it a serious public health problem in the Kingdom, we further investigated the knowledge, attitudes and behaviours related to vitamin D in Saudi Arabia with both quantitative and qualitative approaches to gain a better understanding of the current situation regarding vitamin D in Saudi Arabia.

The purpose of this final chapter is to draw together the main findings of the study. This final chapter is divided into nine sub-sections. The second section presents a summary of the key findings from each of the four previous chapters. The third section provides a general discussion of the association between vitamin D status and the risk of CHD among adults in Saudi Arabia. In the fourth section, a general discussion of the interrelationships between common CHD risk factors and their connection to the future CHD burden was provided. In section five, a general discussion of the knowledge, attitudes and behaviours related to vitamin D in Saudi Arabia was also provided. In section six, the overall public health implications of the research were discussed. In section seven, the strengths and limitation of the research as a whole was provided. Section eight presents the recommendations on policy and health promotion programs and future research. Finally, in section nine, the overall conclusion is provided.

8.2 Summary of key research findings

The findings of this research have established the relationship between vitamin D status and the risk of CHD among adults in Saudi Arabia and achieved a better understanding of the current situation regarding vitamin D status in the country. In chapter 4, the results showed that the prevalence of vitamin D deficiency (serum 25(OH)D < 10 ng/mL) was significantly higher in CHD cases than in the controls (46% and 3%, respectively). Also, vitamin D deficiency (serum 25(OH)D < 20 ng/mL) was significantly associated with an increased risk of CHD among adults in Saudi Arabia. The results of chapter 5 indicated that vitamin D deficiency (serum 25(OH)D < 20 ng/mL) was significantly associated with an increased risk of diabetes in subjects with CHD; however, no significant association was found between vitamin D deficiency and other cardio-metabolic risk factors (obesity, hypertension and hypercholesterolemia) in the same group. On the other hand, no significant associations were found between vitamin D deficiency and various cardio-metabolic risk factors in subjects without CHD. Thus, the results of this research showed that vitamin D deficiency can increase the risk of CHD through both direct and indirect pathways.

Moreover, our results have demonstrated an association between vitamin D deficiency and the risk of CHD among adults in Saudi Arabia. Since vitamin D deficiency is highly prevalent in Saudi Arabia, further investigation about the knowledge, attitudes and behaviours related to vitamin D among the study sample was undertaken by applying both quantitative and qualitative approaches. The results of chapter 6 showed that the total knowledge score was higher in the control subjects than in the CHD subjects [2.5 (±1.8) and 1.6 (±2.2), respectively]. It also showed that CHD cases had better attitudes toward sun exposure than the controls. The control subjects had a significantly higher intake of multivitamin supplements, butter, oily fish and liver in comparison to CHD cases; however, the CHD cases had a significantly higher intake of milk than the controls. Moreover, the multivariate logistic regression analysis revealed that vitamin D deficiency (serum 25(OH)D < 20 ng/mL) was significantly associated with a low level of knowledge about vitamin D, as well as the low intake of vitamin supplements including vitamin D, calcium, multivitamins and calcium supplements with vitamin D. The results in chapter 7 showed reasonable levels of knowledge in some aspects about vitamin D, such as the impact of vitamin D deficiency on bone health, among the study participants. The results also found that some participants had positive attitudes about exposure to sunlight, but it was limited to the time of day and those who like sunlight were mainly exposing only their faces and hands to it. Furthermore, the study participants had identified a number of barriers that prevented them from sufficient sun exposure, such as hot weather and wearing a hijab as a religious principle. The study results also highlighted some gender differences regarding the adoption of healthy actions to increase vitamin D status; in comparison to male participants, the female participants were more enthusiastic about engaging in behaviours that improve their vitamin D status.

8.3 Association between vitamin D status and the risk of CHD and their relationships with common cardio-metabolic risk factors

The studies described in chapters 4 and 5 aimed to examine the association between vitamin D status and CHD after controlling for potential confounding factors. It also attempted to examine the indirect association between vitamin D status and the risk of CHD through interrelationships with cardio-metabolic risk factors, including diabetes, obesity, hypertension and hypercholesterolemia in subjects with and without CHD. The results indicated a significant independent association between vitamin D deficiency and CHD among adults in Saudi Arabia. The subjects with vitamin D deficiency (serum 25(OH)D < 20 ng/mL) were 6.5 times more likely to suffer from CHD than the subjects with adequate vitamin D status. This finding was consistent with several global studies. For example, in developed countries, similar results were reported in New Zealand and the USA (Kendrick et al., 2009; Scragg et al., 1990). Likewise, a number of studies have reported a significant inverse association between vitamin D deficiency and CHD in developing countries such as India and Qatar (El-Menyar et al., 2012; Roy et al., 2015).

The reason for examining the associations between vitamin D status and cardio-metabolic risk factors, such as obesity, diabetes, hypertension and hypercholesterolemia, among both groups, subjects with and without CHD, was to explore the possibly indirect relationship between vitamin D status and CHD by scrutinising the associations between those cardio-metabolic risk factors and vitamin D status. Also, evidence shows that these cardio-metabolic factors are the major risk factors for CHD, so it is important to examine whether vitamin D deficiency would also increase the risk of CHD via the changes in those factors. The results showed that, in subjects with CHD, vitamin D deficiency (serum 25(OH)D < 20 ng/mL) was significantly associated with an increased risk of diabetes. However, no significant association was found between vitamin D deficiency and other cardio-metabolic risk factors (obesity, hypertension and hypercholesterolemia) in subjects with CHD. In subjects without CHD, no significant associations were found between vitamin D deficiency (serum 25(OH)D < 20 ng/mL) and any of the cardio-metabolic risk factors (diabetes, obesity, hypertension and hypercholesterolemia). Several studies worldwide have reported an association between vitamin D deficiency and diabetes (Anderson et al., 2010; Martins et al., 2007; Mattila et al., 2007). Nevertheless, a study that was conducted in Saudi Arabia reported no association between vitamin D status and diabetes (Alhumaidi et al., 2013). The authors of this study stated that they observed high rates of vitamin D deficiency in the control subjects because of failing to apply stringent exclusion criteria. For example, subjects in the control group suffered from medical conditions that led to decreased vitamin D levels in their serum (Alhumaidi et al., 2013). Hence, in this research, we attempted to adhere to strict exclusion criteria (chapter 3, section 3.5.4) to ensure that no other factors would affect vitamin D status in the study samples except for CHD. Therefore, based in our research findings, vitamin D deficiency might be considered as a modifiable risk factor for CHD in Saudi Arabia. Due to the high rates of CHD and associated risk factors in the Kingdom (Al-Nozha, Abdullah, et al., 2007; Al-Nozha, Al-Maatouq, et al., 2004; Al-Nozha et al., 2005; Al-Nozha et al., 2008), the prevention of vitamin D deficiency and improving vitamin D status among the general population is highly desirable.

It has been noticed in the literature that there is no fixed definition for vitamin D deficiency. Different studies have used different cut-off values to define vitamin D deficiency. The main reason for not reaching any agreement to define vitamin D deficiency and adequacy is serum PTH. The production of serum PTH increases when the serum vitamin D levels decrease. The high levels of PTH result in bone loss and fractures (Gallagher & Sai, 2010). Previous studies suggested different cut-off values for vitamin D deficiency, which leads to increased PTH. For example, some studies suggested that when serum 25(OH)D less than 10 ng/mL the production of PTH would increase (Ross et al., 2011), whereas other studies suggested that when serum 25(OH)D is less than 30 ng/mL, the serum levels of PTH increase (Gallagher & Sai, 2010). In the present study, we defined vitamin D deficiency as serum 25(OH)D < 10 ng/mL. However, because of the small sample size of the study and for analysis purposes, we combined vitamin D deficiency and insufficiency and used this cut off in all regression analyses (serum 25(OH)D < 20 ng/mL). In fact, our results were largely consistent with the available evidence, regardless of the definition used for vitamin D deficiency.

The findings of chapter 4 and 5 have important implications in Saudi Arabia. Since CHD is known as one of the most deadly diseases in the world, and we have demonstrated in chapter 2 that CHD and the associated risk factors are highly prevalent in Saudi Arabia (Aljefree & Ahmed, 2015). Also, since the prevalence of vitamin D deficiency is very high in the country (Tuffaha et al., 2015), if there is no intervention strategy in place to prevent and control vitamin D deficiency, it is most likely that the risk of CHD will also increase. Furthermore, increasing the rates of CHD and associated risk factors in the future will double the cost of the treatment and management of CHD and other chronic diseases. Therefore, improving vitamin D status among the general population through increased sun exposure, the consumption of foods that are rich in vitamin D and vitamin D supplements should be considered as an effective and inexpensive way to prevent the incidence of CHD and associated risk factors in the country.

