Australian National University

Cardiovascular disease in East Asian immigrants living in Australia: considerations in relation to vitamin D deficiency, smoking and acculturation

by

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Declaration

I declare that the work contained in this thesis is the result of original research and has not been submitted to any other University or Institution.

The research I conducted and the papers published in this thesis are based on data from a large population-based cohort study and a community-based study. I was the principal researcher for all of the work included in this thesis. I had a central role in the research design, data collection, analysis and interpretation of the findings for the community-based Asian-Australian Health Study. For the work pertaining to the population-based cohort study, I was fully involved in the development of the research questions and led the analysis of the data. I led the preparation of the scientific manuscripts presented here and coordination of co-author input for 4 out of 6 papers published as part of this thesis.

The analyses in this thesis are my own work, except where indicated by references or acknowledgements in the text.

Signed:

Acknowledgements

Undertaking a PhD is something that I have wanted to do for many years. After completing this work, it has been a somewhat challenging but enjoyable journey that has significantly advanced my skill set and experience, particularly with respect to epidemiological study design, systematic review of the literature, and mathematical modeling of population health data. There are many people to thank for their assistance during my PhD candidature. I appreciated the support and guidance of supervisors, colleagues, family and friends both in Australia and in China.

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Lastly I give a big shout out to my family and friends. It is their support, counsel and comradeship that has kept me steady and sound, not just throughout this degree but over the years in my metamorphosis from ordinary university student to epidemiologist.

Abstract

Background: Cardiovascular disease (CVD) is the leading cause of death in Australia and accounts for the second highest disease burden in disability-adjusted life years. Meanwhile, according to a recent report 28.1% of the estimated resident population of Australia was born overseas; this is the highest proportion of immigrants in the past 120 years. Patterns of CVD risk, incidence, and mortality vary significantly across different ethnic population groups. This means that the demographic change in the Australian population due to overseas immigration is likely to alter patterns of CVD in terms of incidence, prevalence, and mortality in both the short and long term. These changes may challenge existing health policies, models of service, and guidelines for prevention and care in Australia. Therefore, it is now important to understand the risk for major CVD and risk factor profiles in immigrants compared to the Australian-born population, and how these factors change according to acculturation. This thesis specifically aims to better understand risk factor profiles and CVD in East Asian immigrants and the effect of increasing acculturation.

Methods: The thesis applied a variety of research methods to address these research aims. First, a systematic review of the literature and meta-analysis was performed to investigate the prevalence of smoking in East Asian populations living in western countries, and then to quantify the effect size for the association between acculturation and smoking prevalence in these populations. Second, a new cross-sectional study was designed and completed, and the data analysed in order to investigate and assess the factors related to vitamin D status, as a possible CVD risk factor, in East Asians living in Canberra. Third, I examined whether mathematical models used for the prediction of vitamin D status were valid and tested the accuracy of different ways of modelling the data to improve prediction, using data already collected in a case-control study as well as published data from the National Health and Nutrition Examination study. Last, an analysis of data from a population-based cohort study that was linked to hospital admissions and mortality records was conducted in order to assess CVD risk profiles according to region of birth and acculturation level and to investigate hospitalisation for CVD as East Asian immigrants become acculturated to the host country.

Results and Discussion: The systematic review and meta-analysis of cross-sectional studies showed that East Asian-born women were far less likely to smoke than East Asian-born men and Australian-born individuals. The prevalence of smoking in East Asian-born men was high compared to western-born counterparts and smoking cessation was uncommon. However, the prevalence of current smoking was generally lower in men, but higher in

women, compared to that of the native country and in association with longer duration of residence. Nevertheless, analysis of baseline cross-sectional data from the population-based 45 and Up Study, in Australia, showed that the prevalence of current smoking among Asian-born men was about the same as their Australian-born counterparts, and increased in relation to longer duration of residence. This contradicts the findings of the meta-analysis, and may be specific to Australia or specific to the 45 and Up Study, where the questionnaire was offered only in English, so that less acculturated immigrants may not have participated. The cross-sectional Asian Australian Health Study, based in Canberra, revealed that vitamin D deficiency in East Asian-born immigrants was common, and greater acculturation was associated with higher vitamin D status in this population. Higher vitamin D status was associated with a lower risk of hypercholesterolemia, but not other markers of cardio-metabolic ill-health in this study. Because of the cross-sectional nature of the study, it is not possible to assess whether this is a causal association; it appeared to be mediated by physical activity. The studies testing the validity of prediction models for vitamin D status, as used in large health studies, showed that these may have poor prediction accuracy and a high risk of bias due to incorrect use of instrumental variables in the modelling. Furthermore, support vector regression modelling was shown to provide more accurate prediction of vitamin D status compared to multiple linear regression. The analysis of linked data from the population-based 45 and Up cohort study indicated that CVD risk factor profiles of East Asian immigrants tended to approximate those of Australian-born with increasing levels of acculturation. The association between region of birth and age at immigration to CVD risk varied across different types of CVD and was likely to be determined by a complex interaction of factors related to both the host country and the country of origin.

Conclusions: This thesis explored the association between acculturation, putative CVD risk factors, CVD related hospitalisation, and all-cause mortality in East-Asian-born immigrants to western countries, mainly Australia. The risk of incident CVD incident is lower in East-Asian immigrant populations than in the Australian-born population. However, changes in the prevalence of various risk factors with increasing acculturation suggest that the pattern of CVD risk in Asian immigrants will change toward that of the Australian-born population over the coming years, as these immigrants become acculturated and adopt unhealthy diets and women are more likely to smoke, but there are healthier patterns of physical activity. Having identified these trends with acculturation, there are real opportunities, with targeted, culturally appropriate health promotion materials, to maximise the opportunities to make the

transition to Australia one that improves, rather than detracts from, the health of this growing immigrant group.

Collaborating authors

I agree that Shuyu Guo made the contribution to the authorship and research of paper(s) on which I am a co-author, to be as shown in this thesis.

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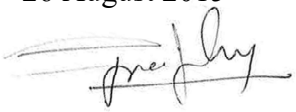
Signature: 

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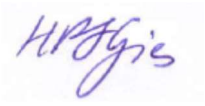
Signature: 

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Chapter 1

Introduction

International immigrants and cardiovascular diseases: an emerging public health challenge

Cardiovascular disease (CVD), usually defined as all of the diseases of the heart and blood vessels, affect the world population without socioeconomic or geographic boundaries (1). Despite the fact that CVD-related morbidity and mortality have been significantly reduced in many high-income countries in recent years, these diseases continue to impose a large health burden and incur considerable health expenditure around world (1, 2).

According to the 2014 WHO Global Status Report on Non-communicable Diseases, 57 million deaths were reported during 2012. Of these, 38 million (68%) were caused by non-communicable diseases, principally CVD (46.2%, 17.5 million deaths), cancer (21.7%, 8.2 million deaths), and chronic respiratory diseases (10.7%, 4.0 million deaths) (3, 4).

In the WHO Global Status Report on Non-communicable Diseases 2010, it was projected that deaths due to CVD, cancers, diabetes, and chronic lung disease would increase by 15% globally, to 44 million, between 2010 and 2020. These diseases contribute nearly 80% of the deaths from non-communicable diseases in middle and low-income countries. Furthermore, they are the diseases for which the overall burden is increasing most rapidly, with estimates of increases of more than 20% over the next decade, in lower-income regions such as Africa, the Eastern Mediterranean, and South-East Asia. (3) In the 2014 WHO report the prediction has been validated: the number of deaths caused by CVD has increased worldwide and in every region since 2000, with the greatest increases in the WHO South-East Asia Region(4).

As shown in the Global Burden of Disease Study 2013 Mortality and Causes of Death Study, ischaemic heart disease and stroke were among the top three causes of years of life lost (YLLs) worldwide (2). It was also reported in the Global Burden of Disease Study 2010 that ischaemic heart disease was the leading cause of loss of disability-adjusted life years (DALYs) worldwide (increased by 29% from 1990) (5).

Concurrent with these increases in CVD-related disease burden, growing international migration is leading to changes in population demographics worldwide (6). More than 214 million people are now estimated to be living outside their home countries. Migration has occurred for a range of reasons, varying from escape from natural disasters, environmental degradation, and/or conflict in home countries, to seeking better working opportunities and education in the host country.

Migrants are exposed to a range of influences that cause them to change gradually over time, adopting, often in a patchwork fashion, behaviours and attitudes that are more similar to the host population than to the country of origin. This forms the root of the concept of acculturation; how this concept applies to health behaviours and risks is a central focus of this thesis.

Population flows across regions that have different health risks and disease prevalence have led to changes in disease patterns and the dynamics of health disparities in host countries (6-8). In the process of acculturation, immigrants may retain cultural characteristics and health-related behaviours from their country of origin while adopting life styles of the host country (9). Indeed, one of the considerable impacts of immigration is on public health. Some of the health problems that immigrants bring with them may not be well known in their host countries (6). Additionally, some biological and genetic determinants of health may persist and pass down to the next generation despite the change in nationality (6).

Australia is one of the most multicultural societies in the world (10). Countries that are receiving a great number of immigrants face emerging challenges caused by the increasing diversity of the population, the consequent cultural profile shifting, and changing health characteristics of its people (11). Health systems in these countries must adapt to a changing profile of health and health risks with culturally appropriate health prevention and promotion initiatives.

The disparity in the prevalence of CVD and its risk factors across different populations makes it a particularly informative disease to study in relation to immigration and changing health risks. The risk of CVD is a function of both environmental and genetic factors. For immigrants, both lifestyle and cultural

perceptions change as they become acculturated to their host societies (12). Understanding the risk of major CVD outcomes and risk factor profiles in immigrants compared to their host populations and how these factors change as they become acculturated to the host society is important to provide an evidence-base to guide policy making and service delivery (6).

Previous studies of CVD risk in overseas-born populations in Australia have been conducted but have focused on changes in only a single risk factor (13, 14), or have retrospectively investigated risk factors and prevalence of specific CVD outcomes according to country of birth (15, 16). In this thesis I consider the effect of acculturation on multiple risk factors for CVD and use data from a large prospective cohort study to examine influences on incidence as well as prevalence of CVD.

Aims and scope of the thesis

The overall aim of this thesis is to examine the profile of CVD risk factors and major CVD outcomes in East Asian immigrants living in Australia in comparison to the Australian-born population. The focus is particularly on the relationship of acculturation to CVD disease risks and outcomes.

In this thesis, CVD is defined as major atherosclerotic and/or arteriovenous thromboembolic diseases. Those cardiovascular conditions that affect lymphatic systems or are caused by other factors (i.e. cardiovascular conditions caused by infections, non-thrombotic disease of veins, lymphatic vessels and lymph nodes and other disorders of circulatory system) were excluded.

This thesis focuses on East Asian-born immigrants. In some sections this thesis examines CVD risk factors and outcomes in Northeast Asian-born and Southeast Asian-born immigrants separately, but in other sections this thesis focuses on North East Asian-born immigrants only, according to the data that are available. While these populations might appear superficially relatively homogeneous, they differ in terms of diet, lifestyle, relationships and other factors. These pre-migration cultural differences may facilitate or hinder levels of acculturation post-migration. Some evidence has suggested that certain CVD risk factors and outcomes are more common in some sub-

groups of East Asian immigrants due to genetic, demographic, socioeconomic and cultural diversity (17). Countries of birth were categorized into several region-of-birth groups according to a modified version of the Standard Australian Classification of Countries (18). This classification categorizes countries into broad groups on the basis of their similarities in social, cultural and economic characteristics. The East Asian immigrants in this thesis include individuals born in Northeast Asia (i.e. China, Hong Kong, Taiwan, South Korea and Japan) and Southeast Asia (i.e. Burma, Cambodia, Thailand, Vietnam, Indonesia, Malaysia, Philippines and Singapore). Immigrants from Southeast Asian countries account for the largest proportion of the population in Australia, followed by those from Northeast Asia (18).

Therefore, in this thesis, Northeast Asia-born and Southeast Asia-born immigrants are examined as two separate groups.

The overall hypothesis of the thesis is that migration of East Asians from their home country to Australia is followed by acculturation which leads to a change in health behaviours that, in turn, lead to a change in cardiovascular disease risk and mortality. This thesis aims to answer the following specific research questions:

1. Does the profile of CVD risk factors change as immigrants become acculturated to the host country?
    - 1.1 Does the prevalence of smoking change in relation to indicators of acculturation in East Asian populations living in western countries?
    - 1.2 What are the factors related to vitamin D deficiency (a possible CVD risk factor) in Northeast Asians living in Australia and is there an association between vitamin D status and level of acculturation?
    - 1.3 Are models used to predict vitamin D status (for example, for use in population-based studies investigating vitamin D deficiency as a risk factor for CVD) valid?
    - 1.4 Does the CVD risk factor profile differ in East Asian immigrants compared to Australian-born and in relation to time indicators of acculturation?
2. Does the risk of CVD change as East Asian immigrants become acculturated to the host country?

2.1 Does the incidence of major CVD-related hospitalisation and all-cause mortality differ in East Asian immigrants compared to Australian-born?

2.2 Does the incidence of major CVD-related hospitalisation and all-cause mortality differ in relation to time indicators of acculturation in East Asian immigrants?

A systematic review and meta-analysis of the literature, one community-based cross-sectional study and both cross-sectional and prospective cohort study data were used to achieve the aims of the research and to answer the five specific questions. These are outlined in Chapter 3 'Research design'.

Thesis structure

This thesis is presented as a compilation of publications, or chapters intended for publication, answering research questions about disparities in CVD risk factor profiles and disease patterns in immigrants compared to the host population in Australia. The thesis is structured such that each research question with its associated studies comprises its own chapter, accompanied by a context statement for the whole thesis.

The context

The context statement consists of this introductory chapter (Chapter 1), followed by a chapter providing background about CVD and CVD risk factors in immigrant groups and potential associations with acculturation (Chapter 2). In Chapter 3 I provide a more in-depth description of the research questions and an overview of the methods used to address them. The thesis concludes with an overall discussion, conclusion and future directions, in Chapter 8.

The studies

Chapter 4 investigates the prevalence of smoking, an important modifiable CVD risk factor, in East Asian immigrants living in a selection of western countries and the association with various acculturation indicators. It consists of 'Paper 1: Acculturation and prevalence of smoking in Asian immigrants in western countries: a systematic review and meta-analysis'. This chapter provides a summary of the evidence on the

prevalence of smoking and the association with different quantitative measures of acculturation from studies in several western countries including Australia.

Chapter 5 is entitled 'Papers 2-4: Vitamin D status as a CVD risk factor in Asian immigrants in relation to acculturation' and consists of two parts. In the first part, Paper 2 focuses on an original research study exploring the inter-relationships between vitamin D status, cardio-metabolic health and acculturation. In a community-based study of 100 Northeast-Asian-born immigrants living in Canberra, Australia, I examined predictors of vitamin D status, and the association with acculturation score and cardio-metabolic biomarkers. The second part of Chapter 5 is made up of Papers 3 and 4, which focus on methodological issues associated with the estimation of vitamin D status in epidemiological studies. I tested the validity of vitamin D prediction models against laboratory-measured vitamin D levels for use in population-based studies, using two different datasets.

Chapter 6 is entitled 'Cardiovascular disease risk factor profiles of 263,356 older Australians according to region of birth and acculturation, with a focus on immigrants born in Asia'. This chapter comprises one published paper (Paper 5) using cross-sectional data from 263,356 participants in the population-based 45 and Up Study cohort. I examined the CVD risk factor profiles of East Asian-born participants with varying degrees of acculturation, compared to participants born in Australia and other immigrant groups.

Chapter 7 is entitled 'Prospective investigation of the risk of incident CVD hospitalisation according to region of birth, in the 45 and Up Study'. This chapter comprises a paper (Paper 6) using baseline data from the 45 and Up Study, with linkage to the NSW Admitted Patient Data Collection and NSW Register of Births, Deaths and Marriage. I compare the risk for various CVD outcomes and all-cause mortality in individuals born in regions other than Australia (including East Asia) compared to Australian-born participants. I further test whether these outcomes are associated with two time indicators for acculturation.

All of the papers have been reproduced with permission of the relevant publishing companies, where relevant, and co-authors. All the papers were prepared during my doctoral candidature.

Student contribution

For five of the six papers, I was the lead researcher of the work. I took primary responsibility for overall management of all aspects of the Asian-Australian Health Study. I ensured the integrity of the research, and organised all parts of the completed manuscripts before and after publication.

Based on the British Medical Journal guidance on contributorship (19), I estimated my specific contribution to each paper as a percentage for conception and drafting, analysis and interpretation, and drafting and revising. These are presented in Table 1 below.

Table 1: Estimate of Shuyu Guo's contribution to each paper included as part of the PhD thesis

Chapter	Title/Publications	Journals	Status	Authorship	Number of co-authors	Conception & designing	Analysis & interpretation	Drafting &revising
4	Acculturation and prevalence of smoking in Asian migrants in western countries: a systematic review and meta-analysis	Not submitted	Not submitted	1st author	3	80	70	60
5	Sun exposure and vitamin D status as Northeast Asian migrants become acculturated to life in Australia	Photobiology & Photochemistry	Published, October 2014	1st author	3	80	70	70
	Tightrope walking: using predictors of 25(OH)D concentration based on multivariable linear regression to infer associations with health risks	PloS One	Published, May 2015	3rd author	3	30	20	10
	A novel approach for prediction of vitamin D status using support vector regression	PloS One	Published, November 2013	1st author	3	80	80	70
6	Cardiovascular disease risk factor profiles of 263,356 older Australians according to region of birth and acculturation, with a focus on migrants born in Asia	PloS One	Published, February, 2015	1st author	3	60	80	70

7	Prospective investigation of the risk of incident CVD hospitalisation according to region of birth, in the 45 and Up Study	Not submitted	Not submitted	1st author	3	60	70	60

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Chapter 2

Background

Preamble

In this chapter I first outline the breadth of CVD considered here and briefly introduce the major categories of disease. I provide a brief description of the evidence for the main known non-genetic risk factors for CVD, focusing on large-scale data and pooled analysis of well-known risk factors. I also summarise the existing evidence of the association with a putative risk factor, vitamin D deficiency.

The next section introduces the concept of acculturation, theoretical models of acculturation and its measurement in epidemiological studies. I consider the current evidence of effects of acculturation on CVD risk and then on each of the known non-genetic risk factors, focusing on smoking and vitamin D deficiency.

This chapter finishes by clearly describing the known epidemiology of CVD in overseas-born populations in Australia and defining the current gaps in our understanding of the effects of acculturation on CVD with a focus on East Asian migrants to Australia.

Definition and classification of cardiovascular diseases

Cardiovascular disease (CVD) is commonly used as an umbrella term for all diseases and conditions of the heart, blood vessel system and also vascular diseases of the brain (1). However, this broad definition groups together pathologically heterogeneous conditions, including major atherosclerotic and thromboembolic diseases, such as myocardial infarction, as well as less severe conditions such as haemorrhoids.

This thesis uses this more restricted definition to include only major atherosclerotic and/or arteriovenous thromboembolic diseases. The main categories of CVD according to this definition are ischaemic heart diseases (IHD), cerebrovascular diseases, heart failure, atrial fibrillation, selected peripheral vascular diseases and other selected CVD with atherosclerotic and thromboembolic aetiology. Circulatory conditions that are known to be caused by non-atherosclerotic diseases such as infectious and infiltrative disease are excluded under this definition. Conditions with a

fundamentally different risk factor profile, such as venous thrombosis, are also excluded.

Atherosclerosis is a leading proximal cause of atherosclerotic and thromboembolic CVD, such as IHD, stroke, or peripheral vascular diseases. It is a pathological state with features including endothelial dysfunction, vascular inflammation, plaque formation, and vascular remodeling. It affects large and medium-sized muscular arteries, such as the coronary arteries, aorta, carotid arteries, and iliofemoral arteries, and results in acute or chronic luminal obstruction and diminished oxygen supply to key organs (2, 3).

According to the Global Burden of Disease Study 2013, the age-standardised death rate from CVD decreased by 22% between 1990 and 2013; however, the number of deaths from CVD increased by 41% over the same period, mainly due to population growth and aging (4). IHD and stroke were the leading and third-ranked causes of loss of disability-adjusted life years (DALYs) worldwide in 2010. DALYs due to IHD increased by 29% and due to stroke increased by 19%, compared to 1990 (5). Approximately 81% of the CVD disease burden (measured by DALYs) was due to IHD (56%) and stroke (25%) in 2010 (6, 7).

In 2011, CVD was the leading cause of death in Australia (across all age groups and in men and women) and was responsible for 31% of all deaths (8). The main categories of CVD in Australia are the major atherosclerotic and/or arteriovenous thromboembolic diseases: ischaemic heart disease (IHD) accounts for 47% of all cardiovascular death; stroke for 19%; heart failure (9%); peripheral vascular disease (4%) (8).The next section will focus on the global burden of IHD and stroke and their prevalence in Australia.

Ischaemic heart diseases (IHD)

The two major clinical forms of ischaemic heart disease are acute myocardial infarction (AMI) and angina pectoris.

The World Health Organization defines AMI based on ‘evidence of myocardial necrosis in a clinical setting, consistent with myocardial ischaemia’ (9-12). The ‘gold

standard' definition (10) includes changes in serum biomarkers (preferably troponin) in combination with symptoms of ischaemia and/or electrocardiographic changes (category A). In resource-constrained settings, where troponin is rarely measured, category B (i.e. ischaemia and electrocardiographic changes) and C (i.e. electrocardiographic changes) definitions of AMI are used (13).

Angina pectoris is characterised by chest pain that may be alleviated by treatment with antianginal medications. Stable angina is not associated with an acute coronary event and is commonly managed in an outpatient setting, while unstable angina is associated with a high risk of AMI and death. The WHO Rose Angina Questionnaire, a brief seven-question tool seeking information on the presence and characteristics of chest pain, is commonly used in community-based studies aiming to measure the prevalence of angina (14, 15). However, there appears to be no gold standard by which to define angina in epidemiological studies.

Ischaemic heart disease was the leading cause of disease burden, accounting for 7% of total DALYs in men and 5% in women, and the leading cause of death, globally, in 2010 (16). Although the global age-standardised IHD mortality has declined since 1990, the IHD DALYs increased by 29% between 1990 and 2010, in which population growth and population aging played important roles (16). The total disease burden of IHD (measured as DALYs) is the summation of years of life lost (YLL) as a result of fatal AMI, and morbidity due to the sequelae of non-fatal IHD (measured as years lived with disability (YLD)). Premature IHD death contributed more than 90% to the total IHD DALYs in 2010 (6).

In high-income countries, IHD YLL decreased remarkably from 1990 to 2010, especially in Australasia (34% decrease) and Western Europe (32% decrease) (6). However, some mid- and low-income regions experienced dramatic increases in YLL from 1990 to 2010, including South Asia (72% increase) and East Asia (78% increase) (6). On the contrary, per capita YLD due to IHD has been increasing across all regions of the globe. This is because, due to medical improvements, IHD patients do not commonly die at a young age in high-income countries but instead live for many years in disability or with compromised health.

In 2011, IHD was the leading cause of death in Australia, accounting for 15% of all-cause mortality and 47% of CVD related mortality (8). There are no reliable national or jurisdictional registry data on IHD incidence. Based on a proxy measure using unlinked hospital and deaths data, the cumulative incidence proportion of acute coronary syndrome (AMI and unstable angina) was 406 per 100,000 population in 2012, a reduction of 24% compared to 2007. According to the Australian Health Survey (AHS), the prevalence of IHD was 3% in Australian adults (aged 18 years and over) in 2011–2012 (17).

Stroke

The WHO definition for stroke is "rapidly developed clinical signs of local (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin" (18).

Stroke can be classified into two major categories: ischaemic stroke and haemorrhagic stroke. Globally in 2010, approximately 77% of first strokes were ischaemic strokes caused by thrombotic or embolic occlusion of a cerebral artery (19). The less common form of stroke, haemorrhagic stroke, is caused by leakage from small intracerebral arteries. However, the incidence of haemorrhagic stroke differs considerably across countries (19, 20). This is thought to be due to differences in dietary habits (e.g., variable intake of salt and preserved food), smoking prevalence, socioeconomic status, and genetic factors (20). Despite being less common, haemorrhagic stroke accounted for a larger proportion of global DALYs (2.5%) compared with ischaemic stroke (1.6%) due to higher mortality rates and more YLLs caused by the younger average age of death (21, 22).

Although mortality from stroke has been decreasing over the past two decades (37% decrease in high-income countries and 20% decrease in low and middle-income countries), the global burden of stroke was 12% higher in 2010 compared to 1990, due to occurrence at a younger age. Thirty-one per cent of strokes occurred in children (aged < 20 years) and young to middle-aged adults (20-64 years) in 2010 (an increase from 25% in 1990). In comparison with the population who is older than 75 years, the proportion of stroke-related DALYs in the total DALYs is greater in

individuals aged less than 75 years, especially in low and middle-income countries (7).

In 2011, stroke was the second most common CVD-related cause of death in Australia (6% of all-cause mortality) (8). The stroke incidence proportion in 2011 was 154 events per 100,000 population, a reduction of 23% compared to 2000. However, the prevalence of self-reported stroke remained the same over the same period (1.5% in 2012) (17).

Heart failure

Heart failure is a pathological state that results from any abnormality in cardiac structure or function that causes a failure of systemic perfusion sufficient to meet metabolic requirements without an excessively elevated diastolic filling pressure. The criteria for heart failure used in the Framingham Heart Study or a hospital discharge diagnosis are commonly used to define heart failure in epidemiological studies (14).

Heart failure is a long-term sequela of IHD but it can also be caused by other CVDs such as cardiomyopathies, hypertensive heart disease, or valvular heart disease. The prevalence of IHD-related heart failure globally increased slightly, from 2.4 per 100,000 to 2.7 per 100,000 in men, but stayed at 1.9 in women, between 1990 and 2010 (6).

There are no national registry data on heart failure incidence or prevalence in Australia. Based on data from the AHS, the prevalence of self-reported heart failure was 1% in the Australian population aged 18 and over, in 2011-2012 (17).

Others

Other kinds of CVD include peripheral vascular disease, hypertensive disease, pulmonary heart disease, cardiomyopathies, valvular heart disease, cardiac arrhythmias, and peripheral vascular disease. Approximately 25% of all CVD-related deaths were caused by ‘other’ kinds of CVD combined in Australia in 2011 (8).

CVD risk factors

The various types of CVD share a range of common risk factors, working through an underlying pathway that leads to atherosclerosis and vessel damage.

The risk factors for the development of CVD can be categorised in various ways, e.g. classical/traditional CVD risk factors, including behavioural/lifestyle factors such as nutrition/diet, physical inactivity, tobacco exposure or perinatal exposures, versus non-traditional risk factors through pathways such as adipocyte dysfunction in brown adipose tissue (23), and changes in adipokines such as adiponectin (24). Here we use the categorisation into modifiable or non-modifiable risk factors, as is used in the GBD studies. Among the non-modifiable risk factors, the effect of ethnicity is shown by the varying incidence of CVD across different ethnic groups (25, 26). This will be carefully discussed in the following sections, since there may also be modifiable elements in "ethnicity". The modifiable risk factors can also be separated into two main categories (with clear links between them): behavioural factors and biomedical factors. The behavioural factors include physical inactivity and smoking, while the biomedical risk factors include high blood pressure, high fasting plasma glucose, dyslipidaemia and, according to some evidence, vitamin D deficiency (27).

According to the Global Burden of Disease and Injury Study (2010) the top eight modifiable risk factors of the CVD disease burden in DALYs were high blood pressure, smoking, high body mass index (BMI), high total cholesterol, high fasting plasma glucose, insufficient physical activity, alcohol use, and dietary factors (5). East Asian populations share the same common major modifiable CVD risk factors as other populations. A study using nationally representative data from 10 Asian countries found a substantial proportion of the CVD burden could be attributed to 5 major modifiable risk factors: high blood pressure, smoking, high BMI, high total cholesterol and diabetes (28). However, the prevalence of modifiable risk factors such as smoking, physical activity and dietary habits may vary considerably among different ethnic groups, affecting biomedical factors and further exaggerating the effect of ethnicity on CVD incidence.

In the remainder of this section, I will briefly address these risk factors except for smoking and vitamin D deficiency. I have chosen to focus on these two risk factors as particular considerations of this thesis.

Smoking accounts for a major proportion of IHD DALYs (31%) (29) and is one risk factor where the prevalence has changed dramatically in Western populations but has been slower to change in Asian populations over time.

Vitamin D deficiency was an emerging novel risk factor for CVD when this thesis was being developed. Although clinical trials have not supported an independent role of vitamin D status in CVD, vitamin D deficiency can also be considered as a marker of multiple CVD risk factors, such as low physical activity, low time outdoors, and high BMI. These risk factors are the key determinants of serum 25(OH)D level.

This means that these two risk factors are useful to examine the broad scope of modifiable risk factors, with a high likelihood of seeing changes with acculturation. More detailed sections on these risk factors are presented separately.

High blood pressure

The WHO definition for hypertension is having any of the following: a systolic blood pressure (SBP) of 140 mm Hg or more; a diastolic blood pressure (DBP) of 90 mm Hg or more; taking antihypertensive medication. According to data from the AHS, the prevalence of hypertension was 32% in Australian adults in 2011-2012 (30).

Hypertension is the leading risk factor for CVD according to the Global Burden of Disease and Injury Study 2010. Fifty-three per cent of IHD DALYs was attributable to high blood pressure worldwide in 2010 (5).

Evidence suggests that hypertension is associated with increased risk of a range of CVD outcomes. In a large-scale prospective study of 1.25 million people, modest associations were found between hypertension and intracerebral haemorrhage (hazard ratio (HR) 1.44 (95% CI 1.32-1.58)), and stable angina (HR: 1.41 (1.36-1.46)) (31).

Controlling or reducing hypertension reduces the risk of CVD. A meta-analysis of randomised controlled trials from the Blood Pressure Lowering Treatment Trialists' Collaboration reported that blood pressure-lowering treatment reduced the risk of cardiovascular events (including stroke, heart attack, heart failure, or cardiovascular death) by 13%-18% for people in different categories of baseline 5-year CVD risk (32).

High body mass index (BMI)

The WHO definition for overweight and obesity based on BMI is: underweight BMI < 18.5, healthy weight BMI ≥ 18.5 and BMI < 25, overweight BMI ≥ 25 and BMI < 30, obese BMI ≥ 30. According to the 2011–12 National Health Measures Survey, 35% of Australian adults were overweight and 28% were obese (30). WHO recommends additional cut-off points to define higher BMI in Asian populations. The suggested categories are: BMI 23–27·5 kg/m^2 for overweight and > 27·5 kg/m^2 for obesity (33).

Higher BMI has been shown to be associated with an increased risk of a range of CVD events and CVD mortality across diverse populations. A meta-analysis of 57 prospective cohort studies reported that each 5kg/m2 increase in BMI was associated with a 40% increase in CVD mortality (HR: 1.41 (1.37-1.45)) (34). A recently published meta-analysis of 95 cohorts with a total of 1.2 million participants reported that the age-adjusted HR of coronary heart disease for those overweight was 1.20 (1.12–1.29) in women and 1.22 (1.12–1.32) in men; and for those obese 1.61 (1.42–1.82) in women and 1.60 (1.43–1.79) in men (35). A meta-analysis of 25 prospective studies including 2 million participants reported that the relative risk (RR) of ischaemic stroke was 1.22 (1.05-1.41) in the overweight and 1.64 (1.36-1.99) in the obese. There was a non-significant association with haemorrhagic stroke (RR for overweight: 1.01 (0.88-1.17); RR for obesity: 1.24 (0.99-1.54)) (36).

Dyslipidaemia

The Australian National Heart Foundation defines dyslipidaemia as a disorder of lipoprotein metabolism that consists of one or more of the following abnormalities in serum lipid concentrations: high total cholesterol (TC ≥ 5.5 mmol/L); high low-

density lipoprotein cholesterol (LDL-C ≥ 3.5 mmol/L); high triglycerides (TG ≥ 2.0 mmol/L); low high-density lipoprotein cholesterol (HDL-C < 1.0 mmol/L for men, and < 1.3 mmol/L for women) (37). According to data from the AHS, 33% of Australian adults had high LDL-C, 23% had low HDL-C cholesterol and 14% had high TG in 2011-2012 (30).

Abnormality of LDL-C has been reported to increase the risk of developing atherosclerosis resulting in IHD, angina, and stroke (37-39). High LDL-C is the primary target for CVD prevention. Evidence from large-scale meta-analysis of 27 randomised trials suggested that, in individuals with low risk of CVD, for each 1 mmol/L reduction in LDL-C, the RR for major vascular events (including major coronary events, strokes, and coronary revascularisation procedures) was 0.79 (0.77-0.81) (40).There is no evidence to support interventions that increase the levels of HDL-C to reduce CVD incidence or CVD mortality (41).

High fasting plasma glucose

WHO defines impaired fasting glucose (IFG) as a fasting plasma glucose concentration between 6.1 mmol/l and 6.9 mmol/l, with a diabetic level defined as 7.0 mmol/L or higher (42). "High fasting plasma glucose" includes both IFG and diabetes. In 2011–12, the estimated prevalence for high fasting plasma glucose was 8.2% in Australian adults, based on self-reported data, HbA1c results, and test results of fasting plasma glucose (5.1% for diabetes, and 3.1% for IFG) (30).

In a meta-analysis of 102 prospective studies, the risk for a wide range of CVD outcomes in individuals with diabetes was around twice that of those without diabetes (HRs: IHD, 2.00, 95% CI (1.83–2.19); ischaemic stroke, 2.27 (1.95–2.65); haemorrhagic stroke, 1.56 (1.19–2.05)). In the same study, in people without diabetes, HRs for IHD were 1.17 (1.08–1.26) for those with IFG, compared to those with fasting blood glucose concentrations in the normal range (3.90–5.59 mmol/L) (43). According to recent findings in a randomised controlled trial, intensive glycaemic control in people with type 2 diabetes significantly reduced the risk of major cardiovascular events (defined as heart attack, stroke, new or worsening congestive heart failure, amputation for ischaemic gangrene, or cardiovascular-related death) (HR: 0.83 (0.70–0.99)) (44). A meta-analysis of thirteen randomised-controlled trials

reported a 20% AMI risk reduction associated with intensive glucose lowering treatment in people with type 2 diabetes (45). However, that evidence suggests intensive glycaemic control has little effect on reducing CVD mortality (44-46).

Physical inactivity

Sufficient physical activity is defined as 'accumulate 150 to 300 minutes of moderate intensity physical activity or 75 to 150 minutes of vigorous intensity physical activity, or an equivalent combination of both moderate and vigorous activities (where vigorous physical activity is weighted by two) each week, according to Australia's Physical Activity and Sedentary Behaviour Guidelines (47). In 2011–12, 56% of the adult population did not meet this physical activity recommendation (30).

Physical inactivity is implicated in increased risk of a range of CVD outcomes from IHD and stroke, to peripheral vascular disease. In addition to the direct effect of insufficient physical activity on cardiovascular health, it also contributes to other CVD risk factors such as overweight or obesity, hypertension, and dyslipidaemia. On the other hand, regular physical activity has a protective effect on decreasing the risk of CVD and other more proximal CVD risk factors. A meta-analysis of prospective cohort studies reported a dose-response relationship between physical activity and risk of IHD. In comparison with those without leisure-time physical activity, the relative risk (RR) of IHD was 0.86 (0.77-0.96) in those engaged in the equivalent of 150 min/week of moderate-intensity leisure-time physical activity. For higher physical activity levels (i.e. 300 min/week of moderate-intensity leisure-time physical activity) the RR of IHD was 0.80 (0.74-0.88) (48). Another meta-analysis reported that, compared with inactivity, moderately intense physical activity had a protective effect on total stroke (with RR ranging from 0.64 (0.48-0.87) to 0.85 (0.78-0.93)) (49).

Dietary risk factors

Dietary risk factors include diets low in fruits, vegetables, nuts, seeds, whole grains, sea food, omega-3 fatty acids, and diets high in sodium. In the GBD 2010 Study, the largest proportion (10%) of global DALYs was attributable to poor diet (22).

The 2013 Australian Dietary Guidelines provide minimum daily intake for five food groups including vegetables, fruit, dairy food , lean meat and grains (50). The guideline also recommends that intake of intake of foods containing saturated fat, added salt, added sugars and alcohol is limited (50). The Australian Health Survey 2011-2013 reported that most Australians failed to meet recommended daily intakes of any of the five food groups (51) and over half of Australians exceeded the recommended free sugar intake (less than 10% of dietary energy) (52).

Observational studies suggested insufficient intake of nutritious foods and consumption of foods high in saturated fat, added salt, added sugars are associated with a range of CVD outcomes (53-55). However, there is no strong evidence from randomised controlled trials that supports the benefits of changing intake of these dietary risk factors.

Smoking as a CVD risk factor

Burden and prevalence of smoking

Tobacco smoking is defined as 'the smoking of tobacco products, including packet cigarettes, roll-your-own cigarettes, cigars or pipes' (56). Smoking causes a considerable disease burden and CVD burden worldwide. In 2010, 31% of IHD DALYs was attributed to tobacco smoking including second-hand smoking (29).

In the AHS (2011-2012), the estimated prevalence of daily smoking in the Australian adult population was 16% overall: 18% of men and 14% of women smoked daily. For each age group, the proportion of men who smoked daily was higher than that for women (30). The highest prevalence of daily smoking was observed in the 45-54 year age group, for both men (23%) and women (17%). There was no significant difference in the prevalence of daily smoking between the 25-34 and 45-54 year age groups. Amongst older people, the lowest prevalence of daily smoking was in the 75 and over age group, with 4% for both men and women. (30).

Evidence in relation to CVD

Smoking is an established independent risk factor for a wide range of CVDs. A comprehensive meta-analysis of 25 prospective cohort studies of older people (aged

60 and over) reported that CVD mortality was increased more than two-fold in current smokers (HR: 2.07 (1.82-2.36)) and was 37% higher in former smokers (HR: 1.37 (1.25-1.49))in comparison with never smokers. The risk for CVD mortality and CVD incidence increased in a dose-response manner according to the number of cigarettes smoked per day, in current smokers. The trend of CVD mortality risk increase per 10 cigarettes was 1.40 (1.33-1.47) (57).

Smoking cessation reduces risk rapidly and is beneficial even in older age groups. Evidence suggests a continuous decrease in risk of CVD events and CVD mortality following cessation of smoking. In those who had stopped smoking for more than 20 years (58), the HR for CVD was only slightly increased (HR: 1.15 (1.02-1.30)) compared to never smokers (57).

Vitamin D deficiency as a CVD risk factor

In addition to the above well-known CVD risk factors, the possible role of vitamin D deficiency in CVD aetiology is a relatively new area of interest. “Vitamin D” is an umbrella term including both cholecalciferol (Vitamin D3) and ergocalciferol (vitamin D2) (59, 60).

Vitamin D formation and metabolism, categories of vitamin D status

Vitamin D can be obtained from foods (e.g. vitamin D-fortified food, oily fish, and eggs) or vitamin D supplements. However, dietary intake accounts for only around 10% of obtained vitamin D for most Australian adults (61). The major source of vitamin D is sunlight-induced vitamin D synthesis in the skin. In this process, vitamin D3 is synthesised through direct action of ultraviolet (UV) radiation in the shorter UVB waveband on 7-dehydrocholesterol in epidermal cells (60). Vitamin D is a prohormone that exerts no significant biological activity. Vitamin D from any source (dietary or sun-induced, whether D2 or D3) is transported to the liver and hydroxylated to 25-hydroxyvitamin D (25(OH)D), which is the major circulating form. This also has minimal biological activity and a further hydroxylation is required, occurring mainly in the kidney, for the active form, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) to be produced. Many extra-renal tissues also express the 1α-hydroxylase enzyme that converts 25(OH)D to $1,25(OH)_2D$, thus producing local,

tissue $1,25(OH)_2D$. Serum 25(OH)D concentration is considered as the main determinant of $1,25(OH)_2D$ tissue levels in various organs and is the usual measure of vitamin D status (62, 63).

There is no general consensus on the cut-off levels of serum 25(OH)D that denote vitamin D deficiency. Based on vitamin D effects on calcium metabolism, bone density and muscle function, with 25(OH)D concentration of 50-60 nmol/L optimal musculoskeletal health can be achieved. Many observational studies have reported an increased risk of various chronic conditions in association with lower serum 25(OH)D levels, including autoimmune diseases, cardiovascular and metabolic diseases (64-66). On the basis of these findings, a higher 25(OH)D cut-off of 75 nmol/L has been recommended by some groups for the prevention of non-bone, chronic diseases. Of note, serious issues with the measurement of serum 25(OH)D (67) and lack of support for a causal effect of higher 25(OH)D levels on disease outcomes have cast some doubt on the need for these higher levels. In this thesis, vitamin D deficiency is defined as deseasonalised serum 25(OH)D level less than 50 nmol/L (68).

Prevalence of deficiency in Australia

The recent AHS reported that the overall prevalence of vitamin D deficiency (serum 25(OH)D concentration <50 nmol/L) was 23% in 2011-2012 (69). However, migrant groups of non-Caucasian ethnicity are at higher risk of vitamin D deficiency (70-72).

The prevalence of vitamin D deficiency ranged from 30% to 50% for people of African origin, and 58% to 67% for those of Asian origin (69). One national population-based study conducted in 1999-2000 indicated that people of non-Caucasian ethnicity were at greatly increased risk of being vitamin D deficient compared to the Caucasian population (odds ratio (OR) = 4.68 (95% confidence interval (CI) 3.14 to 6.95) for males and 3.49 (95CI% 2.60 to 4.68) for females) (73). Both darker skin pigmentation and cultural preferences for lower sun exposure, compared to the host population, have been implicated as major contributors to these differences (70-72).

Asian populations have lighter skin compared to some high-risk ethnic groups such as African migrants. However, behavioural risk factors present in the Asian population,

including sedentary lifestyle and sun-avoidance, increase their risk of vitamin D deficiency (74). Kift and colleagues reported that South Asians living in the United Kingdom reported longer time outdoors than white Caucasians, but their exposure to UV radiation (measured with polysulphone badges) was actually 50% less (75). A likely explanation of this finding is that Asian migrants are commonly sun avoidant, seeking shade when outside and using sun protection (such as clothing or an umbrella) (72, 76). Consistent with this study, Jang and colleagues found in a qualitative study that immigrant women from China and Korea living in Australia reported having a tendency to avoid sun exposure when outdoors, due to their preference for fair skin (74).

Evidence in relation to CVD

The causal relationship between vitamin D deficiency and major CVD and CVD-related mortality has not been well established. According to the Australian National Health and Medical Research Council levels of evidence, there is level III evidence supporting the protective role of higher 25(OH)D levels in cardiovascular disease.

Substantial experimental data provide plausible pathways whereby the association between vitamin D deficiency and increased CVD risk may be explained. The wide distribution of vitamin D receptors (VDRs) in the heart and blood vessels suggests a role for vitamin D in the cardiovascular system. There is an association between low vitamin D status and decreased intestinal calcium resorption, which contributes to low serum calcium levels. This condition stimulates parathyroid hormone (PTH) secretion, which can mediate a variety of adverse cardiovascular effects (77). Vitamin D deficiency may also inhibit insulin secretion, decrease insulin sensitivity and promote inflammation (78), and stimulate activity of the renin-angiotensin-aldosterone system (79, 80). These effects provide plausible pathways whereby vitamin D deficiency may contribute to the aetiology of CVD.