8.4 Complex interrelationships among risk factors and their effects on CHD and the future burden of the disease

In this research we have demonstrated the association between vitamin D deficiency and CHD, which is a novel finding as no previous studies have examined this association among adults in Saudi Arabia. Furthermore, our results indicated that vitamin D deficiency can increase the risk of CHD, not only by direct pathway but also by indirect pathways through influencing the associated risk factors, such as increasing the risk of diabetes. It is worth indicating that no such indirect association was observed between vitamin D deficiency (serum 25(OH)D < 20 ng/mL) and diabetes in subjects without CHD. Since CHD is known as a multifactorial disease, the interactions of these risk factors may display an increasing risk for many chronic diseases. In addition, the international evidence indicated associations between low serum vitamin D levels and increases the risk of diabetes, hypertension, dyslipidaemia and obesity (Anderson et al., 2010; Hintzpeter et al., 2007; Konradsen et al., 2008; Mattila et al., 2007; Muldowney et al., 2011). Hence, the potential interactions between vitamin D status and common CHD risk factors can possibly affect CHD through indirect pathways.

Our research findings showed that vitamin D deficiency is associated with an increased risk of diabetes among CHD cases. However, our results indicated that other cardio-metabolic risk factors (obesity, hypertension and hypercholesterolemia) were not associated with vitamin D status among either group, which is not consistent with many existing studies. Numerous global studies have indicated associations of vitamin D deficiency with obesity (Hintzpeter et al., 2007; Konradsen et al., 2008), hypertension (Anderson et al., 2010) and dyslipidaemia (Muldowney et al., 2011). It is possible that obesity, hypertension and hypercholesterolemia might be underestimated in this study. Since our study samples were collected from hospitals, it is possible that they might have been diagnosed earlier with high blood pressure and high total cholesterol and they were on medications; thus, the prevalence of high blood pressure and high total cholesterol in our sample may not reflect the true prevalence. Also, in this research, BMI was used to measure obesity, since BMI has some limitations in comparison with other obesity indicators, such as total body fat (TBF) and waist-to-hip ratio (WHR) (Burkhauser & Cawley, 2008), it might be the reason for not detecting any association between serum vitamin D levels and obesity. Therefore, the relationships between vitamin D deficiency and obesity, hypertension and high total cholesterol would be more complex than the statistical significance found in this study, especially given the very high prevalence of vitamin D deficiency in the population. Thus, considering the increasing burden of CHD in the future, studies within the country should investigate the interrelationships between vitamin D status and the common risk factors of CHD.

8.5 The knowledge, attitudes and behaviours related to vitamin D among adults in Saudi Arabia

Since the results of chapters 4 and 5 showed a link, either directly or indirectly, between vitamin D deficiency and the risk of CHD among adults in Saudi Arabia and because of the high prevalence of vitamin D deficiency in Saudi Arabia, it prompted us to further investigate the reason for poor vitamin D status in the study population. Therefore, we examined the knowledge, attitudes and behaviours related to vitamin D among the study sample using both quantitative and qualitative approaches. The qualitative data was collected to support the quantitative data and to allow further exploration about the underlying reasons for the high rates of vitamin D deficiency in Saudi Arabia

Thus, studies presented in chapters 6 and 7 aimed to compare the knowledge, attitudes and behaviours (KAP) toward vitamin D between CHD cases and controls in order to understand the upstream determinants of vitamin D deficiency. It also examined the independent associations of vitamin D status with knowledge, attitudes and behaviours related to vitamin D among the study sample after controlling for potential confounders, including CHD status. Furthermore, studies aimed to explore knowledge about vitamin D and attitudes toward sun exposure by using a qualitative approach. It also explored the social and cultural factors that may contribute to the high prevalence of vitamin D deficiency in Saudi Arabia. In order to achieve these aims, quantitative data were collected from the case-control study, as well as data collected by conducting qualitative in-depth interviews which included 22 subjects who participated in the case-control study. The results showed that the total knowledge score was higher in the control subjects than in the CHD subjects. Also, vitamin D deficiency (serum 25(OH)D < 20 ng/mL) was significantly associated with low levels of knowledge about vitamin D among study subjects. Previous studies have reported a significant positive association between the level of knowledge about vitamin D and vitamin D status (Oudshoorn et al., 2011). Low levels of knowledge about vitamin D have been reported in several countries, such as China, UK, Netherland and Kuwait (Al Bathi et al., 2012; Alemu & Varnam, 2012; Kung & Lee, 2006; Oudshoorn et al., 2011). However, the qualitative results of this study showed that the subjects had reasonable levels of knowledge in some aspects about vitamin D, including the impact of vitamin D deficiency on bone health and exposure to sunlight as the key source of vitamin D. Limited knowledge about vitamin D was shown regarding the food sources of vitamin D and the health effects of vitamin D deficiency beyond bone health. Also, doctors, family/friends, media and colleges/universities were identified as the most important sources of information about vitamin D among the study sample, which caused them to be considered as valid channels that should be used appropriately to provide correct information about vitamin D to the general population.

Moreover, the results indicated that CHD cases had better attitudes toward sun exposure than the controls subjects, even though the latter were more knowledgeable about vitamin D than the former cases. This outcome shows contradictory results between knowledge and attitudes and highlights the fact that attitudes and feelings toward sun exposure are not necessarily affected by good levels of knowledge. Similar to our results, a study conducted in China reported unfavourable attitudes towards exposure to sunlight among subjects with good levels of knowledge about vitamin D (Kung & Lee, 2006). The results also indicate low sun exposure behaviours among study samples. It was found that a large portion of both groups was not exposing themselves to sunlight during weekends and weekdays. Also, the results indicated that more than three-quarters of the study samples were only exposing their faces and hands to sunlight, which reflect the low levels of awareness about the required time of exposure to sunlight and body parts exposed in order to obtain a sufficient vitamin levels in the body. Thus, poor sun exposure behaviour was shown in our study, which illustrates the reason for not observing a significant association between sun exposure behaviour and vitamin D when conducting the regression analysis. In fact, it is very important for the Saudi population to expose more parts of their bodies to sunlight, rather than only the face and hands and for a longer period of time in order to improve their vitamin D status since they have darker skin by nature. People with darker skin produce less vitamin D in the skin than people with lighter skin (Holick, 2007). In developed countries, studies suggested that, in order to get a sufficient amount of vitamin D and, at the same time, avoid the harm of excessive sunlight, spending 15 minutes in the sun without wearing sunscreen is required (Khalsa, 2009). However, since Saudi people have darker skin they require longer time of sun exposure in order to have sufficient vitamin D. Furthermore, the qualitative data of this research have shown very important findings regarding the barriers to sun exposure in Saudi Arabia as identified by the participants. One of the barriers was wearing a hijab, which may prevent females from getting sufficient sunlight. In Saudi Arabia, women wear a hijab as a religious principle because it covers the body and stops the skin from absorbing the sunlight. For Saudi men, the situation is similar because traditional male clothes also cover the whole body, except for the face and hands. Thus, covering most of the body with clothing reduces the production of vitamin D because sunlight is blocked from the skin (Holick, 2007). The participants also cited living in high-rise buildings as a barrier to acquiring the proper amount of sunlight. Some participants explained the difference in housing architecture over time because, in the past, houses used to have inner spaces that permitted the entry of sunlight. However, nowadays many people live in high-rise buildings that do not have any open spaces. Even if there were private balconies in the units, it would be difficult for females to expose themselves to sunlight in a culturally appropriate way because such spaces are small and close together; hence, they may be seen by males. A study conducted among immigrants in Australia reported an association between the burden of vitamin D deficiency and living in high-rise buildings (Brand et al., 2008). Also, a previous study in Saudi Arabia indicated that a high proportion of women who are diagnosed with vitamin D deficiency were living in disorganized, busy suburbs that lack the entry of sufficient sunlight into the buildings (Siddiqui & Kamfar, 2007). Moreover, the limited number of public areas for outdoor activities that promote exposure to sunlight and some lifestyle issues, such as a high dependency on cars for transportation and high rates of physical inactivity, were among the barriers for sunlight exposure that the participants identified. The hot weather and high temperatures were the key factors that influenced the participants' feelings and behaviors towards sun exposure, especially since the summer season lasts for nearly the whole year in the western region of the kingdom where the study was conducted.