Meta-analyses of large prospective cohort studies report modest associations between 25(OH)D levels and CVD outcomes such as mortality from IHD and stroke (RR ranged from 1.38-1.64) (62, 81-83). Determinants of 25(OH)D concentration include sex, age, obese/underweight, latitude of residence, season, physical activity levels, and sun exposure habits (72). Genetic factors, such as variants within the vitamin D

receptor (VDR) gene and the vitamin D binding protein gene, also contribute to variation in 25(OH) D levels (84-87). The main problem with observational studies is the 25(OH)D level may be a proxy for its determinants, such as physical inactivity, frailty, and low time outdoors, rather than a risk factor in its own right. Although these factors may be adjusted for as confounders in the analysis, their imprecise measurement may allow for residual confounding (82). It has also been argued that low 25(OH)D concentrations may be a result rather than a cause of adverse health outcomes including CVD (88, 89).

There is no evidence from randomised controlled trials to support that vitamin D supplementation might reduce the risk of or mortality from CVD (90, 91). Meta-analyses of clinical trials also do not indicate that vitamin D supplementation is effective in reducing the biomedical risk factors for CVD, such as high blood pressure (92), high fasting glucose/diabetes (93) and dyslipidaemia (94). However, few randomised trials of vitamin D therapy have used CVD outcomes as endpoints, so that the final conclusions remain unclear.

Acculturation

Origins of the concept

The concept of acculturation originated in anthropology and has been adopted by other disciplines including epidemiology and psychology. It was first introduced in 1936 by anthropologists Redfield, Linton, and Herskovits. It was defined as "a complex process whereby individuals in a minority group modify or retain the features of their culture of origin (i.e. norms, attitudes, values and behaviors) as a consequence of continuous exposure to the host cultural system" (95).

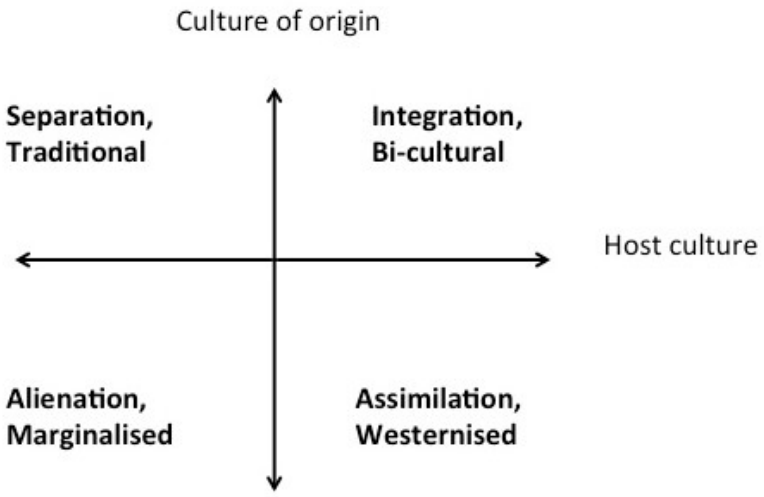
A multicultural society like Australia is composed of culturally diverse ethnic groups, including immigrants and their descendants. These changes in the population to include these ethnic groups with a variety of cultural, socioeconomic and genetic backgrounds results in changes in the population's health profile and the public demand for health services. In this context, the concept "acculturation" takes on special importance in terms of social equity and public health. Therefore, various

theoretical models and quantitative instruments are proposed and developed to quantify the relationship between acculturation and different domains of health.

Acculturation Theoretical Models

Two different theoretical models have been proposed to provide the underlying conceptual framework for the process of acculturation. These are the linear model (96) and the two- or multi-dimensional models (95). In the linear model, there is only one dimension; this is based on the assumption that immigrants acquire host culture and at the same time lose their original culture (96). The two-dimensional model, developed by Berry and his colleagues, describes a more complex process whereby immigrants may retain their original culture and at the same time adopt features of the host culture. Figure 2.1 is a diagrammatic representation of acculturation modified from a publication by Flannery and colleges (97), which shows acculturation in two cultural dimensions: culture of origin (vertical line) and host culture (horizontal line). The two-dimensional model gives rise to four outcomes of acculturation, as a consequence of retaining or losing original cultural features and acquiring or resisting the host cultural features: integration, segregation, assimilation, and marginalisation (97). Multi-dimensional models are based on the assumption that different domains of acculturation such as attitudes, values and behaviours may change separately in different manners, thus, they must be examined individually (95).

Figure 2.1: A diagrammatic representation of the two-dimensional model of acculturation



Instruments to Measure Acculturation in Epidemiology

Various quantitative instruments have been developed to measure the level of acculturation. These instruments have been used to examine the relationship between acculturation and health-related issues in epidemiological studies in North America, Europe and Australia. Such studies have provided evidence of an association with several health outcomes. Based on the theoretical models, there are two categories of quantitative instruments used to measure acculturation: multi-item scales and non-scale measurement tools (98-101).

Non-scale measurements include time measurements and language measurements. These measurements can be used separately or in combination. Time measurements, such as the length of residence in the host country and age at migration, and language measurements, such as language proficiency and language preference, are straightforward to use and commonly used as indicators of acculturation in population-based studies (102, 103). These instruments offer great flexibility to explore health effects in separate dimensions and to some extent correlate with scale-measurements. However, the underlying mechanism of the association between these variables and health outcomes may be very complicated. Therefore these instruments cannot directly reflect the changes in different domains of health in association with acculturation. For instance, changes in language preference and skill may reflect higher levels of acculturation, but these changes can also result from media availability or necessity of language skills for certain subgroups of migrants. Non-scale instruments reflect changes in terms of losing one cultural orientation and gaining another, which presents the acculturation process as a linear process. This type of instrument potentially obscures protective factors related to maintaining elements of the culture of origin (e.g. maintenance of healthy dietary habits, continuation of social support, and social norms around smoking) (104, 105).

Multi-item scales have been designed based on two-dimensional theoretical models or multi-dimensional models (106-108). For instance, the Suinn-Lew Self-Identity Acculturation Scale was created specifically for Asian migrants and is widely used to measure acculturation levels. This scale contains 21-26 items including scale attitudes such as food preferences and media use, self-identity, and behaviours such as

language use (107). Scale items for underlying domains are combined into a composite score (two-dimensional theoretical models) or evaluated based on different domains of acculturation (multi-dimensional models). Although acculturation is measured by changes in values, beliefs, attitudes and behaviours as part of the process, when it is used as a composite score, the effects of different acculturation dimensions on health outcomes may not be very clear. The acculturation process may be better captured with these multi-item scale instruments by examining multiple dimensions such as attitudes, values, and ethnic interactions, separately. (105)

A validation study compared the empirical performance of these theoretical models using different measures. The results suggest that neither linear model nor two-dimensional model demonstrate empirical superiority (97). As both acculturation models are valid, researchers may select the acculturation model that best suits the research questions and study populations (97). In this thesis, linear models were used due to the availability of relevant data.

Acculturation and CVD risk

The diversity of Australia's population has been reshaped over many years by immigration. According to the 2011 census, over a quarter (28.1%) of Australia's population was born overseas (109). Historically, the majority of overseas-born people were from the United Kingdom and other European countries. In the past decade, the pattern has changed. Asian countries have significantly contributed to recent migration streams, representing 33% of all overseas-born populations in 2013 (109).

Health characteristics of migrants may be different from those of host population due to their diverse cultural backgrounds (110). Generally, migrants demonstrate good or even better health on arrival and for some years following migration compared with the host population. This better health is reflected in lower mortality, lower incident hospitalisation for various diseases, and a lower prevalence of some lifestyle-related risk factors (111, 112). Two popular hypotheses have been put forward to explain this phenomenon: 1) The 'healthy migrant effect', that generally only those in good health can migrate to the host country due to health requirements and eligibility criteria in

most countries (113-115); and 2) the "salmon bias" that migrants may return to countries of origin after retirement or severe illness, meaning that their deaths occur in the home country and are not taken into account by mortality reports and hospitalisation records in the host country (116). Thus, the mortality rate and incidence rates of severe diseases in migrant groups may be artificially lowered. However, direct evidence supporting these hypotheses, particularly the "salmon bias," is limited (117). The health advantages seen on arrival are known to become less evident with increasing duration of residence in the host countries (113, 118).

Some studies suggest that the health status of migrants is influenced by the culture and social norms of the home countries, and varies according to age, socioeconomic status, language, and satisfaction with their job and life in the host countries (119). Acculturation models and CVD risks have been studied in various immigrant communities in Australia (120, 121). However, there are limited data on East Asian immigrants (110, 122-124). The majority of these studies were cross-sectional and based on survey data or were conducted more than ten years ago. Based on the limited evidence, inconsistent patterns of CVD-related mortality and hospitalisation were found in different migrant groups, compared to the Australian-born population. Given the recent changes in patterns of migration, these studies may be out-dated and not accurately reflect the CVD patterns in overseas-born populations in Australia, especially for those born in Asian countries who have arrived in the past decade. This thesis specifically addresses this gap in the evidence for migrant populations.

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Chapter 3

Methods

Research questions

The research questions that this thesis seeks to answer have already been noted in chapter 1, and are repeated here for the convenience of the reader:

1. Does the profile of CVD risk factors change as migrants become acculturated to the host country?
    - 1.1 Does the prevalence of smoking change in relation to indicators of acculturation in Asian populations living in western countries?
    - 1.2 What are the determinants of vitamin D deficiency (a possible CVD risk factor) in Northeast Asians living in Australia and is there an association between vitamin D status and level of acculturation?
    - 1.3 Are models used to predict vitamin D status (for example, for use in population-based studies investigating vitamin D deficiency as a risk factor for CVD) valid?
    - 1.4 Does the CVD risk factor profile differ in East Asian migrants compared to Australian-born individuals and in relation to time indicators of acculturation?
2. Does the epidemiology of CVD change as East Asian migrants become acculturated to the host country?
    - 2.1 Does the incidence of major CVD-related hospitalisation differ according to time indicators of acculturation in East Asian migrants compared to Australian-born?

These questions are addressed by chapters comprising multiple studies that have been published (or prepared for publication) in peer-reviewed journals, as outlined below. The specific methodology for each paper is fully described in that paper.

Research question 1.1: Does the prevalence of smoking change in relation to indicators of acculturation in Asian populations living in western countries?

Smoking is a major cause of CVD (1). The prevalence of smoking varies widely across the world (2). Previous studies report a marked sex-related disparity of smoking prevalence in East Asian countries and in East Asian immigrants (3). Understanding how smoking prevalence and the quit ratio change in relation to the acculturation process is important for developing tobacco control policies targeted to multicultural communities in Australia and other western countries. I undertook a

systematic review of the published research literature regarding smoking prevalence in Asian populations living in a selection of western countries (Chapter 4). I conducted a meta-analysis to calculate summary estimates of the odds of being a smoker in acculturated Asian migrants compared to counterparts who had retained a traditional life style (Chapter 4). In this study, different methods to measure acculturation were included and the associations with the different measures were tested for heterogeneity.

Research question 1.2: What are the determinants of vitamin D deficiency (a possible CVD risk factor) in Northeast Asians living in Australia and is there an association between vitamin D status and level of acculturation?

In Chapter 5, I present the findings from a community-based cross-sectional study, the Asian Australian Health Study. I designed and conducted this study, which included 100 Northeast-Asian Australians living in Canberra. The data collection instruments and protocols were based on a previous study of older people living in Canberra (4). This study allowed me to assess the determinants of vitamin D status in this population and to compare these to similar studies within mainly Caucasian populations. I also assessed the association between acculturation and vitamin D status and the determinants of vitamin D status. In this study, acculturation level was quantified using a modified Suinn-Lew Asian Self-identity Acculturation Scale (5).

Research question 1.3: Are models used to predict vitamin D status (for example, for use in population-based studies investigating vitamin D deficiency as a risk factor for CVD) valid?

Emerging evidence from observational studies suggested that vitamin D deficiency may be a risk factor for CVD (6). As direct measurement of biomarkers for vitamin D status may not be feasible in large epidemiological studies, previous studies have developed prediction models for vitamin D status based on parameters derived from questionnaire data and measured vitamin D status in a subsample of the study population (7), using multiple linear regression models. There has been little consideration of the validity of such models and the potential bias introduced by their use.

The problem of potential misclassification of predictors was briefly discussed in the Asian Australian Health Study, and particularly applies to factors such as self-reported skin type. We found that Asian participants reported their skin type as fairer than categorised by an objective measure of skin type. Furthermore, variables such as physical activity are typically self-reported with considerable error leading to potential non-differential misclassification bias.

In the first paper that is included in Chapter 5 we explored the problem of the use of potentially invalid instrumental variables. Here we used mathematical models, in conjunction with simulations and analysis of real data, to estimate the potential bias introduced by the use of variables that are inappropriately specified as being instrumental variables.

The second paper in Chapter 5 introduces new modelling techniques that may provide an improvement over multiple linear regression for prediction accuracy. Using data from a large case-control study (the Ausimmune Study) I conducted a validation study to compare the prediction accuracy using a novel modelling method, support vector regression, with that from traditional multiple linear regression models.

Research question 1.4: Does the CVD risk factor profile differ in East-Asian migrants compared to Australian-born individuals and in relation to time indicators of acculturation?

In Chapter 6, I analysed cross-sectional baseline data from a large population-based study in New South Wales, Australia. Here I described the risk factor profiles in several migrant groups and their association with several indicators of acculturation, with a focus on East-Asian migrants. I used two time indicators to measure acculturation: duration of residence in Australia and age at migration.

Research question 2.1: Does the incidence of major CVD-related hospitalisation differ according to time indicators of acculturation in East-Asian immigrants compared to Australian-born individuals?

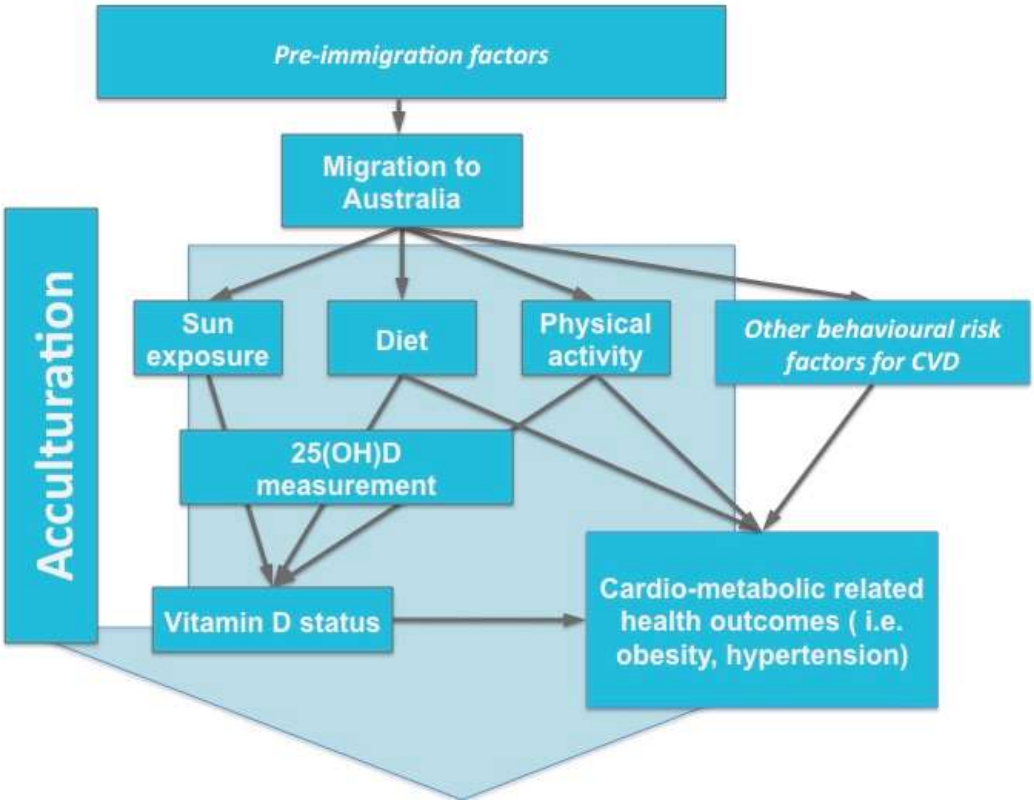
In Chapter 7, I used baseline questionnaire data from participants in the 45 and Up Study that had been probabilistically linked to the NSW Admitted Patient Data Collection (APDC) and the NSW Register of Births, Deaths and Marriages. The

linked data allowed me to assess the incidence of a range of CVD outcomes and all-cause mortality in migrant subgroups compared to Australian-born individuals, with a focus on Asian-born migrants. I also explored the association between two time indicators (duration of residence in Australia and age at migration) and major CVD hospitalisation.

Conceptual framework

The conceptual framework of this thesis is presented in Figure 3.1. Note that some pre-immigration factors, such as migration status and socioeconomic status in the country of origin are not available in the data sources. Thus, pre-immigration factors in the conceptual model will not be examined systematically in this thesis.

Figure 3.1. Thesis conceptual framework



Research methodology

The research questions were investigated using four broad research methods as below:

1. Systematic review of literature and meta-analysis
2. Collection and analysis of data from cross-sectional studies
3. Mathematical modelling for prediction of vitamin D status and assessment of accuracy and bias
4. Analysis of linked data from a population-based cohort study

Systematic review of literature and meta-analysis

Systematic reviews are a means of investigating information from the published literature to provide summary evidence (8). A meta-analysis uses statistical methods to combine the results from different studies to identify patterns of results from multiple studies (9).

In chapter 4, I used a systematic review and meta-analysis to address research question 1.1. Using the methods inherent in the systematic identification and extraction of data I provided a summary of the prevalence of smoking in Asian populations in western countries that have similar overall smoking prevalence to that of Australia (i.e. United States, Canada, New Zealand, and United Kingdom). A meta-analysis was also performed to quantify the effect size for the association between acculturation and smoking prevalence in East-Asian populations in a selection of Western countries. I had primary responsibility for all elements of this study.

Studies were sourced by searching PubMed, Web of Science, PsycINFO, and the Cochrane library database, after which a two-stage filtering process and a quality appraisal process were performed by two investigators (myself and Dr Ning Ding) to select studies that met the inclusion criteria and were of sufficient quality.

A detailed review of the studies identified considerable difference in the methods used to quantify the level of acculturation, including use of multi-item scales, language indicators and time indicators. To compare studies, we took acculturation as a categorical variable and used the most adjusted odds ratios (ORs) and respective 95% confidence intervals (CIs) as the statistics of effect size. Meta-analysis using a

random-effects model was conducted in the statistical package Stata (10). We also performed sub-group analysis to quantify the heterogeneity caused by the use of different indicators of acculturation. Heterogeneity between studies was assessed by the I^2 test.

Collection and analysis of data from cross-sectional studies

In this thesis, I undertook a community-based cross-sectional study, the Asian Australian Health Study. This formed the basis of the third paper (i.e. Paper 4) in Chapter 5 and allowed me to assess the determinants of vitamin D status in East-Asians living in Canberra, including the effect of acculturation. This study involved the recruitment of a study sample of Northeast-Asian adults and the collection of data from questionnaires, physical examination, and a daily sun diary. In addition, I collected dosimeter measurements of exposure to UV radiation, and fasting blood samples provided data on serum 25(OH)D levels, lipid profile, and serum glucose. The questionnaire was adapted from that used in the 45 and Up Study and the "Measuring sun exposure: a validation study" (4) and also included the modified Suinn-Lew Asian Self-identity Acculturation Scale (5). The study design was based on a previous study of sun exposure and vitamin D in older adults in Canberra Australia (4). I recruited the study sample, collected and analysed the data, and wrote the preliminary draft of the paper. In designing the methodology for the Asian-Australian Health Study, I considered the purpose of the study, the sample size needed to obtain the required sample size to detect a difference in sun exposure according to previously described differences in migrant groups, and the appropriate questionnaire design. All questions were tested in a pilot study and available in both the participant's native language and in English.

Backwards stepwise regression, followed by purposeful selection of covariates, was used to generate the model for the determinants of vitamin D status. Exact logistic regression was used to compare proportions of participants with vitamin D deficiency according to acculturation levels. Analyses were performed in SAS version 9.3 (SAS Institute, Inc, Cary, NC, USA)(11). I developed the methods, collected all of the data, and undertook all analyses and initial drafts of the paper for this work.

For chapter 6, I used data that had already been collected in the baseline phase of the 45 and Up Study to assess CVD risk profiles according to region of birth and acculturation level. The 45 and Up Study is a large population-based cohort study of people aged 45 years and over, living in New South Wales, Australia (12). Study participants were recruited following random sampling from the Medicare Australia database and completed a self-administrated baseline questionnaire between January 2006 and December 2008. With a large sample size, the 45 and Up Study provided an opportunity to investigate CVD risk profiles in several migrant subgroups separately. Access to the baseline data was provided by the Cardiovascular Research Network (CVRN) who work on the data from the 45 and Up Study.

Prevalence ratios for CVD risk factors in overseas-born versus Australian-born participants were calculated using modified Poisson regression, focusing on Asian immigrants and adjusting for age, sex, and socioeconomic factors. The same statistical methods were also used to examine the association between acculturation indicators and CVD risk factors in Asian immigrants. I was the lead author of this study and contributed to the development of the research question, data analysis and manuscript writing.

Validation studies of prediction models for vitamin D status

A validation study was undertaken to determine the accuracy of different measurements of vitamin D status compared to its 'gold standard' (13).

Prediction models are increasingly used for diagnosis (to estimate the probability of the presence of a particular health outcome) and prognosis (the probability of developing a certain health outcome in the future). Recently, several publications have used prediction models for vitamin D status to estimate an individual's serum 25(OH)D concentration or vitamin D status (in the categories "deficient," "insufficient," "sufficient"). The models are based on predictors of measured 25(OH)D level in a similar population, or a subsample of the study population. The predicted vitamin D status or 25(OH)D "score" is then used to test associations with disease outcomes, such as CVD or cancer (6, 14).

In this thesis, the validity and potential pitfalls of vitamin D prediction were evaluated with respect to three aspects: the probability of misclassification, the choice of suitable predictors, and the accuracy of prediction. Thus in Chapter 5, the first paper considers the objectively measured skin colour data with the self-reported data from Asian Australian Health Study in order to examine the misclassification of skin colour in Asian migrants. I developed the methods, collected all of the data, and undertook all analyses and initial drafts of the paper for this work. In the second paper, we created a mathematical model of a vitamin D prediction model and considered the effect of different ways in which an instrumental variable could be an invalid instrument and the bias that would be introduced. We then tested that with Monte Carlo simulations and real data from National Health and Nutrition Examination Survey 2005-06. I was a co-investigator of this study and contributed to the study design, development of the methodology, and the literature review.

New modelling techniques may represent an improvement on prediction. In the third part of Chapter 5, I conducted a study to compare a novel modelling method with the traditional multiple linear regression models. This was validated using data from the Ausimmune Study, a multi-centre incident case-control study investigating the role of environmental factors, including past and recent sun exposure and vitamin D, in the development of early demyelinating disease. Detailed, high-quality data on potential vitamin D determinants had already been collected in the Ausimmune Study and the best predictive models using multiple linear regression models had already been determined in a previous study (15). I compared the sensitivity and specificity of predicted vitamin D status using support vector regression, with that using the multiple linear regression model, with reference to a gold standard of measured 25(OH)D concentration. I was the lead author of this study and contributed to the study concept, development of the methods, data analysis and manuscript writing.

Analysis of linked data of a population-based cohort study and administrative databases

A cohort study is a form of observational study, which is commonly used in epidemiology (13). In a cohort study, an outcome or disease-free study population is first identified by the exposure or event of interest and followed in time until the

disease or outcome of interest occurs (13). The linkage of baseline data from a cohort study to administrative records is increasingly used in epidemiological studies. This method provides a means of enriching study datasets with a wide range of data not being collected directly from study participants and offers more accurate information on the health outcomes of participants than would be available from self-report (16).

In this thesis, the baseline dataset of the 45 and Up Study was linked to two administrative data collections: the New South Wales (NSW) Admitted Patient Data Collection (APDC) and Births, Deaths and Marriages Registrations. APDC is a complete census of all public and private hospital admissions in NSW. The information collected includes patient demographics, sources of referral to the service and referral to on hospital discharge records (separation), and clinical information. Death registrations capture all deaths in NSW. The linked data contain details of admissions and death records of the participants in the 45 and Up Study from 1 July 2000 to 31 December 2011. I was the lead author of this study and contributed to the development of the research question, data analysis and manuscript writing.

Considerations in the measurement of vitamin D status and its determinants

Laboratory methods for vitamin D status

Limitations of vitamin D assays are well documented, with significant variability in results between assay methods and laboratories noted in the literature (17). The Vitamin D External Quality Assessment Scheme (DEQAS) has been monitoring the analytical reliability of 25(OH)D assays since 1989 (18). In the Asian-Australian Health study, 25(OH)D levels were tested using liquid chromatography-tandem mass spectrometry (LC-MS/MS) in Canterbury Health Laboratories, New Zealand. Canterbury Health Laboratories participate in DEQAS, and LC-MS/MS is widely considered to be the best assay for accurate and precise measurement of 25(OH)D (19).

Statistical considerations

We used the raw 25(OH)D values to examine the determinants of vitamin D status and the association with cardio-metabolic risk factors, which also fluctuate over

seasons. Levels of 25(OH)D vary across the year due to changes in UV radiation exposure; to ensure comparability across participants in the evaluation of the association between acculturation and vitamin D status, we removed the seasonal contribution from the measures 25(OH)D values using a sinusoidal regression (20).

Methods to measure determinants of vitamin D

This thesis used several different approaches, including both subjective (e.g. sun diaries) and objective (e.g. UV radiation dosimeters) tools, to measure the most important determinant of vitamin D status: sun exposure.

Measurement of Sun exposure

There are two main categories of methods commonly used to estimate sun exposure: geographic estimates and personal estimates. In ecological epidemiological studies geographic data such as latitude of residence and measured ambient UV radiation are used as proxies for personal exposure to UV radiation. However, these geographic parameters cannot reflect the considerable variation in personal sun behaviours. This is especially important in studies with a considerable proportion of immigrant populations where sun exposure behaviour may be very different from the "average". Here individual-level data are required. In considering which tool to use for measuring sun exposure, the relevant timing of exposure is important. In relation to vitamin D status, previous studies have shown that sun exposure over the previous 6-8 weeks is most important (21). For assessment of sun exposure or vitamin D over the lifetime, in relation to disease risk, longer-term measures of sun exposure, such as silicone skin casts or personal residence calendars may be more appropriate (14).

In this thesis, the focus was on short term measurement of sun exposure, in relation to vitamin D status. Various forms of personal dosimeters for UV radiation exposure have been developed. The two most common forms are spore-containing biofilm dosimeters (22) and polysulphone dosimeters (23). More recently, electronic dosimeters have been developed (24). The electronic dosimeters used in our study are comparatively new, and are not yet widely used. They provide the most precise measure of personal exposure to UV radiation. Before the study, dosimeters were calibrated by the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) and calibration factors specific to each dosimeter were used for

conversion between raw data and a dose that is measured in standard erythemal doses (SEDs) (4). Data from dosimeter readings are sensitive to weather variation during the short period of study and may not accurately reflect a participant's sun exposure pattern over a relevant period of weeks. We thus calculated average UV radiation exposure standardised to the ambient UV radiation (data from ARPANSA) for the 28 days prior to blood collection. Standardising in this way to the ambient UV radiation of the previous 28 days reduces the influence on the vitamin D-relevant UV radiation exposure of rainy/cloudy days during the week of dosimeter wearing. Combining dosimeter readings with recent past levels of ambient UVR enables us to evaluate sun exposure over a longer period than usually possible, providing more stable estimates for the period relevant to vitamin D synthesis.

Daily sun diary

Diaries have been used in collecting data on a varied range of health behaviours, including sun exposure and physical activity. Sun diaries are advantageous because they make record of specific events on the day of occurrence (25) and provide data additional to that from dosimeters by including information on clothing, time of day that participants were outdoors, and use of sunscreen. When the diary is used alone (without dosimeter data), the times people report spending outdoors can be converted into personal ambient exposure and into personal dose, provided data are available for the local terrestrial doses of UV radiation (4, 25, 26).

We evaluated the daily average outdoors time and daily physical activity based on the data over the diary days. The daily sun diary has been previously validated against electronic UV radiation dosimeters (4).

Ethics

As the thesis reported on studies that conducted and collected data in Canberra, ACT, Australia, I obtained ethical clearance from the Human Research Ethics Committee (HREC) at the Australian National University. The reference number for the ANU HREC approval is 2012/191. In accordance with ANU HREC requirements, informed consent was sought and obtained from all individuals participating in the studies for which primary data were collected.

The 45 and Up Study has overarching approval from the University of New South Wales (UNSW) Human Research Ethics Committee (HREC), including use of data from the baseline questionnaire. As this PhD is conducted using the data from the 45 and Up Study linked to administrative hospital data and death data, I also received approval to use data from this study and conduct the linked data analysis from the New South Wales Population and Health Services Research Ethics Committee and the ANU HREC.

Funding

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Chapter 4

Paper 1: Acculturation and prevalence of smoking in Asian immigrants in western countries: a systematic review and meta-analysis

Acculturation and prevalence of smoking in Asian migrants to western countries: a systematic review and meta-analysis

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Abstract

Background: There is wide variability in the prevalence of tobacco smoking across different countries and according to sex. In many East Asian countries, the prevalence is high in men low in women, compared to many western countries. East Asian immigrants to western countries undergo a process of acculturation, including in health behaviours. This study describes variation in smoking prevalence among East Asian immigrants living in western countries and quantifies the association between acculturation and smoking behaviours.

Methods: We undertook a systematic review and meta-analysis of smoking prevalence and cessation of smoking in East Asian immigrants to western countries, by searching PubMed, Web of Science, PsycINFO and the Cochrane library database for studies that reported, disaggregated by sex and ethnic subgroup: current smoking prevalence; and/or the proportion of ever- and former smokers; and/or a smoking cessation; and/or the association between a quantitative measure of acculturation and current smoking or smoking cessation

Results: Thirty-nine cross-sectional studies published in peer-reviewed journals from 2000 to 2014 met the inclusion criteria. The prevalence of current smoking ranged from 12% to 42% in men and 0.6% to 17% in women, in population-based studies. Nearly half of former-smokers had quit. The prevalence of current smoking was generally lower in men, but higher in women, compared to that of the native country. Results from the meta-analysis showed an inverse association between acculturation and prevalence of current smoking for men (odds ratio (OR) =0.60, 95% CI 0.53 to 0.68) and a positive association for women (OR=1.79, 95% CI 1.53 to 2.08). Greater effect sizes were observed where multi-item scales were used to measure acculturation (e.g. for men, OR=0.48, 95% CI 0.37 to 0.62).

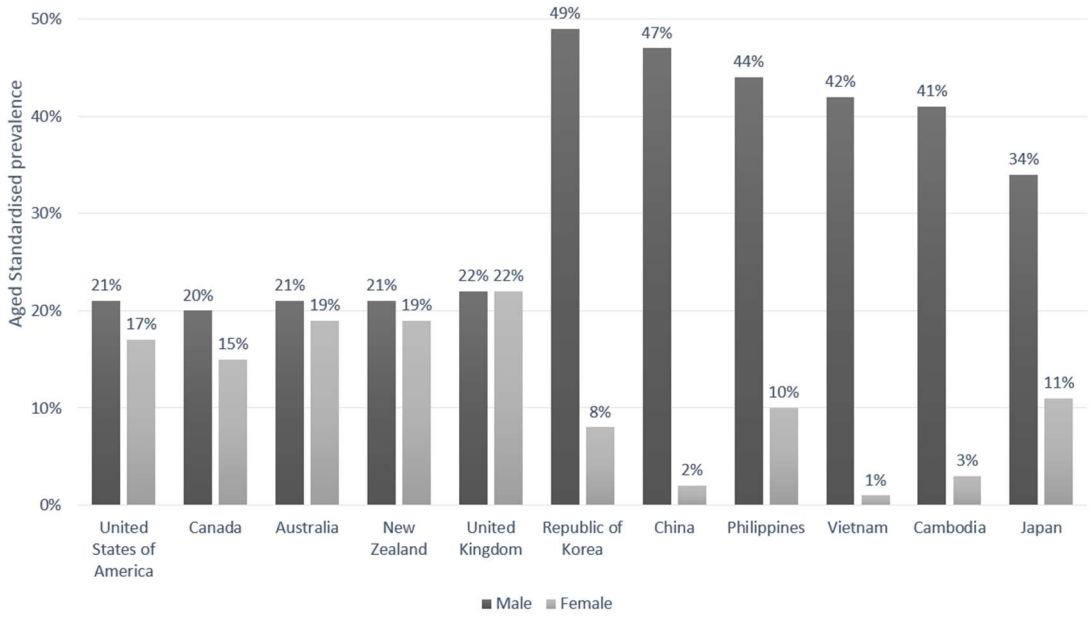
Conclusions: Smoking prevalence decreases with greater acculturation in immigrant Asian men, but increases in women, presumably in response to the different sex-specific social norms around smoking in Asian countries compared to the western countries considered here. Our results have implications for tobacco control programs in multicultural communities in western countries.

Introduction

Smoking is the cause of 5 million preventable deaths worldwide each year and is a major contributor to the global disease burden (1, 2). For example, 71% of all lung cancer deaths, 42% of chronic respiratory disease and nearly 10% of cardiovascular disease around the world are attributable to smoking (2, 3). A recent study summarises smoking prevalence and cigarette consumption intensity from 1980-2012 across 187 counties (4). The prevalence of smoking varies widely across the world (see Figure 1). In western countries such as the United States of America (USA), Canada, Australia, New Zealand and the United Kingdom (UK), concerted efforts to adopt smoke-free-air and legislation, tobacco control policies and campaigns (5-8) have resulted in a declining prevalence of smoking, at least in part because it has become less socially acceptable (8-10). In some East Asian countries there is a strong gender difference in the prevalence of smoking. It can be particularly high among men, where almost 50% currently smoke (52.9% in China, 49% in Korea, 32.4% in Japan and 47.4% in Vietnam), but less than 10% in women (11). Several factors may contribute to the gender difference in smoking prevalence. It may be explained by the opposite social norms around smoking: for men, smoking is widely accepted and a common social lubricant, while for women there are powerful taboos against smoking in these countries (12-14). Also, evidence suggests that due to the different social norm around smoking for men and women in Asian countries, smoking prevalence may be under-reported in Asian-born women (15).

The East Asian population is one of the fastest growing immigrant groups in western countries such as USA, Canada, Australia, New Zealand and UK (16-18). Surprisingly, despite the high prevalence of smoking in East Asian countries, national surveys in Australia and USA indicate that Asian immigrant groups have the lowest prevalence of smoking of all of the population sub-groups (19, 20). However, national survey data that treat Asians as an aggregate group may be problematic. Firstly, averaging the prevalence across men and women may obscure high levels of smoking among Asian men; and secondly, such aggregate data overlook the substantial differences between immigrants from different Asian countries. Indeed, studies based within individual communities, that have used culturally sensitive data collection

Figure 1: Age-standardised prevalence of smoking in National Health Surveys in Asian and Western countries



† Age standardized to the World Standard Population

methods, have shown a much higher prevalence of smoking among male immigrants from several East Asian ethnic groups compared to the male population of the host country (21, 22). Data from a representative sample of the population, disaggregated for individual subgroups (ethnicity, sex), are required to evaluate the true prevalence of smoking among East Asian immigrant groups.

Although limited, current evidence suggest that the prevalence of smoking in East Asian men living in western countries is much lower than in their countries of origin (23, 24). Several studies have also reported striking differences between East Asian immigrants and non-immigrants still living in their countries of origin in the percentage of people who have ever smoked that subsequently stop smoking (the quit ratio) (25, 26). For example, one study reported that less than 12% of former smokers stopped smoking in Chinese living in China were less than 12%, compared to a quit ratio of 53.5% in Chinese living in California (25). It is possible then that this high quit ratio accounts for the lower prevalence of current smoking in East Asian immigrant populations compared to their counterparts living in the countries of origin (25).

Smoking behaviour amongst immigrants is influenced by the culture of their home countries, as well as the policies and social norms of the host country (12, 27-29). A previous meta-analysis by Choi and colleagues reported that the degree of acculturation to the host country has emerged as an important predictor of smoking behaviour in East Asian immigrants living in the USA (27). Acculturation refers to the complex process whereby individuals in a minority group modify or retain the features of their culture of origin (i.e. norms, attitudes, values and behaviors) while exposed to the cultural systems of the host country (28). Typical measures of acculturation include proficiency and use of the host country language, duration of residence, and age at migration, although purpose-specific multi-item scales are also available (30).

During the past decade, several studies have examined smoking prevalence and smoking cessation among Asian migrants, including in relation to various measures of acculturation (31-34). Here we conducted a systematic review of that literature focusing on studies from USA, Canada, Australia, New Zealand and UK as these are somewhat similar western countries that have achieved marked success in reducing the prevalence of smoking over recent years and have high levels of Asian immigration. We update and extend the meta-analysis of Choi and colleagues by extending the study to other western countries and recent publications, and exploring the effects of using different indicators of acculturation. The review was limited to literature on immigrants from Northeast and Southeast Asia and excluded studies of South Asian immigrants who commonly consume tobacco in smokeless form (11), so that smoking data do not indicate the true pattern of tobacco use in this group.

The objectives of this study were to 1) describe sex- and ethnic subgroup-specific smoking behaviours (prevalence of current smoking and the proportion of ever smokers who have stopped smoking) amongst East Asian migrants living in USA, Canada, Australia, New Zealand and UK (systematic review of published studies); and 2) undertake a meta-analysis to quantify the association between indicators of acculturation and smoking behaviours in East Asian immigrants, separately according to sex.

Methods

Literature search and inclusion/exclusion criteria and data extraction

Two authors (SG and ND) independently identified studies published between 2000 and 2014, using PubMed, Web of Science, PsycINFO, EMBASE, and the Cochrane library database search engines. Combinations of key words included: smoking, tobacco and migrants, acculturation and East Asian (including words for specific subgroups) and USA, Canada, Australia, New Zealand and UK. We also searched for additional articles from the reference lists of the retrieved articles and review articles on smoking and other risk factors in East Asian populations living in western countries. Inclusion criteria included that the study: (1) reported current smoking prevalence, proportion of ever smokers and former-smokers, or smoking cessation; or (2) measured the association between acculturation and smoking using quantitative instruments, disaggregated by sex. We included studies where the acculturation effect was examined in East Asian subgroups separately, or in one broad "East Asian group" when the sample size limited analyses in separate ethnic subgroups. Qualitative studies, those focusing on perceptions or reasons for smoking, review articles, commentaries, case reports, methodology papers, studies of adolescents, and studies of South Asian or Pacific Islander populations were excluded. If two papers were based on the same dataset, the paper that included results for more immigrant groups was selected. Two authors (SG and ND) independently screened studies for inclusion, retrieved potentially relevant studies, and determined study eligibility. Any discrepancies were resolved by consensus.

Quality appraisal

Two reviewers (SG and ND) independently assessed study quality using a scale adapted from the 'Newcastle/Ottawa Scale (NOS)' (Appendix 1). Each study was evaluated using a point system on 1) the representativeness of the sample, i.e. a study sample selected from within a specific community (community-based) vs. a population-based study sample; 2) whether culturally sensitive tools were used for data collection; 3) whether validated measurement tools were used to identify the exposure variables (ethnicity or acculturation levels); 4) whether the prevalence/odds ratio was adjusted for age; and, 5) whether clear definitions for current smoking and former smoking were given. The number of criteria satisfied was used as a measure of

study quality; studies satisfying 5, 4, 3 or 0-2 criteria were evaluated as very good, good, satisfactory or unsatisfactory, respectively.

Definition of smoking behaviour

The outcome variables of interest were the prevalence of current tobacco smoking and a measure of smoking cessation, primarily the quit ratio (proportion of ever smokers who have stopped smoking). The most commonly used definition for current smoking in studies conducted in USA was based on the United States Centers for Disease Control and Prevention recommended criteria, according to which a current-smoker is defined as an individual who had smoked at least 100 cigarettes over the life time and reported smoking every day/some days; never smokers had smoked less than 100 cigarettes over the lifetime; and a former-smoker had smoked 100 or more cigarettes over the life time, but was not currently smoking. Ever smokers comprised current-smokers and former-smokers. In studies from Australia or Canada, smoking prevalence was based on self-reported categories of never, ever or current smoker.

Smoking cessation was defined as either the quit ratio (former smokers/ever smokers), or where that was not available or where the measure of association was an odds ratio (OR), the odds for former smokers compared to current smokers.

Measures of acculturation

A number of quantitative instruments are used to measure acculturation. Multi-item scales include measures across different domains that are combined into a composite score (35, 36). Other indicators include time measures such as duration of residence in the host country and age at migration (37), and language indicators such as English proficiency or language preference (38). Categorisation of duration of residence in the host country most commonly uses cut points of 10 or 15 years, with those resident for longer than this categorized as being acculturated. For multi-item scales, cluster analysis is also used in the literature to identify acculturated and traditional groups. Typically, acculturation is dichotomised into acculturated vs. traditional, although a third, intermediate category, bicultural may also be used. In the cross-sectional studies included in this meta-analysis, acculturation was recorded as acculturated vs. traditional.

Statistical analysis

For the meta-analysis, the ORs and respective 95% confidence intervals (CIs) were used as the measures of effect size; these values were retrieved directly from the article or calculated from data available in the paper if necessary. We used the most adjusted OR available from each study.

Studies were excluded from the meta-analysis if ORs could not be extracted or ORs for smoking were not reported separately in men and women. We used forest plots to summarize the distributions of ORs and 95% CIs, stratified by sex and acculturation measure. The Cochran Q test was used to estimate the p value for heterogeneity (39). The I^2 statistic was calculated to demonstrate the degree of heterogeneity (the percentage of variation across studies that is not due to chance) (40). When statistical pooling was required, a random-effects model was used for heterogeneous results, because we assume that different acculturation measurements may lead to different effect size estimations. We then conducted sub-group analysis according to the measure of acculturation used and further tested for heterogeneity within study-level factors (i.e. ethnicity, definition of non-smokers, sampling methods and covariates). Sub-group analysis was conducted only in men, because the limited number of studies in women restricted further stratification. We tested for possible publication bias using Egger's tests and by visual inspection for asymmetry in funnel plots. The analysis was performed using Stata 12 (StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP.).

Results

Characteristics of studies

The initial search identified 957 original articles, after excluding duplications. We excluded 691 papers, since the review of titles and abstracts indicated that they were not relevant (i.e. not about smoking prevalence or acculturation). The full texts of the remaining 266 articles were obtained for detailed review; 227 of these were excluded because they focused only on young adults or adolescents, reported similar findings derived from the same dataset, did not report sex-specific or ethnic group-specific data, or the articles were qualitative studies or reviews. Of the remaining 39 studies, most were rated as very good (17 studies) or good (13 studies). Nine studies were

rated as satisfactory. Most of the studies with satisfactory scores were either community-based studies or conducted in English only. None of the studies was rated as unsatisfactory (Appendix 2).