The results showed differences in vitamin D-related behaviors between CHD cases and controls. The control subjects had a significantly higher intake of multivitamin supplements compared to CHD cases. The results also indicated that vitamin D deficiency was significantly associated with low intake of vitamin supplements including vitamin D, calcium, multivitamin, and calcium supplements with vitamin D. These results emphasize the importance of vitamin D supplements as an affordable way to improve vitamin D status among the Saudi population, especially after considering the aforementioned barriers for sun exposure that were identified in this research, such as hot weather and wearing a hijab. Increase general population awareness about the intake of vitamin D supplements is essential in order to enhance vitamin D status and prevent CHD and its associated risk factors. It is also worth mentioning that no significant association was found between vitamin D deficiency and the intake of foods rich in vitamin D in this study, which might be due to the fact that only 10% to 20% of vitamin D in the human body is acquired from dietary sources (Geleijnse, 2011).

Another important theme that emerged in the KAP qualitative study was that, in comparison to their male counterparts, female participants were more health conscious and more enthusiastic about engaging in behaviours that improve their vitamin D status t. Similar results have been reported in previous studies (Courtenay et al., 2002; Wardle et al., 2004). This implies that gender differences regarding the awareness of vitamin D should be addressed by health promotion programs in order to encourage males to improve their vitamin D status, especially since CHD is more common among males than females. Hence, our results suggest that the low levels of knowledge about vitamin D, low intake of vitamin supplements and insufficient sun exposure might be the main reasons for the high prevalence of vitamin D deficiency in Saudi Arabia.

8.6 Overall implications of the research

The results of this thesis have several implications on economy, practice and policy. CHD is one of the world's major causes of death and disability. The expenditure of health care services for CHD is very high and costs governments millions of dollars every year. For example, in Australia, the health expenditure for CVD was $7,605 million in 2008-2009, with spending on CHD the highest among the CVD group ($2,028 million), followed by stroke (AIHW, 2017). In Saudi Arabia, information on the health expenditure for CVD is not available; however, the health expenditure for non-communicable diseases, including diabetes, CVD, hypertension and cancer, was about $1.9 billion per year (Almalki et al., 2011). Thus, prevention and reducing the risk of CHD is vital and can result in decreased numbers of CHD incidents every year.

In this research, we have demonstrated an inverse association between vitamin D status and CHD among adults in Saudi Arabia. These findings are consistent with several studies worldwide (Roy et al., 2015; Scragg et al., 1990). We have also demonstrated the association between vitamin D deficiency and diabetes among subjects with CHD and suggesting that by improving vitamin D status through appropriate intervention may reduce the risk of CHD. However, considering the limitations of this study, further studies with representative samples are required to confirm these results. The results of this research were the first investigation between vitamin D status and the risk of CHD in Saudi Arabia and provided an opportunity for further understanding of the current situation of CHD and vitamin D status in Saudi Arabia.

Vitamin D deficiency is highly prevalent in Saudi Arabia (Tuffaha et al., 2015). There is also a high prevalence of CHD risk factors, such as obesity, diabetes, dyslipidaemia, high blood pressure and high rates of physical inactivity in the country (Al-Nozha, Abdullah, et al., 2007; Al-Nozha et al., 2005; Al-Nozha et al., 2008).). As a consequence of the high burden of these health conditions, the incidence of CHD increases accordingly among relatively younger generations of Saudi Arabians. Thus, expenses in the treatment and management of CHD and the associated risk factors in the country will both increase. The consumption of vitamin D through food sources and supplementation or by simply increasing sun exposure is inexpensive and can be considered as a cost-effective public health method in the prevention of CHD and associated risk factors in Saudi Arabia.

The findings of this thesis have important implications on practice. The results revealed low sun exposure behaviours among the study subjects and most of those who do not mind sun exposure were only exposing their faces and hands to sunlight. Hence, public health messages in Saudi Arabia should provide advice for the required time of sun exposure according to people's skin colour and clothing style in order to obtain sufficient vitamin D, especially for women who wear a hijab. Furthermore, when considering barriers for sun exposure that were identified among our study subjects, food fortification with vitamin D can be an important tool to reduce vitamin D deficiency in the country. Even though our results showed no significant association between the consumption of foods rich in vitamin D and vitamin D status, previous studies indicated that the intake of milk fortified with vitamin D has significantly increased vitamin D status among Chinese women (Chee, Suriah, Chan, Zaitun, & Chan, 2003). In Saudi Arabia, some basic foods are already fortified with vitamin D, including milk, cheese and breakfast cereals (Sadat-Ali et al., 2013). However, people unaware of these products and previous studies showed a low consumption of milk in Saudi Arabia (Farghaly et al., 2007). Also, the intake of vitamin D supplementation can be considered as an affordable and inexpensive way to improve vitamin D status. Public health messages should increase people awareness about the intake of vitamin D supplements in order to improve vitamin D status in both genders.

The results of this research also have important implications on policy. Our results showed that limited public areas were a barrier that preventing people in Saudi Arabia from getting sufficient sun exposure. The development of policies to expand the number of public areas with required facilities is important to encourage people to increase their exposure to sunlight. In addition, for women wearing a hijab, it is important to provide suitable private places such as gyms and health care centres to increase exposure to sunlight. Gyms and health care centres that provide services for women in Saudi Arabia usually have an open area that include pools and allow female participants to expose to sunlight and obtain a tan while maintain their privacy. These places, such as gyms and health care centres, should be available at affordable prices. Moreover, our results also suggested that male participants were less aware of the benefits of vitamin D. Also, males who were diagnosed with vitamin D deficiency were less motivated to adapt any action to improve their vitamin D levels. Health promotion accomplishments should adopt strategies to address gender differences regarding the awareness of vitamin D and encourage males to practice behaviours to prevent vitamin D deficiency and, as a result, reduce the incidence of CHD. Furthermore, the results indicated that colleges and universities were a good source of information about vitamin D. Therefore, curriculum developers in nutrition and science related subjects in universities and colleges should focus more on providing additional information about the health effects of vitamin D deficiency instead of solely educating students on bone health. Even though the relationship between vitamin D status and chronic disease is relatively new in medical research, it is imperative for general population health. Also, our results showed that doctors, media, family/friends and colleges/universities were the most valid channels to provide efficient information about vitamin D to the Saudi population. Thus, public health message providers should efficiently use these channels to increase awareness and deliver valid information regarding vitamin D.

8.7 Strengths and limitations of the study

This research has several strengths. The main strength of this study was that it has demonstrated an independent association between vitamin D status and the risk of CHD, which has never been explored before in the Saudi population. Also, this research revealed an indirect relationship between vitamin D status and the risk of CHD by examining the association between cardio-metabolic risk factors and vitamin D status among the study sample, which added more value to this research. Moreover, a wide range of confounding factors was adjusted in order to demonstrate the association between vitamin D status and CHD. The confounding factors that were included in the regression were socio-demographic variables, cardio-metabolic risk factors, behavioural risk factors, the use of vitamin D supplements, the use of sunscreen and time spent outdoors for sun exposure, which increased the validity of the findings. Likewise, the previously mentioned confounding factors were also controlled for in order to demonstrate the associations between vitamin D status and cardio-metabolic risk factors among the study sample.

Another strength of this study was that it used a mixed method to comprehensively examine the knowledge, attitudes and behaviours related to vitamin D among adults in Saudi Arabia. To date, there is a shortage of studies examining the knowledge, attitudes and behaviours related to vitamin D in the Middle East in general. Also, no previous studies have examined the associations of vitamin D status with the knowledge, attitudes and behaviours related to vitamin D in Saudi Arabia, as well as a comparison of knowledge, attitudes and behaviours related to vitamin D between subjects with and without CHD in the Kingdom.

Furthermore, the qualitative KAP study provided an in-depth exploration of the underlying reasons for the high prevalence of vitamin D deficiency in the country, as there are limited KAP qualitative studies that explored the social and cultural factors that contribute to vitamin D deficiency in Saudi Arabia. Furthermore, this research was not restricted to a specific gender, as it investigated both males and females. In addition, the measurement of CHD risk factors was conducted in the hospitals where the study was undertaken and was not self-reported, which further strengthens the results.

On the other hand, this research has a number of limitations. The study used a case-control design that only infers the association between the study variables; however, it cannot draw the cause-effect relationship. Nevertheless, it provides stronger evidence than the cross-sectional design. It is also important to recognize that, due to some restrictions related to time and funding for the accomplishment of this PhD research in the required timeframe, it was not possible to use a cohort or experimental design. Moreover, selection bias might be another issue in this research because the cases and controls were collected from different hospitals. It is important to clarify that the collection of study subjects were conducted during the Muslim pilgrimage season. Since the KAMC hospital (where the cases were recruited) is located close to the pilgrimage site in Makkah city, its outpatient clinics were closed to the delivery of health services to pilgrims alone. Hence, the control subjects were recruited from two different hospitals in Makkah and Jeddah cities as it was not possible to collect control subjects from KAMC hospital. In fact, the majority of control subjects (153 subjects) were recruited from another hospital in the same city (Tunsi private hospital in Makkah) and a small number was recruited from KAU hospital in Jeddah (42 subjects). Also, there is a short distance between the two cities (Jeddah and Makkah) of only 70 km, which means that their residents were more likely to share the same socio-demographics. Moreover, in order to minimise the impact of selection bias in this study, socio-demographic variables were controlled for in the final regression to demonstrate the association between vitamin D status and CHD. Similarly, as a result of recruiting cases and controls from different hospitals, the analysis of blood samples was conducted in different laboratories which made it difficult to have strict control on quality assurance of the analytical method; hence, it may potentially introduce some bias.

In addition, the study participants were asked to provide some information, including their smoking history, which may introduce some recall bias. Unfortunately, information about factors that are also important for the development of CHD, such as sitting time or sedentary behaviour and sleeping problems were not collected in this study, future studies need to consider these factors. Furthermore, because of the limited budget in this research, a single measurement of 25 (OH)D was conducted to all study participants, which only shows the current status of vitamin D, whereas multiple measurements of 25 (OH)D would better reflect the average of serum 25 (OH)D. Likewise, the assay method used to measure vitamin D serum levels [chemiluminescence microparticle immunoassay (CMIA)] might over-estimate vitamin D deficiency among study subjects in comparison to the gold standard assay method Liquid chromatography-tandem mass spectrometry (LC-MS/MS). Another limitation for this research was in relation to the recruitment of case subjects. The case subjects included in this study were considered as first incident patients who were diagnosed with CHD at the time of the study, as well as cases who were diagnosed earlier prior to data collection for this study. For patients who were previously diagnosed with CHD, we do not have information regarding the duration of time since they were diagnosed with CHD. However, only 30% of cases were diagnosed earlier with CHD; the remaining 70% were considered as first incident cases with an acute event. Moreover, the very high OR ratio obtained when we conducted multivariate logistic regression analysis to examine the association between vitamin D status and CHD using three categories of vitamin D

[25(OH)D < 10 ng/mL, 10 to <19.9 ng/mL, and ≥ 20 ng/mL] was most likely due to the small sample size. However, we also conducted the regression analysis using only two categories of vitamin D status [25(OH)D < 20 ng/mL, and ≥ 20 ng/mL] to enhance the statistical precision because of the small sample size. The qualitative study has also some limitations. The qualitative interviews were conducted while patients were visiting their doctors in the same hospitals; hence, some subjects were in a hurry to return to work. Also, it is difficult to generalize the results because of the qualitative nature of the study.

8.8 Recommendations and future research

The results of this study added to the growing body of research and support previous evidence that suggest the low serum vitamin D levels might be associated with an increased risk of CHD. The findings of this research have some recommendations for public health initiatives and interventions in Saudi Arabia, as well as recommendations for future research.

It is essential for public health initiatives in Saudi Arabia to provide accurate information to the general population regarding the required duration of sun exposure according to skin colour and increase their awareness of the importance of sun exposure in order to obtain sufficient vitamin D. By using the various channels identified in this research, such as doctors, media and colleges/universities, it is vital to increase awareness about the health effects of vitamin D deficiency and its association with increased the risk of CHD and associated risk factors. Also, increasing people awareness of the importance of the intake of vitamin D supplements is very important to improve vitamin D status in the country and, as result, prevent CHD.

Furthermore, considering the limitations of this study, further studies with a larger sample size and representative sample are needed to further investigate the association between vitamin D status and the risk of CHD in Saudi Arabia. Also, to examine the association between vitamin D status and obesity in future research, it is better to use other obesity indicators, such as total body fat (TBF) and waist-to-hip ratio (WHR). Likewise, further studies are needed to investigate the possible associations between vitamin D status and hypertension and hypercholesterolemia among adults in Saudi Arabia. Prospective studies with a long follow-up period are needed to support our findings and to determine if the intake of vitamin D supplements is associated with a decreased risk of CHD among healthy subjects in Saudi Arabia. Furthermore, the majority of published research on the relationship between vitamin D deficiency and CHD, including this research, arise from observational studies. A limited number of RCTs are conducted to examine the effect of vitamin D supplements on the risk of CHD. The available evidence from RCTs either consisted of a small dosage of vitamin D supplements or a small sample size; hence, they failed to establish any causal relationship. Therefore, well designed RCTs with a large sample size and lengthy duration are required among different populations in order to conclude causality of the association between vitamin D status and CHD.

8.9 Conclusion

The findings of this research revealed that vitamin D deficiency can increase the risk of CHD among adults in Saudi Arabia via direct and indirect pathways by affecting the associated risk factors, such as increasing the risk of diabetes. Furthermore, the results of this research showed that low levels of knowledge about vitamin D, the low intake of vitamin supplements and insufficient sun exposure behaviours might be the major reasons for the high prevalence of vitamin D deficiency in Saudi Arabia. These results emphasize the importance of increase awareness and knowledge about different aspects regarding vitamin D, particularly, the sources of vitamin D and the health effects of vitamin D deficiency. It also affirms the importance of the intake of vitamin D supplements as an inexpensive source of vitamin D, especially after several barriers to sunlight exposure have been identified among our study sample. The results also highlight the importance of accurate sun exposure behaviours in order to obtain sufficient vitamin D. The results of this thesis increased our knowledge about vitamin D as a potential modifiable risk factor of CHD and added a better understanding of the current situation regarding vitamin D status in Saudi Arabia. These results will enable the development of appropriate public health interventions that target the prevention of CHD and associated risk factors in the Kingdom.

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Appendix 1: Information sheet and informed consents for the case-control study in Arabic