A total of 39 cross-sectional studies were thus included in the systematic review (Figure 2). These were all of a cross-sectional design, mainly from the USA, with only 5 studies conducted elsewhere: Australia (n=2), Canada (n=2), UK (n=1) (Table 1). Studies included immigrants from China, Japan, Korea, Vietnam, Philippines and Cambodia. A total of 35 studies reported current smoking prevalence by sex and ethnic subgroup, separately. Fifteen studies examined the association between acculturation indicators and current smoking and were included in the meta-analysis addressing this association.

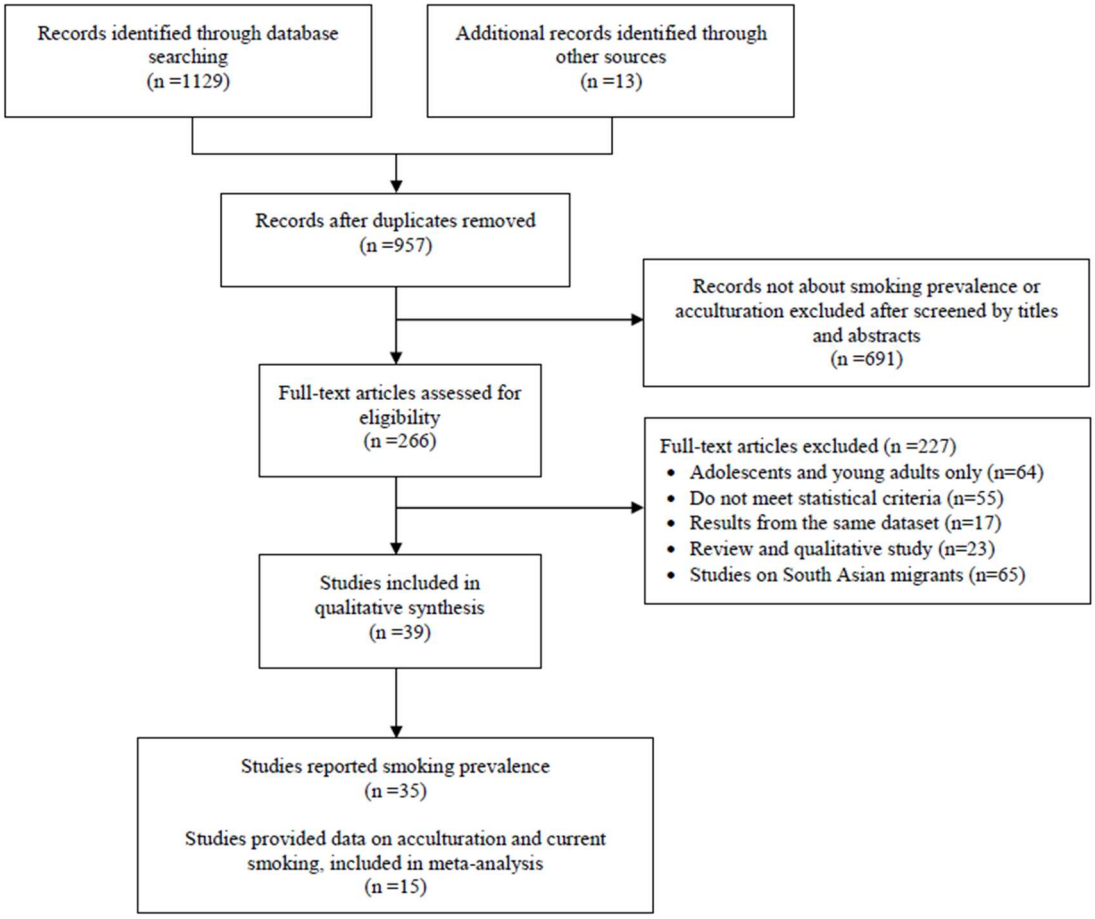
Current smoking and smoking cessation according to sex and ethnicity

Overall, the prevalence of smoking was lower in the population-based studies (range=12% to 42% in men and 0.6% to 17% in women) than in the community-based studies (range=21% to 61% in men and 0.8% to 19% in women). The greatest sex disparity was in the Vietnamese subgroup (14 studies), with the prevalence of current smoking in men 3.6 to 52 times higher than that in women (Figure 1). The smallest disparity between men and women was in the Japanese subgroup (5 studies) with differences of 3% to 13%, largely because of the higher prevalence among women than in other ethnic groups.

There was considerable variability in the prevalence of smoking between and within ethnic subgroups. In population-based samples, men of Korean (26%-39%) and Vietnamese (24%-42%) origin reported higher smoking prevalence than men from other Asian ethnic groups, such as Chinese (11%-24%). Women of Japanese descent reported relatively high smoking prevalence, with results ranging from 4% to 17% compared to Vietnamese (0.6%-3%) and Chinese (1%-7%) women. Notably, surveys conducted in English reported relatively low smoking prevalence compared to studies conducted in the participant's native language (Table 1).

Generally, smoking cessation was high in almost all of the immigrant groups. In most of reviewed studies, nearly half of former-smokers had quit (Table 1).

Figure 2: Flow diagram showing the selection of studies for inclusion in the qualitative and quantitative reviews



Association between Acculturation and Smoking Behaviour

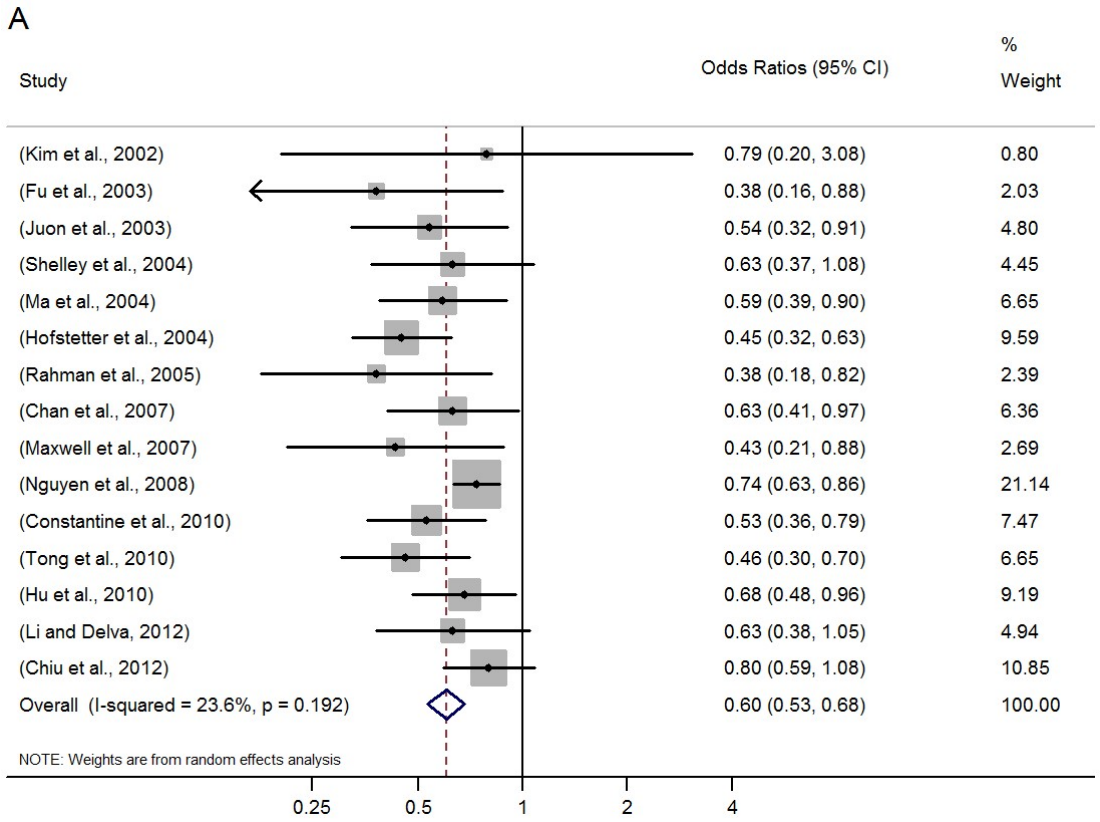
Table 1 shows a summary of the 15 studies that reported the association between some measure of acculturation and current smoking. Most studies used a language measure of acculturation (n=11); three used a time acculturation indicator and two used multi-item scales with multiple domains, followed by factor/cluster analysis to assess linguistic, cultural and structural aspects of acculturation; three studies used both time and language indicators. Five of the 15 studies reported sex-specific effect sizes, while 10 studies reported results only for men. Three studies included participants from multiple ethnic groups (i.e. Chinese, Vietnamese, Korean, Filipino and Japanese); 4 included only Chinese-origin migrants; 4 studies included people only of Vietnamese origin, 3 included only Korean-origin migrants; and 1 included only Filipino-origin migrants.

In general, longer duration of residence in the host country, higher English proficiency/preference or higher acculturation score were each inversely associated with the prevalence of current smoking in men, but positively associated with current smoking in women. The results were similar in studies that used scale and non-scale measures, although a null association was more commonly seen where a time indicator (i.e. duration of residence in host countries) was used as the acculturation measure.

We undertook a quantitative analysis, stratified by sex, on the 15 studies that provided data on a total of 16,652 men and 12,724 women, to evaluate the overall association between acculturation (as assessed by duration of residence in the host countries, language proficiency/preference and multi-item scales) and current smoking. The overall summary result showed an inverse association between acculturation and prevalence of current smoking for men (OR=0.60, 95% CI 0.53 to 0.68) (Figure 3A) and a positive association for women (OR=1.79, 95% CI 1.53 to 2.08) (Figure 3B). There was some heterogeneity (I^2=23.6%; p_{heter}=0.19) in the analysis of the data for men, but not for the analysis of data for women (I^2=0.0%; p_{heter}=0.88) (Figure 3A and 3B).

We further explored possible causes of the heterogeneity, in subgroup analyses (Figure 4). There was significant heterogeneity between the subgroups according to type of acculturation measure (p_{heter}<0.05). Greater effect sizes were observed where multi-item scales were used to measure acculturation (OR=0.48, 95% CI 0.37 to 0.62, I^2=0.0%, p_{heter}=0.53) than where time indicators (OR=0.71, 95% CI 0.57 to 0.87, I^2=0.0%, p_{heter}=0.42) or language indicators (OR=0.65, 95% CI 0.58 to 0.73, I^2=13.3%; p_{heter}=0.32) were used. When we stratified on covariates in adjusted analyses, we found that ORs for current smoking were stronger among studies that adjusted for age and socio-demographic variables (OR=0.54, 95% CI 0.46 to 0.63, I^2=0.0%, p_{heter}=0.59) or adjusted for other health behaviours in addition to age and socio-demographic variables (OR=0.56, 95% CI 0.44 to 0.71, I^2=0.0%, p_{heter}=0.81) than studies adjusted for age only (OR=0.75, 95% CI 0.66 to 0.86, I^2=0.0%, p_{heter}=0.65) (Table 2). Non-significant heterogeneity was observed according to sampling method (p_{heter}=0.07) or definition on non-smokers (p_{heter}=0.73).

Figure 3: Forest plots of studies on the association between acculturation (traditional as the reference category) and smoking in men (A) and women (B)



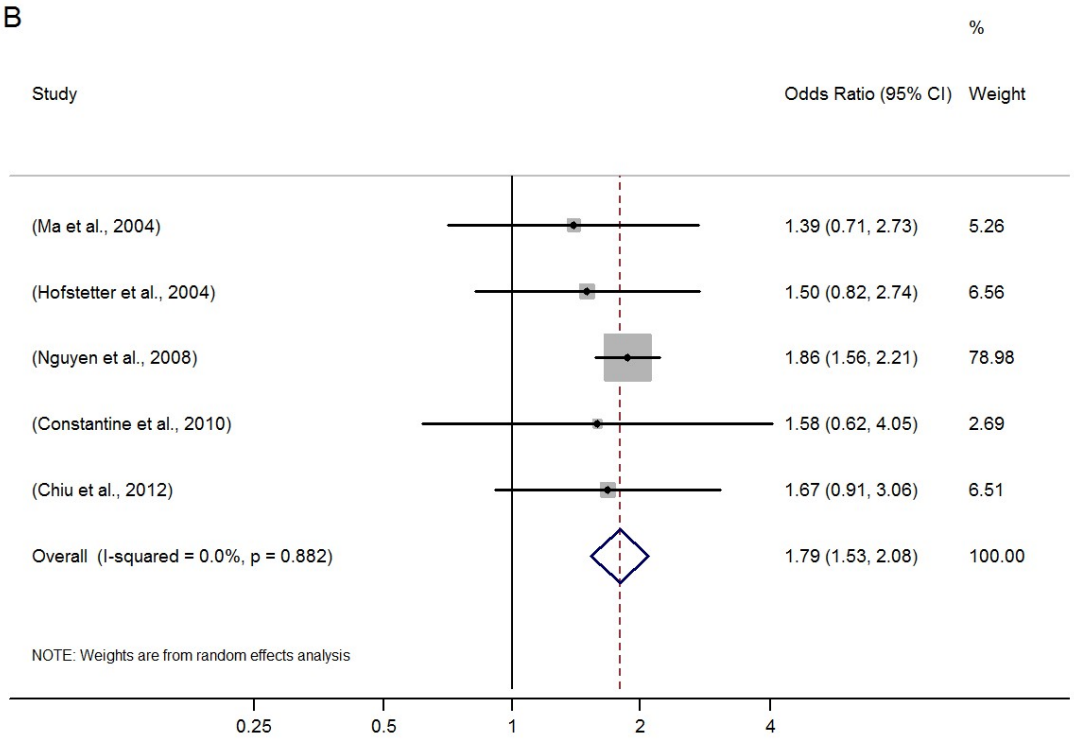


Table 1: Smoking prevalence and association with acculturation in adult Asian immigrants by sex and ethnic subgroup in papers included in this review

Study	Location/data source	Sampling (age)	Sex	N	Definition of current-smoker	Current smoker (%)	Quit rate (%)	Acculturation measure	Adjusted for	Current vs non OR (95%CI)	Former vs current OR (95%CI)
Single Ethnic Group											
Chinese											
	United States										
Li et al 2012 (34)	USA, National Latino and Asian American Survey(2002-2003)	Population-based	Male	284	US CDC definition	16.2	-	English proficiency	Age, education, marital status, health insurance, ethnicity, religion, social capital, Years in USA	1.59 (0.44-5.79)	-
Hu et al., 2010(32)	2004-2005 Houston and Dallas	Population based (≥18 yrs)	Male	652	US CDC definition	16.7	66.8	Length of stay (>15yrs) vs. (≤5 yrs), (6-10 yrs), (11-15 yrs), Born in US	Age, income, education, marital status,	3.41 (3.05-3.81) 1.16 (1.03-1.30) 1.36 (1.22-1.51) 2.64 (2.33-2.99)	-
			Female	402		4.8	24.5			-	-
Fu et al., 2003(41)	2000-2001 Philadelphia's Chinatown	Clinic based (medical/dental practices); (≥18 yrs)	Male	228	US CDC definition	25.0	54.0	English proficiency	Age, clinic site, education, income	0.38 (0.16-0.85)	0.47 (0.17–1.32)
			Female	311		3.0	50.0			-	-
Shelley et al., 2004(42)	New York	Population based (18-74 yrs)	Male	402	US CDC definition	29.0	45.0	Speaks English in the home or reads English newspapers most days or every day	Age, education, residence, marital status, employment, health insurance, knowledge, visited health professional in the past 12 months	0.63 (0.37-1.09)	0.77 (0.32-1.86)
			Female	310		4.0	33.0			-	-
Yu et al., 2002(43)	Chicago's Chinatown	Population based (≥18 yrs)	Male	312	US CDC definition	33.6	43.9				
			Female	332		2.1	46.2				

Baluja et al., 2003(44)	1995–1996 and 1998–1999, Current Population Survey (CPS) tobacco use	Population based (≥18 yrs)	Male	1547 (total of both sexes)	US CDC definition	12	-			
			Female			2	-			
Carr et al., 2005(45)	California Chinese American Tobacco Use Survey (CCATUS)	Population based (≥18 yrs)	Male	1057	US CDC definition	14.3	59.4			
			Female	869		2	63.6			
Chae et al., 2006(46)	2002-2003 National Latino and Asian American Study (NLAAS)	Population based (≥18 yrs)	Male	Total 488	US CDC definition	23.6	44.4			
			Female			2.4	50.0			
Taylor al., 2007 (47)	2005 Seattle, Washington	Population based (20-64 yrs)	Male	184	US CDC definition	21.0	-			
			Female	211		1.0	-			
Parikh et al., 2009(48)	2003 New York City Chinese Health Survey (NYC CHS)	Population based (55-75 yrs)	Male	336	US CDC definition	23.6	-			
			Female	181		1.0	-			
Maxwell et al.,2012(49)	2005 California Health Interview Survey (CHIS)	Population based (≥18 yrs)	Male	1285	US CDC definition	15	-			
			Female	758		3	-			
	Canada									
Chiu et al., 2012(50)	Pooled data from 1996 National Population Health Survey & 2001-2007 Canadian Community Health Survey	Population based (≥18 yrs)	Male	1468	Self-reported current smoker (smokes cigarettes every day)	14.2	-	Years of living in Canada (<15 yrs vs. ≥15 yrs)	Age	0.80 (0.59-1.08)	-
			Female	1570		3.4	-			1.67 (0.92-3.09)	-
Newbold and Neligan, 2012(51)	2000/01, 2003, 2005 Canadian Community Health Survey	Population based (≥18 yrs)	Male	6% of CCHS pool	Self-reported current smoking	10.2	-	Years of living in Canada (<15 yrs) (≥15 yrs)	Age, Sex, Income, Education	0.34 (0.30-0.38) 0.29 (0.24-0.35)	1.27 (1.10-1.47)
			Female				-				

	Australia										
Donato-Hunt et al., 2012(52)	2004-2005 Sydney	Population based (≥18 yrs)	Male	211	Self-reported daily smoking	12	-				
			Female	281		2	-				
Lin and Ward, 2000(53)	1998 Sydney	Clinic based (18-70 yrs)	Male	411	Self-reported daily smoking	25	-				
			Female	673		4	-				
	United Kingdom										
Aspinall et al.,2014(54)	2009/10-2011/12 Integrated Household Survey	Population based (≥18 yrs)	Male	1222	Self-reported smoking status	21.4	49.1				
			Female	1528		5.8	60.3				
	2012 GP Patient Survey	Population based (≥18 yrs)	Male	2888	Self-reported smoking status	17	48.5				
			Female	3232		6	50				
Japanese											
	United States										
Baluja et al., 2003(44)	1995–1996 and 1998–1999, Current Population Survey (CPS) tobacco use supplements	Population based (≥18 yrs)	Male	960 both sexes	US CDC definition	30	-				
			Female			17	-				
Ueshima et al., 2003(55)	1997-1998 Hawaii	Population based (40-59 yrs)	Male	136	US CDC definition	13.2	-				
			Female	131		4.4	-				
Haiman et al., 2006(56)	1993-1996 Hawaii and California	Population based (45-75 yrs)	Male	24,970	Self-reported current smoker	15.5	77.9				
			Female	28,188		9.3	70.0				
Kaholokula et al., 2006(57)	1993-1996 Hawaii, Kohala Health Research (KHR)	Community based (≥18 yrs)	Male	93	US CDC definition	11.8	82.0				
			Female	97		3.7	83.3				
Maxwell et al.,2012(49)	2005 California Health Interview Survey (CHIS), California	Population based (≥18 yrs)	Male	1285 both sexes	US CDC definition	13	-				
			Female			16	-				
Korean											
	United States										
Kim et al., 2000(58)	Chicago	Population based (40-69 yrs)	Male	104	US CDC definition	38.5	50.0	English proficiency	Age, education, religion, years of residence	0.79 (0.20-3.04)	-
			Female	159		3.8	64.5				

Hofstetter et al., 2004(59)	2000-2001 California	Population based (≥18 yrs)	Male	1266	US CDC definition	31.7	55.8	Siunn Liew-ASIA Scale	Age, education, working, social support	0.49 (0.33-0.64)	
			Female	1564		4.5	49.6			1.50 (0.82-2.74)	
Juon et al., 2003(60)	1998-1999 Maryland	Community based (18-89 yrs)	Male	333	US CDC definition	26.1	61.6	Length of stay >20 years	Age, education, marital status, employment, having hypertension, having annual checkup, alcohol use	0.32 (0.13-0.77)	0.75 (0.33-1.66)
			Female	438		3.7					
Lee et al., 2000(61)	Continental US	Population based (17-90 yrs)	Male	201	US CDC definition	26.9	40.0				
			Female	141		8.5	42.8				
Lew et al., 2001(62)	1994-1995, Alameda County, California	Population based (≥18 yrs)	Male	304	US CDC definition	39.0	44.3				
			Female	372		6.0	53.8				
Baluja et al., 2003(44)	1995–1996 and 1998–1999, Current Population Survey (CPS) tobacco use supplements	Population based (≥18 yrs)	Male	1101 total both sexes	US CDC definition	33.0	-				
			Female			10.1	-				
Carr et al., 2005(63)	2003 California Korean American Tobacco Use Survey (CKATUS)	Population based (≥18 yrs)	Male	1055	US CDC definition	27.9	55.9				
			Female	863		4.3	55.2				
Filipino											
	United States										
Li et al 2012 (34)	USA, National Latino and Asian American Survey(2002-2003)	Population-based	Male	235	US CDC definition	25.0	-	English proficiency	Age, education, marital status, health insurance, ethnicity, religion, social capital, Years in USA	3.85 (1.01-14.75)	-

Maxwell et al.,2007(64)	2004-2005 California	Community based (40-75 yrs)	Male	318	US CDC definition	34.6	49.5	English usage with friends	Age, education, marital status, income, health insurance, years in USA, knowledge, belief score, other health behaviours	0.43 (0.21-0.88)	1.31 (1.01-1.69)
Baluja et al., 2003(44)	1995–1996 and 1998–1999, Current Population Survey (CPS) tobacco use supplements	Population based (≥18 yrs)	Male	2477 total both sexes	US CDC definition	19	-				
			Female			5	-				
Kaholokula et al., 2006(57)	1993-1996 Hawaii, Kohala Health Research (KHR)	Community based (≥18 yrs)	Male	71	US CDC definition	23	66.2				
			Female	113		13.8	57.4				
Chae et al., 2006(46)	2002-2003 National Latino and Asian American Study (NLAAS)	Population based (≥18 yrs)	Male	235	US CDC definition	24.4	52.9				
			Female	225		7.0	68.3				
Maxwell et al., 2012(49)	2005 California Health Interview Survey (CHIS)	Population based (≥18 yrs)	Male	659	US CDC definition	25	-				
			Female	568		6	-				
	Canada										
Newbold and Neligan, 2012(51)	2000/01 and 2003 Canadian Community Health Survey	Population based (≥18 yrs)	Male		US CDC definition	21.3	-				
			Female			5.3	-				
Vietnamese											
	United States										
Li et al 2012 (34)	USA, National Latino and Asian American Survey(2002-2003)	Population-based	Male	243	US CDC definition	29.4	-	English proficiency	Age, education, marital status, health insurance, ethnicity, religion, social capital, Years in USA	0.21 (0.05-0.95)	-

Rahman et al.,2005(65)	2000-2001 Santa Clara County, California	Population based (≥18 yrs)	Male	364	US CDC definition	31.9	48.7	English fluency, language spoken at home, language spoken outside with friends	Age, education, marital status, income, years lived in USA, other health behaviours	0.38 (0.18-0.83)	
Chan et al., 2007(66)	2002 Seattle, Washington	Population based (≥18 yrs)	Male	509	US CDC definition	37	42.1	English fluency	Age, education, residence, marital status, health insurance, knowledge and attitudes	0.63 (0.41-0.98)	-
Nguyen et al., 2009(67)	2002-2005 Clara county, California	Population based (≥18 yrs)	Male	2084	Self-reported current smoking	29.8	39.3	Primary spoken language	Age	0.74 (0.64-0.87)	
			Female	2170		1.1	50			1.86 (1.01-3.43)	
Tong et al., 2010(68)	2007-2008 California	Population based (≥18 yrs)	Male	1101	US CDC definition	25	50.0	Language used in the interview	Age, education, marital status, income, health insurance, religion, depression symptom, media exposure knowledge, belief score, other health behaviours	0.46 (0.30-0.70)	
			Female	1078		1	66.7				
Duong et al.,2001(22)	1999, Gulf Coast region	Community based (≥18 yrs)	Male	77	US CDC definition	44.2	-				
			Female	124		1.6	-				
Baluja et al., 2003(44)	1995–1996 and 1998–1999, Current Population Survey (CPS) tobacco use supplements	Population based (≥18 yrs)	Male	1338 (total of both sexes)	US CDC definition	29	-				
			Female			3	-				

Xu et al., 2005(69)	2003 Bayou La Batre, Alabama	Community based (≥18 yrs)	Male	135	US CDC definition	39.3	-				
			Female	143		2.1	-				
Chae et al., 2006(46)	2002-2003 National Latino and Asian American Study (NLAAS)	Population based (≥18 yrs)	Male	243	US CDC definition	29.5	41.8				
			Female	217		0.6	78.5				
Coronado et al.,2008(70)	2006-2007 Seattle, Washington	Population based (20-79 yrs)	Female	1523	US CDC definition	1.5	-				
Liao et al., 2010(71)	2002 REACH Risk Factor Survey	Community based (≥18 yrs)	Male	1055	US CDC definition	31.0	19.6				
Liao et al., 2010(71)	2006 REACH Risk Factor Survey	Community based (≥18 yrs)	Male	906	US CDC definition	21.0	45				
Maxwell et al.,2012(49)	2005 California Health Interview Survey (CHIS),California	Population based (≥18 yrs)	Male	480	US CDC definition	31	-				
Kim et al., 2012(33)	2009 Massachusetts	Population based (18-84 yrs)	Male	78	US CDC definition	24.4	51.2				
			Female	85		1.2	74.4				
	Canada										
Newbold and Neligan, 2012(51)	2000/01 and 2003 Canadian Community Health Survey	Population based (≥18 yrs)	Male	2.0% of CHSS pool	Self-reported smoking daily	20.7	-	Years of living in Canada (<15 yrs)	Age, Sex, Education, income	0.67 (0.55-0.81)	0.65 (0.53-0.80)
			Female				-	(≥15 yrs)		0.84 (0.72-0.99)	
	Australia										
Donato-Hunt et al., 2012(52)	2004-2005, Sydney	Population based (≥18 yrs)	Male	208	Self-reported smoking cigarettes every day/occasionally	30	-				
Cambodian											
	United States										
Liao et al., 2010(71)	2002 REACH Risk Factor Survey	Community based (≥18 yrs)	Male	418	US CDC definition	50.1	19				

Liao et al., 2010(71)	2006 REACH Risk Factor Survey	Community based (≥18 yrs)	Male	334	US CDC definition	29	48				
Friis et al., 2012(72)	2009-2010 Long Beach, California	Population based (≥18 yrs)	Male	523	US CDC definition	24.4	39.2				
			Female	891		5.4	34.1				
Koch-Weser et al., 2012(73)	2001 -2002 Lowell, Massachusetts	Community based (≥18 yrs)	Male	132	US CDC definition	45.1	-				
			Female	247		10.3	-				
Multiple Ethnic Groups:											
Cambodian and Vietnamese											
	United States										
Constantine et al., 2010(74)	2006-2007 Minnesota	Community based (≥18 yrs)	Male	143	US CDC definition	13.8	74.6	Fluency with US culture (Multi-item scale followed by factor analysis)	Age, education, Social network	0.53 (0.36-0.79)	
			Female	208		1.5	75			1.58 (0.61-4.01)	
Korean, Chinese, Vietnamese, and Cambodian											
	United States										
Ma et al., 2004(75)	1999-2000 Delaware Valley Region	Community based (≥21 yrs)	Male	57	US CDC definition	61.1	-	a. Frequency of reading /using native language b. Years living in USA (5 yrs)	Age, education	a. 0.59 (0.39-0.91) b. 0.85 (0.55-1.30)	-
			Female	43		19	-			a. 1.39 (0.71-2.73) b. 0.60 (0.32-1.12)	-

Table 2: Association between acculturation and smoking according to study-level factors in men

	No of studies	OR (95% CI)	I^2 for heterogeneity%	P value for heterogeneity
Acculturation indicator				
Language	10	0.65 (0.58-0.73)	13.3	0.32
Time	3	0.71 (0.57-0.87)	0.0	0.42
Scale	2	0.48 (0.37-0.62)	0.0	0.53
Heterogeneity between groups p<0.05				
Ethnicity				
Chinese	4	0.70 (0.57-0.88)	0.0	0.40
Korean	3	0.48 (0.37-0.64)	0.0	0.65
Vietnamese	4	0.68 (0.59-0.78)	55.8	0.08
Filipino	1	0.43 (0.21-0.88)	-	-
Multi-ethnicity	3	0.57 (0.45-0.74)	30.6	0.23
Heterogeneity between groups p=0.14				
Sampling method				
Population-based	11	0.66 (0.60-0.73)	34.9	0.13
Community-based	5	0.52 (0.42-0.66)	0.0	0.88
Heterogeneity between groups p=0.07				
Definition of non-smokers				
never-smokers	8	0.63(0.56-0.71)	41.3	0.10
former-smokers & never-smokers	7	0.64 (0.54-0.75)	6.1	0.38
Heterogeneity between groups p=0.73				
Covariates in adjusted analyses				
Age	2	0.75 (0.66-0.86)	0.0	0.65
Age+ socio-demographic factors	7	0.54 (0.46-0.63)	0.0	0.59
Age+ socio-demographic factors+ health behaviours	6	0.56 (0.44-0.71)	0.0	0.81
Heterogeneity between groups p<0.01				

Figure 4: Forest plots of studies measuring the association between acculturation and smoking in men, separately by different indicators of acculturation

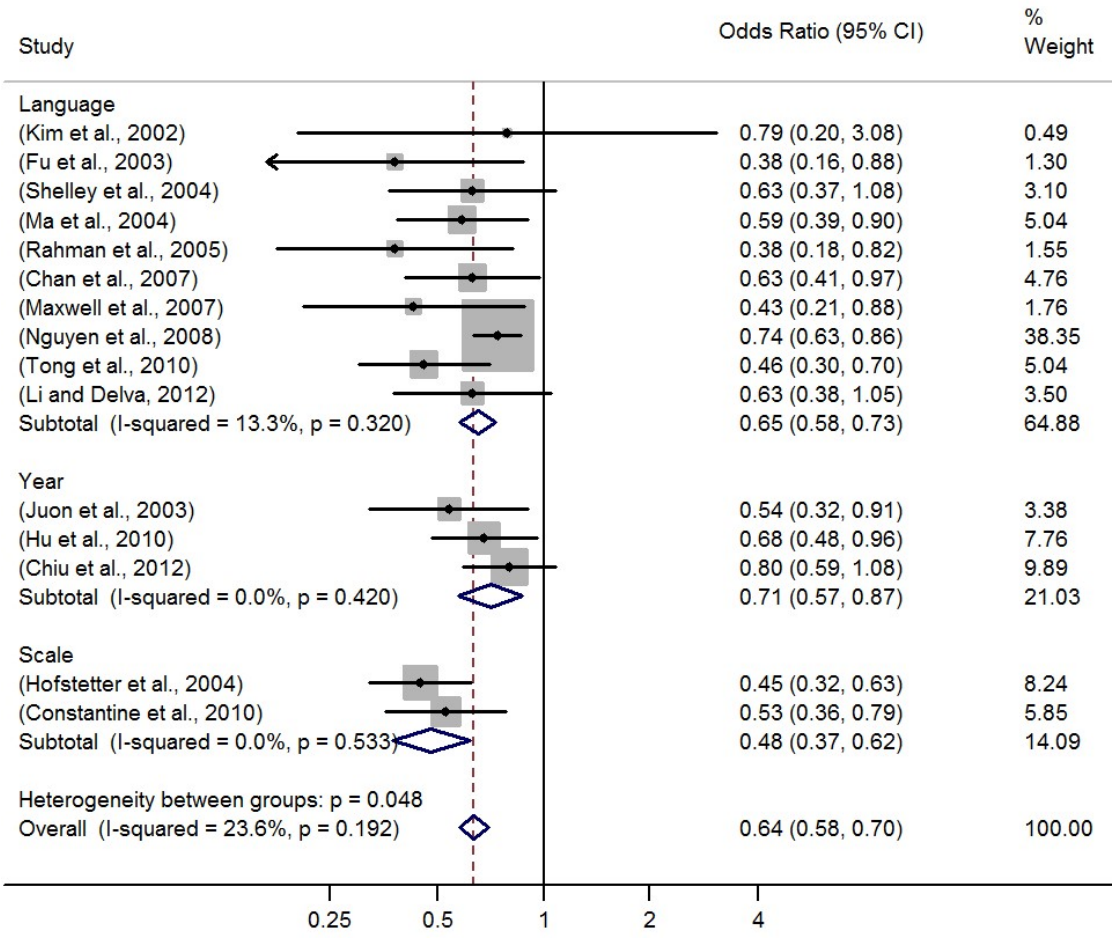


Figure 5: Forest plots of studies measuring the association between acculturation and smoking cessation (men only)

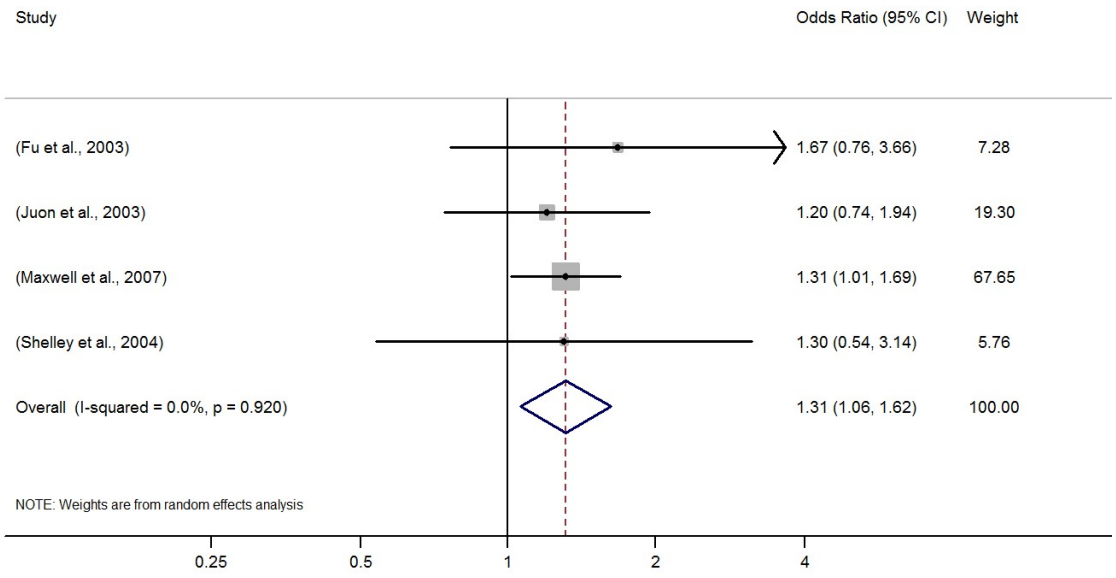
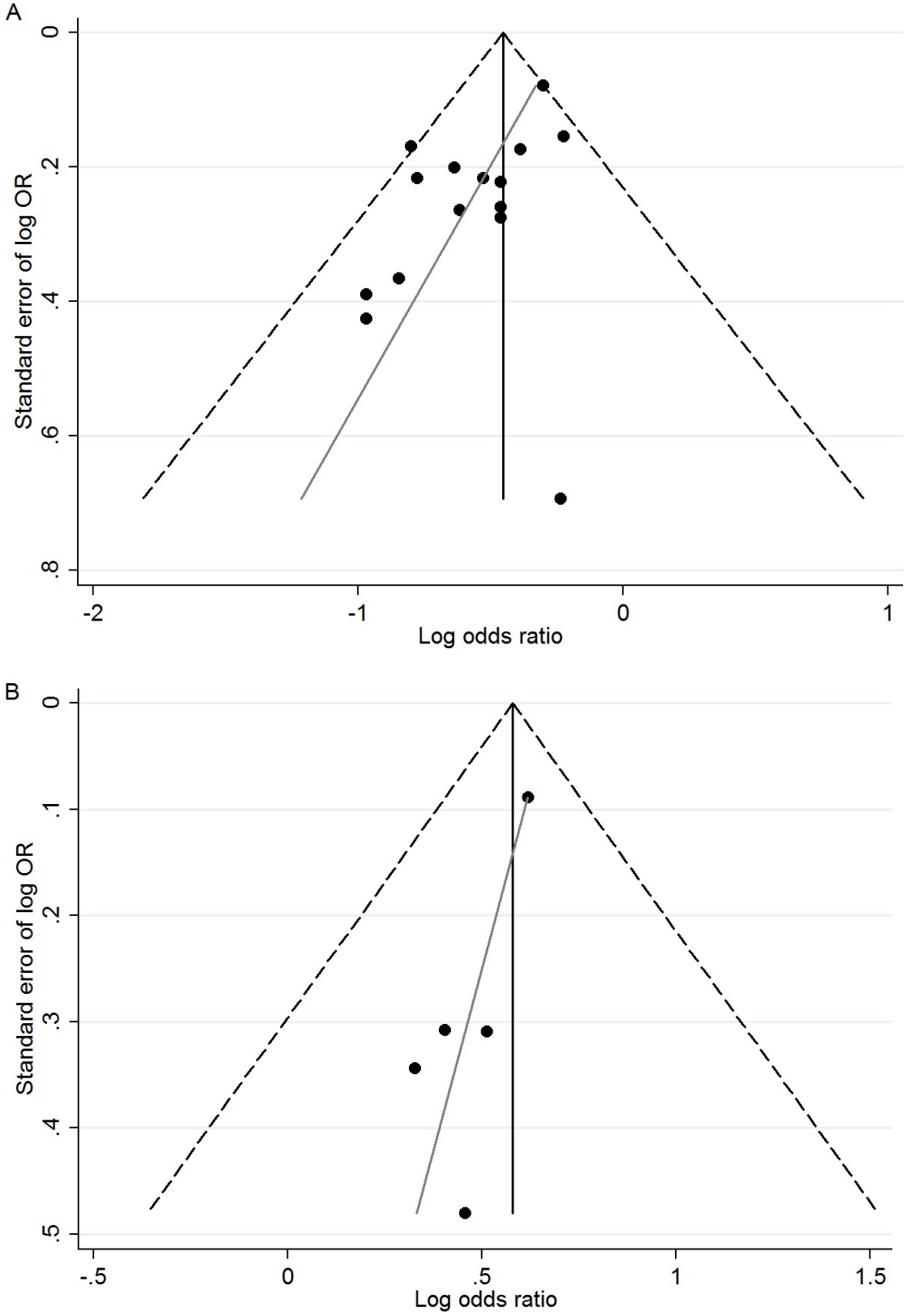


Figure 6: Funnel plots for publication bias with pseudo 95% confidence limits for studies in men (A) and women (B), the grey line is the fitted regression line from Egger test for small study effect



Association between acculturation and smoking cessation

Four of the 15 studies conducted a subset analysis to examine the association between acculturation and smoking cessation among male ever smokers, by comparing the proportion of former smokers to that of current smokers. This association was examined in women in only 1 of the four studies, due to the limited number of female ever smokers. We conducted a meta-analysis on the association between acculturation and smoking cessation in men, including these four studies. There was a weak but statistically significant positive association, i.e. greater acculturation was associated with a higher ratio of former vs. current smokers (OR=1.31, 95% CI 1.06 to 1.62, I^2=0.0%; p_{heter}=0.92) (Figure 5).

Publication bias

We detected considerable asymmetry of effect estimates among small studies in men (Figure 6A) and also slight asymmetry in studies in women (Figure 6B). However, we found no evidence for significant publication bias by Egger's test (Men: p=0.07; Women: p=0.25).

Discussion

In this systematic review, we found that, in general, amongst East Asian immigrants to the USA, UK, Canada, New Zealand, and Australia, men were more likely to be current smokers than women. In men, the prevalence of current smoking was lower than, or comparable to, that of the host countries for Chinese, Japanese and Filipino migrants, but remained high in Korean and Vietnamese men. High levels of smoking cessation were observed for most ethnic subgroups.

Most of the studies included in this systematic review were community-based, local surveys, with small sample sizes in each ethnic sub-group. Although random sampling methods were commonly used, and the data collection instruments were available in a range of languages, few studies used a general population sampling frame, making it difficult to fully assess the generalisability of the prevalence estimates. On the other hand, national surveys were mainly conducted in English (19, 76); consequently, these also have sampling bias, manifested as lower smoking prevalence in these studies compared to community-based studies. All the studies

included in the analysis were cross-sectional. To test the causal effects of acculturation on smoking would require longitudinal studies with prospective data.

This meta-analysis was constrained by the measures of acculturation in the existing studies, primarily the linear model, which describes acculturation as a linear process whereby immigrants acquire customs of the host countries and at the same time lose the customs of their original culture (77). The linear model does not capture the different dimensions of acculturation. The two-dimensional model, developed by Berry and colleagues, shows four outcomes of acculturation: integration, segregation, assimilation, and marginalisation (28). As a common outcome of acculturation, integration or biculturalism allows immigrants to maintain customs and behaviours from the country of origin while adopting customs of the host country (28). Biculturalism may explain the finding of much lower prevalence of smoking in Asian-born women who have been living in western countries for a long duration and are proficient in the language of the host country, compared to that in the host population. However, this meta-analysis was constrained by the available measures, which did not allow the bi-dimensional or multi-dimensional models to be explored.

Our meta-analysis showed that higher levels of acculturation were associated with lower prevalence of current smoking in East Asian men (a weak-to-moderate effect size), but higher prevalence of current smoking in East Asian women (moderate effect size). However, the studies included in the meta-analysis were not homogeneous for study population, recruitment methods, measure of acculturation or the adjustment of covariates. Although there was a largely consistent direction of effect, the magnitude of the association in men varied according to the indicator that was used to measure acculturation and also which covariates had been adjusted for in the final models of the individual studies. Based on limited evidence, men who had been smokers and were more acculturated to the host country were more likely to quit smoking.

Our findings build on those of a previous meta-analysis (27) by including more recently published data, and providing results stratified by different indicators of acculturation, thus providing a more accurate and robust estimation of the size of the effect of acculturation on smoking. The previous meta-analysis also found an inverse association between acculturation and current smoking prevalence in Northeast Asia

and Southeast Asia men and a positive association in East Asian women in their summary of 9 studies from 1997 to 2004. There was a five-fold increase in the likelihood of smoking in acculturated compared to traditional women. However, our results suggest a more moderate effect size.