بسم الله الرحمن الرحيم

إذن خطي بالموافقه علي المشاركه في البحث الطبي

Consent for the agreement in participation in medical research

- أنت مدعو/ أنتي مدعوه من قبل الباحثه نجلاء محمد حمادي الجفري إلي المشاركه في بحث علمي تحت عنوان "العلاقه بين فيتامين د و أمراض القلب الوعائيه لدي البالغين في المملكه العربيه السعوديه: دراسة الحالات والشواهد" كـ جزء من متطلب رسالة الدكتوراه للباحثه في جامعة جريفيث في أستراليا.
- المملكه العربيه السعوديه تتعرض لكميات وافره من أشعة الشمس خلال فصول السنه نظراً لظروفها المناخيه وطبيعتها الجغرافيه، في حين أثبتت الدراسات العلميه المحليه أن نقص فيتامين د التغذوي هو حاله شائعه بين السعوديين البالغين سواء كانوا رجالاً أم نساء. العديد من الدراسات حول العالم أظهرت أن نقص فيتامين د التغذوي يؤثر سلبياً علي جهاز القلب الوعائي. في المملكه العربيه السعوديه، لا توجد دراسات سابقه عن العلاقه بين مستويات فيتامين د الغذائي و أمراض القلب الوعائيه.
- الهدف من الدراسه الحاليه هو إختبار العلاقه بين مستويات فيتامين د الغذائي و خطر الإصابه بأمراض القلب الوعائيه بالإضافه الي دراسة العلاقه بين مستويات فيتامين د الغذائي و عوامل الخطوره لأمراض القلب التي تشمل: السمنه، السكّر، إرتفاع ضغط الدم، إرتفاع دهون الدم، بين السعوديين المصابين بأمراض القلب الوعائيه (حاله) ومقارنتهم بـ سعوديين غير مصابيين بأمراض القلب الوعائيه (شاهد). هذه الدراسه أيضاً تختبر العلاقه بين مختلف عوامل الخطوره متضمناً السمنه، السكّر، إرتفاع ضغط الدم، إرتفاع دهون الدم، التدخين، ممارسة الرياضه، الأنماط الغذائيه مع أمراض القلب الوعائيه في نفس عينة الدراسه.
- للمشاركه في هذا البحث، يجب أن تكون: سعودي الجنسيه أو مقيم في السعوديه لفتره لا تقل عن خمس سنوات و أن تبلغ من العمر 18 سنه أو أكثر.
- مشاركتك في البحث هو أمر تطوعي، إذا قبلت/قبلتي المشاركه في البحث ف لك حق الإنسحاب في أي وقت. قرارك بالمشاركه في البحث العلمي لن يؤثر عليك بأي طريقه ولن يكون هناك أي خساره أو فوات لمنفعه تستحقها. أيضاً، في حالة حدوث أي تغيرات في البحث سيتم إبلاغك وللمشارك الحريه في الإستمرار بالمشاركه في الدراسه.
- هذه الدراسه توفر الأساسيات لتطوير برامج لتعزيز الصحه العامه لـ عموم المجتمع السعودي و المرضى المصابين بأمراض القلب الوعائيه، مما يساعد علي تخفيض خطر الإصابه بأمراض القلب وعوامل الخطوره المصاحبه لها بالإضافه لنقص فيتامين د الغذائي في المملكه العربيه السعوديه. أيضاً، المنفعه المفترضه للمشاركه في البحث تستمد من نتائج البحث حيث أن جميع المشاركين في البحث سوف يحصلوا علي النتائج المتعلقه بـ مستويات فيتامين د الغذائي، مؤشر كتلة الجسم (مقياس للسمنه)، و ضغط الدم بدون دفع أي تكاليف. بالإضافه إلي أن المشاركين في البحث سوف يتم تبليغهم بإستلام نتائج البحث عن طريق البريد أو الايميل. وبالنسبه للأشخاص المصابين بنقص فيتامين د الغذائي سوف يتم إرشادهم لمراجعه الطبيب المختص.
- لا يوجد ضرر جسماني أو معنوي يتوقع حدوثه للمشاركين في البحث. قد يكون هناك القليل من الإنزعاج خلال عملية تجميع عينات الدم خلال الوريد.
- أي معلومات سوف يتم الحصول عليها خلال الدراسه ستكون سريه ولن يتم كشفها إلا في حالة أخذ إذن مباشر من المشارك/المشاركه في البحث أو إذا تطلب عن طريق القانون. أي معلومات تخص هوية المشاركين في

البحث مثل الأسماء، أرقام التلفون، عنوان سيتم الإحتفاظ بها بسريه بعيداً عن أي معلومات أخري يتم أخذها من المشاركين والوصول إلي هذه المعلومات سيكون محظور إلا علي عدد قليل من المشرفين علي البحث. المعلومات الخاصه بهوية المشلركين مهمه للباحث حيث ستمكنه من إستدعاء المشاركين في البحث للمشاركه في المرحله الثانيه من الدراسه وتمكن الباحث أيضاً من ربط النتائج المتحصل عليها من المرحله الأولي والثانيه من الدراسه. بعد ذلك كل المعلومات الخاصه بالتعريف علي هوية المشاركين في البحث سيتم حذفها وجميع إستمارات الإستبيان و إستمارات جمع البيانات سيتم ترميزها برموز خاصه لحفظ هوية المشاركين. لا يوجد أي نتائج قانونيه متعلقه بـ مشاركتك في البحث وجميع المعلومات التي سيتم تجميعها ستكون بغرض خدمة البحث العلمي فقط.

- إذا وافقت/وافقتي علي المشاركه في الدراسه الحاليه، سيطلب منك عدة أمور للقيام بها تتضمن: قراءة وتوقيع النموذج الحالي (طلب الموافقه علي المشاركه في البحث العلمي أو الموافقه المتنوره المستنيره)، إكمال المقابله الشخصيه مع مقابليين متدربين بإستخدام إستبيان منظم معد مسبقاً، أخذ مقاييس الطول والوزن، أخذ قياسات ضغط الدم، و سحب عينة دم لمره واحده فقط.
- عينة الدم التي سيتم سحبها (10 ملليليتر) سيتم تعريضها لعملية الطرد المركزي أولاً ثم حفظها مجمده علي درجة حراره °80 - لحين الإنتظار تحليل عينات الدم بواسطه المختبر. سيتم التخلص من عينات الدم بعد أن يتم تحليلها.
- إذا لديك أي أسئله أو إستفسارات تتعلق بالبحث أو بحقوق المشارك، أو التبليغ في حالة حدوث ضرر:

  الأستاذه نجلاء الجفري : هاتف (+966543165165)

  najlaa.aljefree@griffithuni.edu.au

  اللجنه المحليه: البريد الإلكتروني IRB@kamc.med.sa

  اللجنه الدوليه: جامعة جريفيث (أستراليا) research-ethics@griffith.edu.au

  الهاتف (61737354375)
- بالتوقيع علي الموافقه المتنوره المستنيره أقرّ أنا المشارك/ المشاركه في البحث بالموافقه علي الإطلاع علي الملف الطبي الخاص بي لغرض الحصول علي بيانات تخص الدراسه الحاليه.
- بالتوقيع علي الموافقه التنوره المستنيره أقرّ أنا المشارك/المشاركه في البحث، أني قد قرأت وفهمت جميع المعلومات المدونه أعلاه، و أوافق علي المشاركه في الدراسه الحاليه.
- أقرّ أنا الباحث الرئيسي بصحة المعلومات المدونه أعلاه والتعهد بتزوييد اللجنه المحليه بأي تغييرات محتمله في حال حدوثها وقبل العمل بها.

المشارك/ الإنسان موضوع البحث: التوقيع:

أستاذه نجلاء الجفري التوقيع:

التاريخ: / / هـ الموافق: / / م

Appendix 2: Information sheet and informed consents for the case-control study in English

Association between vitamin D status and coronary heart disease in Saudi Arabian adults

INFORMATION SHEET

Who is conducting the research?

Chief investigator 1: A/Prof Faruk Ahmed, School of Medicine (Public Health), (61-7) 555 27874, f.ahmed@griffith.edu.au

Chief investigator 2: Dr. Patricia Lee, School of Medicine (Public Health), (61-7) 555 27865, patricia.lee@griffith.edu.au

Research student: Mrs. Najlaa Aljefree, School of Medicine (Public Health), (61-7) 555 27865, najlaa.aljefree@griffithuni.edu.au

Why is the research being conducted?

This project is being conducted through Griffith University, as part of a PhD project for Mrs. Najlaa Aljefree. Saudi Arabia has plentiful sunlight throughout the year, however national studies have shown that vitamin D deficiency is highly prevalent among Saudi adults of both genders. Accumulative data indicated that vitamin D deficiency may negatively affect the cardiovascular system. No previous studies have been carried out among Saudi adults that focus on the relationship between vitamin D status and coronary heart disease (CHD).

The purpose of this study is to investigate the relationship between vitamin D status and the risk of CHD as well as vitamin D status and cardio metabolic risk factors including, obesity, diabetes, hypertension and dyslipidemia among Saudis diagnosed with CHD (cases) and compare them to Saudis free from the disease (controls). This study is also investigating the relationship of various risk factors including, obesity, diabetes, hypertension, dyslipidemia, smoking, dietary patterns and physical activity with CHD among the same population.

What you will be asked to do:

If you volunteer to participate in this study, you are asked to read and sign this consent form, complete interviews in person by trained interviewers using a structured questionnaire, complete anthropometric measurements including weight and height, complete blood pressure measurements, and provide a single blood sample. A single blood sample (10 mL) will be collected and centrifuged first then the separated serum will kept frozen at - 80°C while waiting for analysing using a reverse phase HPLC with a UV detection technique by the laboratory staff.

The basis by which participants will be selected or screened:
To be a participant in this study, you must be a native Saudi or resident in Saudi Arabia for at least five years and adult 18 years and above.

The expected benefits of the research:
This study can provide the basis for an appropriate health promotion and public health interventions for the general population and patients diagnosed with CHD, which would help reduce the risk of CHD and its associated risk factors as well as vitamin D deficiency in Saudi Arabia. In addition, the main benefits from participating in this study will be derived from the results as all the study subjects will receive feedback regarding their vitamin D status, BMI and blood pressure without charge. Participants will be advised about the possibility to receive a summary of the study findings by email or post**.** Also, subjects who identified with vitamin D deficiency will be advised to see a doctor.

Risks to you:

No significant physical or psychological risk/harm to the participants will be introduced in this study. There will be a very minimal risk involved for the subjects participating in this research, including a slight wound and inconvenience during the collection of blood samples through venepuncture.