Socio-demographic factors such as sex, age, education and income are established to determinants of smoking behaviour (78). Smoke-free laws and smoking-related policies such as tax and packaging may promote smoking cessation in both immigrants and the host populations (79). Our findings suggest that among immigrants, acculturation and social norms in the host country may be additional factors that affect smoking behaviour in East Asian immigrant men and women in opposite ways. In a qualitative study on American Korean men, Kim and colleagues reported that cultural pressure to conform, the social environment in the native country and gender identity were responsible for the high prevalence of smoking in Korean men, while female smoking was generally forbidden (63). Following immigration, both men and women acculturated to the norms of the host society. The diminishing social acceptability of smoking triggered quit attempts and led to smoking cessation in men (12). Our findings on smoking cessation in men also support this effect of acculturation on smoking habits. However, western culture promotes liberty and equality in acculturated women, which includes equal levels of social tolerance to male and female smokers (29). The prevalence of smoking in women thus increases toward that of their male counterparts, following immigration to a country with this type of culture. It is also possible that smoking prevalence in Asian-born women may be under-reported due to the social norm around smoking in their countries of origin and in the immigrant community. One study compared self-reported smoking prevalence with cotinine-verified smoking prevalence in Korean women and found that less than half of cotinine-verified female smokers self-reported smoking (15). Therefore, the higher self-reported smoking prevalence in acculturated women may be due to less misreporting.

Our results point to two groups at increased risk of smoking-related diseases: newly arrived East Asian men, and acculturated East Asian women. This provides a guide for health promotion programs designed to reduce smoking rates in multicultural communities. Newly immigrant Asian men who have lower English proficiency but

the high smoking prevalence of their native country may be least able to access public health information written in English. Indeed, greater proficiency with the English language was associated with a lower prevalence of current smoking in men (31, 38, 41). It is important that health interventions are culturally sensitive and offered in the participants' native languages (80, 81).

In East Asian countries, the prevalence of smoking in men is high and smoking cessation uncommon; less than 20% of ever smokers stop smoking (11, 82). Smoking behaviours are likely influenced by a combination of social norms and cultural factors as well as the broader social context (e.g. state-level policies or neighbourhood of residence) that increases vulnerability to smoking. The declining prevalence of smoking in Western countries, both over time and, as evidenced here, in association with immigration for some population groups, reflects the effects of smoke-free-air laws and high tobacco taxes (5, 7), but particularly, effective public health education campaigns that alter social norms and culture around smoking.

Footnotes

Contributors: SG, RL and GJ developed the initial strategy for the review; SG undertook the literature search with support from ND and GJ; SG and ND reviewed individual articles; SG wrote the first draft of this paper; RL and GJ undertook revisions of the paper. All authors agree with the results and conclusions.

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Appendix 1: Newcastle-Ottawa Scale adapted for cross-sectional studies

Scoring: a score of 1 was applied if the study met the criterion that is starred in each group and 0 if it did not.

Selection

1) Representativeness of the sample:
   a) Representative of the target population.(all subjects or random sampling) *
   b) Selected population group, e.g. community-based study
   c). No description of the sampling strategy

2) Used culturally sensitive tools (interviews/questionnaires in participants' native language).
   a) Yes *
   b) No.

3) Ascertainment of the exposure (ethnicity or acculturation level):
   a) Validated measurement tool. *
   b) Non-validated measurement tool
   c) No description of the measurement tool.

Comparability

4) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.
   a) Prevalence/odds ratio was adjusted for age. *
   b) Prevalence/odds ratio was not adjusted for age.

Outcome

5) Assessment of the outcome:
   a) Uses a standardised definition for current smoking and former smoking *
   b) Self report categories of smoking status
   c) No description.

This scale has been adapted from the Newcastle-Ottawa Quality Assessment Scale for cohort studies to perform a quality assessment of cross-sectional studies for the systematic review, "Acculturation and prevalence of smoking in Asian migrants in western countries: a systematic review and meta-analysis".

The quality of the studies was defined as follows:

Very Good Studies:	5 points
Good Studies:	4 points
Satisfactory Studies:	3 points
Unsatisfactory Studies:	0 to 2 points

Appendix 2: Cross-sectional studies on smoking prevalence and acculturation included in the systematic review and meta-analysis

Study	Representativeness of the sample	Used culturally sensitive tools	Ascertainment of exposure	Based on design and analysis	Assessment of outcome	Total quality score
Lee et al., 2000 (61)	*	*	*	*	*	5
Lin and Ward, 2000(53)		*	*	*		3
Kim et al., 2000(58)	*	*	*	*	*	5
Duong et al.,2001(22)		*	*		*	3
Lew et al., 2001(62)	*	*	*	*	*	5
Yu et al., 2002(43)		*	*	*	*	4
Baluja et al., 2003(44)	*	*	*	*		4
Fu et al., 2003(41)		*	*	*	*	4
Ueshima et al., 2003(55)			*	*	*	3
Juon et al., 2003(60)		*	*	*	*	4
Ma et al., 2004(75)		*	*	*	*	4
Shelley et al.,2004(42)	*	*	*	*	*	5
Carr et al., 2005(83)	*	*	*	*	*	5
Carr et al., 2005(84)	*	*	*	*	*	5
Rahman et al.,2005(65)	*	*	*	*	*	5
Xu et al., 2005(69)		*	*		*	3

Haiman et al., 2006(56)	*		*	*		3
Chae et al., 2006(46)	*	*	*	*	*	5
Kaholokula et al., 2006(57)			*	*	*	3
Chan et al., 2007(66)	*	*	*	*	*	5
Hofstetter et al., 2007(85)	*	*	*	*	*	5
Maxwell et al.,2007(64)		*	*		*	3
Taylor al., 2007(47)		*	*	*	*	4
Coronado et al.,2008(70)	*	*	*	*	*	5
Nguyen et al., 2009(67)	*	*	*	*		4
Parikh al., 2009(48)	*	*	*	*	*	5
Constantine et al., 2010(74)		*	*	*	*	4
Hu et al., 2010(32)	*	*	*	*	*	5
Tong et al., 2010(68)	*	*	*	*	*	5
Liao et al., 2010(71)		*	*	*		3
Chiu et al., 2012(50)	*	*	*	*		4
Li et al., 2012(34)	*	*	*	*	*	5
Kim et al., 2012(33)		*	*	*	*	4
Maxwell et al.,2012(49)	*	*	*	*	*	5
Newbold and Neligan, 2012(51)	*	*	*	*		4
Donato-Hunt et al., 2012(52)	*	*	*	*		4

Friis et al., 2012(72)	*	*	*	*	*	5
Koch-Weser et al., 2012(73)		*	*	*	*	4
Aspinall et al.,2014(54)	*	*	*			3

Chapter 5

Paper 2: Tightrope walking: using predictors of 25(OH)D concentration based on multivariable linear regression to infer associations with health risks

Paper 3: A Novel Approach for Prediction of Vitamin D Status Using Support Vector Regression

Paper 4: Sun Exposure and Vitamin D Status as Northeast Asian Immigrants Become Acculturated to Life in Australia

Overall introduction

In Chapter 2 I reviewed the health issue of vitamin D deficiency and the purported link to increased risk of CVD. Vitamin D deficiency, measured by serum 25(OH)D reflects more than vitamin D status since major determinants include time outdoors, obesity and physical activity. Thus vitamin D deficiency may reflect an overall poor health status and other risk factors for CVD, such as physical inactivity and overweight/obesity.

The common approach to estimate Vitamin D status is to measure serum 25(OH)D concentration using laboratory assays. The cost of these assays limits their use in large-scale epidemiological studies. Several past studies (1-3) have developed prediction models to produce a vitamin D "score" using cross-sectional survey data, and then used this score to test the association with CVD risk. However, this approach could potentially lead to incorrect results and inconsistencies in the evidence.

In the first two papers of chapter 5, we use published data to explore potential errors in prediction models, to facilitate better interpretation of the epidemiological evidence linking vitamin D deficiency to CVD. One caveat is that these papers are not based within Asian populations, but on available datasets, which include a general US population sample, or a largely Caucasian population in Australia.

In the papers, 'Tightrope walking: using predictors of 25(OH)D concentration based on multivariable linear regression to infer associations with health risks' and 'A Novel Approach for Prediction of Vitamin D Status Using Support Vector Regression', I identify several potential problems that may introduce both bias and confounding when using predicted vitamin D scores in population based studies. These issues include using invalid instrumental variables and prediction inaccuracy, suggesting that prediction models were unlikely to accurately and precisely estimate vitamin D status for consideration of the relationship to CVD risk.

With these methodological investigations in mind, we designed the third study 'Sun Exposure and Vitamin D Status as Northeast Asian Immigrants Become Acculturated to Life in Australia'. Here vitamin D status was measured as the serum 25(OH)D

concentration from fasting blood samples, using a well-standardised method rather than estimated from a prediction model. Emerging evidence from observational studies suggests that Asian-born immigrants are at higher risk of vitamin D deficiency than people who are born in Australia (4). Elucidating the determinants of vitamin D deficiency and the association between vitamin D deficiency and acculturation in East-Asian immigrants represents a first step in evaluating vitamin D deficiency-related CVD risk in this population.

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RESEARCH ARTICLE

Tightrope Walking: Using Predictors of 25 (OH)D Concentration Based on Multivariable Linear Regression to Infer Associations with Health Risks

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Abstract

The debate on the causal association between vitamin D status, measured as serum concentration of 25-hydroxyvitamin D (25[OH]D), and various health outcomes warrants investigation in large-scale health surveys. Measuring the 25(OH)D concentration for each participant is not always feasible, because of the logistics of blood collection and the costs of vitamin D testing. To address this problem, past research has used predicted 25(OH)D concentration, based on multivariable linear regression, as a proxy for unmeasured vitamin D status. We restate this approach in a mathematical framework, to deduce its possible pitfalls. Monte Carlo simulation and real data from the National Health and Nutrition Examination Survey 2005–06 are used to confirm the deductions. The results indicate that variables that are used in the prediction model (for 25[OH]D concentration) but not in the model for the health outcome (called instrumental variables), play an essential role in the identification of an effect. Such variables should be unrelated to the health outcome other than through vitamin D; otherwise the estimate of interest will be biased. The approach of predicted 25 (OH)D concentration derived from multivariable linear regression may be valid. However, careful verification that the instrumental variables are unrelated to the health outcome is required.

Introduction

Evidence suggests that higher vitamin D status is associated with a decreased risk of various cancers and chronic diseases, beyond its essential role in bone health [1]. In epidemiologic studies examining vitamin D deficiency as a risk factor for disease, vitamin D status is measured as the serum concentration of 25-hydroxyvitamin D (25[OH]D) [2]. However, for

large-scale health surveys, measuring 25(OH)D concentration for each participant is not always feasible because of the logistics of blood collection and the costs of vitamin D testing.

To overcome this problem, it has been common to use an indicator of vitamin D status, such as latitude or level of solar ultraviolet radiation, as a proxy for 25(OH)D [3–5]. Recent studies have however shifted toward using multivariable linear regression models to predict 25 (OH)D concentration [6]. Briefly, the relationship between measured 25(OH)D concentration and determinants is identified by multivariable linear regression within a subset of participants. Based on the estimates derived, the unobserved 25(OH)D concentration is predicted and then the predicted value is used to analyze the association with the health outcome of interest. This methodology has been used to demonstrate a protective association between vitamin D sufficiency and risk of various cancers [6–9].

Here we firstly restate this approach in a simple but general mathematical framework. We deduce that the variables, called instrumental variables, which appear only in the multivariable linear regression for the prediction, but not in the health outcome equation, are vital for the correct identification of the association between 25(OH)D concentration and the health outcome. If the instrumental variables are in fact associated with the health outcome, and therefore are invalid as instruments, the estimated effect may be significantly biased. We then use Monte Carlo simulation and real data from the National Health and Nutrition Examination Survey (NHANES) to demonstrate this potential bias. Overall, we highlight problems that may occur when using this methodology to gain a better understanding of the potential for misleading results due to the use of invalid instrumental variables.

Predictors of 25(OH)D Concentration Based on Linear Regression

Recent studies using predicted 25(OH)D concentrations based on multivariable linear regression to investigate associations between vitamin D status and health outcomes, such as incidence of cancers, diabetes, or Crohn's disease are summarized in Table 1.

This is a two-stage, two-dataset method.

Stage I (using a subset of the main dataset). The determinants of 25(OH)D concentration are identified based on the analysis of a subset of the full dataset which is assumed to be representative of the whole sample. Measured 25(OH)D concentration is available in this subset. The following model is estimated:

$$D = ax + dz + e, \tag{1}$$

where x and z are the possible determinants of 25(OH)D concentration, D, and e is the error term. For the sake of simplicity, x and z are assumed to be single variables, however, the derivation can be generalized to the case of multiple regression by allowing x and z to be vectors. Furthermore, either x or z is assumed to be uncorrelated with e, and so the parameter estimates, $\hat{a}$ and $\hat{d}$ are unbiased.

Stage II (Using the Main Dataset). In the Full Dataset, the Missing 25(OH)D Concentration ("Score") Is Predicted as

$$\hat{D} = \hat{a}x + \hat{d}z. \tag{2}$$

The predicted 25(OH)D score, $\hat{D}$, is used as a proxy for the real 25(OH)D concentration, even for those with measured values.

Table 1. Summary of papers employing predicted 25(OH)D score to examine associations between vitamin D status and health outcomes.

Reference	Health outcome	Statistical model in *Stage II*	Instrumental variables(s)
Giovannucci et al, 2006 [6]	Cancer incidence and mortality	Cox	Geographical residence, Dietary vitamin D intake, vitamin D supplements, Race
Ng et al, 2009 [9]	Colorectal cancer	Cox	Geographical region
Liu et al, 2010 [15]	Type 2 diabetes	Cox	Month of blood sampling, total vitamin D intake, physical activity score, smoking status, total energy intake, BMI[a]
Jimenez et al, 2012 [19]	Tooth loss and periodontitis	Cox	UVB radiation flux at residence, dietary and supplemental intake of vitamin D
Gilbert et al, 2012 [29]	Risk factors for prostate cancer (PSA level, BMI, Family history of prostate cancer)	Linear and Logistic	Sun exposure, dietary intake, Anthropometric, clinical and demographic factors[b]
Liu et al, 2013[16]	Endometrial cancer	Cox	Vitamin D intake from food, vitamin D intake from supplements, UVB flux based on state of residence, physical activity, alcohol intake
Ananthakrishnan et al, 2012 [18]	Crohn's disease	Cox	Dietary and supplemental vitamin D intake, exposure to sunlight, race, regional ultraviolet-B radiation intensity
Harris et al, 2013 [17]	Endometriosis	Cox	Race, geographical region, season of blood draw, dietary vitamin D intake
Joh et al, 2013 [8]	Renal cancer	Cox	UVB radiation flux at residence, dietary and supplement intake of vitamin D, postmenopausal hormone use

[a] Adjusted for waist circumference in *Stage II*;

[b] Since backwards stepwise regression was employed, the instrumental variables used varied across regressions.

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Here we use the Cox proportional hazard model in *Stage II* as an example, as it has been widely used in the research-to-date that has employed this approach. The form of the model is:

$$H(t) = h_0(t)\exp(\alpha x + \beta y + \theta \hat{D}), \quad (3)$$

where $H(t)$ and $h_0(t)$ are the hazard rate and the baseline hazard respectively.

In this example, x is a common covariate in *Stage I* and *II* and in practice includes, for example, age and sex; y appears only in *Stage II* and is a factor associated with the health outcome but not with 25(OH)D concentration, for example, vegetable and fruit intake and family history of the disease. The variable z is excluded from *Stage II*. The exclusion of z (hereafter, referred to as an "instrumental variable") from Eq (3) is necessary to avoid a problem with multicollinearity that arises because $\hat{D}$ is a linear combination of x and z (using the predictive model derived in *Stage 1*) [10]. If x, z and $\hat{D}$ are all introduced, most computer software packages will drop one of them and the estimation will be equivalent to that of Eq (3). Among papers utilizing this approach, variables such as geographic residence, vitamin D intake, race, alcohol intake and variants of genes, are used as instrumental variables Table 1.

There are two important requirements of a valid instrumental variable. First, it must be significantly associated with the 25(OH)D concentration, D, conditioning on x; and, second it should not be a risk factor for the disease of interest except through its effect on D. If the first requirement is not satisfied, the estimated standard error of the association between the 25 (OH)D score and the health outcome may be very large and/or the effect estimate will be inconsistent. However, this problem is easily detected and avoided in practice, since whether z is statistically significant in *Stage I* can be easily checked. We will not discuss this problem further.

We examine the effect of violation of the second requirement, that an instrumental variable should not be a risk factor for the disease except through its effect on *D*. This cannot be detected statistically and may result in bias in the estimate of interest.

Consider theoretically,

$$H(t) = h_0(t)\exp(\alpha x + \beta y + \delta z + \theta \hat{D}); \quad (4)$$

Here, *z* is employed as an instrumental variable although it is not valid, and Eq (3) is estimated. As demonstrated in S1 Appendix, the bias in the estimated effect of 25(OH)D concentration on the health outcome is $\delta/\hat{d}$ where $\hat{d}$ is the estimate of the association between measured 25 (OH)D concentration and *z*. The intuitive explanation is illustrated in Fig 1. That is, the bias occurs because the direct association between *z* and the health outcome, $H(t)$, forms part of the association between 25(OH)D concentration, *D*, and the health outcome, $H(t)$. Thus, on the one hand, the bias is positively associated with δ (i.e. the larger the effect estimate of the association between *z* and the health outcome, the greater is the contribution of that association to the association of *z* with 25(OH)D, *D*). On the other hand, the stronger the association between *z* and *D*, the greater is the 'proportion' of the association between *z* and the health outcome that is working via the 25(OH)D concentration, and the smaller the 'proportion' that is the direct association between *z* and the health outcome. As a result, the bias is inversely associated with *d*.

These deductions can be generalized to generalized linear models (GLMs), such as linear, logistic, or Poisson regression [11,12]. In these cases, $\alpha x + \beta y + \theta \hat{D}$ is the linear predictor in the GLM framework.

In order to assess the empirical importance of correctly choosing the instrumental variables, we implemented Monte Carlo simulations to generate a series of virtual datasets as well as examining real data from NHANES 2005–2006 to examine the association between 25(OH)D concentration and systolic blood pressure.

Methods and Materials

Monte Carlo Simulation

Data Generating. The Monte Carlo design assumes the 25(OH)D concentration is generated according to the following linear equation

$$D = a_0 + a_1 x + d_1 z_1 + d_2 z_2 + e. \quad (5)$$

We set $a_0 = 0.1$, $a_1 = 0.4$, $d_1 = 0.2$ and $d_2 = 0.3$. The covariates, *x*, z_1 and z_2 are all drawn independently from the standard normal distribution, and the error term *e* from a uniform distribution between -0.5 and 0.5.

The hazard of the health outcome is defined as a function of *x*, y, z_1 and *D*.

$$H(t) = h_0(t)\exp(\alpha_1 x + \beta y + \delta_1 z_1 + \theta D), \quad (6)$$

We set $\alpha_1 = 0.1$, $\beta = 0.3$, $\delta_1 = 0.4$, $\theta = 0.5$ and $h_0(t) = 1$. The covariate *y* was drawn from the standard normal distribution independently.

The method for the generation of the survival time for the proportional hazard models is introduced in S2 Appendix. Furthermore, in order to show how the bias changes with either of d_1 or δ_1, d_1 was set to change from -1 to 1 with a step size of 0.1 with δ_1 fixed at 0.4; and δ_1 was set to change from -1 to 1 with a step size of 0.1 with d_1 fixed at 0.2. For each level of d_1 and δ_1 1,000 datasets with 5,000 observations were generated. Note, z_2 is always a valid instrumental

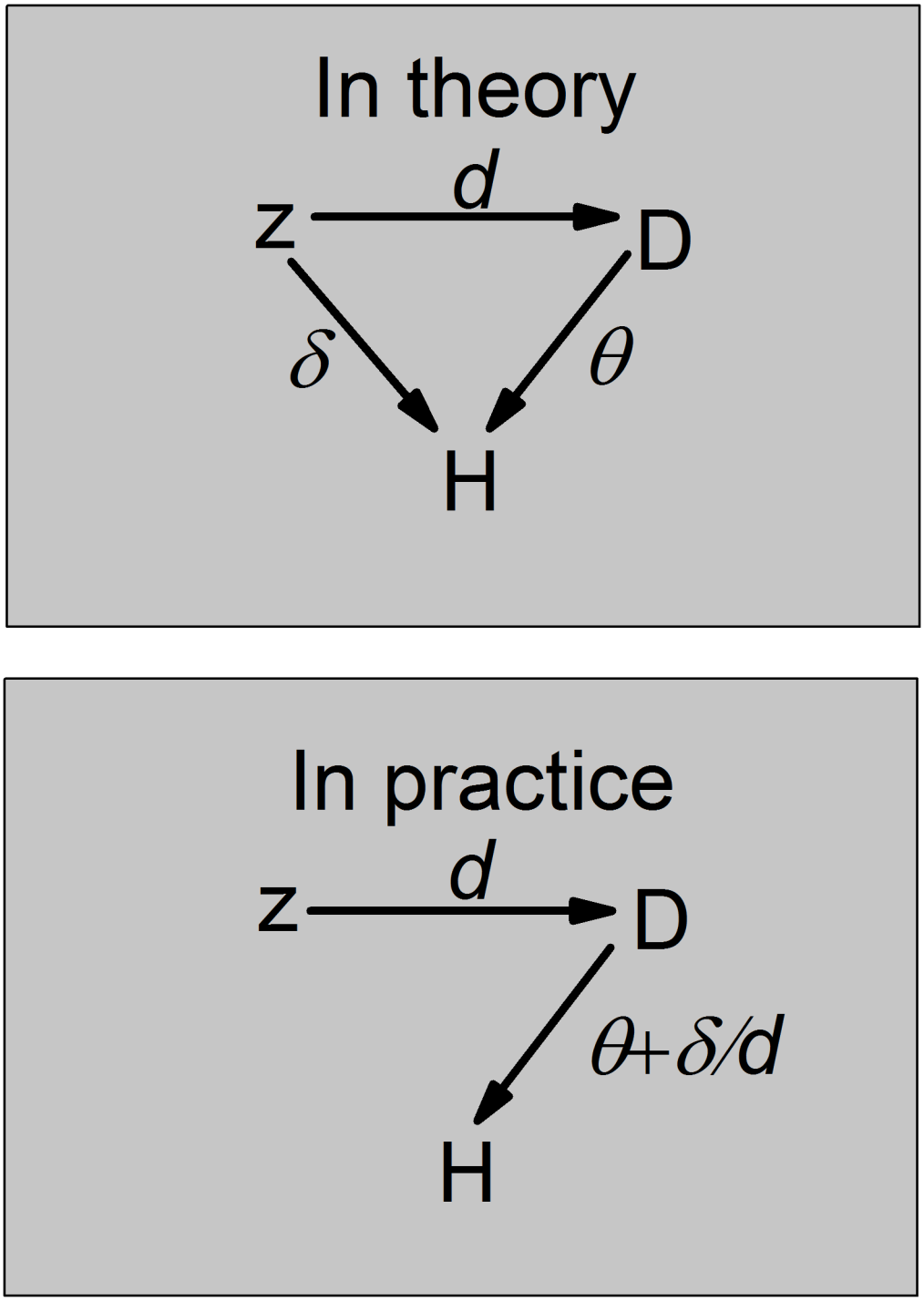

Fig 1. The effect of omitting *z* from the health outcome equation. In theory, the total effect of *z* on health outcome, H, is $\delta + \theta d$. In practice, using *z* as an instrumental variable causes bias in the estimated effect of the 25(OH)D score, *D*, on the health outcome, because the direct effect of *z* on the health outcome is incorrectly captured as being mediated by *D*.

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variable; however only when $\delta_1 = 0$, is z_1 valid because only in this case is z_1 not an explanatory factor for the health outcome.

Estimating. When estimating, three specifications were employed. In Specification I, only z_1 is used as an instrumental variable. In other words, z_1 is included in the equation to predict 25(OH)D score, but not in the equation testing the association with the health outcome. In Specification II, both $\mathbf{z_1}$ and $\mathbf{z_2}$ are used as instrumental variables, and in Specification III, only $\mathbf{z_2}$ is used as an instrumental variable. Hence, only Specification III is correct and the estimates arising should be unbiased.

The means of the estimated association with the health outcome over the 1,000 datasets for each level of d_1 and δ_1 were compared with each actual value.

Source of Real Data

The methodology for NHANES 2005–06 is well-described elsewhere [13]. Briefly, the survey is designed to assess the health and nutritional status of adults and children in the United States. NHANES 2005–06 was the seventh NHANES and included more than 10,000 participants from 30 sites across the United States. The data from this survey are used here as 25(OH)D concentration is available on a large sample size.

We chose to examine the association between 25(OH)D concentration and systolic blood pressure (as the health outcome of interest) as an example. It is unclear that there is any causal relationship between 25(OH)D level and blood pressure. Nevertheless the association is used here to demonstrate the potential bias caused by the use of an invalid instrumental variable. Exclusion of data from participants with missing values for 25(OH)D concentration or with fewer than three readings of systolic blood pressure and children (aged$<$18 years), resulted in a final sample of 4,002 participants. The missing data for 25(OH)D concentration and systolic blood pressure were missing at random [14]; specifically, missingness was associated with gender and overweight or obesity status

Statistical Methods

The dependent variable, systolic blood pressure, is continuous; thus ordinary least squares regression (OLS) is used for *Stage II*. This also provides an opportunity to test the generalizability of our theoretical analysis.

First, we estimated the association between 25(OH)D concentration and systolic blood pressure. The results were used as the benchmark against which to check whether there was bias caused by use of invalid instrumental variables. Covariates included age, sex (reference category = 'Female'), and overweight or obesity status (reference category = 'BMI$\leq$25').

Next, we developed a predictive model for 25(OH)D concentration using a multivariable OLS linear regression model (*Stage I*). The determinants of 25(OH)D concentration included sex, and overweight or obesity.

In *Stage II*, we used the same dataset but set all of the values of 25(OH)D concentration to be missing, and replaced these with a predicted 25(OH)D score derived from *Stage I*. We used OLS regression again, using sex and the predicted 25(OH)D score to assess the association between 25(OH)D score and systolic blood pressure (*Stage II*). Thus, the instrumental variable of interest was overweight or obesity status (included in *Stage I*, but not *Stage II*). There are many potential explanatory variables in both stages; however, use of only overweight/obesity is sufficient to illustrate the outcome of using an invalid instrumental variable.

All analyses were performed using Stata 11.

Table 2. *Stage-II* estimates of the coefficient for each of the variables (x, y, D) included in the Cox proportional hazard models for different specifications, Monte Carlo simulations, sample size 5000, $d_1 = 0.2$ and $\delta_1 = 0.4$.

Variable	Pre-set value	Estimated value	95% CI	*P*-value
		Specification I[a]		
x	0.10	-0.68	(-0.74, -0.61)	<0.001
y	0.30	0.29	(0.26, 0.32)	<0.001
D	0.50	2.42	(2.27, 2.57)	<0.001
		Specification II[b]		
X	0.10	-0.13	(-0.18, -0.09)	<0.001
y	0.30	0.27	(0.25, 0.30)	<0.001
D	0.50	1.02	(0.93, 1.10)	<0.001
		Specification III[c]		
x	0.10	0.10	(0.05, 0.15)	0.003
y	0.30	0.30	(0.27, 0.32)	<0.001
z_1	0.40	0.39	(0.36, 0.43)	<0.001
D	0.50	0.49	(0.40, 0.59)	<0.001

[a] z_1 is the only instrumental variable, but it is invalid;

[b] z_1 and z_2 are the invalid and valid instrumental variables respectively;

[c] z_2 is the only instrumental variable, and it is valid. Specification III is correct.

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Results

Monte Carlo Simulation

The effect estimates for the different variables, based on virtual samples for all three specifications, are in Table 2. The results confirmed that valid instrumental variables are essential for the estimates to be unbiased. If the instrumental variable is invalid, the bias in the estimated effect of 25(OH)D on the health outcome (θ) can be large, even if all of the coefficients in these models are reasonably small. For example, when d_1 and δ_1 were 0.2 and 0.4 respectively, the bias was 2 ($\delta_1/d_1 = 0.4/0.2$), with the estimated coefficient nearly five-fold higher than the "real" (pre-set) value of θ (see Specification I Table 2). For Specification II (using z_1 and z_2 as instrumental variables), the bias in the estimate of the association between 25(OH)D and the health outcome, (θ) remained significant ($p<0.001$) but was smaller. Only when the instrumental variable is valid are the estimates statistically identical to the pre-set values (Specification III).

Fig 2(A) shows that the bias in the estimate of θ is inversely correlated with the magnitude of the association between z_1 and 25(OH)D concentration. The results, when d_1 is very close to 0, are not shown because the bias is theoretically infinite. The bias caused by the invalid instrumental variable decreases with increasing δ_1. When δ_1 is zero, z is a valid instrumental variable and the estimate is unbiased. Further, the comparison between Specification I and II suggests that, although the introduction of a valid instrumental variable improves the performance of the model, bias is still present.

Fig 2(B) shows that the estimate of θ increases almost linearly with the association between z and the health outcome. Again, bias is absent only if δ_1 is equal to zero. A valid instrumental variable is helpful to identify the presence of an association between the 25(OH)D score and the health outcome, but the effect estimate is biased.

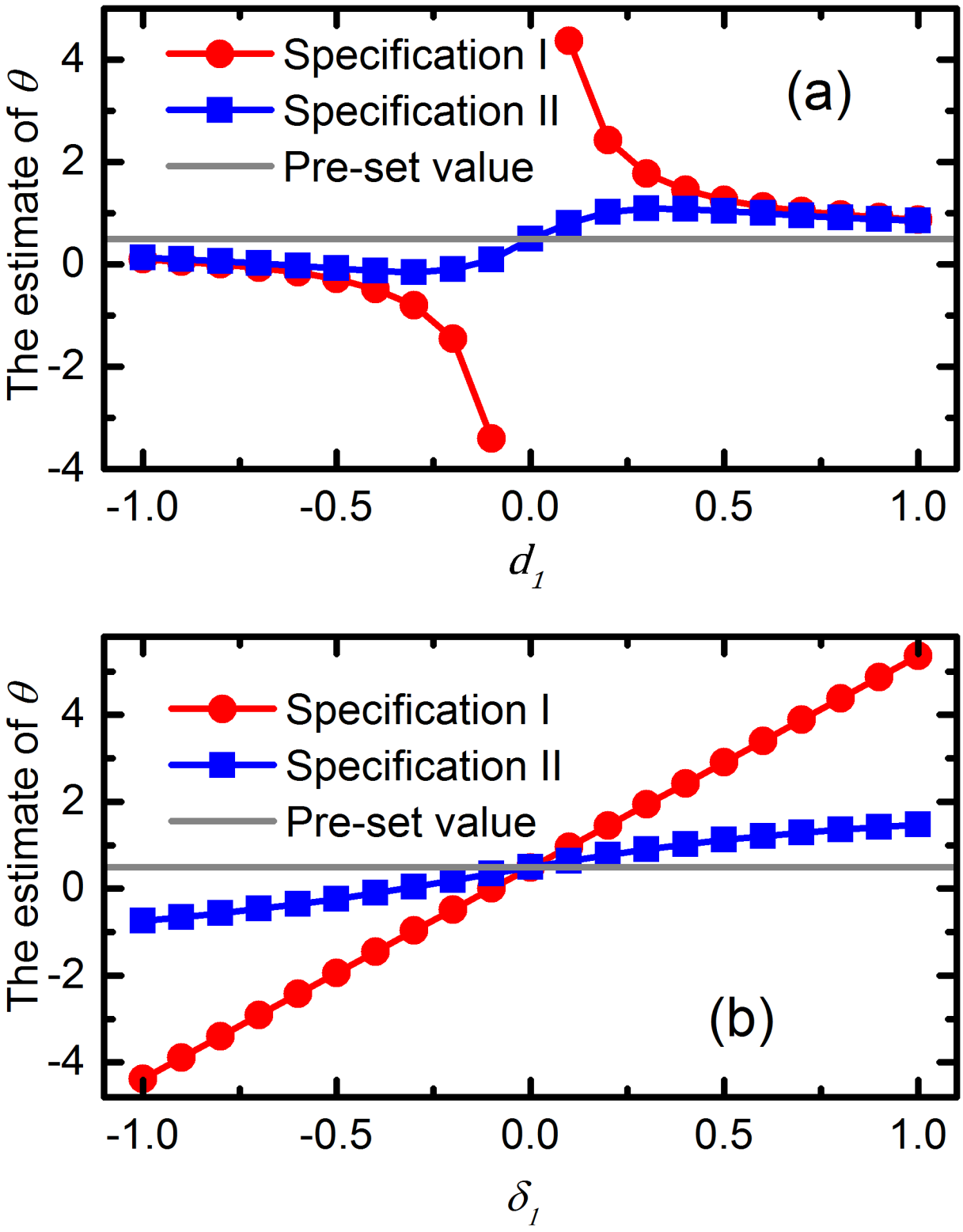

Fig 2. Estimates of the association between the 25(OH)D concentration and the health outcome (Θ) according to the change in (a) d_1, with $\delta_1 = 0.4$ and (b) δ_1, with $d_1 = 0.2$; sample size 5000, Specification I and II.

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Table 3. Summary of characteristics according to vitamin D status (based on measured serum 25(OH)D concentration) among 4,002 adults of the National Health and Nutrition Examination Survey (2005–06), American adults who had three readings of systolic blood pressure.

	Severe deficiency<10 ng/mL	Mild deficiency10~20 ng/mL	Adequacy> = 20 ng/mL	*P*-value
Overall n(%)	365 (9.1)	1427 (35.6)	2210 (55.3)	
Gender[a]				0.14
Male, n (%)	141(7.3)	711(36.6)	1089(56.1)	
Female, n(%)	224(10.9)	716(34.7)	1121(54.4)	
Age (years), mean(SD)[b]	41.3 (18.3)	44.1 (19.0)	45.4 (18.8)	<0.001
Overweight or obesity status[a]				<0.001
BMI>25, n (%)	277(10.2)	1050(38.6)	1390(51.2)	
BMI≤25, n(%)	88(6.9)	377(29.3)	820(63.8)	
Systolic blood pressure (mmHg) mean(SD)[b]	124.1 (19.5)	123.4 (18.0)	120.7 (17.3)	<0.001

[a] P values were derived from Kolmogorov-Smirnov tests;

[b] P values for trend (two-sided) were derived from trend tests.

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Real Data

Table 3 presents summary data on the 4,002 adults in NHANES 2005–06 who had complete information on blood pressure and 25(OH)D concentration. Severe vitamin D deficiency was more common in participants who were overweight or obese compared to those of normal weight ($p<0.001$). Mean systolic blood pressure increased across categories of lower vitamin D status ($p<0.001$).

The results in the first column of Table 4 show that the measured 25(OH)D concentration was inversely associated with systolic blood pressure after controlling for age, sex, and overweight or obesity status ($\beta = -0.16$ (95% CI: -0.21, -0.11; $p<0.001$)). In addition, systolic blood pressure was positively and significantly associated with overweight status: when BMI was greater than 25, the systolic blood pressure was higher by 3.13 (95% CI: 2.08, 4.18; $p<0.001$) mm Hg.

The results of the OLS linear regression in *Stage I* based on the measured 25(OH)D concentration, shown in Column (2) of Table 4, suggested that overweight or obesity status was a

Table 4. Multivariable association between measured 25(OH)D concentration and systolic blood pressure; determinants of 25(OH)D concentration (*Stage I*); and multivariable association between predicted 25(OH)D score and systolic blood pressure (*Stage II*) among 4,002 adults of the National Health and Nutrition Examination Survey (2005–06), US, OLS.

Variable	Systolic blood pressure			*Stage I*: measured 25(OH)D concentration			*Stage II*: Systolic blood pressure		
	Coefficient	95% CI	*P*-value	Coefficient	95% CI	*P*-value	Coefficient	95% CI	*P*-value
Measured 25(OH)D concentration	-0.16	(-0.21, -0.11)	<0.001						
Predicted 25(OH)D score							-1.15	(-1.48, -0.82)	<0.001
Age	0.42	(0.40, 0.45)	<0.001	0.02	(0.01, 0.04)	<0.001	0.45	(0.42, 0.47)	<0.001
Male (vs. female)	3.71	(2.74, 4.67)	<0.001	-0.28	(-0.86, 0.30)	0.35	3.43	(2.45, 4.41)	<0.001
Overweight or obesity (BMI>25 vs≤25)	3.13	(2.08, 4.18)	<0.001	-3.16	(-3.79, -2.53)	<0.001			
Constant	102.63	(100.80, 104.45)	<0.001	22.89	(21.05, 23.74)	<0.001	130.19	(124.55, 132.45)	<0.001
Adjusted R^2	0.24			0.02			0.24		

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significant predictor of 25(OH)D concentration. Compared to a BMI of ≤25, a BMI of greater than 25 was associated with a 3ng/ml lower measured 25(OH)D concentration (β = -3.16; 95% CI: -3.79, -2.53 ng/mL; $p<0.001$). The *Stage II* estimate for the association between the predicted 25(OH)D score and systolic blood pressure, where overweight or obesity status was employed as the instrumental variable, was β = -1.15 (95% CI: -1.48, -0.82; $p<0.001$) (Column (3) of Table 4). This is significantly different from the estimate based on the measured 25(OH)D concentration (Column (1) of Table 4) ($p<0.001$).

In addition, because the coefficient of the association between overweight or obesity status and systolic blood pressure was 3.13, and that between overweight or obesity status and 25 (OH)D concentration was -3.16 (See Column (1) and (2) of Table 4 respectively), the bias is theoretically -0.99 (= 3.13/-3.16) when overweight or obesity status is used as the instrumental variable. Thus, the estimated effect of the predicted 25(OH)D score on systolic blood pressure is β = -1.15 (= [-0.16] +[-0.99]), that is, the sum of the estimated effect of the measured 25(OH) D concentration in Column (1) of Table 4 and the bias. This is statistically identical with the estimate in column (3) of Table 4, -1.15 (95% CI: -1.48, -0.82).

Discussion

The results indicate that the prediction of 25(OH)D concentration based on multivariable linear regression may be correct, but care needs to be taken when applying this methodology. Even if only one of the instrumental variables used is invalid, the estimates of the association between 25(OH)D concentration and the health outcome will be unreliable. It should be noted that the second requirement of a valid instrument variable, that it should not be a risk factor for the disease, cannot be test mathematically or statistically and can only be judged according to biological findings from past research. Thus, the reasons for the choice of instrumental variables should be discussed, and the lack of correlation with the health outcome confirmed. Previous studies using this methodology have not provided an adequate consideration of the potential biases that could occur. For example, several papers used variables such as physical activity, BMI, smoking status, alcohol intake and race as instrumental variables, despite substantial evidence these factors are strongly associated with many diseases, including the outcomes of interest [6,15–18]. Vitamin D intake has also been used as an instrumental variable [8,19], but may also be associated with disease risk as a marker of a healthier lifestyle and thus lower disease risk [20].

In some studies, stratification by a potential confounder, or meta-analysis of findings have been used to indicate a greater likelihood of a "real" finding. However, a stratified analysis cannot demonstrate that the results are "correct" or robust. For example, where BMI is used in the predictive model for 25(OH)D score, then the effect estimate of 25(OH)D score on the health outcome, e.g. digestive cancer, may be compared across strata of BMI. Higher BMI is a known risk factor for digestive cancer and is therefore an invalid instrumental variable. In this case, if the effect estimates from the two strata are the same or similar, then the conclusion may be that the association between 25(OH)D score and the health outcome is the same for both strata, or, alternatively, that the bias caused by the invalid instrumental variable plus the real association is the same for both strata. But it is not possible to distinguish between these two possible conclusions. Similarly, meta-analysis does not help although it is useful to estimate the summary effects over a number of previous studies particularly when the sample size in any single study is insufficient. If all of the individual studies use invalid instrumental variables, all of the effect estimates are biased, and the weighted average of these biased estimations will be similarly biased.

Most recently, variants of genes that affect 25(OH)D synthesis or substrate availability (e.g. *CYP2R1*, *GC* and *DHCR7*) have been used as instrumental variables either individually or through creation of a genetic score that acts as a proxy for long-term 25(OH)D levels [21]. This method does not predict 25(OH)D levels per se, but may be more disease-relevant than a single 25(OH)D measurement for which intraclass correlation coefficients range from 0.42–0.72 between 2 direct measures taken 2–14 years apart [6,22–24]. The substrate from which vitamin D is synthesised is 7-dehydrocholesterol (7-DHC) located in epidermal cells of the skin. The *DHCR7* gene encodes the enzyme 7-DHC reductase and both 7-DHC and 7-DHC reductase are part of the cholesterol biosynthesis pathway. Using a genetic synthesis score, a recent meta-analysis showed a modest association between higher genetically instrumented 25(OH)D concentration and lower systolic blood pressure A valid instrument has an effect on the outcome only through the factor that it is a proxy for, in this case 25(OH)D concentration. In the recent study, the synthesis score was highly correlated with measured 25(OH)D concentration, but also had an overall association with higher serum total cholesterol ($p = 0.04$), suggesting a possible separate pathway of effect of this genetic score on higher systolic blood pressure. Thus genetic 25(OH)D scores should also be used as instrumental variables with caution, given the pleiotropic effects of some vitamin D pathway genes, e.g. *GC* and its association with lipid metabolism, inflammation and metabolic feedback loops.

In practice, it is common to generate a dichotomous variable based on the predicted score to categorize participants as suffering from vitamin D deficiency or not, and this further complicates the situation. In this situation, the bias caused by use of an invalid instrumental variable will be further distorted by the distribution of the predicted 25(OH)D score. The direction of the bias cannot be determined theoretically.

The method discussed here is similar to the method of Two-Stage Least Squares (2SLS) which is widely used to estimate causal relationships in economics [25,26]. Differences between the two methods include that 25(OH)D concentration is available in the main data for Stage 1, but not Stage II, while 2SLS usually uses the same dataset in both stages. The 2SLS method aims to solve the bias caused by omitted confounders; an instrumental variable can be used only if it: 1) has a strong association with the variable (exposure) of interest; and 2) is not an independent risk factor for the outcome. These two criteria also apply for the methodology using a predicted 25(OH)D score.

Although applying the predicted 25(OH)D score method to identify the association between 25(OH)D concentration and health outcomes is not straightforward, there are clinical applications for predicted data. Recently there have been large increases in vitamin D testing in several countries due to concern about possible widespread vitamin D deficiency and purported links to a wide range of health risks [27], with considerable costs to healthcare systems [28]. One solution to reduce unnecessary tests is to predict those who are at high risk of vitamin D deficiency using available data, and test only these people. However, when predicted levels are used in large-scale epidemiological studies seeking to clarify links between vitamin D status and disease risks, there is considerable risk of bias in the estimates of effect arising from incorrect specification of an instrumental variable. This must be fully considered and discussed in studies using this methodology.

Supporting Information

S1 Appendix. The mathematical framework for a predictive model of 25(OH)D concentration, based on multivariable linear regression.
(DOCX)

S2 Appendix. Generating virtual survival times.
(DOCX)

Author Contributions

Conceived and designed the experiments: ND RL. Performed the experiments: ND SG. Analyzed the data: ND SG KD RL FX. Contributed reagents/materials/analysis tools: ND SG RL FX. Wrote the paper: ND KD SG FX RL.

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S1 Appendix

The mathematical framework for a predictive model of 25(OH)D concentration, based on multivariable linear regression

The 25(OH)D concentration is a linear function of variables x, z and the error term as follows

$$D = ax + dz + e_{,,} \tag{A.1}$$

Theoretically, the relationship between 25(OH)D concentration (D) and the health outcome is assumed to be:

$$H(t) = H_0(t)\exp(\Gamma) = H_0(t)\exp(\alpha x + \beta y + \delta z + \theta D), \tag{A.2}$$

where y is the determinant of health outcome but not of the 25(OH)D concentration. Substitute A.1 into A.2, we have.

$$H(t) = H_0(t)\exp[(\alpha + a\theta)x + \beta y + (\delta + \theta d)z + \theta e]. \tag{A.3}$$

In practice, the 25(OH)D concentration is predicted based on the regression (A.1) and let us assume the estimates are all unbiased and consistent. $\widehat{D} = ax + dz$ (*Stage I*). However, in *Stage II*, the health outcome equation is mis-specified as

$$H(t) = H_0(t)\exp(\Gamma) = H_0(t)\exp\big(\alpha x + \beta y + \theta\widehat{D}\big), \tag{A.4}$$

Thus,

$$H(t) = H_0(t)\exp[(\hat{\alpha} + a\hat{\theta})x + \beta y + \hat{\theta}dz]. \tag{A.5}$$

Comparing the coefficients before z in equation (A.3) and (A.5), we have

$$\delta + \theta d = \hat{\theta}d. \tag{A.1}$$

Thus, $\hat{\theta} = \theta + \delta/d$ and the bias in the estimate of interest is δ/d.

Further, comparison of the coefficients before x in equation (A.3) and (A.5), shows

$$\alpha + a\theta = \hat{\alpha} + a\hat{\theta}. \tag{A.2}$$

Then, $\hat{\alpha} = \alpha + a\big(\theta - \hat{\theta}\big) = \alpha - a\delta/d$ and the bias is $-a\delta/d$. Thus, invalid instrumental variables bias the estimates of the covariates which appear in both stages too.

S2 Appendix

Generating virtual survival times

Since all of the variables are assumed to be time-invariant, the survival function of the proportional hazards model is given by

$$S(t|X,Y,D) = \exp(-H_0(t)\exp(\Gamma)) \quad \text{(B.1)}$$

where $H_0(t) = \int_0^t h_0(u)du$ is the cumulative baseline hazard function. Thus, the survival time, denoted by T, is in fact a random variable with distribution function S. So, $U = S(T)$ follows a uniform distribution on the interval from 0 to 1. Then

$$U = \exp(-H_0(T)\exp(\Gamma)). \quad \text{(B.2)}$$

If the baseline hazard $\mathrm{h}_0(t) > 0$ for all t, then H_0 is invertible and the survival time T of the proportional hazard model can be expressed as:

$$T = H_0^{-1}(-\ln(U) \times \exp(-\Gamma)). \quad \text{(B.3)}$$

With the help of equation (B.3), the random variable of survival time can be generated.

If the baseline hazard rate is a constant, $h_0(t) = \lambda$ (the exponential model), then $H_0(t) = \int_0^t \lambda du = \lambda t$. So, $H_0^{-1}(t) = \lambda^{-1}t$. Thus, $T = -\lambda^{-1}\ln(U) \times \exp(-\Gamma)$.

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A Novel Approach for Prediction of Vitamin D Status Using Support Vector Regression

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Abstract

Background: Epidemiological evidence suggests that vitamin D deficiency is linked to various chronic diseases. However direct measurement of serum 25-hydroxyvitamin D (25(OH)D) concentration, the accepted biomarker of vitamin D status, may not be feasible in large epidemiological studies. An alternative approach is to estimate vitamin D status using a predictive model based on parameters derived from questionnaire data. In previous studies, models developed using Multiple Linear Regression (MLR) have explained a limited proportion of the variance and predicted values have correlated only modestly with measured values. Here, a new modelling approach, nonlinear radial basis function support vector regression (RBF SVR), was used in prediction of serum 25(OH)D concentration. Predicted scores were compared with those from a MLR model.

Methods: Determinants of serum 25(OH)D in Caucasian adults (n = 494) that had been previously identified were modelled using MLR and RBF SVR to develop a 25(OH)D prediction score and then validated in an independent dataset. The correlation between actual and predicted serum 25(OH)D concentrations was analysed with a Pearson correlation coefficient.

Results: Better correlation was observed between predicted scores and measured 25(OH)D concentrations using the RBF SVR model in comparison with MLR (Pearson correlation coefficient: 0.74 for RBF SVR; 0.51 for MLR). The RBF SVR model was more accurately able to identify individuals with lower 25(OH)D levels (<75 nmol/L).

Conclusion: Using identical determinants, the RBF SVR model provided improved prediction of serum 25(OH)D concentrations and vitamin D deficiency compared with a MLR model, in this dataset.

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Introduction

There have been increasing concerns about vitamin D deficiency around the world. Epidemiological evidence suggests that hypovitaminosis D is linked to various chronic diseases such as colorectal, prostate and breast cancers[1,2,3], as well as cardiovascular diseases and diabetes[4,5,6]. Vitamin D status is assessed by the serum concentration of 25-hydroxyvitamin D (25(OH)D), an accepted biomarker[7]. However measuring 25(OH)D requires blood sampling and laboratory resources for quantitative assays. This approach may not be feasible for testing hypotheses of vitamin D status as a risk factor for chronic disease in large epidemiological studies.

An alternative approach for estimating vitamin D status is to derive a predictive model based on measurements of 25(OH)D concentration and questionnaire data on known determinants, from a subset of the study cohort. Values for the remainder of the cohort are then predicted, based on their questionnaire data[8,9,10]. Past studies have used multiple linear regression (MLR) modelling to develop these predictive models. However, the final models typically explain only a small proportion of the total variability in 25(OH)D concentration, that is, the coefficient of determination (R^2) values from such predictive models have ranged from 0.13 to 0.42[8,9,10,11,12,13]. In some publications, predicted and actual 25(OH)D levels have been compared in a validation sample, with Spearman(9,10) or Pearson(12) correlation coefficients ranging from 0.23 to 0.51.

Recent studies on vitamin D status prediction are shown in **Table 1**. These models, based on MLR, have a number of potential limitations. For example, outliers can be highly influential in MLR models, with large differences in parameters dependent on inclusion or exclusion of these values. Moreover, MLR reflects a relationship between the means of the dependent variable and the independent variables[14], although in chronic

disease epidemiology, we may be most interested in very low 25(OH)D values. Thus the 25(OH)D scores predicted using MLR models may not accurately reflect an individual's actual vitamin D status, biasing any risk factor associations. Nevertheless, vitamin D prediction models could have considerable potential, both in studies examining vitamin D status in relation to disease risks and in screening for risk of vitamin D deficiency and thus the need for testing – but require improved prediction accuracy. Newer modelling techniques may provide better fit and more accurate assignment of participants to categories of vitamin D status, e.g. deficient, insufficient, sufficient, or optimal.

Support vector regression (SVR) algorithm

Data modelling methods based on machine learning, such as Artificial Neural Networks (ANN) and Support Vector Machines (SVM), have been extensively used in bioinformatics and molecular biology[15,16,17]. More recently, these techniques have been introduced to solve medical classification and medical prediction problems and aid clinical decision making[18,19,20,21]. In the epidemiology domain, machine learning algorithms also have the potential for prediction, classification and risk factor identification. For example, this type of modeling has been used for risk prediction of common diseases such as diabetes and pre-diabetes[22].

The SVM algorithm was originally developed by Vapnik and co-workers at AT&T Bell Laboratories in the 1990s[23,24]. The underlying theory and algorithm were introduced by Elisseeff *et al.* [25]. SVM methods include support vector classification (SVC) for classification and support vector regression (SVR) for prediction.

The SVR method differs from that of MLR in the underlying theoretical settings. The basic idea of regression methods is to construct an optimal regression hyperplane with n-1 dimensions that best fits the data in an n-dimensional space. If we take the simplest example, a two-dimensional data space can be generated by two variables in a dataset; the regression hyperplane is a straight line (with one dimension). As for other conventional methods, the MLR algorithm fits a model using the least mean squares approach to define the linear hyperplane[26,27]. However, the real world is much more complicated than a linear correlation. Furthermore, the regression hyperplane based on a least mean squares approach is greatly affected by outliers. In the SVR method, these problems are solved by 1) using integrating kernel functions (i.e polynomial, sigmoid and radial basis functions) to add more dimensions to lower dimensional space or add nonlinearity to the model; and 2) introducing user-specified parameters to control the trade-off of prediction errors and flatness of the regression plane (see Methods section). **Figure 1** illustrates the difference between MLR and SVR prediction models.

In this paper, we examine the utility of an SVR algorithm, in comparison with a MLR algorithm, in predicting serum 25(OH)D concentration based on the determinants of vitamin D status already identified in a population of Australian Caucasian adults.

Materials and Methods

Study population

Data included here are from 494 participants from the control group of the Ausimmune Study[28]. The Ausimmune Study is a multi-centre, case-control study examining risk factors for multiple sclerosis. The control group was randomly selected from the Australian Electoral Roll in four different study regions. Participants completed a questionnaire including self-reported recent sun exposure and sun protection behaviours, physical activity, smoking history, diet and the use of supplements. Skin types were defined by spectrophotometric measurements of skin reflectance to calculate melanin density for exposed skin sites (dorsum of hand, shoulder) and non-exposed skin sites (upper inner arm, buttock) using a spectrophotometer (Minolta 2500d)[29]. Height, weight, waist and hip circumference were also measured. Serum 25(OH)D levels were determined by liquid chromatography dual mass spectrometry at a central laboratory. Because the number of non-Caucasian participants was small (n = 26), only data from the Caucasian participants in the control group were included for the purpose of developing the vitamin D prediction model.

Statistical analysis

The MLR model. The important determinants of vitamin D status were defined using MLR and forward purposeful selection of covariates, as previously described[30]. Briefly, 12 variables were retained in the MLR environmental and phenotypic determinants model: latitude, ambient ultraviolet radiation levels, ambient temperature, hours in the sun 6 weeks before the blood draw (log transformed to improve the linear fit), frequency of wearing shorts in the last summer, physical activity (three levels: mild, moderate, vigorous), sex, hip circumference, height, left back shoulder melanin density, buttock melanin density and inner upper arm melanin density. A square root transformation of the dependent variable (serum 25(OH)D concentration) in the MLR model was performed because of heteroscedasticity of the residuals[30].

The SVR model. Given a dataset with n independent variables and m observations, the MLR model can be written as $y = f(x) = W.X + b$ where W represents the vector of the coefficients, X represents the vector of the independent variables, and b is the intercept. To estimate the best fit, we minimize the sum of the squared errors:

$$\min \sum_{i=1}^{m} (y_i - \hat{y}_i)^2 = \min \sum_{i=1}^{m} (y_i - (\hat{W} \cdot X_i + \hat{b}))^2,$$

(where i represents the i^{th} observation).

When the correlation between x and y is linear, the form of the SVR algorithm is similar to that of MLR: $y = f(x) = W.X + b$. However, the SVR method has two additional parameters: C and ε. The parameter C is introduced to adjust the error sensitivity of the training data in order to avoid over-fitting; setting C to a high value results in fewer prediction errors in the training data:

$$\min \sum_{i=1}^{m} (y_i - (\hat{W} \cdot X_i + \hat{b}))^2 + C \sum_{j=1}^{n} |W_j^2|,$$

(where j represents the j^{th} variable), The second parameter ε is the regularization constant, which controls the flatness of the final model [31].The goal of SVR is to determine an optimal function that has less than ε deviation from the target values for the training data, so that we do not count errors that are less than ε, and at the same time the regression hyperplane needs to be as flat as possible.

By using different kernel functions, which transform data into a high dimensional space or add non-linearity, the SVR algorithm allows application of nonlinear regression[32]. The Radial Basis

Table 1. Recent studies using a multiple linear regression prediction model for 25(OH)D concentration.

Reference	Cohort	Sample	Model covariates	R^2 for the model	Validation
Giovannucci et al,	Health Professionals	Male	Geographical region	28%	Measured plasma 25(OH)D level rose across increasing
2006 [8]	Follow-Up Study (HPFS),	40–75	Dietary vitamin D intake		deciles of predicted 25(OH)D score ($p_{trend}<0.001$)
	US	Training set: 1095	Vitamin D supplements		
		Validation set: 542	Race		
			BMI		
			Physical activity level		
Chan et al., 2010	Adventist Health Study-2	Male & Female	Race	White: 22%	N/A
[11]	(AHS-2),	Black: 209	BMI	Black: 31%	
	US, Canada	White: 236	Skin type	Total: 42%	
			UV season		
			Latitude		
			Erythemal zone		
			Total vitamin D intake		
			Duration of sun exposure		
			Percentage of body exposed		
Liu et al., 2010	Framingham Offspring	Male & Female	Age	25.75%	Spearman rho for measured 25(OH)D concentration vs.
[9]	Study,	50–70	Sex		predicted score = 0.51 ($p<0.001$)
	Massachusetts, US	Training set: 883	BMI		
		Validation set: 845	Total vitamin D intake		
			Smoking status		
			Total energy intake		
Millen et al.,	Women's Health Initiative	Female	Langleys	21%	Pearson correlation coefficient for measured plasma
2010	Clinical Trial (WHI-CT),	50–79	Race		25(OH)D vs. predicted score r = 0.45, 95%CI: 0.40,0.49
[12]	US	Training set: 3055	Age		The predictive model was poor at categorizing women in the
		Validation set: 1528	Waist circumference		severely deficient (3%) and sufficient (3%) range of vitamin
			Recreational physical activity		D status.
			Total vitamin D intake		
Peiris et al., 2011	Veterans Administration	Male	Triglyceride	12.9%	The model correctly classified vitamin D deficiency status
[13]	Center patients		Race		for 70.6% patients; only 30.6% of those who were actually
	Southeastern US		Total cholesterol		deficient were correctly identified as deficient.
			BMI		
			Calcium level		
			Number of missed appointments		
Bertrand et al.,	Nurses' Health Study	NHS: female, 30–55 y	Race	NHS: 33%	Spearman rho for measured 25(OH)D concentration vs.
2012 [10]	(NHS)	Training set:2246	UV-B flux	NHSII: 25%	predicted score were 0.23, 95%CI: 0.16,0.29 for NHS, 0.42,
	Nurses' Health Study II	Validation set:818	Dietary vitamin D intake	HPFS: 28%	95%CI:0.34, 0.49 for NHSII, 0.30, 95%CI: 0.21 0.37
	(NHSII)	NHSII: female, 25–42 y	Supplementary vitamin D intake		(adjusted for batch, age and season of blood draw)
	Health Professionals	Training set:1646	BMI		
	Follow-up Study (HPFS)	Validation set: 479	Physical activity		
		HPFS: Male, 40–75 y	Alcohol intake		
		Training set: 1255	Post-menopausal hormone use		
		Validation set: 841	Season of blood draw		

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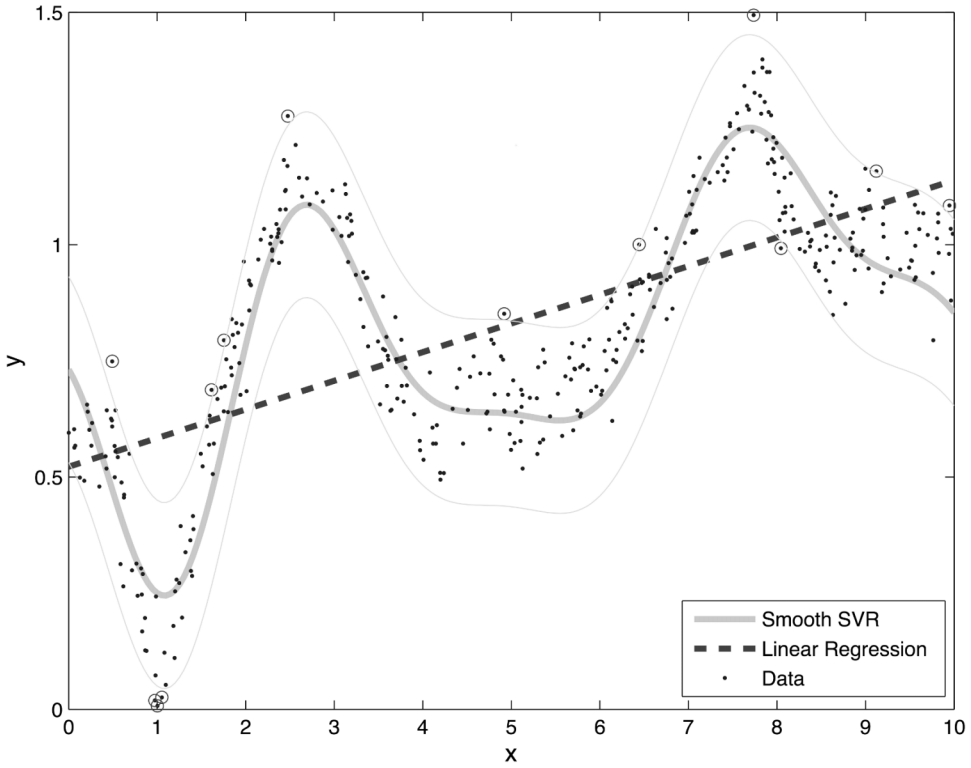

Figure 1. Performance demonstration of SVR and MLR in a simple scenario (two-dimensional case). The black dots indicate actual simulation data set. The solid curve denotes SVR regress line and the dot line represents the MLR regression line. The simulation data set is randomly generated by MATLAB.
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Function (RBF) SVR method adopts the RBF kernel function, also known as the Gaussian kernel, which is the same as a Gaussian distribution function. Compared to linear SVR, the RBF SVR method has one more parameter, γ, which determines the degree of nonlinearity[33].

For the RBF SVR modelling, the data were randomly separated into two independent samples: the 'training sample' (n = 294) was used to develop the parameters of the vitamin D prediction model and the 'validation sample' (n = 174) was used for all statistical analyses noted below. The same 12 variables were included in the model as for the MLR modelling, described above. Parameters were determined by grid search, i.e. exhaustive searching through a set of parameters, followed by cross validation. The parameters with the best model performance were selected.

Model comparison. Predicted values from the MLR model were derived by summing coefficients multiplied by the individual values of the covariates[8]. Predicted values from the SVR model were derived by running the model with the individual values of the covariates. We compared the predictions from the RBF SVR and MLR models to measured 25(OH)D values in the ''validation sample'' Results were reported as means, standard deviations (SDs), minima and maxima. Mean absolute differences, i.e. the mean of the absolute differences between the individual predicted and measured 25(OH)D values, were calculated as an indication of the magnitude of error. Differences between results from the RBF SVR and MLR models were analysed with the Wilcoxon signed rank test. The correlation between predicted and measured serum 25(OH)D concentrations was analysed using a Pearson correlation coefficient (r). Bland-Altman plots were used to provide the mean bias (the average of the difference between measured 25(OH)D and prediction scores from the two compared modelling methods) across the range of 25(OH)D levels, and 95% limits of agreement between the methods.

We tested the accuracy of classification into categories of vitamin D status using predicted 25(OH)D scores. Data in the validation sample were analysed by generating the receiver operating characteristic (ROC) curve. Sensitivities and specificities were generated for a range of cut offs for the ROC curve. In chronic disease epidemiology studies, ''exposures'' are often categorised into quintiles. Thus, here individuals in the validation set were also classified according to quintile of predicted 25(OH)D scores and measured 25(OH)D concentration, for the purpose of testing the performance of the two models.

Data analysis for the RBF SVR model was performed using Matlab R2001b. Analyses for the MLR model, Pearson correlation, Wilcoxon signed rank test, Bland-Altman plots and ROC curves were performed using Stata 12.0 (Statacorp, Texas).

Results

Means, SDs, minima and maxima of predicted 25(OH)D scores for the two models are presented in **Table 2**. A summary, as the mean absolute difference between measured and predicted 25(OH)D for the two models, is also given. The mean absolute difference between measured and predicted 25(OH)D concentrations generated by the RBF SVR model was significantly smaller than that for the MLR model (p = 0.012). Figure 2 demonstrates the correlation between the measured and predicted 25(OH)D concentration for the MLR (Figure 2A) and RBF SVR (Figure 2B) models. Consistent with this, the Pearson correlation coefficients indicated better correlation between predicted scores and measured 25(OH)D concentrations for the RBF SVR model (r = 0.74)

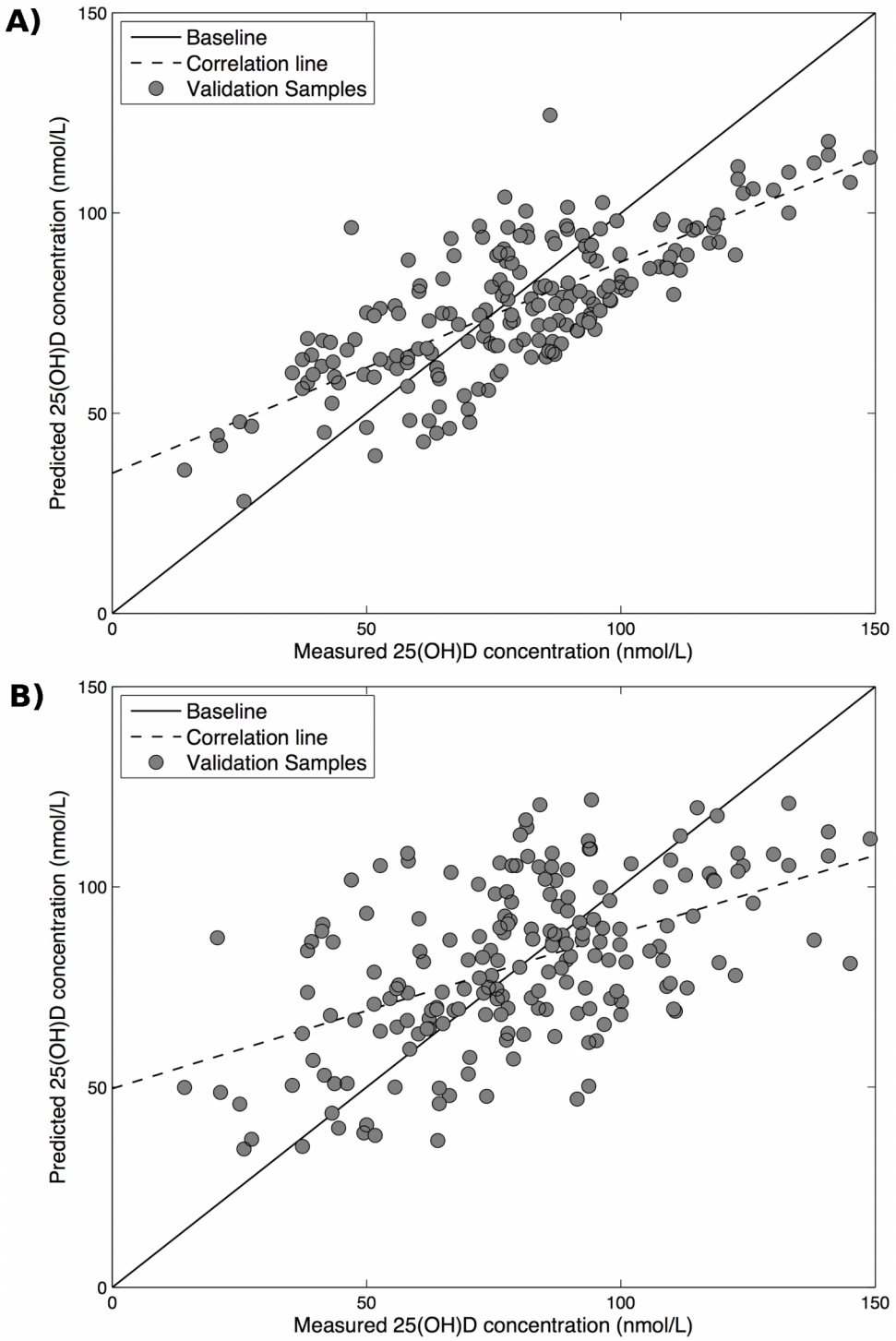

Figure 2. Correlation of measured 25(OH)D concentration (nmol/L) and predicted 25(OH)D concentration using (A) a multiple linear regression model; and (B) a radial basis function support vector regression model.
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than for the MLR model (r = 0.51). Bland Altman plots showed that there was tighter agreement between measured 25(OH)D concentration and predicted scores for the RBF SVR model than for the MLR model: 95% limits of agreement were −49.20, 48.37 (Figure 3A) and −38.26, 31.03 (Figure 3B) for the MLR and RBF SVR models, respectively. There was a slight negative bias across the range of measured 25(OH)D concentrations that was greater for the RBF SVR than the MLR predicted scores (−3.62 nmol/L, −0.37 nmol/L, respectively). Predicted scores from both models showed a greater tendency to negative bias at higher 25(OH)D concentrations.

We compared the sensitivity of the two modelling techniques for correctly classifying individuals as being vitamin D deficient vs. sufficient, using different cut-points. When vitamin D deficiency

Table 2. Predicted 25(OH)D concentration and mean absolute difference between predicted and measured 25(OH)D level (nmol/L).

	Mean	Standard deviation	Minimum	Maximum
Measured 25(OH)D level	81.71	28.33	14.2	163.3
Predicted level MLR	81.3	20.41	34.54	121.71
Predicted level RBF SVR	78.10	18.87	28.01	129.91
Mean absolute difference MLR	19.04	15.23	0.18	76.39
Mean absolute difference RBF-SVR	15.65	8.91	0.05	49.33

RBF SVR, radial basis function support vector regression (nonlinear support vector regression).
MLR, multiple linear regression.
Mean absolute difference is the average of the absolute differences between the predicted and measured values.
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was defined as 25(OH)D level of <75 nmol/L (vs. ≥75 nmol/L), both models had reasonable sensitivity, but the RBF SVR model performed significantly better (P<0.01, Figure 4). The sensitivity for the RBF SVR model was 81.6% compared to the MLR model of 67.1%. The area under the curve (AUC) for the MLR ROC curve was 0.79 (95% confidence interval (CI) 0.73–0.86) compared with an area under the curve of 0.87 (95%CI, 0.82–0.92) for RBF SVR. Using a 25(OH)D level of 50 nmol/L as the cut off point, the AUC for the MLR ROC curve was 0.79 (95%CI, 0.68–0.89) compared with an AUC of 0.86 (95%CI, 0.79–0.94) for RBF SVR, P = 0.064. Notably, however, only 13% of the test sample were vitamin D deficient according to this cut off point (25(OH)D <50 nmol/L) with 25(OH)D levels measured using an LC-MS/MS assay. The superior performance of the RBF SVR model was less apparent with the limited number of 'positive' cases. As previously reported, 25(OH)D levels from a Diasorin Liaison assay were also available for these samples[34] with the results negatively biased compared to results from the LC-MS/MS assay, i.e. a greater proportion of the sample <50 nmol/L. We thus also tested the performance of the two modelling methods using the Liaison 25(OH)D results. Here the AUC for the curve generated from the MLR results was 0.69 (95%CI, 0.62–0.76), compared to that for the RBF SVR of 0.83 (95%CI, 0.77–0.89). That is, the RBF SVR model performed significantly better than the MLR model, P<0.0001.

In epidemiological studies, exposures are often categorised into quintiles for analysis, so we classified predicted 25(OH)D scores and measured 25(OH)D concentration by quintile to determine how well the two prediction models performed in each quintile group. For the MLR model 50.2% of the predicted 25(OH)D scores, compared to 66.1% of predicted scores for the RBF SVR model, fell into the same quintile as the measured 25(OH)D values. Figure 5 shows the percentage of correct classification in each quintile. As is illustrated in Figure 5, both MLR and RBF SVR models performed well in predicting 25(OH)D concentration

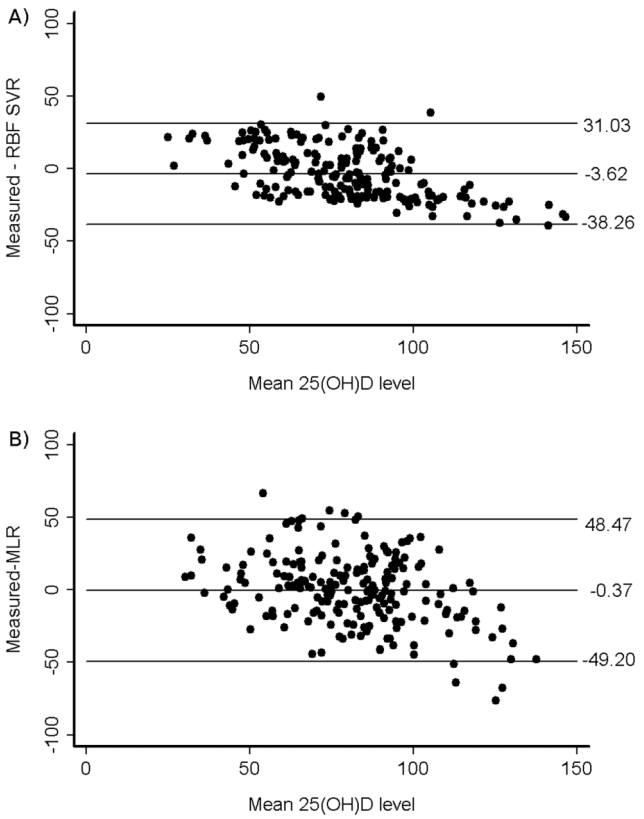

Figure 3. Bland – Altman plots of measured 25(OH)D concentration compared to predicted scores from (A) a MLR model; (B) a RBF SVR model. The solid lines indicate the mean bias (middle line) and 95% limits of agreement (top and bottom lines). All measurements are in nmol/L.
doi:10.1371/journal.pone.0079970.g003

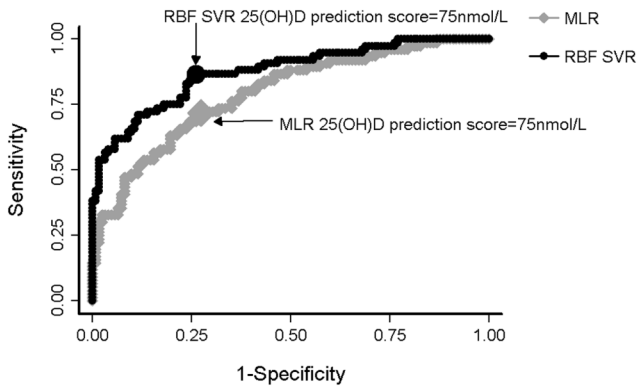

Figure 4. ROC curves of MLR and RBF SVR. ROC curves showing true-positive rates (sensitivity) plotted against the false-positive rate for different cut off points of the quantified components of MLR (gray diamonds) and RBF SVR (black circles). The points highlighted are 25(OH)D scores of 75 nmol/l for MLR and RBF SVR. The area under the curve is 0.79 and 0.87 for MLR and RBF SVR respectively.
doi:10.1371/journal.pone.0079970.g004

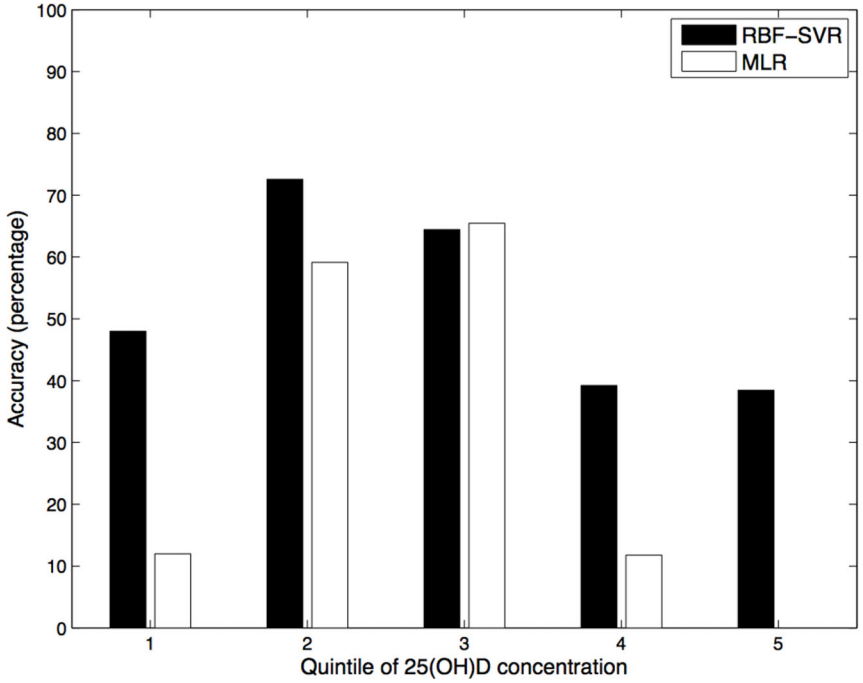

Figure 5. Accuracy of predicted 25(OH)D score in each quintile of 25(OH)D concentration.
doi:10.1371/journal.pone.0079970.g005

in the second and third quintile (Q2 and Q3). Although both prediction models were limited in their detection of extreme values the RBF SVR model had superior performance compared to the MLR model for correct prediction in quintiles 1, 4 and 5. The MLR model had very poor performance in predicting the highest serum 25(OH)D score; the prediction accuracy for Q5 was 0%.

Figure 6 illustrates the percentage of individuals classified into each quintile according to actual and predicted 25(OH)D concentration. The quintile distribution of predicted 25(OH)D concentration derived from RBF SVR model is much more accurate than the MLR model, according to the quintile distribution of measured 25(OH)D concentration.

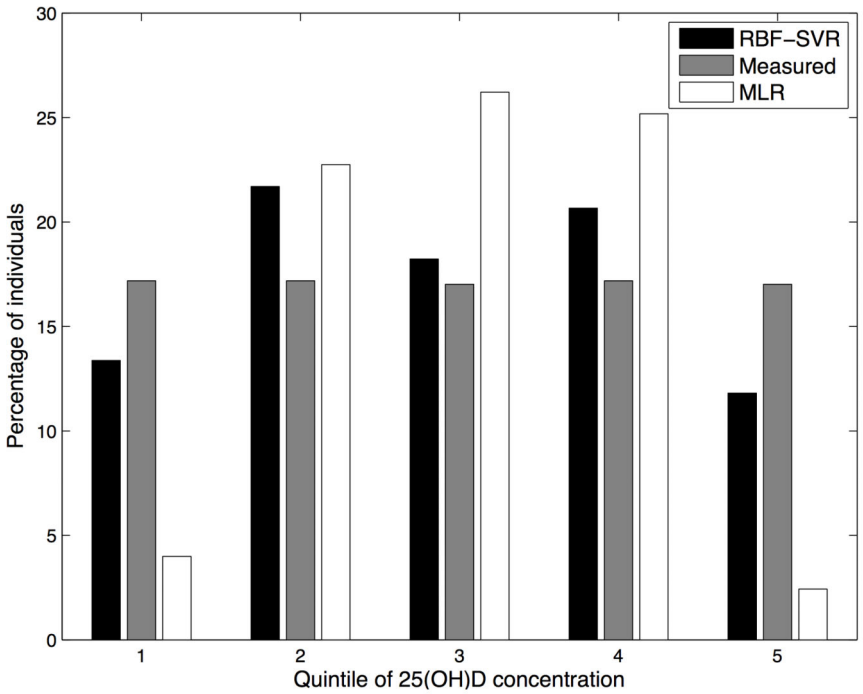

Figure 6. Percentage of individuals classified by quintiles of measured 25(OH)D concentration and predicted 25(OH)D score.
doi:10.1371/journal.pone.0079970.g006

Discussion

We compared the performance of MLR and RBF SVR models for the prediction of vitamin D status, using a set of predetermined explanatory variables. Using the RBF SVR for prediction of serum 25(OH)D concentration resulted in lower mean absolute error in comparison with the MLR model. In the validation sample we observed better correlation between predicted scores and measured 25(OH)D concentration for the RBF SVR model compared to the MLR model. Furthermore, the RBF SVR method demonstrated higher sensitivity in classifying vitamin D status as deficient/sufficient and the AUC for the RBF SVR ROC curve was significantly larger than that for the MLR ROC curve.

This is the first study in which serum 25(OH)D concentration has been modelled using RBF SVR, with previous studies focussing on MLR models. For example, Bertrand *et al*[10] reported a MLR model using data from three US cohorts, with Spearman correlation coefficients between predicted and measured 25(OH)D of 0.23, 0.40, and 0.24, respectively. In the Women's Health Initiative, Millen *et al.*[12] reported a comparable correlation (0.45), using a MLR model. In the Framingham Offspring Study, Liu *et al.*[9] observed a correlation of 0.51 between predicted and measured levels. Using the results from these prediction models imposes several limitations on the accurate estimation of "exposure" in chronic disease epidemiology. Such models have substantial unexplained variability ($R^2 = 0.13$–0.42) and the predicted scores are only moderately correlated with actual 25(OH)D levels. In previous studies, the predicted scores were based on data that were incomplete for known determinants of vitamin D status, such as sun sensitivity characteristics (e.g. skin colour, ability to tan), actual sun exposure and sun exposure behaviours (e.g. time spent outdoors and protective clothing). Proxies such as physical activity and ethnicity were used instead of actual sun exposure and skin colour, allowing considerable measurement error and misclassification on key determinants.

In our study, time spent outdoors and direct measurements of untanned skin colour were included as predictors in the MLR model. But even so, the MLR model using these environmental and phenotypic factors explained only a modest proportion of the total variability in serum 25(OH)D levels ($R^2 = 0.36$) and the Pearson correlation coefficient (for predicted vs. measured values) was 0.51. The performance of our MLR model was consistent with the prediction models reported in the previous studies, suggesting intrinsic limitations of the MLR models.

Here we did not use the R^2 value to evaluate the performance of the RBF SVR model, because this method is not based on a least mean squares approach. However, using the RBF SVR model, we observed a correlation of 0.74 between predicted scores and measured 25(OH)D concentration. Moreover, the RBF SVR model had higher sensitivity and performed better than MLR in correctly identifying individuals with vitamin D deficiency. Interestingly, the difference in sensitivity and AUC between the two models was less when the prevalence of vitamin D deficiency was low, i.e. with a cut-point of 50 nmol/L using the 25(OH)D results from the LC-MS/MS assay.

Millen *et al.*[12] concluded that predicted 25(OH)D scores do not adequately reflect serum 25(OH)D concentrations, and Peiris *et al.*[13] argued that vitamin D status cannot be reliably predicted and that common laboratory tests are required, especially for high-risk groups. Our study indicates that 25(OH)D scores developed using an RBF SVR model much better reflect actual serum 25(OH)D concentration. Although the RBF SVR model had some limitations in predicting extreme values, generally, the estimated vitamin D status was consistent with the measured 25(OH)D concentration. One limitation of our analyses was that only one validation dataset was available. Future studies testing the RBF SVR model in a range of other populations would further advance the understanding of its utility as a tool in epidemiological studies. After validation in population-based datasets, tools developed from SVM models could also be of value to primary care physicians and others to assess the risk of vitamin D deficiency to provide a more rational basis for vitamin D testing.

Conclusion

Our results demonstrated a statistically significant superiority of an RBF SVR model in comparison with a MLR model for the prediction of serum 25(OH)D concentrations in the Ausimmune Study dataset. The accuracy of 25(OH)D scores from the RBF SVR model was greater. Thus the RBF SVR method has considerable promise for the prediction of vitamin D status for use in chronic disease epidemiology and potentially other situations.

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Author Contributions

Conceived and designed the experiments: SG RL AP AIG. Performed the experiments: SG. Analyzed the data: SG. Contributed reagents/materials/analysis tools: RL. Wrote the paper: SG RL. Obtained permission for use of Ausimmune dataset: RL AP. Contributed comments to drafts of the paper: AIG.

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Sun Exposure and Vitamin D Status as Northeast Asian Migrants Become Acculturated to Life in Australia

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ABSTRACT

Vitamin D deficiency is more common in Northeast-Asian immigrants to western countries than in the local population; prevalence equalizes as immigrants adopt the host country's culture. In a community-based study of 100 Northeast-Asian immigrants in Canberra, Australia, we examined predictors of vitamin D status, its association with indicators of acculturation (English language use; time since migration) and mediators of that association. Participants completed a sun and physical activity diary and wore an electronic ultraviolet radiation (UVR) dosimeter for 7 days. Skin colour was measured by reflectance spectrophotometry. Serum concentrations of 25-hydroxyvitamin D (25(OH)D) and cardio-metabolic biomarkers were measured on fasting blood. In a multiple linear regression model, predictors for 25(OH)D concentration were season of blood collection, vitamin D supplementation, UVR exposure, body mass index, physical activity and having private health insurance ($R^2 = 0.57$). Greater acculturation was associated with lower risk of vitamin D deficiency (de-seasonalized 25(OH)D level <50 nmol L^{-1}) (Adjusted Odds Ratio (AOR): 0.22 [95%CI 0.04–0.96]); this association was statistically mediated by physical activity and time outdoors. Vitamin D deficiency was associated with higher total cholesterol levels (>5.0 mmol L^{-1}) (AOR: 7.48 [95%CI 1.51–37.0]). Targeted public health approaches are required to manage the high prevalence of vitamin D deficiency in migrants retaining a traditional lifestyle.

INTRODUCTION

Vitamin D deficiency is common in migrants from Asia, the Middle East and Africa who relocate to Australia (1,2). In Australia, the most recent national health survey reported that the overall prevalence of vitamin D deficiency (serum 25-hydroxyvitamin D [25(OH)D] concentration <50 nmol L^{-1}) was 23%, but ranged from 30% to 50% for people of African origin, and 58% to 67% for those of Asian origin (3). Both darker skin pigmentation and cultural preferences for lower sun exposure, compared to the host population, have been implicated as major risk factors for these discrepancies.

Australia is among one of the most multicultural societies in the world: 27% of Australians are born overseas, and a high proportion of these are from Asia (4). As duration of residence increases, migrants tend to adopt the lifestyle of the host country, a process known as acculturation. This process changes the health risk profile, typically with increasing prevalence of obesity, hypertension and diabetes (5–7), but also higher physical activity levels (5,8) and higher vitamin D status (2).

In a recent cross-sectional study in Chinese and Korean women in Sydney, Australia greater acculturation was associated with higher vitamin D status. However, lack of information on several key determinants of vitamin D status, such as skin type and body mass index, restriction of blood sampling to the spring and summer months, and the availability only of recalled time in the sun in each season, limited a detailed assessment of the determinants of vitamin D status and possible mediators of the observed association with acculturation in these migrant women.

Here we extend these analyses using objective measures of skin type and sun exposure, measuring acculturation using a validated scale, in both men and women from a broader range of Northeast Asian origins living in Canberra, Australia, with data collected across a full year. We explore: (1) the determinants of vitamin D status (measured as the serum 25-hydroxyvitamin D [25(OH)D] level); (2) the association between acculturation and vitamin D status, and its potential mediators; and (3) the inter-relationships between vitamin D status, cardio-metabolic health, and acculturation.