Your confidentiality:

Any information that is obtained in connection with this study will remain strictly confidential and will be disclosed only with your permission or as required by law. Any identifying information such as your full name, phone number and address will be stored separately from the information you provide and the access to this information is restricted to a small number of senior members of this study team. We need to retain your identifying information so that the researcher can invite you to participate in the second phase of this project and to enable the researcher to match the two parts of the results of this study. After that, all your identifying information will be removed and all surveys and data sheets will be labelled with a unique barcode number. No legal ramifications can be taken as result of your answers. All data collected is for research and educational purposes only.

Your participation is voluntary:

Your participation in this project is voluntary. If you volunteer to participate in this study, you can withdraw at any time without comment or penalty by contacting the researcher. Your decision to participate will not affect you in any way or negatively impact any other personal consideration or right you usually expect.

Questions / further information:

If you have any questions regarding this study, you may reach the principle researcher, Mrs. Najlaa Aljefree at (+966 543165165).

The ethical conduct of this research

Griffith University conducts research in accordance with the National Statement on Ethical Conduct in Human Research. However, if you do have any concerns or complaints about the ethical conduct of the project you may contact the Manager, Research Ethics on (617) 373 54375 or **research-ethics@griffith.edu.au**.

Privacy Statement – non disclosure

"The conduct of this research involves the collection, access and/or use of your identified personal information. The information collected is confidential and will not be disclosed to third parties without your consent, except to meet government, legal or other regulatory authority requirements. A de-identified copy of this data may be used for other research purposes. However, your anonymity will at all times be safeguarded. For further information consult the University's Privacy Plan at http://www.griffith.edu.au/about-griffith/plans-publications/griffith-university-privacy-plan or telephone (07) 3735 4375."

Association between vitamin D status and coronary heart disease in Saudi Arabian adults

CONSENT FORM

Research Team:

Chief investigator 1: A/Prof Faruk Ahmed, School of Medicine (Public Health), (61-7) 555 27874, f.ahmed@griffith.edu.au

Chief investigator 2: Dr. Patricia Lee, School of Medicine (Public Health), (61-7) 555 27865, patricia.lee@griffith.edu.au

Research student: Mrs. Najlaa Aljefree, School of Medicine (Public Health), (61-7) 555 27865, najlaa.aljefree@griffithuni.edu.au

By signing below, I confirm that I have read and understood the information package and in particular have noted that:

- I understand that my involvement in this research will include read and sign this consent form, complete interviews by trained interviewers, complete anthropometric and blood pressure measurements, and provide a single blood sample;
- I have had any questions answered to my satisfaction;
- I understand the risks involved;
- I understand that there will be no direct benefit to me from my participation in this research;
- I agree that the researchers can seek access to my medical records for use in this research
- I understand that the information gained from this research may result in improved methods for diagnosis or treatment, but as an individual I do not have ownership of these results, research records, or the sample that I give
- I understand that my participation in this research is voluntary;
- I understand that if I have any additional questions I can contact the research team;
- I understand that I am free to withdraw at any time, without explanation or penalty;
- I understand that I can contact the Manager, Research Ethics, at Griffith University Human Research Ethics Committee on (617) 373 54375 (or research-ethics@griffith.edu.au) if I have any concerns about the ethical conduct of the project; and
- I agree to participate in the project.

Name	
Signature	
Date	

Appendix 3: Survey

Association between vitamin D status and coronary heart disease in Saudi Arabian adults: a case-control

Patient ID		**Group (A) or (B)**	
Interviewer ID			
Hospital name		Date of interview	

Part one:

I. Socio-demographics

Please answer the following questions:

1- What is your age group?
□ 20-29 years □30-39 years □40-49 years
□50-59 years □60-65 years □>65 years
2- What is your gender?
□Male □Female
3- If you are female and married; are you pregnant? **(females only)**
□Yes □No
4- Are you currently breastfeeding your baby? **(females only)**
□Yes □No
5- What is your marital status?
□Single □Married □Divorced □Widowed
6- What is your education level?
□No formal education □Up to primary level □Secondary level
□ High school □ Bachelor or diploma degree □ Master or PhD degree
7- What is your employment status?
□ Employed full time □ Employed part time □ Unemployed
□ Student □ Self-employed □ Retired □House wife
8- What is your personal monthly income?
□ <5000 SR □5000-10,000 SR □10,001-15,000 SR
□15,001 SR-25,000SR □≥25,001SR
9- What is your family monthly income?
□ <5000 SR □5000-10,000 SR □10,001-15,000 SR
□15,001 SR-25,000SR □25,001SR-35,000SR □≥35,001SR
10- Do you have Saudi citizenship?
□Yes □No
11- If not, what is your citizenship? And how long you have been in Saudi Arabia?

citizenship	
Number of years	

12- Do you live in rural or urban area?

□Rural □Urban □Semi-rural

13- In what city do you live in Saudi Arabia?

Name of city	

II. Behavioural risk factors and family history of the disease:

Please answer the following questions:

1- Did any of your male family members have CVD prior to age 55 years? And how many?

□Yes □No

If Yes, what family members:

□grandfather □father □uncle _____

□cousin _____ □brother _____

2- Did any of your female family members have CVD prior to age 65 years? And how many?

□Yes □No

If Yes, what family members:

□grandmother □mother □aunty _____

□cousin _____ □sister _____

3- Do you smoke cigarettes?

□ Current smoker □ previous smoker □ Non-smoker

4- If you are currently smoker, how many cigarettes do you smoke per day? And how old were you when you first became a regular smoker?

Number of cigarettes per day	
Years of age	

5- If you are a previous smoker, at what age did you stop? And how long you had been smoking before you quitted?

Years of age when quitting	
Years of smoking	

6- Do you consider yourself as a regular water pipe (Shisha) smoker?

□Yes **(Go to Q7)** □No **(Go to Q9)**

7- How many water pipes do you usually smoke per week?

□1-2 per week □3-6 per week □≥6 per week

8- How old were you when you first became a water pipe smoker?

Years of age	

9- How often do you do moderate-intensity exercise such as walking, swimming or running?

□Never □Rarely □ 1-2 times/week

□3-4 times/week □>5 times/week

10- And how many minutes each time?

Number of minutes	

11- How often do you do vigorous exercise that cause sweating or hard breathing like heavy lifting, aerobics, or fast bicycling?
□Never □Rarely □ 1-2 times/week
□3-4 times/week □>5 times/week
12- And how many minutes each time?

Number of minutes	

Part two:

I. Knowledge about vitamin D:

Please answer the following questions:

1- Have you ever heard/learnt about vitamin D?
□Yes □No
2- Where have you heard or learnt about vitamin D?
□ Newspaper/Magazine □ Radio □ TV □ Doctor
□ Friends/Relatives □ School/university □ Internet
□ Other health professionals (dietician) □ I don’t know
3- Vitamin D helps which of the following health effects? (tick all that apply)
□ Prevention of kidney disease □ Healthy bones
□ Prevention of cancer □ I don’t know
4- Where do you think the body gets vitamin D from? (tick all that apply)
□Diet □Sun exposure □supplements
□ I don’t know
5- What type of food is a good source of vitamin D? (tick all that apply)
□ Red meat □ vegetables □ Milk □ Fatty fish (salmon, sardines)
□ Olive oil □ Eggs □ Fruits □ I don’t know

II. Attitudes toward vitamin D:

Please answer the following questions:

1- Do you think vitamin D is important for your health?
□Yes □No □ I don’t know
2- How do you feel about sun exposure?
□ I like to expose to sun light all the time □ I like to expose to sun light sometimes □ I rarely expose to sun light
□I avoid expose to sun light
3- Do you often use a parasol to shade from the sun?
□Yes □No

4- How much do you agree or disagree with the following statement: "I'm concerned that my current vitamin D level might be too low".

□ Strongly disagree □ Disagree □ neither agree or disagree

□ Agree □ Strongly agree

III. Vitamin D related behaviours:

1- Do you work mainly:

□ Indoors □ Outdoors

2- How much time do you often spend outdoors per day on weekdays?

□ Not at all □ <30 min □30-60 min

□60-90 min □>90 min

3- How much time do you often spend outdoors per days on weekends?

□ Not at all □ <30 min □30-60 min

□60-90 min □>90 min

4- How often do you wear sunscreen while outdoors in the sun?