MATERIALS AND METHODS

Study sample. Northeast Asian Australians with Chinese, Japanese and Korean ancestry ($n = 100$), aged 18–80 years were recruited through community organizations, distribution of information brochures, and snowball recruiting between May 2012 and April 2013. Data were collected during two face-to-face interviews 7–10 days apart, in either English or the participant's native language. At Interview 1, participants completed a self-administered questionnaire (see Supporting Information) and had physical measurements taken. Between Interviews 1 and 2 participants wore an electronic dosimeter measuring exposure to ultraviolet radiation (UVR) at the wrist, concurrently completed a daily sun diary for seven consecutive days (see Supporting Information) and had fasting blood collected by a commercial pathology provider. Diaries and dosimeters were collected at Interview 2.

Data collection. Questionnaire: Data collected included date of birth, ancestry, country of birth, the year migrated to Australia, language spoken at home, current smoking (yes/no), university education (yes/no), use

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of multivitamin supplements (yes/no), frequency of intake of fish and/or cheese and whether they had private health insurance (yes/no) (questions available at www.45andUp.org.au). Acculturation was assessed using items from the modified Suinn-Lew Asian Self-identity Acculturation Scale (9), including language preference, location raised, and self-rated acculturation. *Use of Vitamin D supplements:* Participants were specifically asked whether or not they took a vitamin D supplement at Interview 1. Many participants could not recall the dose of vitamin D in their supplement; we thus defined intake of a vitamin D supplement as a binary variable (i.e. yes/no), for use in these analyses. *Physical measurements:* Height, weight, waist circumference and sitting blood pressure were measured as previously described (10). *Skin colour:* Self-reported untanned skin colour was determined according to the response to the questionnaire question "What best describes the colour of the skin on the inside of your upper arm, that is, your skin colour without any tanning? (Very Fair/ Fair/ Light Olive/ Dark Olive/ Brown"). Natural skin colour was also measured using a reflectance spectrophotometer (Minolta CM-2500d) at the left inner upper arm, halfway between the axilla and the medial epicondyle. Melanin density was calculated from the average of three reflectance readings at 400 nm (R_{400}) and 420 nm (R_{420}) (11). *Exposure to UVR:* Electronic dosimeters worn at the wrist measured UVR every 10 s from 6 am to 8 pm for the 7 days they were worn. Dosimeters were calibrated by the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) and calibration factors specific for each dosimeter were used to convert the raw data to a dose, measured in standard erythemal doses (SEDs) (12). Dosimeter readings were used to calculate daily average personal UVR exposure in SEDs/day for the week: $SEDs_{daily} = [(SEDs_{weekdays} \times 5) + (SEDs_{weekends} \times 2)]/7$ where $SEDs_{weekdays}$ is the average daily UVR exposure on weekdays and $SEDs_{weekends}$ is the average daily UVR exposure on weekends. If data were missing for a day, measurements were averaged over the available days. We included data only from participants who had records for at least three weekdays and one weekend day in the analysis. *Daily sun diary:* For each one hour period between 6 am and 8 pm, participants recorded time spent outdoors in 15 min blocks, clothing worn, and the level (walking, moderate, vigorous) and duration of outdoor and indoor physical activity. We estimated average daily time outdoors by summing the medians of each 15 min block (i.e. 0–15 min = 7.5 min) and averaging over the diary days. The daily sun diary has been previously validated against electronic UVR dosimeters (13). Average daily physical activity time (metabolic-equivalent [MET]-adjusted) was calculated as the total time spent in each physical activity level, with vigorous physical activity weighted twice, summed and averaged over the diary days (13). *Blood samples:* Fasting blood glucose, high sensitivity C-reactive protein (hs-CRP), triglyceride and cholesterol (total, high-density lipoprotein [HDL], low-density lipoprotein [LDL]) were measured in a commercial pathology laboratory. Serum samples for 25(OH)D levels were stored at −70°C and analysed in one batch at study completion using a liquid chromatography tandem mass spectrometry assay (LC-MS/MS), with a mean CV of 14.3% (Canterbury Health Laboratories Christchurch, New Zealand). Canterbury Health Laboratories participates in the Vitamin D External Quality Assessment Scheme (DEQAS).

Data analysis. Previous studies have shown that 25(OH)D concentration best correlates with sun exposure in the previous month (14). We calculated average UVR exposure standardized to the ambient UVR (data from ARPANSA) of the 28 days prior to blood collection (standardized average UVR exposure, $SEDs_{STD}$) using the following equation:

$$SEDs_{STD} = SEDs_{daily} \times \frac{UV_{28}}{UV_7}$$

where UV_7 is the average ambient UVR during the week of badge wearing and UV_{28} is average ambient UVR for the 28 days prior to blood collection. Standardizing in this way to the ambient UVR of the previous 28 days also reduces the influence on the vitamin D-relevant UVR exposure of rainy/cloudy days during the week of dosimeter wearing.

We used the raw 25(OH)D values to examine the determinants of vitamin D status and the association with cardio-metabolic risk factors. Levels of 25(OH)D vary across the year due to changes in UVR exposure; to ensure comparability across participants in the evaluation of the association between acculturation and vitamin D status, we deseasonalized the 25(OH)D values using a sinusoidal regression (15) of the form:

$$25(\mathrm{OH})\mathrm{D} = \beta_0 + \beta_1 \cos(\frac{2\pi T}{12}) + \beta_2 \sin(\frac{2\pi T}{12})$$

where T represents the month of blood draw. De-seasonalized 25(OH)D levels were obtained by adding the residuals to the model mean, β_0. The aim of de-seasonalization is to remove the effect of data collection occurring at different times of the year, so that comparisons between participants can be made as though they were all interviewed in the same month. Vitamin D deficiency was defined as 25(OH)D level <50 nmol L^{-1} (3). *Cardio-metabolic health*: Body Mass Index (BMI) was calculated as weight(kg)/height(m)^2 and categorized using cut-offs for Asians: ≤23 kg m^{-2} (normal weight), >23–25 kg m^{-2} (overweight), >25 kg m^{-2} (obese). We dichotomised the markers of cardio-metabolic

Table 1. Descriptive characteristics of Northeast Asian Australian study participants and their association with 25(OH)D concentration

	N (%)*	25(OH)D Mean (SD) nmol L^{-1}	25(OH)D < 50 nmol L^{-1} *n* (%)
Age group			
18–29	43	58.6 (23.6)	15 (38.5)
30–39	17	46.3 (21.2)	11 (68.8)
40–49	21	58.7 (18.9)	6 (30.0)
≥50	19	76.8 (21.0)	2 (10.5)
Sex			
Male	46	56.2 (22.5)	17 (39.5)
Female	54	56.0 (27.1)	17 (33.3)
University degree or higher			
No	14	53.0 (30.2)	6 (46.2)
Yes	86	56.6 (27.4)	28 (34.6)
Private health insurance			
No	42	51.8 (23.1)	19 (51.3)
Yes	58	65.6 (22.3)	15 (26.3)
Acculturation			
Traditional	42	50.5 (20.5)	23 (60.5)
Bicultural	32	66.2 (24.5)	6 (19.4)
Acculturated	26	67.5 (22.0)	5 (20.0)
Season of interview			
Spring	33	48.2 (13.0)	17 (53.1)
Summer	21	80.3 (17.7)	1 (5.0)
Autumn	29	62.5 (26.0)	8 (30.8)
Winter	17	55.4 (25.7)	8 (50.0)
Daily UVR exposure (SEDs)†			
<0.1	33	52.6 (25.6)	16 (55.2)
0.1–<0.5	38	55.8 (18.7)	14 (38.9)
≥0.5	29	73.3 (21.8)	4 (13.8)
Daily outdoors time (hours)†			
<0.5	21	48.1 (24.2)	12 (70.6)
0.5–<1	43	57.7 (20.2)	15 (34.9)
≥1	36	69.3 (24.1)	7 (20.6)
Daily physical activity (hours, MET adjusted)†			
<1	41	53.8 (24.3)	18 (48.7)
1–<2	31	57.7 (19.7)	12 (38.7)
≥2	28	72.2 (22.8)	4 (15.4)
BMI			
<23	56	62.6 (24.6)	19 (36.5)
23–25	24	60.0 (25.7)	8 (34.8)
>25	20	53.6 (61.3)	7 (36.8)
Melanin density			
Low	33	56.8 (23.7)	15 (48.4)
Medium	33	60.8 (25.3)	10 (31.3)
High	34	62.8 (21.9)	9 (30.0)
Intake of vitamin D supplements			
No	79	51.1 (25.1)	27 (36.0)
Yes	21	75.2 (28.9)	1 (5.3)
Intake of multi-vitamin supplements			
No	59	56.9 (21.8)	22 (39.3)
Yes	41	65.1 (25.2)	13 (31.6)

*Since $N = 100$, this column represent the number as well as the proportion †Average daily UVR exposure/physical activity/time outdoors over one week, calculated from diary data

risk as follows: Pre-hypertension/hypertension, systolic blood pressure >120 mmHg or diastolic blood pressure >80 mmHg (16); adverse metabolic profile, fasting blood glucose >5.5 mmol L^{-1}; total cholesterol >5.0 mmol L^{-1}; LDL >3.0 mmol L^{-1}; HDL <1.0 mmol L^{-1}; triglyceride >1.7 mmol L^{-1}; hsCRP >1.0 mmol L^{-1}. Acculturation was recorded according to the total score over the following variables: *language preference*: 2 = only English/mostly English, 1 = Asian language and English equally well, 0 = Asian only/mostly Asian language; *location raised*: 2 = in Australia only/mostly in Australia, 1 = equally in Asia and Australia, 0 = in Asia only/mostly in Asia; *self-rated acculturation*: 2 = mostly or very westernized, 1 = bicultural, 0 = mostly or very Asian. Categorisation into three groups was as follows: Traditional (score<2), Bicultural (score 2–4) and Acculturated (score>4).

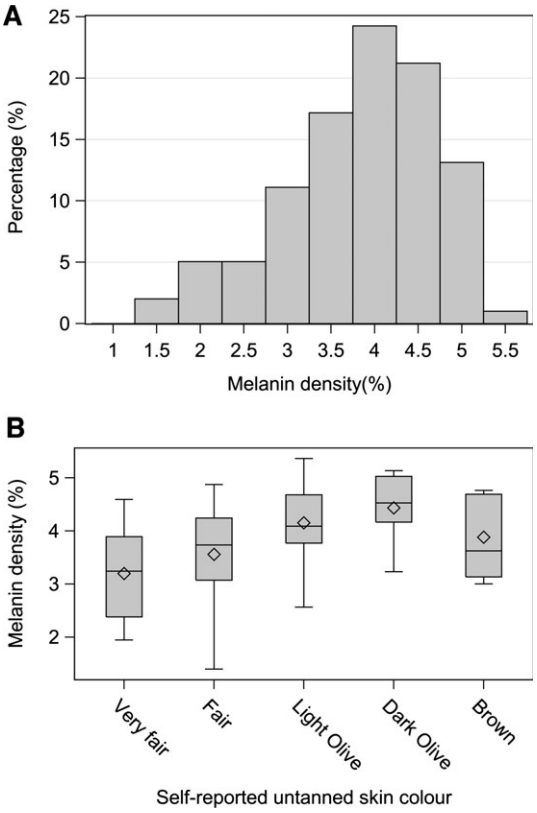

Figure 1. (A) Distribution of skin melanin density (of inner upper arm); (B) Box-plots of melanin density (of inner upper arm) by self-reported "untanned skin colour".

Statistical analysis. Descriptive statistics (mean and standard deviation, number and proportion) were used to describe socio-demographic characteristics and relevant health behaviours. Fisher's exact tests were used to compare characteristics of acculturation groups. For seasonally varying variables such as SEDs, physical activity and time spent outdoors, we used Cochran-Mantel-Haenszel Statistics to adjust for season. We categorised the following variables into tertiles: melanin density, fish intake and cheese intake. Smoking status was not used in the analyses as only two of the participants were current smokers. We used backwards stepwise regression and then purposeful selection of covariates (17) to generate the model for the determinants of vitamin D status, using the likelihood ratio test to assess whether addition of previously removed variables significantly improved the model fit. The relative contribution of each factor was estimated using the R^2 contribution averaged over orderings among regressors calculated using the "relaimpo" package for R Software (18). Because of the small sample size, we used exact logistic regression for the remaining analyses: the association between vitamin D deficiency and acculturation level and the possible (statistical) mediators of that association; the association between cardio-metabolic risk factors and vitamin D deficiency, and between cardio-metabolic risk factors and acculturation, including the possible mediating role of vitamin D status (tested by adjusting for vitamin D status and examining the effect on the odds ratio). Adjusted odds ratios (AOR, adjusted for age, sex, university education, private health insurance, with additional adjustment for BMI, intake of supplements, duration of physical activity and time spent outdoors as indicated for specific analyses) with 95% confidence intervals (CI) were calculated. We additionally adjusted for season where seasonally varying variables (i.e. time spent outdoors, physical activity) were included as explanatory factors in the model. Except where previously noted, analyses were performed in SAS version 9.3 (SAS Institute, Inc, Cary, NC).This study was approved by the Human Research Ethics Committee of the Australian National University. All participants gave written informed consent.

RESULTS

General findings

Descriptive data are provided in Table 1. Of the 100 participants, the majority (96%) completed the sun dairy and wore the UVR dosimeter as instructed. Diary data were available for 694 of 700 days; dosimeter data were available for 616 days (12% of data were lost due to dosimeter malfunction). Most (94%) participants provided a blood sample.

Table 2. Predictors of 25(OH)D concentrations among Northeast Asian Australians living in Canberra, Australia

Predictors	Mean change in 25(OH)D per unit increase in predictor β (95%CI), P-value	Relative contribution %*
Season (vs. Spring)		
Summer	26.48 (16.85, 36.11), $P < 0.0001$	35.48
Autumn	7.14 (−1.92, 16.21), $P = 0.12$	
Winter	5.50 (−5.64, 16.63), $P = 0.32$	
Intake of vitamin D supplements in previous 4 weeks (vs. No)		
Yes	20.50 (11.01, 29.99), $P < 0.0001$	25.81
UVR exposure (SEDs, standardized to the average ambient UVR over the previous 28 days)	9.72 (3.34, 16.10), $P = 0.003$	17.74
BMI (vs. <23 kg m^{-2})		
23–25 kg m^{-2}	−10.05 (−18.84, 1.25), $P = 0.03$	9.68
≥25 kg m^{-2}	−3.76 (−12.65, 5.14), $P = 0.40$	
Physical activity (Hours, MET adjusted)	3.04 (−0.40, 6.48), $P = 0.08$	8.06
Private health insurance (vs. No)		
Yes	6.50 (−13.96, 0.96), $P = 0.09$	3.23

*Relative contribution %, proportion of R^2 attributable to the variable of interest.

Forty-eight percent of these Northeast Asian participants reported "Very fair" or "Fair" skin colour. Although self-reported untanned skin colour was moderately correlated with objectively measured melanin density ($r_s = 0.31$; 95%CI 0.12, 0.48; $P < 0.001$) (Fig. 1), the latter ranged from 1.5 to 5.4, indicating medium skin color. Thus these participants tended to report their skin type as fairer than objective measurement would indicate.

The mean (SD) 25(OH)D concentration was 60.2 (SD = 23.5) nmol L^{-1} and levels were approximately normally distributed. Thirty-six percent of participants had vitamin D deficiency (<50 nmol L^{-1}), while 28% of participants had a de-seasonalized 25(OH)D level of less than 50 nmol L^{-1}. In this study sample, 8% had 25(OH)D levels <30 nmol L^{-1} and 3% were <25 nmol L^{-1}. Vitamin D deficiency was present in 26% of participants whose blood was sampled in summer/autumn compared to 54% for spring/winter. Notably, a high proportion of participants reported taking a vitamin D-containing supplement.

Determinants of 25(OH)D concentration

In the final model, the most important determinants of 25(OH)D concentration were season of blood draw and taking a vitamin D supplement. Other factors, such as having private health insurance, and higher UVR exposure and MET-adjusted duration of physical activity, were also important (Table 2). Overweight, but not obesity, was associated with lower serum 25(OH)D concentration. Melanin density was not an independent predictor for 25 (OH)D concentration in this study, because there was limited variation of skin colour in the Northeast Asian group. Acculturation level was associated with 25(OH)D concentration but was not retained in the final model that contained vitamin D supplementation, UVR exposure and physical activity. The model accounted for 56.8% of the variance in serum 25(OH)D concentration.

Acculturation and vitamin D deficiency

Table 3 shows the characteristics of study participants according to their acculturation status. Compared to the traditional group, participants who were more adapted to an Australian lifestyle were more likely to have private health insurance, be physically active and spend more time outdoors. Participants with higher acculturation level tended to have more UVR exposure during weekends ($P = 0.05$), but there was no difference in average daily UVR exposure. After adjustment for age, sex, university education and private health insurance (see Table 4), participants in the acculturated group, but not the bicultural group, were less likely to be vitamin D deficient compared to the traditional group (AOR: 0.22 [95%CI 0.04–0.96]). After adjusting for MET-adjusted duration of daily physical activity or daily time spent outdoors, or both, the odds ratio for vitamin D deficiency was attenuated and no longer statistically significant (Table 4). This suggests that these factors were, at least statistically, mediators of the association between vitamin D deficiency and acculturation.

Vitamin D deficiency, acculturation and cardio-metabolic health

After additional adjustment for physical activity and BMI, the only measured cardio-metabolic factor that was significantly associated with vitamin D deficiency was higher total cholesterol level (AOR: 7.48 [95%CI 1.51–37.0]; the wide confidence interval reflects uncertainty in the estimate due to the small sample size. To explore a possible dose response relationship between 25(OH)D level and hypercholesterolemia (>5.0 mmol L^{-1}), we categorized 25(OH)D level into quartiles (category medians: 32, 49, 67, 91 nmol L^{-1}). The odds of having hypercholesterolemia increased across decreasing quartiles of 25(OH)D level, but the

Table 3. Characteristics and cardio-metabolic health in Northeast Asian Australians according to their acculturation levels

	Traditional *n* (%) *N* = 42	Bicultural *n* (%) *N* = 32	Acculturated *n* (%) *N* = 26	*P* value
Socio-demographic characteristics				
Age				
Mean (SD)	34.1 (9.8)	41.7 (12.8)	34.0 (16.5)	0.02
Sex				
Female	18 (43.9)	22 (68.6)	14 (53.9)	0.09
University degree or higher				
Yes	38 (90.5)	28 (87.5)	20 (76.9)	0.28
Private health insurance				
Yes	16 (38.1)	23 (71.9)	19 (73.1)	0.003
Health behaviors				
Daily sun exposure (SEDs)				
<0.1	17 (40.5)	10 (31.3)	6 (23.1)	0.15*
0.1–<0.5	17 (40.5)	9 (28.1)	12 (46.2)	
≥0.5	8 (19.1)	13 (40.6)	8 (30.8)	
Weekend sun exposure (SEDs)				
<0.1	26 (61.9)	11 (34.4)	9 (34.6)	0.05*
0.1–<0.5	7 (16.7)	9 (28.1)	10 (38.5)	
≥0.5	9 (21.4)	12 (37.5)	7 (26.9)	
Daily time outdoors (hours)				
<0.5	12 (28.8)	8 (25.0)	1 (3.9)	<0.0001*
0.5–<1	21 (50.0)	14 (43.8)	8 (30.8)	
≥1	9 (21.4)	10 (31.2)	17 (65.3)	
Daily physical activity (hours, MET adjusted)				
<1	27 (64.3)	11 (34.4)	3 (11.5)	<0.0001*
1–<2	11 (26.2)	12 (37.5)	8 (30.8)	
≥2	4 (9.5)	9 (28.1)	15 (57.7)	
Intake of vitamin D supplements				
Yes	6 (14.3)	9 (28.2)	6 (23.1)	0.32
Intake of multivitamin supplements				
Yes	17 (40.5)	16 (50.0)	8 (30.8)	0.34
Cardio-metabolic biomarkers				
BMI				
23–25	10 (23.8)	10 (31.3)	4 (15.2)	0.61
>25	7 (16.7)	6 (18.8)	7 (26.6)	
Pre-hypertension				
Yes	6 (14.3)	10 (31.3)	10 (38.5)	0.05
Blood glucose				
>5.5 mmol L^{-1}	6 (14.3)	1 (3.1)	2 (7.7)	0.24
Total Cholesterol				
>5.0 mmol L^{-1}	13 (31.0)	11 (34.4)	9 (34.6)	0.93
LDL				
>3.0 mmol L^{-1}	10 (23.8)	12 (37.5)	7 (26.9)	0.42
HDL				
<1.0 mmol L^{-1}	11 (26.2)	8 (25.0)	4 (15.4)	0.62
Triglyceride				
>1.7 mmol L^{-1}	2 (4.8)	3 (9.4)	4 (15.4)	0.33
hsCRP				
>1.0 mmol L^{-1}	11 (26.2)	13 (40.6)	9 (34.6)	
Vitamin D status				
25 (OH)D				
<50 mmol L^{-1}	23 (60.5)	6 (19.4)	5 (20.0)	0.0003
De-seasonalized 25 (OH)D				
<50 mmol L^{-1}	17 (44.7)	8 (25.8)	3 (12.0)	0.02

25(OH)D, 25-hydroxyvitamin D; BMI, body mass index. *Adjusted for season.

Table 4. The association between acculturation levels and vitamin D deficiency (de-seasonalized 25(OH)D < 50 mmol L^{-1}), with consideration of potential mediating factors

Model	Adjusted for	Bicultural AOR (95% CI)	Acculturated AOR (95% CI)
Model 1	Age, sex, education, private health insurance, season	0.61 (0.17–2.22)	0.22 (0.04–0.96)*
Model 2	Model 1 + Vitamin D supplements	0.64 (0.16–2.44)	0.23 (0.04–1.05)
Model 3	Model 1 + BMI	0.48 (0.12–1.84)	0.18 (0.03–0.86)*
Model 4†	Model 1 + Physical activity	0.91 (0.22–3.70)	0.47 (0.08–2.85)
Model 5†	Model 1 + Time spent outdoors	0.77 (0.20–2.89)	0.33 (0.06–1.86)
Model 6†	Model 1 + Physical activity and time spent outdoors	1.03 (0.25–4.18)	0.59 (0.10–3.44)

AOR, Adjusted Odds Ratios, using traditional group as reference, *$P < 0.05$ †Models additionally adjusted for season

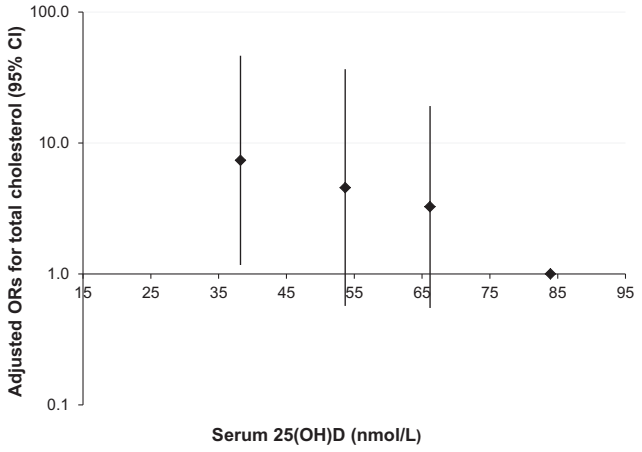

Figure 2. The association between de-seasonalized 25(OH)D level and adjusted odds ratios of having high cholesterol levels (>5.0 mmol L^{-1}).

effect was statistically significant only for lowest, compared to the highest, quartile (Fig. 2).

DISCUSSION

In this cross-sectional study of a sample of people of Northeast Asian origin living in a temperate Australian city, the strongest predictors for serum 25(OH)D concentration were season of blood draw, use of vitamin D supplements and personal UVR exposure. More acculturated participants were less likely to be vitamin D deficient (de-seasonalized 25(OH)D level <50 nmol L^{-1}) and this association was, statistically, mediated by physical activity and time outdoors. Vitamin D deficiency was associated with an increased risk of hypercholesterolemia.

Vitamin D deficiency (<50 nmol L^{-1}) was common in this population, with higher prevalence in spring/winter than in summer/autumn, as has been previously described for Sydney, Australia (2) and more generally for the Australian population (3). In the Australian Health Survey, 63.7% of Australians born in North East Asia were vitamin D deficient (<50 nmol L^{-1}) compared to 17.0% of those born in Australia. There were few comparable vitamin D studies available for the general white Caucasian population in Canberra. In a small study ($n = 47$) of volunteers aged 45 years and over where a similar LC-MS/MS assay was used, the mean 25(OH)D level was 72.1 (SD = 20.6) nmol L^{-1}, and 13% of the sample had levels <50 nmol L^{-1} (13). In another study (adults 18 + years) the mean (raw) 25 (OH)D concentration was 48.5 (SD = 18.4) nmol L^{-1} and 56.3% of participants had levels <50 nmol L^{-1} (19). However, in that study, fewer people participated in summer and we have previously reported that the Diasorin Liaison assay used underestimates 25(OH)D levels compared to the LC-MS/MS assay (20). The results from the two studies using LC-MS/MS assays are consistent with the results of the Australian Health Survey in showing that vitamin D deficiency is more common in Northeast Asian compared to white Caucasian participants. Both studies appear to be biased toward lower prevalence of vitamin D deficiency than in the Australian population, although region-specific data for separate ethnicities in the Australian Health Survey are not yet available.

Interestingly, men did not have better vitamin D status than women. In other studies of Northeast Asians living in Australia, women are considered to be an "at risk" group for vitamin D deficiency (2,21). Furthermore, here vitamin D deficiency was more common in younger, compared to older, Northeast Asian Australians. The latter findings are consistent with those from the Australian Health Survey, where vitamin D deficiency was most common in the 18–34 years age group and slightly more common in men than women (24.2% vs. 22.7%) (3). Studies in China report that vitamin D deficiency is common in all age groups, most likely due to the high prevalence of physical inactivity and lack of sun exposure (22,23).

We report, for the first time, the relationship between average daily sun exposure standardised to ambient UVR levels over the previous month in relation to serum 25(OH)D levels in Northeast Asian Australians. Dosimeter readings provide an accurate record of UVR exposure compared to self-reported questionnaire or diary measures of time outdoors, but are affected by short term changes in ambient UVR levels; standardising to ambient UVR levels over a longer time period provides more relevant data in relation to vitamin D status. Kift and colleagues reported that South Asians living in the United Kingdom reported longer time outdoors than white Caucasians, but their UVR exposure in SEDs (measured with polysulphone badges) was actually 50% less (24). A likely explanation of this finding is that Asian migrants are commonly sun avoidant, seeking shade when outside and using sun protection (such as clothing or an umbrella) (2, 25). This highlights the importance of objective measurement of actual UVR exposure, rather than self-reported time in the sun, as a measure of sun exposure.

In this study, season was the strongest predictor of 25(OH)D levels, with vitamin D supplementation also important. Northeast Asians may prefer vitamin D supplementation to additional sun exposure, to raise their 25(OH)D levels. Indeed vitamin D supplementation was more effective than sun exposure advice for improving vitamin D status in non-western immigrants in one randomized controlled trial (26). The use of a vitamin

D-containing supplement was very common in the participants in this study. However, as we do not have information about the dose of vitamin D, the results should be considered with care. As in a previous Australian study (14), dietary vitamin D intake was not a significant predictor of vitamin D status. However, our dietary assessment was not specifically designed to measure vitamin D intake and our null findings for this facet of the study should thus be treated with caution. Nevertheless, the dietary intake of vitamin D in Australian populations (27) and in the Asian traditional diet (28) is generally low (80–120 and 40–80 IU day^{-1}, respectively), as few of the commonly consumed foods are rich in vitamin D.

Melanin density was not an independent predictor of vitamin D status in the final model. However, we noted that Northeast Asian participants in this study tended to underestimate the darkness of their skin. This finding may have implications for public health messages about sun protection that provide advice according to skin type. Individuals who perceive their own skin type as being fair or very fair are likely to stay out of the sun and use more rigorous sun protection than may be inappropriate for their actual skin type.

As in a previous study (2), acculturated Northeast Asian Australians tended to engage in more leisure-time physical activities than those with a more traditional lifestyle. Our results indicate that greater time outdoors and physical activity are likely mediators of the better vitamin D status of acculturated Northeast Asians compared to those with a traditional lifestyle.

In this study, there was a reduced risk of hypercholesterolemia with higher 25(OH)D levels. This association has not been consistently found (29,30) and trials of vitamin D supplementation do not indicate a convincing beneficial effect for cardiovascular disease outcomes. The association observed here may be the result of residual confounding by physical activity or other factors (31). Further, we found no association between markers of cardio-metabolic health and level of acculturation

Strength and limitations

We have focused on Northeast Asian Australian men and women of younger age, a group that has not been well-studied in previous investigations. Measurements of 25(OH)D concentration and cardio-metabolic biomarkers were from fasting blood samples, using well-standardised methods. We used several different approaches to measure sun exposure (i.e. UVR dosimeters, sun diaries) and related variables (e.g. skin colour) using both objective and subjective methods. Combining dosimeter readings with recent past levels of ambient UVR allowed us to estimate sun exposure over a longer period than is commonly done, providing more stable estimates for the period relevant to vitamin D synthesis. The major limitations of the study were that the sample size was relatively small, with this being reflected in the wide confidence intervals around some estimates. Moreover, our measurement of dietary intake of vitamin D was relatively crude and misclassification of intake may have led to the null findings of dietary intake as a significant determinant of vitamin D status.

CONCLUSION

In this study of Northeast Asian Australians living in Canberra, we report high prevalence of vitamin D deficiency particularly during spring/winter. Season, use of vitamin D supplements, and average sun exposure (in SEDs) were key determinants of vitamin D status. Vitamin D sufficiency was more common in acculturated compared to traditional migrants, in association with higher levels of sun exposure and physical activity.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Data S1. Questionnaire for interview, Asian Australian Health Study.

Data S2. Sun exposure and physical activity diary, Asian Australian Health Study.

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Asian Australian Health Study

Sun/Physical Activity Diary

Participant ID number:
Dosimeter ID:
First entry date:
Last entry date:

Your badge-wearing timeline

DAY	0	1	2	3	4	5	6	7	END
DATE									
ACTIVITIES	-First meeting with researcher -Collect badge and diary	**-Wear Badge** -Complete sun/physical activity diary	**-Wear Badge** -Complete sun/physical activity diary	**-Wear Badge** -Complete sun/physical activity diary	**-Wear Badge** -Complete sun/physical activity diary	**-Wear Badge** -Complete sun/physical activity diary	**-Wear Badge** -Complete sun/physical activity diary	**-Wear Badge** -Complete sun/physical activity diary	-Last meeting with researcher -Return badge and diary

INSTRUCTIONS

Please complete a new page of this sun/physical activity diary for each day of the 7-day period during which you wear the UV badge. You will be required to record your time spent outside, sunscreen use, physical activity levels, and the type of clothing worn during each hour block of the day.

To record your **time spent outside**, please cross the box that best represents the number of minutes you spent outside during each hour block. To record **sunscreen use,** please first indicate whether you applied sunscreen by circling 'yes' or 'no' in response to *question b* at the top of each page. If you circle 'yes', shade the figure in the upper right-hand corner of the page to indicate where you applied the sunscreen, and in the space provided, also record the hour blocks during which you applied the sunscreen. To record your **physical activity levels**, please refer to instructions in the 'Physical Activity Key' at the bottom of this page. To record the type of **clothing** worn, please refer to the instructions in the 'Clothing Key' on page 3.

Physical Activity Key

In your daily diary you will be asked to record the level of physical activity performed and the duration of that activity.

For each hour block you should decide which number below best represents your level of physical activity. If the activity was performed outside, record the number in the 'outside' column, and likewise, if the activity was performed inside, record the number in the 'inside' column. If the physical activity level is rated greater than 0 (i.e. 1, 2 or 3), the duration of the activity (in minutes) should also be recorded in the space provided.

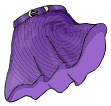
Examples:

-Nancy went for a 20 minute jog during the 7-8am block. So, in the 7-8am row, she writes the number 3 in the 'outdoors' column, and 20 minutes in the duration column next to it. In the 'indoors' column, she will write 0, as she performed no physical activity indoors.
-Joe sat at an office desk from 10-11am, so in the 10-11am row, he records 0 in both the indoors and outdoors column, leaving the duration columns blank.

Number	Physical activity level	Description
0	No physical activity	No physical activity performed
1	Mild physical activity	Walking continuously for at least 10 mins (for recreation or exercise or to get to and from places)
2	Moderate physical activity	Activities such as gentle swimming, social tennis, vigorous gardening or work around the house. Please **do not** include walking.
3	Vigorous physical activity	Activities that made you breathe harder or puff and pant, like jogging, cycling, aerobics, competitive tennis, but **not** household chores or gardening.

Clothing Key

In your daily diary you will be asked to record the scores of dress coverage level that best represent the clothing you are wearing. *Use the guide below to decide which letter-number codes best represent the clothing you are wearing during each time block. E.g. If you are wearing a jumper and jeans, with no hat, you will record 3, 3, and 0 in the spaces provided on your daily diary.*

Upper Body							
Kind	**No clothing on upper body**	**Bikini**	**Swimsuit**	**Singlet top**	**Short-sleeved top**	**Long-sleeved top**	
Level	**0**	**1**		**2**		**3**	
Lower Body							
Kind	**Speedos/briefs**	**Shorts**	**Short skirt**	**Medium skirt**	**Medium shorts or ¾ pants**	**Long trousers/jeans**	**Long skirt**
Level	**0**	**1**		**2**		**3**	
Headwear							
Kind	**No headwear**	**Beanie Cap**	**Cap**	**Legionnaire's cap**	**Wide-brimmed hat**	**Bucket hat**	
Level	**0**	**1**	**2**	**3**			

Example page

DAY 1 02/04/2012

a) Did you wear the badge today: (Yes)/No Please document any problems you had with the UV badge (e.g. it was covered by clothing for around 10 minutes while I was outside at midday; the badge fell off at 5pm; the badge got wet etc)._____

b) Did you apply any sunscreen today? (Yes)/No *If yes:* What time did you apply the sunscreen and to what parts of your body?_____
Time: 8-9 am Parts: hands, arms, neck, face

c) Did you use an umbrella to protect yourself from sunshine today? Yes (No) *If yes* When did you use umbrella, e.g. 10-11am_____

d) Please complete the following table:

	TIME OUTSIDE IN THE SUN (Cross the box that best represents the amount of time you spent in the sun)					**CLOTHING** (Insert the letter/number codes that best represent the type of clothing worn. See p. 3 for details)			**PHYSICAL ACTIVITY** (Insert number denoting level of physical activity and provide duration in *minutes* of activity. See p.2 for details)			
									INDOORS		**OUTDOORS**	
	0 mins	**<15 mins**	**15-30 mins**	**31-45 mins**	**46-60 mins**	**Upper body**	**Lower body**	**Headwear**	Level (0-3)	Duration (0-60mins)	Level (0-3)	Duration (0-60mins)
6-7 am	☒	☐	☐	☐	☐	2	2	0	0	0	0	0
7-8 am	☒	☐	☐	☐	☐	2	2	0	0	0	0	0
8-9 am	☐	☐	☒	☐	☐	2	3	0	0	0	1	17
9-10 am	☐	☒	☐	☐	☐	2	3	0	1	12	0	0
10-11 am	☐	☒	☐	☐	☐	2	3	0	1	14	0	0
11-12 am	☒	☐	☐	☐	☐	2	3	0	0	0	0	0
12-1 pm	☐	☐	☒	☐	☐	2	3	0	0	0	1	20
1-2 pm	☐	☒	☐	☐	☐	2	3	0	0	0	2	10
2-3 pm	☒	☐	☐	☐	☐	2	3	0	0	0	0	0
3-4 pm	☒	☐	☐	☐	☐	2	3	0	0	0	0	0
4-5 pm	☒	☐	☐	☐	☐	2	3	0	0	0	0	0
5-6 pm	☐	☐	☐	☐	☒	2	3	0	3	50	0	0
6-7 pm	☐	☐	☒	☐	☐	2	3	0	0	0	1	17
7-8 pm	☒	☐	☐	☐	☐	2	3	0	0	0	0	0

4

DAY 1 _____

a) Did you wear the badge today: Yes/No Please document any problems you had with the UV badge (e.g. it was covered by clothing for around 10 minutes while I was outside at midday; the badge fell off at 5pm; the badge got wet etc)._____

_____

b) Did you apply any sunscreen today? Yes/No *If yes:* What time did you apply the sunscreen and to what parts of your body?_____

_____

c) Did you use an umbrella to protect yourself from sunshine today? Yes/No *If yes* When did you use umbrella, e.g. 10-11am_____

d) Please complete the following table:

	TIME OUTSIDE IN THE SUN (Cross the box that best represents the amount of time you spent in the sun)					**CLOTHING** (Insert the letter/number codes that best represent the type of clothing worn. See p. 3 for details)			**PHYSICAL ACTIVITY** (Insert number denoting level of physical activity and provide duration in *minutes* of activity. See p.2 for details)			
	0 mins	**<15 mins**	**15-30 mins**	**31-45 mins**	**46-60 mins**	**Upper body**	**Lower body**	**Headwear**	**INDOORS** Level (0-3)	Duration (0-60mins)	**OUTDOORS** Level (0-3)	Duration (0-60mins)
6-7 am	☐	☐	☐	☐	☐							
7-8 am	☐	☐	☐	☐	☐							
8-9 am	☐	☐	☐	☐	☐							
9-10 am	☐	☐	☐	☐	☐							
10-11 am	☐	☐	☐	☐	☐							
11-12 am	☐	☐	☐	☐	☐							
12-1 pm	☐	☐	☐	☐	☐							
1-2 pm	☐	☐	☐	☐	☐							
2-3 pm	☐	☐	☐	☐	☐							
3-4 pm	☐	☐	☐	☐	☐							
4-5 pm	☐	☐	☐	☐	☐							
5-6 pm	☐	☐	☐	☐	☐							
6-7 pm	☐	☐	☐	☐	☐							
7-8 pm	☐	☐	☐	☐	☐							

DAY 2 _____

a) Did you wear the badge today: Yes/No Please document any problems you had with the UV badge (e.g. it was covered by clothing for around 10 minutes while I was outside at midday; the badge fell off at 5pm; the badge got wet etc)._____

_____

b) Did you apply any sunscreen today? Yes/No *If yes:* What time did you apply the sunscreen and to what parts of your body?_____

_____

c) Did you use an umbrella to protect yourself from sunshine today? Yes/No *If yes* When did you use umbrella, e.g. 10-11am_____

d) Please complete the following table:

	TIME OUTSIDE IN THE SUN (Cross the box that best represents the amount of time you spent in the sun)					**CLOTHING** (Insert the letter/number codes that best represent the type of clothing worn. See p. 3 for details)			**PHYSICAL ACTIVITY** (Insert number denoting level of physical activity and provide duration in *minutes* of activity. See p.2 for details)			
	0 mins	**<15 mins**	**15-30 mins**	**31-45 mins**	**46-60 mins**	**Upper body**	**Lower body**	**Headwear**	**INDOORS** Level (0-3)	Duration (0-60mins)	**OUTDOORS** Level (0-3)	Duration (0-60mins)
6-7 am	☐	☐	☐	☐	☐							
7-8 am	☐	☐	☐	☐	☐							
8-9 am	☐	☐	☐	☐	☐							
9-10 am	☐	☐	☐	☐	☐							
10-11 am	☐	☐	☐	☐	☐							
11-12 am	☐	☐	☐	☐	☐							
12-1 pm	☐	☐	☐	☐	☐							
1-2 pm	☐	☐	☐	☐	☐							
2-3 pm	☐	☐	☐	☐	☐							
3-4 pm	☐	☐	☐	☐	☐							
4-5 pm	☐	☐	☐	☐	☐							
5-6 pm	☐	☐	☐	☐	☐							
6-7 pm	☐	☐	☐	☐	☐							
7-8 pm	☐	☐	☐	☐	☐							

DAY 3 _____

a) Did you wear the badge today: Yes/No Please document any problems you had with the UV badge (e.g. it was covered by clothing for around 10 minutes while I was outside at midday; the badge fell off at 5pm; the badge got wet etc)._____

_____

b) Did you apply any sunscreen today? Yes/No *If yes:* What time did you apply the sunscreen and to what parts of your body?_____

_____

c) Did you use an umbrella to protect yourself from sunshine today? Yes/No *If yes* When did you use umbrella, e.g. 10-11am_____

d) Please complete the following table:

	TIME OUTSIDE IN THE SUN (Cross the box that best represents the amount of time you spent in the sun)					**CLOTHING** (Insert the letter/number codes that best represent the type of clothing worn. See p. 3 for details)			**PHYSICAL ACTIVITY** (Insert number denoting level of physical activity and provide duration in *minutes* of activity. See p.2 for details)			
	0 mins	**<15 mins**	**15-30 mins**	**31-45 mins**	**46-60 mins**	**Upper body**	**Lower body**	**Headwear**	**INDOORS** Level (0-3)	Duration (0-60mins)	**OUTDOORS** Level (0-3)	Duration (0-60mins)
6-7 am	☐	☐	☐	☐	☐							
7-8 am	☐	☐	☐	☐	☐							
8-9 am	☐	☐	☐	☐	☐							
9-10 am	☐	☐	☐	☐	☐							
10-11 am	☐	☐	☐	☐	☐							
11-12 am	☐	☐	☐	☐	☐							
12-1 pm	☐	☐	☐	☐	☐							
1-2 pm	☐	☐	☐	☐	☐							
2-3 pm	☐	☐	☐	☐	☐							
3-4 pm	☐	☐	☐	☐	☐							
4-5 pm	☐	☐	☐	☐	☐							
5-6 pm	☐	☐	☐	☐	☐							
6-7 pm	☐	☐	☐	☐	☐							
7-8 pm	☐	☐	☐	☐	☐							

DAY 4 _____

a) Did you wear the badge today: Yes/No Please document any problems you had with the UV badge (e.g. it was covered by clothing for around 10 minutes while I was outside at midday; the badge fell off at 5pm; the badge got wet etc)._____

_____

b) Did you apply any sunscreen today? Yes/No *If yes:* What time did you apply the sunscreen and to what parts of your body?_____

_____

c) Did you use an umbrella to protect yourself from sunshine today? Yes/No *If yes* When did you use umbrella, e.g. 10-11am_____

d) Please complete the following table:

	TIME OUTSIDE IN THE SUN (Cross the box that best represents the amount of time you spent in the sun)					**CLOTHING** (Insert the letter/number codes that best represent the type of clothing worn. See p. 3 for details)			**PHYSICAL ACTIVITY** (Insert number denoting level of physical activity and provide duration in *minutes* of activity. See p.2 for details)			
	0 mins	**<15 mins**	**15-30 mins**	**31-45 mins**	**46-60 mins**	**Upper body**	**Lower body**	**Headwear**	**INDOORS** Level (0-3)	Duration (0-60mins)	**OUTDOORS** Level (0-3)	Duration (0-60mins)
6-7 am	☐	☐	☐	☐	☐							
7-8 am	☐	☐	☐	☐	☐							
8-9 am	☐	☐	☐	☐	☐							
9-10 am	☐	☐	☐	☐	☐							
10-11 am	☐	☐	☐	☐	☐							
11-12 am	☐	☐	☐	☐	☐							
12-1 pm	☐	☐	☐	☐	☐							
1-2 pm	☐	☐	☐	☐	☐							
2-3 pm	☐	☐	☐	☐	☐							
3-4 pm	☐	☐	☐	☐	☐							
4-5 pm	☐	☐	☐	☐	☐							
5-6 pm	☐	☐	☐	☐	☐							
6-7 pm	☐	☐	☐	☐	☐							
7-8 pm	☐	☐	☐	☐	☐							

DAY 5 _____

a) Did you wear the badge today: Yes/No Please document any problems you had with the UV badge (e.g. it was covered by clothing for around 10 minutes while I was outside at midday; the badge fell off at 5pm; the badge got wet etc)._____

_____

b) Did you apply any sunscreen today? Yes/No *If yes:* What time did you apply the sunscreen and to what parts of your body?_____

_____

c) Did you use an umbrella to protect yourself from sunshine today? Yes/No *If yes* When did you use umbrella, e.g. 10-11am_____

d) Please complete the following table:

	TIME OUTSIDE IN THE SUN (Cross the box that best represents the amount of time you spent in the sun)					**CLOTHING** (Insert the letter/number codes that best represent the type of clothing worn. See p. 3 for details)			**PHYSICAL ACTIVITY** (Insert number denoting level of physical activity and provide duration in *minutes* of activity. See p.2 for details)			
	0 mins	**<15 mins**	**15-30 mins**	**31-45 mins**	**46-60 mins**	**Upper body**	**Lower body**	**Headwear**	**INDOORS** Level (0-3)	Duration (0-60mins)	**OUTDOORS** Level (0-3)	Duration (0-60mins)
6-7 am	☐	☐	☐	☐	☐							
7-8 am	☐	☐	☐	☐	☐							
8-9 am	☐	☐	☐	☐	☐							
9-10 am	☐	☐	☐	☐	☐							
10-11 am	☐	☐	☐	☐	☐							
11-12 am	☐	☐	☐	☐	☐							
12-1 pm	☐	☐	☐	☐	☐							
1-2 pm	☐	☐	☐	☐	☐							
2-3 pm	☐	☐	☐	☐	☐							
3-4 pm	☐	☐	☐	☐	☐							
4-5 pm	☐	☐	☐	☐	☐							
5-6 pm	☐	☐	☐	☐	☐							
6-7 pm	☐	☐	☐	☐	☐							
7-8 pm	☐	☐	☐	☐	☐							

DAY 6 _____

a) Did you wear the badge today: Yes/No Please document any problems you had with the UV badge (e.g. it was covered by clothing for around 10 minutes while I was outside at midday; the badge fell off at 5pm; the badge got wet etc)._____

_____

b) Did you apply any sunscreen today? Yes/No *If yes:* What time did you apply the sunscreen and to what parts of your body?_____

_____

c) Did you use an umbrella to protect yourself from sunshine today? Yes/No *If yes* When did you use umbrella, e.g. 10-11am_____

d) Please complete the following table:

	TIME OUTSIDE IN THE SUN (Cross the box that best represents the amount of time you spent in the sun)					**CLOTHING** (Insert the letter/number codes that best represent the type of clothing worn. See p. 3 for details)			**PHYSICAL ACTIVITY** (Insert number denoting level of physical activity and provide duration in *minutes* of activity. See p.2 for details)			
									INDOORS		**OUTDOORS**	
	0 mins	**<15 mins**	**15-30 mins**	**31-45 mins**	**46-60 mins**	**Upper body**	**Lower body**	**Headwear**	Level (0-3)	Duration (0-60mins)	Level (0-3)	Duration (0-60mins)
6-7 am	☐	☐	☐	☐	☐							
7-8 am	☐	☐	☐	☐	☐							
8-9 am	☐	☐	☐	☐	☐							
9-10 am	☐	☐	☐	☐	☐							
10-11 am	☐	☐	☐	☐	☐							
11-12 am	☐	☐	☐	☐	☐							
12-1 pm	☐	☐	☐	☐	☐							
1-2 pm	☐	☐	☐	☐	☐							
2-3 pm	☐	☐	☐	☐	☐							
3-4 pm	☐	☐	☐	☐	☐							
4-5 pm	☐	☐	☐	☐	☐							
5-6 pm	☐	☐	☐	☐	☐							
6-7 pm	☐	☐	☐	☐	☐							
7-8 pm	☐	☐	☐	☐	☐							

DAY 7 _____

a) Did you wear the badge today: Yes/No Please document any problems you had with the UV badge (e.g. it was covered by clothing for around 10 minutes while I was outside at midday; the badge fell off at 5pm; the badge got wet etc)._____

_____

b) Did you apply any sunscreen today? Yes/No *If yes:* What time did you apply the sunscreen and to what parts of your body?_____

_____

c) Did you use an umbrella to protect yourself from sunshine today? Yes/No *If yes* When did you use umbrella, e.g. 10-11am_____

d) Please complete the following table:

	TIME OUTSIDE IN THE SUN (Cross the box that best represents the amount of time you spent in the sun)					**CLOTHING** (Insert the letter/number codes that best represent the type of clothing worn. See p. 3 for details)			**PHYSICAL ACTIVITY** (Insert number denoting level of physical activity and provide duration in *minutes* of activity. See p.2 for details)			
	0 mins	**<15 mins**	**15-30 mins**	**31-45 mins**	**46-60 mins**	**Upper body**	**Lower body**	**Headwear**	**INDOORS** Level (0-3)	Duration (0-60mins)	**OUTDOORS** Level (0-3)	Duration (0-60mins)
6-7 am	☐	☐	☐	☐	☐							
7-8 am	☐	☐	☐	☐	☐							
8-9 am	☐	☐	☐	☐	☐							
9-10 am	☐	☐	☐	☐	☐							
10-11 am	☐	☐	☐	☐	☐							
11-12 am	☐	☐	☐	☐	☐							
12-1 pm	☐	☐	☐	☐	☐							
1-2 pm	☐	☐	☐	☐	☐							
2-3 pm	☐	☐	☐	☐	☐							
3-4 pm	☐	☐	☐	☐	☐							
4-5 pm	☐	☐	☐	☐	☐							
5-6 pm	☐	☐	☐	☐	☐							
6-7 pm	☐	☐	☐	☐	☐							
7-8 pm	☐	☐	☐	☐	☐							

Australian National University

PARTICIPANT ID: _____

Asian Australian Health Study Questionnaire

Thank you for your interest in this study. Participation is completely voluntary, and you may withdraw from the study at any time without explanation. If you wish to take part, first ensure that you have read the participant information brochure, then complete the consent form and this questionnaire. Please complete this questionnaire with a blue or black pen and bring it, together with the consent form, to your first visit with the researcher. Thank you.

General questions about you

1. Are you male or female?

☐0 Male ☐1 Female

2. What is your date of birth?

Day Month Year

☐☐ / ☐☐ / ☐☐☐☐

3. What is today's date?

Day Month Year

☐☐ / ☐☐ / ☐☐☐☐

4. How tall are you without shoes?

_____ cm _____ feet _____ inches

5. About how much do you weight?

_____ kg _____ stone _____ lbs

6. What is the highest qualification you have completed?

(please put a cross in the most appropriate box)

☐0 no school certificate or other qualifications
☐1 school or intermediate certificate (or equivalent)
☐2 higher school or leaving certificate (or equivalent)
☐3 trade/apprenticeship (e.g. hairdresser, chef)
☐4 certificate/diploma (e.g. child care, technician)
☐5 university degree or higher

7. In which country were you born?

☐0 Australia
☐1 UK ☐2 Ireland ☐3 Italy
☐4 Greece ☐5 New Zealand ☐6 Germany
☐7 Philippines ☐8 Korea ☐9 Vietnam
☐10 China (including Hong Kong, Macau and Taiwan)
☐11 Japan ☐13 Singapore ☐14 Malaysia
☐15 Other (please specify)_____

8. What year did you first come to live in Australia for one year or more? (e.g. 1970)

☐☐☐☐

9. What is your ancestry?

(please cross up to 2 boxes)

☐0 Australia
☐1 UK ☐2 Ireland ☐3 Italy
☐4 Greece ☐5 New Zealand ☐6 Germany
☐7 Philippines ☐8 Korea ☐9 Vietnam
☐10 China (including Hong Kong, Macau and Taiwan)
☐11 Japan ☐13 Singapore ☐14 Malaysia
☐15 Other (please specify)_____

Australian National University

Questions about culture

10. Do you speak a language other than English at home?

☐ 1 Yes ☐ 0 No

11. What language do you prefer?

☐ 1 Asian only
☐ 2 Mostly Asian, some English
☐ 3 Asian and English about equally well
☐ 4 Mostly English, some Asian
☐ 5 Only English

12. Where were you raised?

☐ 1 In Asia only
☐ 2 Mostly in Asia, some in Australia
☐ 3 Equally in Asia and Australia
☐ 4 Mostly in Australia, some in Asia
☐ 5 In Australia only

13. If you consider yourself a member of the Asian group, how much pride you have in this group?

☐ 1 Extremely proud
☐ 2 Moderately proud
☐ 3 Little pride
☐ 4 No pride but do not feel negatively toward group
☐ 5 Feel negatively toward group

14. Rate yourself on how much you believe in Asian values (i.e. marriage, family, education, work):

1	2	3	4	5
Do not believe		Neutral		Strongly believe

15. Rate yourself on how well you believe in Australian (western) values:

1	2	3	4	5
Do not believe		Neutral		Strongly believe

16. Rate yourself on how well you fit in with other Australians who are not Asian:

1	2	3	4	5
Do not fit		Neutral		Fit very well

17. How would you rate yourself?

☐ 1 Very Asian
☐ 2 Mostly Asian
☐ 3 Bicultural
☐ 4 Mostly westernized
☐ 5 Very westernized

Questions about your life style

18. Have you been a regular smoker?

☐ 1 Yes ☐ 0 No ▼ *if no go to question 19*

How old were you when you started smoking regularly? ☐☐ years old

Are you a regular smoker now? ☐ 1 Yes ☐ 0 No

if *NO* - how old were you when you stopped smoking regularly ☐☐ years old

About how much do / did you smoke on average each day?

☐☐ cigarettes per day
☐☐ pipes and cigars per day

19. How many TIMES did you do each of these activities LAST WEEK?
(put "0" if you did not do this activity)

Times in last week

Walking continuously, for at least 10 minutes ☐☐
(for recreation or exercise or to get to or from places)

Vigorous physical activity ☐☐
(that made you breathe harder or puff and pant, like jogging, cycling, aerobics, competitive tennis, but not household chores or gardening)

Moderate physical activity ☐☐
(like gentle swimming, social tennis, vigorous gardening or work around the house)

20. How much TIME did you spent ALTOGETHER doing each of these activities LAST WEEK?
(put "0" if you did not do this activity)

Walking continuously, for at least 10 minutes
(for recreation or exercise or to get to or from places)

hours ☐☐ minutes ☐☐

Vigorous physical activity
(that made you breathe harder or puff and pant, like jogging, cycling, aerobics, competitive tennis, but not household chores or gardening)

hours ☐☐ minutes ☐☐

Moderate physical activity
(like gentle swimming, social tennis, vigorous gardening or work around the house)

hours ☐☐ minutes ☐☐

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Questions about your health

21. About how many hours a week are you exposed to someone else's tobacco smoke?

hours per week ☐☐ at home

hours per week ☐☐ in other places *(e.g. work, going out, cars)*

22. Have you taken any medications, vitamins or supplements for most of the last 4 weeks, including HRT and the pill?

☐1 Yes ☐0 No

▼*If yes, was it:*

☐1 multivitamins+ minerals ☐2 multivitamins alone

☐3 fish oil ☐4 glucosamine ☐5 omega 3

☐6 paracetamol ☐7 aspirin for the heart ☐8 aspirin for other reasons

☐9 Lipitor ☐10 Avapro, Karvea ☐11 warfarin, Coumadin

☐12 Pravachol ☐13 Coversyl, Coversyl plus ☐14 Lasix, frusemid

☐15 Zocor, Lipex ☐16 Cardiezem, Vasocordol ☐17 Micardis

☐18 Nexium ☐19 Norvasc ☐20 Fosamax

☐21 Somac ☐22 Tritace ☐23 Caltrate

☐24 Losec, Acimax omeprazole ☐25 Noten,Tenormin atenolol ☐26 Oroxine thyroxine

☐27 Ventolin salbutamaol ☐28 Zyloprim, Progout 300 allopurinol ☐29 Diabex, Diaformin metformin

☐30 Zoloft, Sertraline ☐31 Cipramil, citaloprim ☐32 Efexor, venlafaxine

☐33 Other_____

23. Has a doctor EVER told you that you have:

(If YES, please cross the box and give your age when the condition was first found)

	Yes	Age condition was first found
(a) skin cancer (not melanoma)	☐	☐☐ years
(b) melanoma	☐	☐☐ years
(c) prostate cancer/breast cancer	☐	☐☐ years
(d) other cancer	☐	☐☐ years

Type of cancer (please describe):

(e) heart disease	☐	☐☐ years

Type of heart disease (please describe):

(f) high blood pressure	☐	☐☐ years
(g) stroke	☐	☐☐ years
(h) diabetes	☐	☐☐ years
(i) blood clot(thrombosis)	☐	☐☐ years
(j) asthma	☐	☐☐ years
(k) hayfever	☐	☐☐ years
(l) depression	☐	☐☐ years
(m) anxiety	☐	☐☐ years
(n) Parkinson's diseases	☐	☐☐ years
(o) none of these	☐	

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24. In the last month have you been treated for:

(If YES, please cross the box and give your age when the treatment started)

	Yes	Age started treatment
(a) cancer	☐	☐☐ years
(b) heart attack or angina	☐	☐☐ years
(c) other heart disease	☐	☐☐ years
(d) high blood pressure	☐	☐☐ years
(e) high blood cholesterol	☐	☐☐ years
(f) blood clotting problems	☐	☐☐ years
(g) asthma	☐	☐☐ years
(h) osteoarthritis	☐	☐☐ years
(i) thyroid problem	☐	☐☐ years
(j) osteoporosis or low bone density	☐	☐☐ years
(k) depression	☐	☐☐ years
(l) anxiety	☐	☐☐ years
(j) none of these	☐	

Questions about your diet

25. About how many times each week do you eat:

(please count all meals and snacks. Put '0' if never eaten or eaten less than once a week)

	times eaten each week
(a) beef, lamb or pork	☐☐
(b) chicken, turkey or duck	☐☐
(c) processed meat (include bacon, sausages, salami, devon, burgers, etc)	☐☐
(d) fish or seafood	☐☐
(e) cheese	☐☐

26. About how many of the following do you usually eat:

Slices or pieces of brown/wholemeal bread each week (also include multigrain, rye bread, etc) ☐☐

bowls of breakfast cereal each week ☐☐

If you eat breakfast cereal is it usually: (please cross)

☐1 bran cereal (allbran, branflakes,etc.)
☐2 muesli
☐3 biscuit cereal (weetbix, shredded wheat etc.)
☐4 other(cornflakes, rice bubbles, ect.)
☐5 oat cereal (porridge,etc.)

27. What type of milk do you mostly have?

☐1 whole milk ☐2 reduced fat milk ☐3 skim milk

☐4 soy milk ☐5 other milk ☐6 don't drink milk

28. About how many serves of vegetables do you usually eat every day?

A serve is half a cup of cooked vegetables or one cup of salad (please include potatoes and put "0" if less than one a day)

number of serves of cooked vegetables each day ☐☐

number of serves of raw vegetables each day ☐☐

29. About how many serves of fruit or glasses of fruit juice do you usually have each day?

A serve is 1 medium piece or 2 small pieces or 1 cup of diced or canned fruit pieces (put "0" if you eat less than one serve a day)

number of serves of fruit each day ☐☐

number of serves of fruit juice each day ☐☐

30. Please put a cross in the box if you NEVER eat:

☐1 red meat ☐2 dairy product ☐3 sugar

☐4 seafood ☐5 chicken/poultry ☐6 any meat

☐7 wheat product ☐8 cream ☐9 pork/ham

☐10 eggs ☐11 fish ☐12 cheese

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Questions about social and sun exposure

31. Which of the following do you have? (excluding Medicare)

- ☐ 1 Private health insurance – with extras
- ☐ 2 Private health insurance – without extras
- ☐ 3 Department of Veterans' Affairs white or gold card
- ☐ 4 Health care concession card
- ☐ 5 None of these

32. What best describes the colour of the skin on the inside of your upper arm, that is, your skin colour without any tanning?

- ☐ 0 very fair
- ☐ 1 fair
- ☐ 2 light olive
- ☐ 3 dark olive
- ☐ 4 brown
- ☐ 5 black

33. What would happen if your skin was repeatedly exposed to bright sunlight during summer without any protection? Would it:

- ☐ 0 Get very tanned?
- ☐ 1 Get mildly or occasionally tanned?
- ☐ 2 Get moderately tanned?
- ☐ 3 Never tan, or only get freckled?

34. About how many hours a DAY would you usually spend outdoors on a weekday and on the weekend?

hours per day ☐☐ weekday

hours per day ☐☐ weekends

35. How many times have you used a tanning bed in your life?

- ☐ 0 Never
- ☐ 1 1-10
- ☐ 2 11-20
- ☐ 3 21 or more

36. How often do you try to get a tan (ie, lay out in the sun)?

- ☐ 0 Never
- ☐ 1 Rarely
- ☐ 2 Sometimes
- ☐ 3 Most of the time
- ☐ 4 Always

37. How often do you seek shade from the sun?

- ☐ 0 Never
- ☐ 1 Rarely
- ☐ 2 Sometimes
- ☐ 3 Most of the time
- ☐ 4 Always

38. How often do you wear sun-protective clothing (i.e. hat, long sleeves)

- ☐ 0 Never
- ☐ 1 Rarely
- ☐ 2 Sometimes
- ☐ 3 Most of the time
- ☐ 4 Always

39. How often do you use sunscreen?

- ☐ 0 Never
- ☐ 1 Rarely
- ☐ 2 Sometimes
- ☐ 3 Most of the time
- ☐ 4 Always

40. About how many HOURS in each 24 hour DAY do you usually spend doing the following?
(please put "0" if you do not spend any time doing it)

hours per day		hours per day	
☐☐	sleeping (including naps)	☐☐	sitting
☐☐	watching television or using a computer	☐☐	standing

41. How many TIMES in the LAST WEEK did you:
(please put "0' if you did not spend any time doing it)

	time in the last week
spend time with friends or family who do not live with you?	☐☐
talk to someone (friends, relatives or others) on the telephone?	☐☐
go to meetings for social clubs, religious groups or other groups you belong to?	☐☐

42. How many people outside your home, but within one hour of travel, do you feel you can depend on or feel very close to?

☐☐ people

END OF QUESTIONNAIRE

Thank you kindly for your participation!

Chapter 6

Paper 5: Cardiovascular Disease Risk Factor Profiles of 263,356 Older Australians According to Region of birth and Acculturation, with a Focus on Migrants Born in Asia

PLOS | ONE

RESEARCH ARTICLE

Cardiovascular Disease Risk Factor Profiles of 263,356 Older Australians According to Region of Birth and Acculturation, with a Focus on Migrants Born in Asia

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Abstract

Risk factors for cardiovascular disease (CVD), such as obesity, diabetes, hypertension and physical inactivity, are common in Australia, but the prevalence varies according to cultural background. We examined the relationship between region of birth, measures of acculturation, and CVD risk profiles in immigrant, compared to Australian-born, older Australians. Cross-sectional data from 263,356 participants aged 45 and over joining the population-based 45 and Up Study cohort from 2006–2008 were used. Prevalence ratios for CVD risk factors in Australian- versus overseas-born participants were calculated using modified Poisson regression, adjusting for age, sex and socioeconomic factors and focusing on Asian migrants. The association between time resident in Australia and age at migration and CVD risk factors in Asian migrants was also examined. Migrants from Northeast (n = 3,213) and Southeast Asia (n = 3,942) had lower levels of overweight/obesity, physical activity and female smoking than Australian-born participants (n = 199,356), although differences in prevalence of overweight/obesity were sensitive to body-mass-index cut-offs used. Compared to Australian-born participants, migrants from Northeast Asia were 20–30% less likely, and from Southeast Asia 10–20% more likely, to report being treated for hypertension and/or hypercholesterolaemia; Southeast Asian migrants were 40–60% more likely to report diabetes. Northeast Asian-born individuals were less likely than Australian-born to have 3 or more CVD risk factors. Diabetes, treated hypertension and hypercholesterolaemia occurred at relatively low average body-mass-index in Southeast Asian migrants. The CVD risk factor profiles of migrants tended to approximate those of Australian-born with increasing acculturation, in both favourable (e.g., increased physical activity) and unfavourable directions (e.g., increased female smoking). Minimizing CVD risk in migrant populations may be achieved through efforts to retain the healthy facets of the traditional lifestyle, such as a normal body mass index and low prevalence of smoking in women, in addition to adopting healthy aspects of the host country lifestyle, such as increased physical activity.

Introduction

In recent years, advances in clinical and public health interventions have resulted in significant progress in reducing cardiovascular disease (CVD) related morbidity and mortality in many developed countries[1]. However, CVDs remain the leading cause of morbidity and mortality worldwide, accounting for 30% of all deaths[2]. There is also troubling evidence that the prevalence of risk factors for CVD, such as overweight/obesity, diabetes, hypertension and physical inactivity is increasing[2]. While these risk factors are individually important, there is a steady increase in risk of all-cause and cardiovascular disease mortality as the number of risk factors present increases[3,4].

International migration from non-western to western countries is increasing[5]. Migrants from diverse cultural backgrounds have health characteristics that are different from the populations of their host countries[6]. Evidence suggests that the prevalence of CVD risk factors may vary considerably among heterogeneous migrant groups according to birth place[6–8], and also differ according to degree of acculturation, measured by such factors as duration of residence in the host country, age at migration and proficiency in the host language[9,10].

Australia is among one of the most multicultural societies in the world, with 27% of the population born overseas. Asian migrants were one of the most rapidly growing population groups in the latter part of the 20th century[11]. Understanding the CVD risk profile and how this changes as migrants become acculturated to the host country is important to provide an evidence-base to guide programs to improve health outcomes in migrants.

Recent studies of migrants to Australia have examined changes in only a single risk factor [12–15], with information on multiple CVD risk factors available only within studies that are now over 10 years old [6,16–18]. Furthermore, CVD risk profiles of recently arrived migrant groups from Asia have not been explored in detail. Thus research to date may not accurately reflect the current CVD risk situation among overseas-born populations in Australia.

We used cross-sectional data from the 45 and Up Study to compare multiple CVD risk factors in Australian-born and overseas-born participants according to region of birth, with an emphasis on Asian migrants, and examined the association between acculturation variables and these risk factors in Asian migrants.

Methods

Study Population

The 45 and Up Study is a large population-based cohort study of people aged 45 years and over, living in New South Wales, Australia [19]. This age group has a high prevalence of CVD risk factors and related morbidity and mortality. A total of 266,097 individuals, recruited following random sampling from the Medicare Australia database, completed a self-administrated baseline questionnaire and informed consent distributed between January 2006 and December 2008. Baseline questionnaire data included information on socio-demographic and lifestyle factors, self-reported medical history, height and body weight, and physical activity. Participants were also asked about their country of birth, and, for those born outside of Australia, they were also asked to provide the year they moved to Australia.

The data for the project were obtained from a third party, namely the Sax Institute, which is the data custodian for the 45 and Up Study. Data are available through application to the Sax Institute (details are available at https://www.saxinstitute.org.au/our-work/45-up-study/) or through contacting 45andUp.research@saxinstitute.org.au.

Region of birth

Based on the question "In which country were you born?", "overseas-born" was defined as being born in a place other than Australia. Countries of birth were categorized into five major groups according to a modified version of the Standard Australian Classification of Countries (SACC, 2011)[20]: Australia, Europe, Northeast Asia (i.e. China, Hong Kong, Taiwan, South Korea and Japan), Southeast Asia (i.e. Burma, Cambodia, Thailand, Vietnam, Indonesia, Malaysia, Philippines and Singapore) and Other.

Socio-demographic variables

Five age categories were created: 45–49, 50–59, 60–69, 70–79, 80+. Marital status was categorized as "Married/living with a partner", "Single", and "Other (divorced, widowed or separated)". Education was categorized as: "None", "Intermediate/ high school/ trade/certificate diploma", "University or higher". Location of residence was defined as: "Major cities", "Regional", "Remote or very remote". Household annual pre-tax income was categorized as $<$\$20,000, \$20,000-\$39, 999, \$40,000-\$69,999, $\geq$\$70,000. Health insurance was dichotomized as "has private health insurance" and "no private health insurance".

Acculturation variables

Two variables related to acculturation were examined: duration of residence in Australia and age migrated to Australia. Duration of residence in Australia was categorized as: 0–10, 11–20, 21–30, $>$30 years (with 0–10 as the reference, "less acculturated" group); age migrated to Australia was categorized as 0–10, 11–20, 21–30, $>$30 years, (with $>$30 as the reference group).

Previous CVD incidents and CVD risk factors

Previous CVD was identified as self-reported heart disease, stroke or thrombosis according to the response to the question "Has a doctor ever told you that you have (following conditions)?" (yes/no). We examined 6 additional major CVD risk factors:

Current Smoking: Smoking status was categorized as current smoker, past smoker or never smoked based on the questions "Have you ever been a regular smoker?" "Are you a regular smoker now?" For multivariate analysis, current smoking and past smoking were used as two different risk factors, with never-smokers as the reference group.

Diabetes, *Current Treatment for Hypertension & Hypercholesterolaemia*: Data on diabetes were based on the self-report response to the question "Has a doctor ever told you that you have diabetes?" (yes/no). For female participants, if the age of giving birth to the last child was older than the age they were diagnosed with diabetes and they were not currently being treated for diabetes, they were categorized as "no diabetes", to exclude gestational diabetes in this risk category. Current treatment for hypertension and current treatment for hypercholesterolaemia were recorded as being present if participants reported that they had been treated for these conditions in the previous month.

Overweight/Obesity: Body mass index (BMI) was calculated from self-reported height and weight. Obesity/overweight was defined as BMI$\geq$25kg/m^2 and used as a dichotomous variable (overweight/obesity vs. normal weight). We also conducted sensitivity analyses using the categorisation recommended by the World Health Organization for participants born in Asia [21], i.e. overweight/obesity defined as BMI $\geq$23kg/cm^2.

Physical Inactivity: Respondents were asked "How many times did you do each of these activities last week? Walking continuously for at least 10 minutes/ Vigorous physical activity/ Moderate physical activity" "If you add up all the time you spent doing each activity last week,

how much time did you spent altogether doing each type of activity? Walking continuously for at least 10 minutes/ Vigorous physical activity/ Moderate physical activity". Physical activity level was dichotomized as physically inactive versus physically active (<150 minutes vs. ≥150 minutes of at least moderate-intensity physical activity, as recommended by the National Physical Activity Guidelines for Australians [22]).

CVD risk profiles: In addition to examining individual risk factors, we examined the combination of 6 major risk factors: current smoking, diabetes, current treatment for hypertension, current treatment for hypercholesterolaemia, BMI≥25 kg/m^2 and physical inactivity (i.e. presence of 0, any 1 only, any 2 only and ≥3 risk factors).

Statistical analysis

Of the 266,097 participants in the 45 and Up Study dataset used, 2741 (1%) were excluded from all analyses, because of missing data on country of birth. Missing data on CVD risk factors (BMI, n = 20356; physical activity, n = 13619; smoking status, n = 847) were categorized as "missing", and included in the descriptive statistical analysis, but excluded from multivariate analysis that used the specific risk factor as the outcome variable.

The prevalence of previous CVD, individual CVD risk factor and CVD risk profiles were calculated by region of birth and for men and women separately. Given the high prevalence of overweight, physical inactivity and metabolic disorders in both Australian-born participants and migrants, odds ratios do not accurately reflect relative risks. Since logistic regression is thus not suitable for these analyses, modified Poisson regression models with a robust error variance[23] were used to estimate the association of region of birth and individual CVD risk factor and CVD risk profiles, using Australian-born participants as the reference group. Each model was stratified by sex. Prevalence ratios (PR) with 95% confidence intervals (CI) were estimated.

The two acculturation variables (i.e. duration of residence in Australia, age of migration) were used as categorical variables to examine the association with CVD risk factors, for Asian-born participants, stratified by sex and region of birth and adjusted for age and socio-demographic variables. Tests for linear trend for the acculturation variables of interest were performed by assigning the median value of each category to participants in that group and modelling as a continuous variable. Cumulative residual plots were used to investigate the linear functional form of continuous variables in the models. Missing values for covariates were included in the models as separate categories.

Previous CVD itself is a major risk factor for CVD morbidity and mortality in future. Patients who have had a heart attack, coronary angioplasty or other heart or blood vessel diseases may also substantially change their life styles. Thus, we performed additional sensitivity analysis to separately examine the results in participants with and without self-reported previous CVD.

All analyses were conducted using SAS 9.3 [24].

The conduct of the 45 and Up Study was approved by the University of New South Wales Human Research Ethics Committee (HREC). Ethical approval for this sub-study was provided by the NSW Population and Health Services Research Ethics Committee and the Human Research Ethics Committee of the Australian National University.

Results

Sample characteristics

A total of 263,356 participants were included in the analyses; 25% were overseas-born immigrants (3,213 from Northeast Asia, 3,942 from Southeast Asia, 41,061 from Europe, 15,963

from other regions). Table 1 shows the socio-demographic characteristics of these participants by region of birth (data for migrants from other regions are not presented).

Compared to Australian-born participants, overseas-born individuals tended to live in major cities. Individuals from Southeast Asia and Northeast Asia were younger and more likely than others to have a university degree and more likely than others to report a lower household income. Table 2 shows the acculturation characteristics of overseas-born individuals according to their region of birth. Compared to European migrants, most Asian-born participants had lived in Australia less than 30 years and migrated to Australia after the age of 30.

Self-reported CVD by region of birth

The overall prevalence of self-reported previous CVD within the cohort was 19.5% for men and 11.0% for women. Table 3 shows the crude prevalence of previous CVD (i.e. heart disease, stroke or thrombosis) in Australian-born and overseas-born participants. After adjustment for

Table 1. Socio-demographic characteristics of participants in the 45 and Up Study whose data were included in this analysis, by region of birth.

Country of Birth	Australia (n = 199356) %(n)	Northeast Asia (n = 3213) %(n)	Southeast Asia (n = 3942) %(n)	Europe (n = 41061) %(n)
Sex				
Female	55 (108593)	55 (1760)	57 (2347)	49 (20222)
Male	45 (90403)	45 (1453)	43 (1595)	51 (20839)
Age				
Mean ± SD	62 ± 11.08	59 ± 10.78	59 ± 10.78	65 ± 11.32
45–49	12 (23661)	18 (563)	16 (650)	8 (3153)
50–59	34 (66995)	43 (1393)	47 (1835)	26 (10561)
60–69	28 (55324)	18 (567)	22 (849)	32 (13327)
70–79	16 (32535)	13 (418)	8 (318)	19 (7735)
80+	10 (20087)	8 (272)	7 (290)	15 (6285)
Education				
None	12 (23178)	8 (243)	11 (428)	14 (5724)
Intermediate/High school/Trade/certificate/diploma	66 (13026)	48 (1544)	47 (1841)	61 (25365)
University or higher	22 (43110)	42 (1355)	40 (1592)	22 (9084)
Annual household pre-tax income				
<$20,000	19 (37548)	25 (824)	25 (973)	22 (9226)
$20,000-$39,999	18 (35484)	15 (466)	15 (588)	18 (7287)
$40,000-$69,999	18 (36157)	17 (541)	18 (713)	16 (6458)
≥$70,000	24 (47728)	18 (576)	18 (740)	21 (8553)
Marital status				
Current married/live with partner	74 (148116)	80 (2577)	76 (2994)	73 (30100)
Other	19 (37179)	14 (457)	17 (676)	21 (8589)
Never married	6 (12920)	5 (169)	6 (251)	5 (2123)
Location of residence				
Major cities	40 (79514)	91 (2939)	83 (3280)	54 (22149)
Regional	37 (74514)	6 (200)	12 (471)	34 (13761)
Remote or very Remote	23 (45286)	2 (72)	5 (191)	13 (5140)
Private health insurance				
No	33 (65036)	35 (1133)	45 (1779)	42 (2734)
Yes	67 (134314)	65 (2080)	55 (2163)	58 (3887)

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Table 2. Acculturation characteristics of overseas born participants by region of birthRegion of Birth.

	Northeast Asia (n = 3213) %(n)	Southeast Asia (n = 3942) %(n)	Europe (n = 41061) %(n)
Years lived in Australia			
0–10	14 (402)	11 (380)	8 (2574)
11–20	39 (1140)	22 (775)	5 (1738)
21–30	26 (774)	41 (1467)	11 (3697)
>30	21 (633)	26 (945)	77 (26317)
Age migrated to Australia			
0–10	7 (202)	8 (285)	27 (9208)
11–20	6 (189)	9 (312)	17 (5693)
21–30	20 (594)	28 (991)	32 (10969)
>30	67 (1964)	56 (1979)	25 (8456)

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sex, age and socio-economic variables, the prevalence of CVD was significantly lower for all overseas-born immigrant groups than for Australian-born participants. Northeast Asian migrants had the lowest risk of previous CVD events with an adjusted prevalence ratio (APR) of 0.61 (95%CI 0.54–0.68) compared to Australian-born participants.

CVD risk factors by region of birth

Asian-born women, but not men, had significantly lower current smoking prevalence than their Australian-born counterparts (Figs. 1 and 2). However, both women and men from Northeast Asia and Southeast Asia were less likely to have smoked in the past. In contrast, European migrants had higher prevalence of both current and past smoking than Australian-born participants.

Northeast Asian migrants were significantly less likely than Australian-born individuals to report current treatment of hypertension and hypercholesterolaemia, but their risk for diabetes was similar (Figs. 1 and 2). Southeast Asian-born participants had generally higher prevalence of all of these three metabolic risk factors compared to Australian-born participants.

Asian-born participants, especially women from Northeast Asia, had a lower average BMI than Australian-born and European-born individuals (Fig. 3). After adjustment for age and socio-economic factors, all of the overseas-born migrant groups were less likely to have a BMI of $\geq$25kg/m^2 compared to Australian-born participants. The magnitude of the differences was larger for individuals from Northeast Asia (APR: 0.53 (0.49–0.57) for men and 0.37

Table 3. Prevalence of self-reported previous cardiovascular diseases in participants in the 45 and Up Study.

	Previous cardiovascular disease% (n)			PR[1] (95%CI)		
Region Of Birth	**All**	**Male**	**Female**	**All**	**Male**	**Female**
Australia	15 (29948)	19 (17769)	11 (12179)	1	1	1
Northeast Asia	8 (294)	10 (150)	6 (114)	0.61 (0.54–0.68)	0.54 (0.47–0.62)	0.69 (0.58–0.82)
Southeast Asia	10 (375)	14 (222)	7 (153)	0.76 (0.69–0.83)	0.79 (0.70–0.89)	0.72 (0.62–0.84)
Europe	16 (6735)	21 (4344)	13 (2391)	0.92 (0.90–0.94)	0.89 (0.87–0.92)	0.90 (0.87–0.94)

[1]PR, prevalence ratio, adjusted for age, education, income, private health insurance, marital status and location of residence

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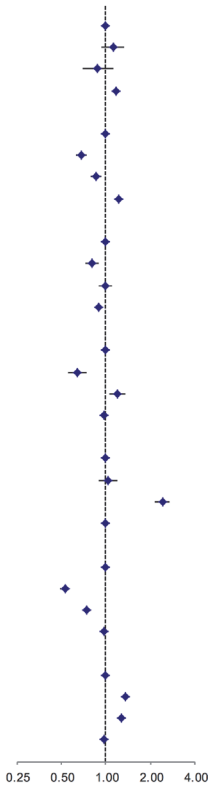
Prevalence of CVD Risk Factors in Male Participants by Region of Birth

CVD Risk Factors	Region of Birth	Prevalence %(n)	PR[1]	PR[2]	(95% CI)
Smoking					
Current smoking	Australia	7.4 (6713)	1.00	1.00	
	Northeast Asia	8.0 (116)	1.01	1.12	(0.94 - 1.34)
	Southeast Asia	9.3 (149)	1.12	0.88	(0.70 - 1.12)
	Europe	7.3 (1491)	1.22	1.17	(1.11 - 1.23)
Past smoking					
	Australia	42.8 (38714)	1.00	1.00	
	Northeast Asia	26.5 (385)	0.64	0.69	(0.63 - 0.75)
	Southeast Asia	33.4 (532)	0.79	0.86	(0.79 - 0.94)
	Europe	54.3 (11458)	1.21	1.22	(1.19 - 1.24)
Treated for hypertension					
	Australia	24.9 (5132)	1.00	1.00	
	Northeast Asia	19.3 (280)	0.82	0.81	(0.73 - 0.90)
	Southeast Asia	25.4 (405)	0.98	1.00	(0.90 - 1.11)
	Europe	24.3 (5132)	0.90	0.90	(0.88 - 0.92)
Treated for hypercholesterolaemia					
	Australia	16.2 (14689)	1.00	1.00	
	Northeast Asia	10.7 (155)	0.69	0.64	(0.55 - 0.75)
	Southeast Asia	19.9 (318)	1.26	1.20	(1.07 - 1.36)
	Europe	16.9 (3564)	0.99	0.98	(0.95 - 1.01)
Diabetes					
	Australia	10.9 (9817)	1.00	1.00	
	Northeast Asia	11.1 (162)	1.10	1.04	(0.90 - 1.21)
	Southeast Asia	4.8 (114)	2.29	2.41	(2.16 - 2.70)
	Europe	12.2 (2574)	1.03	0.99	(0.95 - 1.03)
BMI ≥25kg/m^2					
	Australia	65.8 (59404)	1.00	1.00	
	Northeast Asia	34.1 (496)	0.51	0.53	(0.49 - 0.57)
	Southeast Asia	40.8 (650)	0.70	0.74	(0.70 - 0.79)
	Europe	62.3 (13143)	0.96	0.97	(0.96 - 0.98)
Physical Inactivity					
	Australia	41.7 (37686)	1.00	1.00	
	Northeast Asia	61.7 (897)	1.46	1.37	(1.32 - 1.43)
	Southeast Asia	53.4 (852)	1.30	1.26	(1.20 - 1.33)
	Europe	42.4 (8935)	1.00	0.98	(0.96 - 0.99)



PR[1]: prevalence ratio, adjusted for age

PR[2]: prevalence ratio, adjusted for age, education, annual income, private health insurance, marital status and region of residence

The forest plot illustrates PR[2] (95%CI) on a log-scale

Fig 1. Prevalence of CVD risk factors in male participants according to region of birth.

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(0.33–0.40) for women) than for those from Southeast Asia (APR: 0.63 (0.59–0.67) for men and 0.58 (0.55–0.62) for women) and Europe (APR: 0.97 (0.96–0.98) for men and 0.95 (0.94–0.97) for women).

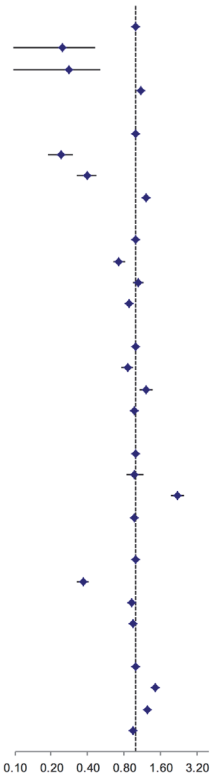
As studies in Asian populations have shown that a BMI of ≥23kg/m^2 is associated with increased risk of diabetes, hypertension and other cardiovascular outcomes, we also examined the relationship of cultural background to overweight/obesity defined according to the WHO-recommended BMI cut-off for Asian participants (BMI≥23kg/m^2). With the different BMI cut-off, men from Southeast Asia had a significantly higher prevalence of overweight/obesity (APR: 1.06 (1.02–1.09)), while women from Southeast Asia were similar to their Australian-born counterparts. Northeast Asian-born participants were still less likely to be overweight, but the magnitude of the difference was smaller. Individuals from both Northeast Asia and Southeast Asia were more likely to be physically inactive than Australian-born and European-born participants.

CVD risk profiles by region of birth

After adjustment for age and socio-economic factors, compared to Australian-born participants both Northeast Asian and Southeast Asian migrants were more likely to have none of the

Prevalence of CVD Risk Factors in Female Participants By Region of Birth

CVD Risk Factors	Region of Birth	Prevalence % (n)	PR[1]	PR[2]	(95% CI)
Smoking					
Current smoking	Australia	7.0 (6713)	1.00	1.00	
	Northeast Asia	1.9 (33)	0.23	0.25	(0.18 - 0.35)
	Southeast Asia	3.1 (73)	0.39	0.28	(0.16 - 0.48)
	Europe	7.3 (1491)	1.15	1.11	(1.05 - 1.17)
Past smoking					
	Australia	28.6 (31105)	1.00	1.00	
	Northeast Asia	6.8 (119)	0.23	0.24	(0.20 - 0.29)
	Southeast Asia	9.5 (223)	0.39	0.40	(0.32 - 0.49)
	Europe	34.4 (7036)	1.22	1.22	(1.19 - 1.24)
Treated for hypertension					
	Australia	24.7 (26937)	1.00	1.00	
	Northeast Asia	15.3 (269)	0.73	0.73	(0.66 - 0.81)
	Southeast Asia	21.4 (503)	1.02	1.05	(0.93 - 1.18)
	Europe	24.4 (4997)	0.90	0.89	(0.87 - 0.91)
Treated for hypercholesterolaemia					
	Australia	14.0 (15250)	1.00	1.00	
	Northeast Asia	10.7 (155)	0.92	0.85	(0.75 - 0.98)
	Southeast Asia	15.2 (357)	1.25	1.22	(1.04 - 1.42)
	Europe	15.4 (3165)	1.01	0.99	(0.95 - 1.02)
Diabetes					
	Australia	7.2 (7808)	1.00	1.00	
	Northeast Asia	6.4 (112)	1.05	0.99	(0.82 - 1.18)
	Southeast Asia	11.1 (162)	2.12	2.21	(1.87 - 2.61)
	Europe	8.1 (1650)	1.03	0.98	(0.93 - 1.03)
BMI≥25kg/m^2					
	Australia	52.3 (56981)	1.00	1.00	
	Northeast Asia	19.5 (343)	0.36	0.37	(0.33 - 0.40)
	Southeast Asia	30.7 (721)	0.90	0.93	(0.87 - 1.00)
	Europe	51.3 (10513)	0.96	0.95	(0.94 - 0.97)
Physical Inactivity					
	Australia	38.1 (41561)	1.00	1.00	
	Northeast Asia	61.7 (897)	1.50	1.44	(1.38 - 1.50)
	Southeast Asia	48.7 (1143)	1.26	1.25	(1.16 - 1.34)
	Europe	37.9 (7772)	0.98	0.95	(0.93 - 0.97)



PR[1]: prevalence ratio, adjusted for age

PR[2]: prevalence ratio, adjusted for age, education, annual income, private health insurance, marital status and region of residence

The forest plot illustrates PR[2] (95%CI) on a log-scale

Fig 2. Prevalence of CVD risk factors in female participants according to region of birth.