□ Never □ 1-2 times/week □ 3-4 times/week

□ 5-6 times/week □ always

5- Which parts of your body get exposed to the sun? (tick all that apply)

□ Face □ Hand □ Face & hand

□ both arms □ both legs □ completely covered

6- Do you take vitamin D supplements?

□Yes □No

7- How often do you take it?

□2-3/day □once a day □every 2-3 times/week

□every 4-6 times/week □once a week □< once a week

8- How long you have been taken vitamin D supplements?

□< 3 months □3-6 months □ last year □more than year

9- Do you take calcium supplements?

□Yes □No

10- How often do you take it?

□2-3/day □once a day □every 2-3 times/week

□every 4-6 times/week □once a week □< once a week

11- How long you have been taken calcium supplements?

□< 3 months □3-6 months □ last year □more than year

12- Do you take multivitamin supplements?

□Yes □No

13- How often do you take it?

□2-3/day □once a day □every 2-3 times/week

□every 4-6 times/week □once a week □< once a week

14- How long you have been taken multivitamin supplements?

□< 3 months □3-6 months □ last year □more than year

15- Do you take calcium supplements with vitamin D?

□Yes □No

16- How often do you take it?

□2-3/day □once a day □every 2-3 times/week

□every 4-6 times/week □once a week □< once a week

17- How long you have been taken calcium supplements with vitamin D?

□< 3 months □3-6 months □ last year □more than year

18- How often do you drink milk?

□never □once/week □2 times/week □3-4 times/week

□5-6 times/week □once/day □2 times/day □≥3 times/day

19- How often do you eat butter?

□never □once/week □2 times/week □3-4 times/week

□5-6 times/week □once/day □2 times/day □≥3 times/day

20- How often do you eat eggs?

□never □once/week □2 times/week □3-4 times/week

□5-6 times/week □once/day □2 times/day □≥3 times/day

21- How often do you eat oily fish (salmon, tuna, sardine)?

□never □once/week □2 times/week □3-4 times/week

□5-6 times/week □once/day □2 times/day □≥3 times/day

22- How often do you eat liver?

□never □once/week □2 times/week □3-4 times/week

□5-6 times/week □once/day □2 times/day □≥3 times/day

Appendix 4: Information sheet and informed consents for the qualitative study in Arabic

بسم الله الرحمن الرحيم

إذن خطي بالموافقه علي المشاركه في البحث الطبي

Consent for the agreement in participation in medical research

- أنت مدعو/ أنتي مدعوه من قبل الباحثه نجلاء محمد حمادي الجفري إلي المشاركه في بحث علمي تحت عنوان "العلاقه بين فيتامين د و أمراض القلب الوعائيه لدي البالغين في المملكه العربيه السعوديه: دراسة الحالات والشواهد" كـ جزء من متطلب رسالة الدكتوراه للباحثه في جامعة جريفيث في أستراليا.
- المملكه العربيه السعوديه تتعرض لكميات وافره من أشعة الشمس خلال فصول السنه نظراً لظروفها المناخيه وطبيعتها الجغرافيه، في حين أثبتت الدراسات العلميه المحليه أن نقص فيتامين د التغذوي هو حاله شائعه بين السعوديين البالغين سواء كانوا رجالاً أم نساء. هناك القليل من الدراسات التي أختبرت مستوى المعرفه والمواقف والسلوك تجاه فيتامين د وبحثت بعمق في السلوكيات المتعلقه بفيتامين د مثل التعرض لأشعة الشمس، ممارسة الأنشطه في الهواء الطلق، إستخدام واقي من أشعة الشمس، وكيفية تأثرها بالمعرفه والمواقف تجاه فيتامين د بين السعوديين.
- الهدف من الدراسه الحاليه هو أستكشاف مستوى المعرفه والفهم تجاه فيتامين د، المواقف من التعرض لأشعة الشمس، مصادر المعلومات المتعلقه بـ فيتامين د، الحواجز أمام معالجة نقص فيتامين د، والسلوكيات المتعلقه بفيتامين د بما في ذلك التعرض لأشعة الشمس، الأنشطه في الهواء الطلق، إستخدام الواقي من أشعة الشمس بين السعوديين المصابيين بأمراض القلب الوعائيه (الحالات) ومقارنتهم بالسعوديين الغير مصابين بأمراض القلب الوعائيه (الشواهد).
- للمشاركه في هذا البحث، يجب أن تكون: سعودي الجنسيه أو مقيم في السعوديه لفتره لا تقل عن خمس سنوات و أن تبلغ من العمر 18 سنه أو أكثر.
- مشاركتك في البحث هو أمر تطوعي، إذا قبلت/قبلتي المشاركه في البحث ف لك حق الإنسحاب في أي وقت. قرارك بالمشاركه في البحث العلمي لن يؤثر عليك بأي طريقه ولن يكون هناك أي خساره أو فوات لمنفعه تستحقها. أيضاً، في حالة حدوث أي تغيرات في البحث سيتم إبلاغك وللمشارك الحريه في الإستمرار بالمشاركه في الدراسه.
- هذه الدراسه توفر الأساسيات لتطوير برامج لتعزيز الصحه العامه لـ عموم المجتمع السعودي و المرضى المصابين بأمراض القلب الوعائيه، مما يساعد علي تخفيض خطر الإصابه بأمراض القلب وعوامل الخطوره المصاحبه لها بالإضافه لنقص فيتامين د الغذائي في المملكه العربيه السعوديه. أيضاً، ستساهم هذه الدراسه في إكتشاف مستويات المعرفه والمواقف والسلوكيات المتعلقه بفيتامين د والتعرض لأشعة الشمس في المملكه العربيه السعوديه خاصة بين المرضي المصابين بأمراض القلب الوعائيه.
- لا يوجد ضرر جسماني أو معنوي يتوقع حدوثه للمشاركين في البحث.
- أي معلومات سوف يتم الحصول عليها خلال الدراسه ستكون سريه ولن يتم كشفها إلا في حالة أخذ إذن مباشر من المشارك/المشاركه في البحث أو إذا تطلب عن طريق القانون. أي معلومات تخص هوية المشاركين في البحث مثل الأسماء، أرقام التلفون، عنوان سيتم الإحتفاظ بها بسريه بعيداً عن أي معلومات أخري يتم أخذها من المشاركين والوصول إلي هذه المعلومات سيكون محظور إلا علي عدد قليل من المشرفين علي البحث. المعلومات الخاصه بهوية المشلركين مهمه للباحث حيث ستمكنه من ربط النتائج المتحصل عليها من المرحله

الأولي والثانيه من الدراسه. بعد ذلك كل المعلومات الخاصه بالتعريف علي هوية المشاركين في البحث سيتم حذفها وجميع إستمارات الإستبيان و إستمارات جمع البيانات سيتم ترميزها برموز خاصه لحفظ هوية المشاركين. لا يوجد أي نتائج قانونيه متعلقه بـ مشاركتك في البحث وجميع المعلومات التي سيتم تجميعها ستكون بغرض خدمة البحث العلمي فقط.

- إذا وافقت/وافقتي علي المشاركه في الدراسه الحاليه، سيطلب منك عدة أمور للقيام بها تتضمن: قراءة وتوقيع النموذج الحالي (طلب الموافقه علي المشاركه في البحث العلمي أو الموافقه المتنوره المستنيره)، إكمال المقابله الشخصيه وجه لوجه مع الباحث الرئيسي التي ستقام في نفس المستشفي و ستكون مسجله. المقابله ستستغرق تقريباً 45-30 دقيقه.
- إذا لديك أي أسئله أو إستفسارات تتعلق بالبحث أو بحقوق المشارك، أو التبليغ في حالة حدوث ضرر:

  الأستاذه نجلاء الجفري : هاتف (+966543165165)

  najlaa.aljefree@griffithuni.edu.au

  اللجنه المحليه: البريد الإلكتروني IRB@kamc.med.sa

  اللجنه الدوليه: جامعة جريفيث (أستراليا) research-ethics@griffith.edu.au

  الهاتف (61737354375)
- بالتوقيع علي الموافقه التنوره المستنيره أقرّ أنا المشارك/المشاركه في البحث، أني قد قرأت وفهمت جميع المعلومات المدونه أعلاه، و أوافق علي المشاركه في الدراسه الحاليه.
- أقرّ أنا الباحث الرئيسي بصحة المعلومات المدونه أعلاه والتعهد بتزوييد اللجنه المحليه بأي تغييرات محتمله في حال حدوثها وقبل العمل بها.

المشارك/ الإنسان موضوع البحث: التوقيع:

أستاذه نجلاء الجفري التوقيع:

التاريخ: / / هـ الموافق: / / م

Appendix 5: Information sheet and informed consents for the qualitative study in English

Association between vitamin D status and coronary heart disease in Saudi Arabian adults

INFORMATION SHEET

Who is conducting the research?

Chief investigator 1: A/Prof Faruk Ahmed, School of Medicine (Public Health), (61-7) 555 27874, f.ahmed@griffith.edu.au

Chief investigator 2: Dr. Patricia Lee**,** School of Medicine (Public Health), (61-7) 555 27865, patricia.lee@griffith.edu.au

Research student: Mrs. Najlaa Aljefree, School of Medicine (Public Health), (61-7) 555 27865, najlaa.aljefree@griffithuni.edu.au

Why is the research being conducted?

This project is being conducted through Griffith University, as part of a PhD project for Mrs. Najlaa Aljefree. Saudi Arabia has plentiful sunlight throughout the year, however national studies have shown that vitamin D deficiency is highly prevalent among Saudi adults of both genders. There are limited studies which have assessed the knowledge and attitudes toward vitamin D and explored in-depth how vitamin D related behaviours such as sun exposure, outdoor activities and using of sunscreen can be affected by knowledge and attitudes among Saudis.

The purpose of this study is to explore knowledge and understanding of vitamin D, attitudes of sun exposure, the source of information about vitamin D, barriers to addressing vitamin D deficiency, and behaviours related to vitamin D including sun exposure, outdoor activities and using of sunscreen among Saudis diagnosed with CHD (cases) and compare them to Saudis free from the disease (controls).

What you will be asked to do:

If you volunteer to participate in this study, you are asked to read and sign this consent form and complete in-depth face to face interviews that will be conducted by the researcher in the same hospital and they will be fully transcribed. The interviews will last between 30-45 minutes.

The basis by which participants will be selected or screened:
To be a participant in this study, you must be a native Saudi or resident in Saudi Arabia for at least five years and adult 18 years and above.

The expected benefits of the research:
This study will contribute to new knowledge about understanding of vitamin D, attitudes of sun exposure and behaviours related to vitamin D among Saudi population especially CHD patients. It also can provide the basis for an appropriate health promotion and public health interventions for the general population and patients diagnosed with CHD, which would help reduce the risk of vitamin D deficiency in Saudi Arabia.

Risks to you:

No significant physical or psychological risk/harm to the participants will be introduced in this study.

Your confidentiality:

Any information that is obtained in connection with this study will remain strictly confidential and will be disclosed only with your permission or as required by law. Any identifying information such as your full name, phone number and address will be stored separately from the information you provide and the access to this information is restricted to a small number of senior members of this study team. All your identifying information will be removed alter and all surveys and data sheets will be labelled with a unique barcode number. No legal ramifications can be taken as result of your answers. All data collected is for research and educational purposes only.

Your participation is voluntary:

Your participation in this project is voluntary. If you volunteer to participate in this study, you can withdraw at any time without comment or penalty by contacting the researcher. Your decision to participate will not affect you in any way or negatively impact any other personal consideration or right you usually expect.

Questions / further information:

If you have any questions regarding this study, you may reach the principle researcher, Mrs. Najlaa Aljefree at (+966 543165165).

The ethical conduct of this research

Griffith University conducts research in accordance with the National Statement on Ethical Conduct in Human Research. However, if you do have any concerns or complaints about the ethical conduct of the project you may contact the Manager, Research Ethics on (617) 373 54375 or **research-ethics@griffith.edu.au**.

Privacy Statement – non disclosure

"The conduct of this research involves the collection, access and/or use of your identified personal information. The information collected is confidential and will not be disclosed to third parties without your consent, except to meet government, legal or other regulatory authority requirements. A de-identified copy of this data may be used for other research purposes. However, your anonymity will at all times be safeguarded. For further information consult the University's Privacy Plan at

http://www.griffith.edu.au/about-griffith/plans-publications/griffith-university-privacy-plan
or telephone (07) 3735 4375."

Association between vitamin D status and coronary heart disease in Saudi Arabian adults

CONSENT FORM

Research Team:

Chief investigator 1: A/Prof Faruk Ahmed, School of Medicine (Public Health), (61-7) 555 27874, f.ahmed@griffith.edu.au

Chief investigator 2: Dr. Patricia Lee, School of Medicine (Public Health), (61-7) 555 27865, patricia.lee@griffith.edu.au

Research student: Mrs. Najlaa Aljefree, School of Medicine (Public Health), (61-7) 555 27865, najlaa.aljefree@griffithuni.edu.au

By signing below, I confirm that I have read and understood the information package and in particular have noted that:

- I understand that my involvement in this research will include read and sign this consent form and complete in-depth face to face interviews;
- I have had any questions answered to my satisfaction;
- I understand the risks involved;
- I understand that there will be no direct benefit to me from my participation in this research;
- I understand that my participation in this research is voluntary;
- I understand that the information gained from this research may result in improved methods for diagnosis or treatment, but as an individual I do not have ownership of these results, research records, or the sample that I give
- I understand that if I have any additional questions I can contact the research team;
- I understand that I am free to withdraw at any time, without explanation or penalty;
- I understand that I can contact the Manager, Research Ethics, at Griffith University Human Research Ethics Committee on (617) 373 54375 (or research-ethics@griffith.edu.au) if I have any concerns about the ethical conduct of the project; and
- I agree to participate in the project.

Name	
Signature	
Date	

Appendix 6: Questions for the qualitative study

<u>Questions for semi-structured interview (Qualitative study):</u>

1- Can you tell me what do you know about vitamin D? Where did you hear about this?
2- Have you ever been offered any advice about preventing vitamin D deficiency? Who gave you this advice? Why was the advice given?
3- How do you feel about sun exposure? Do you like going into the sun?
4- Can you tell how often you are exposed to the sun? At what times of the day?
5- Which parts of your body do you usually expose to the sun?
6- What types of activities do allow you to expose to the sun adequately? Do you try to avoid these types of activities?
7- If you are rarely exposed to the sun, what do you do to avoid sun exposure? Can you please explain why?
8- In your opinion, what are the barriers to receiving adequate sun exposure?
9- Do you think that some cultural and religious factors may play a role in the high prevalence of vitamin D deficiency in Saudi Arabia? Can you please explain?
10- Have you heard of fortification? Can you explain what this is?
11- Do you take any vitamin D supplements? If yes, why are you taking them?
12- Can you tell me what the things you would do, to prevent vitamin D deficiency?

Appendix 7: Screen sheet form to collect information regarding exclusion criteria and diagnosis of cases

Association between vitamin D status and coronary heart disease in Saudi Arabian adults: a case-control

<u>Screening sheet</u>

Patient name		Patient ID number	
Age		Date of birth	
Gender		Patient Phone number	
Patient Email		Hospital name	
Screener' name		Date	

1- Is patient identified as a coronary heart disease patient?
□Yes □No

2- If yes, by what clinical diagnoses the patient was identified as CHD patient?

electrocardiogram (EKG)	
stress testing	
echocardiography	
coronary angiography	
Other (specified)	

3- Does patient had a definite or suspected heart attack or stroke?
□Yes □No

4- Does patient had coronary bypass surgery or any other type of heart surgery?
□Yes □No

5- Does patient had any of these conditions (please choose as many as apply):

any type of cancer	
kidney disease	
liver disease	
osteomalacia	
osteoporosis	
hyperparathyroidism	
granulomatous disease	
tuberculosis	
lymphomas	
hyperthyroidism	
celiac disease	
Crohn's disease	
cystic fibrosis	
Whipple's disease	
bypass surgery	

6- Is this patient eligible for the current study?
□Yes □No

7- If yes, in what group this patient fit?

Group (A): cases	
Group (B): controls	

Appendix 8: Data collection sheet to collect results from blood tests and anthropometric and blood pressure measurements

Association between vitamin D status and coronary heart disease in Saudi Arabian adults: a case-control

Data collection sheet

Patient name		**Group (A) or (B)**	
Patient ID number		Date of birth	
Gender/ Age		Patient Phone number	
Patient Email		Hospital name	
Physician's name		Date	

1- Blood glucose: ____________________

2- Blood lipids:

LDL	
HDL	
Cholesterol level	
Triglyceride level	

3- Blood pressure:

SBP	
DBP	

4- Anthropometric measurements:

Height		Weight		BMI	

5- Blood test:

Vitamin D	
Calcium	
PTH	