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six major CVD risk factors. However, among those who had at least one risk factor, Northeast Asian-born individuals were more likely to have only a single risk factor, while individuals from Southeast Asia had similar prevalence of multiple risk factors compared with their Australian-born counterparts (Table 4).

Acculturation and CVD risk factors and risk profiles in Asian migrants

Fig. 4 illustrates the prevalence ratios (using Australian-born participants as the reference group) of CVD risk factors according to duration of residence in Australia and age at migration for participants born in Northeast Asia and Southeast Asia. Data are shown only for the four CVD risk factors for which there was a significant trend in prevalence according to the acculturation variables; data for the other variables are presented in S1 Table.

Younger age at migration and increasing duration of residence in Australia were associated with increasing prevalence of current smoking among Northeast Asian-born (P(trend) = 0.05 and 0.03, respectively) and Southeast Asian-born women (P(trend)<0.01 and <0.01, respectively). In women who migrated to Australia before the age of 10, the prevalence of smoking was more than six times higher in Northeast Asian-born and more than twice as high in Southeast Asian-born women, compared to those who migrated after the age of 30. These trends were not observed in men.

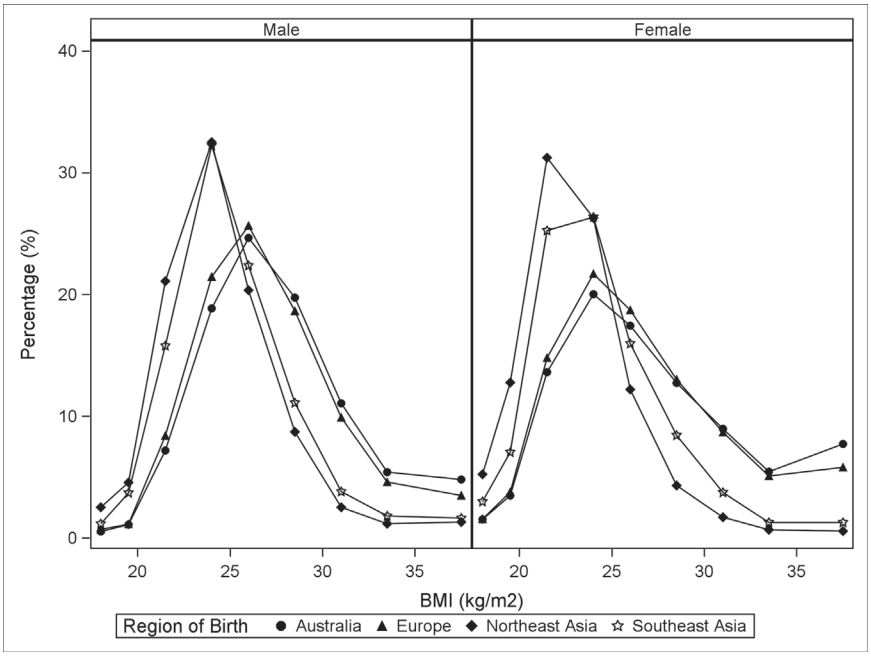

Fig 3. The distribution of body mass index according to region of birth and sex.

doi:10.1371/journal.pone.0115627.g003

Table 4. Prevalence of cardiovascular disease risk profiles by region of birth and sex (fully adjusted).

Number of CVD		Male			Female		
Risk Factors	**Region of Birth**	**Prevalence % (n)**	**PR[1]**	**(95% CI)**	**Prevalence % (n)**	**PR[1]**	**(95% CI)**
0							
	Australia	10.6 (9623)	1.00		17.1 (18622)	1.00	
	Northeast Asia	14.7 (213)	1.32	(1.16–1.50)	23.0 (405)	1.25	(1.14–1.36)
	Southeast Asia	13.4 (213)	1.23	(1.08–1.40)	22.6 (530)	1.26	(1.17–1.36)
	Europe	11.6 (2444)	1.12	(1.07–1.16)	18.8 (3859)	1.19	(1.15–1.23)
1							
	Australia	30.3 (27424)	1.00		30.1 (32809)	1.00	
	Northeast Asia	35.5 (516)	1.18	(1.10–1.26)	43.4 (763)	1.41	(1.34–1.49)
	Southeast Asia	29.8 (476)	0.99	(0.92–1.07)	31.4 (737)	1.03	(0.97–1.10)
	Europe	29.8 (6278)	1.03	(1.00–1.05)	34.0 (6137)	1.05	(1.02–1.07)
2							
	Australia	27.9 (25244)	1.00		23.9 (26034)	1.00	
	Northeast Asia	27.4 (399)	0.98	(0.90–1.07)	15.9 (279)	0.67	(0.60–0.74)
	Southeast Asia	26.0 (414)	0.92	(0.85–1.00)	21.2 (497)	0.89	(0.82–0.96)
	Europe	28.3 (5962)	1.03	(1.00–1.05)	23.3 (4766)	0.97	(0.95–1.00)
> = 3							
	Australia	20.1 (18199)	1.00		15.0 (16385)	1.00	
	Northeast Asia	13.6 (198)	0.66	(0.58–0.75)	8.8 (154)	0.62	(0.53–0.72)
	Southeast Asia	19.8 (315)	0.97	(0.88–1.07)	12.8 (300)	0.89	(0.79–0.99)
	Europe	19.8 (4172)	0.93	(0.90–0.96)	16.0 (3269)	0.96	(0.92–0.99)

[1]PR, prevalence ratio, adjusted for age, education, income, private health insurance, marital status and location of residence

doi:10.1371/journal.pone.0115627.t004

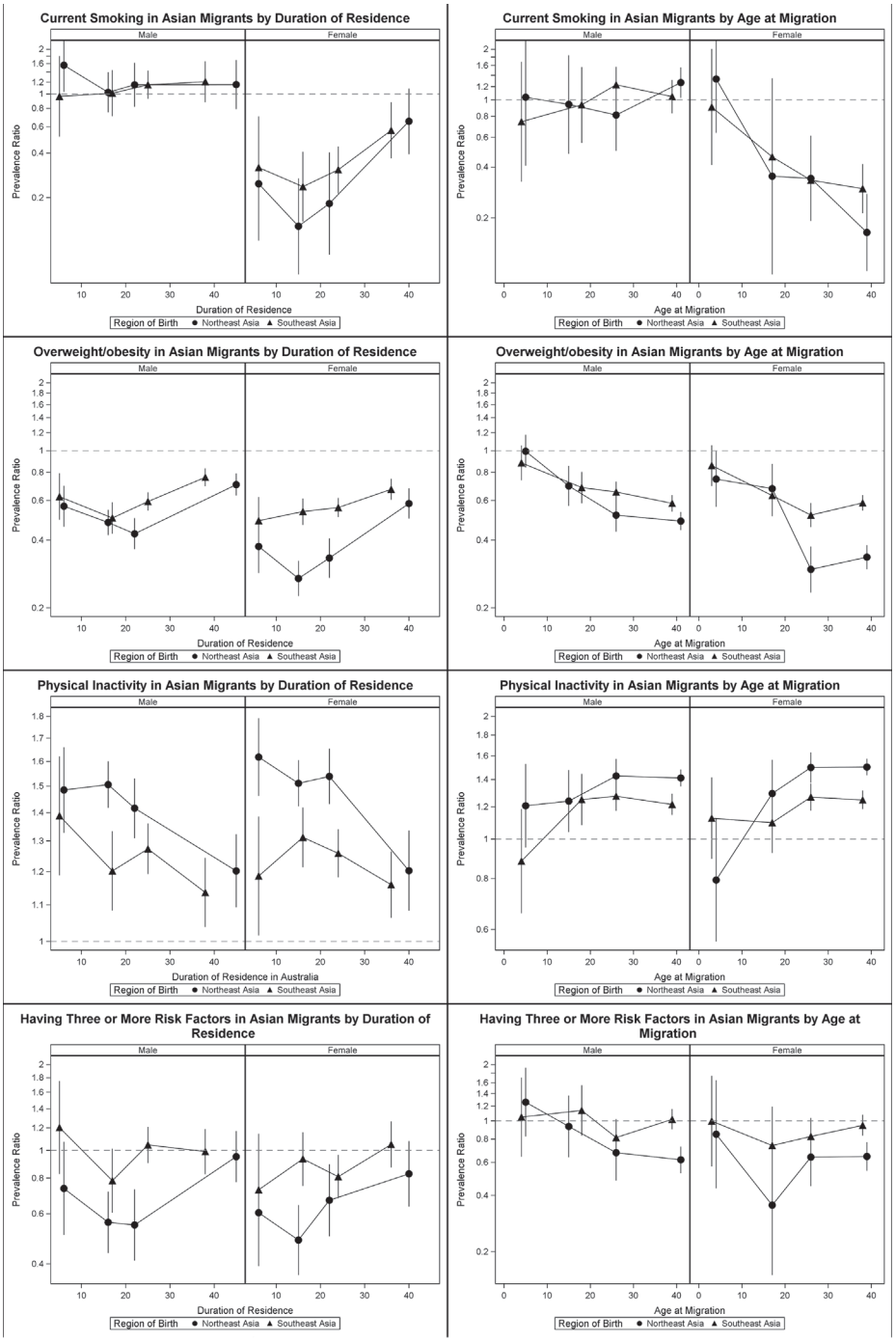

Fig 4. Prevalence ratios of current smoking, overweight/obesity, physical inactivity and having three or more risk factors among men and women migrants from Northeast Asia and Southeast Asia by duration of residence and age of migration compared with Australian-born participants.

doi:10.1371/journal.pone.0115627.g004

The prevalence of overweight/obesity (BMI$\geq$25kg/m^2) was significantly higher with longer duration of residence in Australia and younger age at migration (e.g. before 10 years old) among Northeast Asian-born and Southeast Asian-born individuals. This trend was not linear for some groups. Younger age at migration and increasing duration of residence were

associated with decreasing prevalence of physical inactivity only among Northeast Asian-born men (P(trend) = 0.04 and 0.07, respectively) and women (P(trend)<0.01 and <0.01, respectively).We found no evidence of significant trends in prevalence of diabetes or treatment of hypertension and hypercholesterolaemia in association with the degree of acculturation (S1 Table).

The proportion of people with 3 or more risk factors significantly increased among Northeast Asian-born men (P-trend = 0.04) and Southeast Asian-born women (P-trend = 0.05) with longer duration of residence in Australia.

Results of the sensitivity analysis separating participants into those with and without previous CVD are shown in Table 5. Except for current smoking, the prevalence of each CVD risk factor was higher among participants with previous CVD, for each region of birth and for men and women. However, the association between region of birth and CVD risk factors was similar in participants with and without previous CVD.

Discussion

We have found that the prevalence of self-reported CVD within the 45 and Up Study cohort was significantly lower for all overseas-born immigrant groups than for Australian-born individuals. However, there was significant variation in the risk factor profiles and the proportion of at-risk individuals for each CVD risk factor across different migrant subgroups. Northeast Asian-born participants had significantly more favourable CVD risk profiles. In spite of the lower prevalence of overweight/obesity, Southeast Asian-born participants had a higher prevalence of certain metabolic risk factors, compared with Australian-born participants.

Consistent with our findings, a much lower prevalence of current smoking among Asian-born women in comparison to Asian-born men and individuals of host countries has been reported in studies from the United States [25–27], Canada [28] and Australia[12]. One possible explanation is that there are different social norms regarding gender and smoking in Asian and western countries. Smoking is commonly viewed as a masculine behaviour in many Asian countries, and as not acceptable for women [25,29]. However, despite impressive tobacco control measures in Australia, we found that the prevalence of smoking increased in association with longer duration of residence in Asian-born women from the 45 and Up Study, probably because of changes in social norms around smoking as migrants adopt the host culture.

Our finding of a much lower likelihood of overweight/obesity in Asian-born individuals from the 45 and Up Study is consistent with results from other studies using the same BMI cut-off (25 kg/m^2 or 30 kg/m^2) for Asian migrants and individuals of host countries[14,30]. However when a recommended BMI cut-off for Asians of $\geq$23 was used, a significantly higher proportion of Southeast Asia-born men and a similar proportion of Southeast Asia-born women were overweight or obese compared to their Australian-born counterparts. Northeast Asian-born participants were still less likely to be overweight/obese.

Despite the lower or similar BMI levels in Southeast Asian- versus Australian-born individuals from the 45 and Up Study, Southeast Asian migrants had a higher prevalence of diabetes, hypertension and hypercholesterolemia [15,31,32]. This is consistent with existing evidence which indicates that the prevalence of diabetes and other cardio-metabolic risk factors and visceral adiposity are greater at a lower mean BMI in Asian populations compared to people of European descent [33–36].

Our data also show that migration to Australia at a younger age, and a longer duration of residence in Australia were associated with an increased prevalence of current smoking and overweight/obesity and with increased physical activity in some Asian migrant subgroups within the 45 and Up Study cohort.

Table 5. Sensitivity Analysis of Region of Birth and CVD Risk Factors in participants with and without self-reported previous CV.

		Without previous CVD						With previous CVD					
		Male			Female			Male			Female		
CVD Risk Factors	Region of Birth	Prevalence % (n)	PR[1]	(95% CI)	Prevalence % (n)	PR[1]	(95% CI)	Prevalence % (n)	PR[1]	(95% CI)	% (n)	PR[1]	(95% CI)
Smoking													
Current smoking	Australia	7.9 (5751)	1.00		7.1 (6897)	1.00		5.4 (962)	1.00		5.7 (692)	1.00	
	Northeast Asia	8.3 (108)	1.10	(0.92–1.33)	1.8 (30)	0.24	(0.17–0.34)	5.3 (8)	1.21	(0.64–2.30)	2.6 (3)	0.57	(0.19–1.72)
	Southeast Asia	10.1 (139)	1.10	(0.94–1.29)	3.3 (72)	0.37	(0.30–0.47)	4.5 (10)	0.68	(0.37–2.30)	0.7 (1)	0.57	(0.15–2.13)
	Europe	8.2 (1380)	1.13	(1.07–1.20)	7.5 (1350)	1.11	(1.05–1.17)	6.6 (291)	1.37	(1.21–1.55)	5.8 (141)	1.18	(1.00–1.41)
Past smoking	Australia	40.4 (29365)	1.00		28.5 (27584)	1.00		52.6 (9349)	1.00		28.9 (3521)	1.00	
	Northeast Asia	24.9 (324)	0.69	(0.62–0.75)	6.6 (109)	0.24	(0.20–0.29)	40.7 (61)	0.81	(0.67–0.99)	8.7 (10)	0.32	(0.18–0.58)
	Southeast Asia	30.9 (424)	0.84	(0.78–0.91)	9.3 (205)	0.33	(0.29–0.38)	48.7 (108)	1.00	(0.88–1.15)	11.8 (18)	0.40	(0.26–0.61)
	Europe	51.9 (8660)	1.23	(1.21–1.25)	34.0 (6137)	1.21	(1.18–1.24)	63.5 (2798)	1.20	(1.17–1.23)	37.2 (902)	1.30	(1.23–1.38)
Treated for hypertension													
	Australia	21.8 (15864)	1.00		22.3 (21583)	1.00		37.6 (6680)	1.00		44.0 (5354)	1.00	
	Northeast Asia	17.3 (226)	0.83	(0.74–0.96)	13.9 (228)	0.73	(0.65–0.82)	36.0 (54)	0.94	(0.76–1.17)	36.0 (41)	0.83	(0.65–1.06)
	Southeast Asia	22.9 (315)	1.12	(1.02–1.24)	19.8 (435)	0.88	(0.86–0.91)	40.5 (90)	1.08	(0.92–1.27)	44.4 (68)	1.09	(0.91–1.30)
	Europe	21.5 (3584)	0.90	(0.87–0.93)	21.8 (3943)	1.04	(0.96–1.13)	35.1 (1548)	0.93	(0.89–0.97)	43.5 (1054)	0.96	(0.91–1.01)
Treated for hypercholesterolaemia													
	Australia	13.0 (9476)	1.00		12.2 (11790)	1.00		29.3 (5214)	1.00		28.4 (3460)	1.00	
	Northeast Asia	9.2 (120)	0.69	(0.58–0.82)	9.7 (159)	0.88	(0.76–1.02)	23.3 (35)	0.78	(0.58–1.04)	25.4 (29)	0.87	(0.64–1.19)
	Southeast Asia	17.6 (242)	1.34	(1.19–1.51)	14.3 (313)	1.30	(1.17–1.44)	34.2 (76)	1.10	(0.91–1.32)	28.8 (44)	1.03	(0.81–1.32)
	Europe	13.6 (2268)	0.99	(0.95–1.03)	13.6 (2248)	0.99	(0.95–1.03)	29.4 (1296)	1.02	(0.97–1.07)	29.6 (717)	1.01	(0.95–1.08)
Diabetes													
	Australia	8.9 (6481)	1.00		6.0 (5384)	1.00		18.8 (3336)	1.00		16.2 (1974)	1.00	
	North East Asia	9.9 (129)	1.11	(0.94–1.31)	11.1 (162)	1.05	(0.86–1.27)	22.0 (33)	1.14	(0.85–1.55)	14.9 (17)	0.93	(0.60–1.44)
	South East Asia	12.7 (174)	1.44	(1.25–1.66)	10.1 (221)	1.75	(1.54–1.99)	28.4 (63)	1.50	(1.21–1.86)	25.5 (39)	1.62	(1.22–2.14)
	Europe	10.1 (1692)	0.99	(0.94–1.04)	6.9 (0.55)	0.99	(0.93–1.05)	20.0 (882)	1.05	(0.98–1.12)	17.1 (413)	1.00	(0.91–1.10)
BMI≥25kg/m2													
	Australia	65.9 (47866)	1.00		52.0 (50308)	1.00		64.9 (11538)	1.00		54.8 (6673)	1.00	

(*Continued*)

Table 5. (*Continued*)

		Without previous CVD						With previous CVD					
		Male			Female			Male			Female		
	Northeast Asia	33.7 (440)	0.52	(0.48–0.56)	19.0 (313)	0.36	(0.32–0.40)	37.3 (56)	0.63	(0.51–0.77)	26.3 (30)	0.48	(0.36–0.57)
	Southeast Asia	40.9 (561)	0.63	(0.59–0.67)	30.3 (650)	0.58	(0.54–0.62)	61.8 (89)	0.63	(0.54–0.74)	36.0 (55)	0.64	(0.52–0.79)
	Europe	62.5 (10431)	0.97	(0.96–0.98)	50.8 (9173)	0.95	(0.93–0.96)	61.6 (2712)	0.98	(0.96–1.01)	55.3 (1340)	1.01	(0.97–1.05)
Physical Inactivity													
	Australia	40.4 (29340)	1.00		37.2 (37686)	1.00		47.0 (8346)	1.00		47.5 (5537)	1.00	
	Northeast Asia	61.2 (798)	1.40	(1.34–1.47)	57.7 (949)	1.46	(1.40–1.52)	66.0 (99)	1.27	(1.13–1.42)	61.4 (70)	1.29	(1.12–1.48)
	Southeast Asia	53.8 (738)	1.25	(1.19–1.31)	47.9 (1050)	1.23	(1.17–1.28)	51.4 (114)	1.03	(0.91–1.17)	60.8 (93)	1.29	(1.14–1.45)
	Europe	41.2 (6869)	0.98	(0.96–1.00)	36.8 (6643)	0.95	(0.93–0.97)	46.9 (2066)	0.97	(0.93–1.00)	46.6 (1129)	0.95	(0.91–1.00)

[1]PR, prevalence ratio, adjusted for age, education, income, private health insurance, marital status and location of residence

doi:10.1371/journal.pone.0115627.t005

The age at migration, and the duration of residence in a new country, are both considered to be indirect proxies for acculturation. Previous studies have shown that the prevalence of smoking and overweight/obesity in Asian-born individuals converges toward that of the population born in the host country in association with longer duration of residence and younger age at migration [12,25,37,38]. Despite the negative effect of acculturation on many CVD risk factors, our findings are consistent with others from North America that show a trend toward higher levels of physical activity with greater acculturation in ethnically diverse groups of migrants [39,40].

We found that longer duration of residence in Australia was associated with an increased probability of having three or more risk factors in most of the Asian migrant subgroups within the 45 and Up Study cohort. These findings are consistent with those of Chui et al. in their study of Chinese migrants to Canada [28]. The results suggest that the overall health advantage of being a migrant becomes less evident, in Northeast Asian-born individuals, as they live longer in a western country.

Our findings have implications for the planning of health promotion strategies in migrant populations. Efforts should be made to retain normal BMIs in both men and women and the low prevalence of smoking in women, as migrants become acculturated to the host country. At the same time, migrants could be encourage to adopt the healthy aspects of the lifestyle of the host country, such as increasing physical activity.

A range of cut-points have been used in past studies to summarize time since migration, with "long term" residence of >10 years or >15 years commonly used to define acculturation. Our study focused on a cohort aged 45 years and over, having a relatively high prevalence of CVD risk factors, which is distinct from previous studies and allowed us to examine the relationship of incremental changes in the acculturation variables and CVD risk factors over a longer time frame (e.g. lived in Australia for more than 30 years). We are thus able to provide greater detail on the gradients in risk in older "long term" residents in Australia, showing us that there is a significant change in some CVD risk factors over this longer time period.

Previous studies have suggested that many changes in health behaviours in migrant groups take decades to appear [41].

There are some limitations to this analysis. The 45 and Up Study is a cohort study, with an estimated response rate of 17.9%; hence, the absolute prevalence of CVD risk factors may not directly reflect that of the general population. However, relative risks from internal comparisons within the cohort, such as those reported here, have been shown to be generalizable[42]. Most of the data are self-reported. There may be a higher proportion of undiagnosed and untreated metabolic risk factors, such as impaired glucose tolerance and hypertension, in disadvantaged migrants who are less likely to seek health care. However, validation studies involving 45 and Up Study participants have found good agreement between self-reported and measured BMI[43] and shown that self-reported diagnosis of diabetes has high sensitivity and specificity compared to available administrative data collections [44]. The 45 and Up Study questionnaire was available only in English. Non-English speaking migrants with limited English skills were thus less likely to be involved in this study. Reduced participation of less acculturated and more disadvantaged migrants may lead to more conservative estimates for differences in the prevalence of CVD risk factors [45]. Furthermore, these results were derived from cross-sectional data; we were therefore unable to draw conclusions about the causal relationship between acculturation level and increased cardiovascular risk. The results may be influenced by the cohort effect, such that different waves of migrants may have had different cardiovascular risk profiles prior to immigration.

Conclusion

In this study, we found contrasting CVD risk profiles in migrants from Northeast Asia and Southeast Asia. Northeast Asian migrants had a generally favourable CVD risk profile while Southeast Asian-born participants were equally as likely as Australian-born individuals to have multiple risk factors and to have a higher prevalence of certain metabolic risk factors. With greater acculturation, general increases in CVD risk factors were seen among both Northeast and Southeast Asian migrants, including increases in the prevalence of smoking in women. However, changes in patterns of physical activity with acculturation were generally favourable. Given the substantial increase in migration from Asia to Australia in recent decades, these findings highlight the potential importance of developing health promotion strategies to preserve healthy lifestyles and address specific risk factors, in Asian communities.

Supporting Information

S1 Table. Cardiovascular risk factors for all Asian-born participants by acculturation status.
(XLSX)

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Author Contributions

Conceived and designed the experiments: SG EB RL. Analyzed the data: SG. Contributed reagents/materials/analysis tools: EB RL GJ. Wrote the paper: SG.

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Appendix 1: Cardiovascular risk factors for all Asian-born participants by acculturation status

		Male						Female					
		Northeast Asia			Southeast Asia			Northeast Asia			Southeast Asia		
	Acculturation variables	PR[1]	(95%CI)		PR[1]	(95%CI)		PR[1]	(95%CI)		PR[1]	(95%CI)	
Current smoking	Years lived in Australia												
	0-10	1			1			1			1		
	11-20	0.66	(0.38 -	1.16)	0.90	(0.50 -	1.65)	0.47	(0.15 -	1.54)	0.77	(0.31 -	1.94)
	21-30	0.71	(0.39 -	1.29)	1.02	(0.60 -	1.75)	0.59	(0.17 -	2.05)	1.03	(0.44 -	2.37)
	>30	0.71	(0.36 -	1.37)	0.97	(0.55 -	1.72)	1.82	(0.57 -	5.80)	1.51	(0.64 -	3.59)
	P for trend	0.63			0.99			0.05			0.03		
	Age migrated to Australia												
	0-10	0.79	(0.27 -	2.27)	0.67	(0.37 -	0.24)	6.34	(2.16 -	18.62)	2.55	(1.00 -	6.52)
	11-20	0.70	(0.29 -	1.65)	0.87	(0.48 -	0.45)	1.47	(0.32 -	6.75)	1.36	(0.55 -	3.37)
	21-30	0.83	(0.46 -	1.47)	1.26	(0.87 -	0.85)	2.30	(1.00 -	5.29)	1.22	(0.69 -	2.14)
	>30	1			1			1			1		
	P for trend	0.79			0.90			<0.01			<0.01		
Diabetes	Years lived in Australia												
	0-10	1			1			1			1		
	11-20	1.37	(0.71 -	2.62)	0.94	(0.52 -	1.70)	0.81	(0.45 -	1.46)	1.62	(0.90 -	2.91)
	21-30	1.88	(0.98 -	3.63)	1.13	(0.65 -	1.97)	0.80	(0.42 -	1.54)	1.49	(0.84 -	2.65)
	>30	1.89	(0.95 -	3.76)	0.97	(0.53 -	1.75)	0.80	(0.42 -	1.56)	1.50	(0.82 -	2.75)
	P for trend	0.05			-			0.61			0.34		
	Age migrated to Australia												
	0-10	0.94	(0.44 -	2.03)	0.27	(0.08 -	0.90)	1.33	(0.58 -	3.09)	1.02	(0.51 -	2.05)
	11-20	1.20	(0.70 -	2.06)	0.80	(0.48 -	1.33)	0.48	(0.17 -	1.35)	0.87	(0.50 -	1.53)
	21-30	1.03	(0.62 -	1.72)	0.81	(0.57 -	1.16)	0.76	(0.41 -	1.39)	0.96	(0.70 -	1.33)
	>30	1			1			1			1		
	P for trend	0.70			0.22			0.90			0.55		
Treated for hypertension	Years lived in Australia												
	0-10	1			1			1			1		
	11-20	0.97	(0.63 -	1.48)	0.90	(0.61 -	1.33)	0.91	(0.59 -	1.41)	1.39	(0.96 -	2.00)
	21-30	0.90	(0.57 -	1.43)	0.90	(0.63 -	1.29)	0.95	(0.59 -	1.51)	1.12	(0.79 -	1.61)
	>30	1.11	(0.70 -	1.76)	0.88	(0.60 -	1.29)	1.11	(0.70 -	1.77)	1.15	(0.79 -	1.68)
	P for trend	0.44			0.33			0.54			-		
	Age migrated to Australia												
	0-10	1.64	(0.98 -	2.76)	1.11	(0.65 -	1.89)	1.04	(0.57 -	1.88)	0.69	(0.40 -	1.20)
	11-20	1.34	(0.87 -	2.04)	0.95	(0.65 -	1.40)	0.60	(0.32 -	1.11)	0.59	(0.38 -	0.93)
	21-30	1.26	(0.86 -	1.84)	0.69	(0.52 -	0.92)	1.00	(0.70 -	1.42)	0.82	(0.65 -	1.04)
	>30	1			1			1			1		
	P for trend	-			0.92			0.82			<0.01		
Treated for hypercholesterolaemia	Years lived in Australia												
	0-10	1			1			1			1		
	11-20	1.02	(0.56 -	1.85)	0.73	(0.47 -	1.13)	1.05	(0.62 -	1.81)	1.03	(0.69 -	1.52)
	21-30	0.91	(0.48 -	1.72)	0.87	(0.58 -	1.29)	1.21	(0.68 -	2.13)	0.80	(0.54 -	1.17)
	>30	0.98	(0.51 -	1.88)	0.81	(0.53 -	1.25)	1.16	(0.64 -	2.08)	1.03	(0.69 -	1.54)
	P for trend	0.61			0.42			0.80			0.14		
	Age migrated to Australia												
	0-10	1.06	(0.51 -	2.19)	0.84	(0.44 -	1.58)	0.80	(0.36 -	1.78)	0.37	(0.15 -	0.90)
	11-20	0.98	(0.55 -	1.73)	1.26	(0.87 -	1.84)	0.81	(0.42 -	1.57)	0.93	(0.60 -	1.45)
	21-30	0.95	(0.58 -	1.56)	0.70	(0.51 -	0.96)	1.21	(0.82 -	1.79)	0.79	(0.59 -	1.04)
	>30	1			1			1			1		
	P for trend	0.59			0.99			0.22			-		
BMI≥25kg/m2	Years lived in Australia												
	0-10	1			1			1			1		
	11-20	0.87	(0.68 -	1.12)	0.82	(0.62 -	1.10)	0.75	(0.54 -	1.04)	1.08	(0.82 -	1.43)
	21-30	0.82	(0.63 -	1.07)	0.98	(0.76 -	1.26)	0.90	(0.64 -	1.28)	1.14	(0.88 -	1.49)
	>30	1.43	(1.11 -	1.85)	1.19	(0.92 -	1.55)	1.31	(0.93 -	1.85)	1.26	(0.95 -	1.67)
	P for trend	-			<0.01			<0.01			0.06		
	Age migrated to Australia												
	0-10	2.28	(1.86 -	2.80)	1.51	(1.19 -	1.91)	2.01	(1.42 -	2.83)	1.32	(1.03 -	1.68)

	11-20	1.57	(1.24 -	1.98)	1.15	(0.95 -	1.40)	1.80	(1.33 -	2.43)	1.04	(0.82 -	1.32)
	21-30	1.19	(0.97 -	1.46)	1.20	(1.04 -	1.39)	0.95	(0.72 -	1.26)	0.91	(0.78 -	1.06)
	>30	1			1			1			1		
	P for trend	-			<0.01			-			0.04		
Physical inactivity	Years lived in Australia												
	0-10	1			1			1			1		
	11-20	1.05	(0.92 -	1.19)	0.89	(0.74 -	1.07)	0.94	(0.84 -	1.06)	1.09	(0.92 -	1.30)
	21-30	0.99	(0.86 -	1.13)	0.94	(0.80 -	1.12)	0.99	(0.87 -	1.12)	1.04	(0.88 -	1.23)
	>30	0.89	(0.76 -	1.05)	0.90	(0.75 -	1.09)	0.80	(0.68 -	0.93)	1.02	(0.85 -	1.22)
	P for trend	0.04			-			<0.01			0.56		
	Age migrated to Australia												
	0-10	0.84	(0.66 -	1.07)	0.70	(0.51 -	0.96)	0.53	(0.37 -	0.75)	0.94	(0.74 -	1.20)
	11-20	0.90	(0.75 -	1.08)	1.00	(0.85 -	1.19)	0.87	(0.72 -	1.06)	0.89	(0.74 -	1.07)
	21-30	0.96	(0.86 -	1.08)	0.98	(0.88 -	1.09)	0.95	(0.86 -	1.06)	0.99	(0.90 -	1.09)
	>30	1			1			1			1		
	P for trend	0.07			-			<0.01			0.34		
Risk factors >=3	Years lived in Australia												
	0-10	1			1			1			1		
	11-20	0.79	(0.50 -	1.24)	0.66	(0.42 -	1.04)	0.85	(0.50 -	1.46)	1.33	(0.81 -	2.18)
	21-30	0.78	(0.48 -	1.26)	0.93	(0.62 -	1.39)	1.14	(0.65 -	2.03)	1.14	(0.71 -	1.85)
	>30	1.23	(0.76 -	1.99)	0.87	(0.56 -	1.34)	1.15	(0.65 -	2.05)	1.49	(0.90 -	2.46)
	P for trend	0.04			0.68			-			0.05		
	Age migrated to Australia												
	0-10	1.86	(1.09 -	3.17)	1.01	(0.59 -	1.73)	1.04	(0.48 -	2.24)	0.99	(0.54 -	1.78)
	11-20	1.43	(0.90 -	2.26)	1.08	(0.75 -	1.54)	0.48	(0.20 -	1.14)	0.76	(0.46 -	1.27)
	21-30	1.29	(0.86 -	1.93)	0.81	(0.61 -	1.07)	1.18	(0.78 -	1.78)	0.87	(0.65 -	1.16)
	>30	1			1			1			1		
	P for trend	0.01			0.79			0.68			0.38		
Previous CVD	Years lived in Australia												
	0-10	1			1			1			1		
	11-20	0.52	(0.31 -	0.87)	1.19	(0.52 -	2.72)	1.28	(0.65 -	2.49)	1.11	(0.49 -	2.51)
	21-30	0.50	(0.27 -	0.92)	1.73	(0.78 -	3.81)	0.95	(0.43 -	2.09)	1.28	(0.59 -	2.77)
	>30	1.05	(0.63 -	1.76)	2.24	(1.00 -	4.99)	1.50	(0.72 -	3.09)	1.50	(0.69 -	3.28)
	P for trend	0.63			<0.01			0.25			0.12		
	Age migrated to Australia												
	0-10	1.99	(1.16 -	2.95)	1.40	(0.77 -	2.55)	1.31	(0.58 -	2.97)	1.45	(0.63 -	3.33)
	11-20	1.61	(1.01 -	2.56)	1.16	(0.69 -	1.94)	1.06	(0.52 -	2.17)	0.99	(0.48 -	2.04)
	21-30	1.02	(0.61 -	1.71)	1.39	(1.01 -	1.91)	0.81	(0.42 -	1.56)	1.22	(0.82 -	1.83)
	>30	1			1			1			1		
	P for trend	0.01			0.11			0.96			0.37		

PR1: prevalence ratio, adjusted for age, education, annual income, private health insurance, marital status and loaction of residence

* Statistically significant at the 5% level compared to reference groups

Chapter 7

Paper 6: Prospective investigation of the risk of hospitalisation for incident cardiovascular disease and all-cause mortality according to region of birth in the 45 and Up Study

Prospective investigation of the risk of hospitalisation for incident cardiovascular disease and all-cause mortality according to region of birth in the 45 and Up Study

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Abstract

Background: Retrospective studies indicate that cardiovascular disease (CVD) morbidity and mortality vary among heterogeneous immigrant groups. This prospective study aims to examine the relationship of region of birth and acculturation to incident CVD hospitalisation and all-cause mortality in Australia, with an emphasis on Asian immigrants.

Method: Questionnaire data from the 45 and Up Study, a population-based prospective study of individuals aged ≥45 years, linked to hospitalisation and death data, were analysed. Cox proportional-hazards models were used to examine the association between region of birth and acculturation and CVD hospitalisation, in 214,743 individuals without CVD at baseline, adjusting for potential confounding factors.

Result: Over a median 3.4 years of follow-up, 24,640 incident hospitalisations for major CVD and 12,283 deaths were observed. Compared to Australian-born participants, the hospitalisation incidence for ischaemic heart disease (IHD) and major CVD was substantially lower in Northeast Asia (IHD hazard ratio (HR): 0.50, 0.35-0.71 CVD HR: 0.56, 0.45-0.70) and Southeast Asian-born (IHD HR: 0.70, 0.53-0.94 CVD HR: 0.68, 0.56-0.82), but higher IHD incidence (IHD HR: 1.35, 1.01-1.80) was found in South & Central Asian-born participants. All-cause mortality was significantly lower in Southeast Asian-born (HR: 0.75, 0.58-0.97) and South & Central Asian-born (HR: 0.51, 0.34-0.78) versus Australian-born participants, but not in Northeast Asian-born participants. There was no significant difference in the hospitalisation rate for incident cerebrovascular disease in any immigrant sub-group compared to the Australian-born. There was no evidence of an effect of duration of residence or age at migration on major CVD, other than the reduced risk observed in Northeast Asian-born individuals who migrated at ≥20 years of age compared to Australian-born (HR: 0.45, 0.35-0.59).

Conclusion: In Australia, CVD hospitalisation risks are considerably lower in immigrants of Northeast Asia and Southeast Asian origin, suggesting the effect of location of birth and age at migration varies across different types of CVD and is likely to be determined by a complex interaction of factors related to both the host country and the country of origin.

Introduction

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide (1). Ischemic heart disease (IHD) and cerebrovascular disease comprise the majority of CVD. In recent decades, CVD-related morbidity and mortality have been decreasing in many developed countries including Australia. However, burden of disease attributable to CVD in middle and low income countries have been increasing over the same period (2).

Australia, in common with many other western countries, has experienced substantial international immigration, with 27% of the population born in a foreign country (3). Immigrants from Asian countries comprise one of the most rapidly growing population groups in recent decades (3). Evidence suggests that CVD-related morbidity and mortality may vary considerably among heterogeneous immigrant groups according to their country of birth, and may also differ according to the host country (4). These variations may at least in part be explained by differences in health behaviours and risk factors both in the immigrants' home countries and in the host countries. It has also been reported that the incidence of certain CVD outcomes (i.e. CVD mortality, IHD) increasingly approximates that of the host country with increasing duration of residence, a proxy for acculturation (5, 6).

Three previous studies in Australia have investigated CVD outcomes according to birth place, but these have all been retrospective studies and examined only individual CVD outcomes (5, 7, 8). Furthermore, the pattern of CVD morbidity and mortality in recently arrived immigrant groups from Asia has not been explored in detail.

We used data from a large prospective cohort study, the 45 and Up Study, to compare the risk of incident CVD, as measured by hospitalisation for a range of CVD diagnoses, and all-cause mortality, in Australian-born and overseas-born participants without CVD at baseline, according to sex and region of birth, with an emphasis on Asian immigrants. We further examined how the risk of specific CVD diagnoses varied according to the duration of residence and age at migration in Asian-born participants compared with Australian-born participants.

Methods

Study Population

The 45 and Up Study is a large population-based cohort study of people aged 45 years and over, living in New South Wales, Australia (9). A total of 267,153 individuals, randomly sampled from the Medicare Australia database, completed a self-administrated baseline questionnaire distributed between January 2006 and December 2008 and gave informed consent for follow-up through repeated contact and population health databases. Baseline questionnaire data included information on socio-demographic and lifestyle factors, self-reported medical history, height and body weight, and physical activity. Participants were also asked about their country of birth, and, for those born outside of Australia, the year they moved to Australia.

Questionnaire data from study participants were linked probabilistically to hospitalisations and deaths by the Centre for Health Record linkage (http://www.cherel.org.au/). The NSW Admitted Patient Data Collection is a complete census of all public and private hospital admissions in NSW. The linked data contain details of admissions in participants from 1 July 2000 to 31 December 2011, including dates of admission and discharge, and the primary reason for admission, coded using the International Classification of Diseases 10th revision—Australian Modification (ICD-10-AM) (9). Dates of death from the date of recruitment up to 31 December 2011 were ascertained using linkage to the NSW Register of Births, Deaths and Marriages. Death registrations capture all deaths in NSW. Cause of death information was not available at the time of analysis.

Region of birth

Based on the question "In which country were you born?", "overseas-born" was defined as being born in a place other than Australia. Countries of birth were categorized into major region of birth groups according to a modified version of the Standard Australian Classification of Countries (SACC, 2011) (10) including six major groups: Australia, Europe, Northeast Asia (China, Hong Kong, Taiwan, South Korea and Japan), Southeast Asia (Burma, Cambodia, Thailand, Vietnam, Indonesia, Malaysia, Philippines and Singapore) South and Central Asia (Bangladesh, India, Nepal, Pakistan, Sri Lanka, Afghanistan, and Kazakhstan) and Other.

CVD outcomes and all-cause mortality

We investigated major CVD as a combined group, including IHD (ICD-10-AM I20-I25); cerebrovascular disease (ICD-10-AM I60-I69), pulmonary heart disease and diseases of pulmonary circulation (ICD-10-AM I26-I28), diseases of arteries, arterioles and capillaries (ICD-10-AM I70-I79) and other selected forms of CVD (ICD-10-AM I30-I52, I80-I82, G45, G46 (11)). An incident major CVD was defined as the first hospitalisation with a primary diagnosis of any form of CVD mentioned above based on ICD-10-AM three-character codes, after the date of recruitment into the 45 and Up Study. We also focused on the two major forms of CVD: IHD and cerebrovascular disease.

To analyse incident CVD hospitalisation, participants contributed person-years from the date of recruitment until the first CVD-related hospitalisation, their date of death or the end of follow-up (31 December 2011), whichever occurred first. To analyse all-cause mortality, participants contributed person-years from the date of recruitment until death or end of follow-up (31 December 2011).

Socio-demographic variables

Education was categorised as: none, intermediate/ high school/ trade/certificate diploma, university or higher. Location of residence was defined as: major cities, regional, remote/very remote. Household annual pre-tax income was in Australian dollars and categorized as: <$20,000, $20,000-$39,999, $40,000-$69,999, ⩾$70,000. Health insurance was dichotomized as: has private health insurance, no private health insurance.

Acculturation variables

Two variables related to acculturation were examined: duration of residence in Australia and age at migration to Australia. Duration of residence in Australia was defined as the number of years from the year of arrival in Australia until baseline. Duration of residence in Australia was categorized as: 0-20 years, >20 years; age at migration to Australia was categorized as: 0-20 years, >20 years.

Table1: Characteristics of study population according to region of birth

	Australia	Europe	Northeast Asia	Southeast Asia	South & Central Asia	Other
	N=162152 (n)	N=33018 (n)	N=2934 (n)	N=3525 (n)	N=1586 (n)	N=11528 (n)
Age						
45-54	35 (56634)	24 (7884)	48 (1409)	46 (1627)	42 (671)	40 (4642)
55-64	34 (55621)	36 (11919)	29 (852)	34 (1193)	29 (462)	36 (4181)
65-74	20 (31665)	24 (8065)	13 (395)	13 (459)	17 (275)	15 (1778)
75-84	10 (15597)	12 (4082)	8 (230)	6 (198)	9 (149)	7 (759)
85+	2 (2635)	3 (1068)	2 (48)	1.4 (48)	2 (29)	1.5 (168)
Sex						
Female	58 (93376)	53 (17412)	56 (1656)	62 (2186)	45 (706)	55 (6318)
Male	42 (68784)	47 (15609)	44 (1279)	38 (1339)	55 (880)	45 (5210)
Education						
Less than secondary school	35 (57059)	27 (8998)	13 (383)	18 (645)	9 (150)	17 (1963)
Secondary school graduation	9 (14132)	12 (3931)	19 (572)	18 (624)	13 (209)	16 (1900)
Certificate/ diploma	32 (51461)	35 (11607)	23 (662)	22 (774)	21 (338)	30 (3408)
University degree	23 (37512)	24 (7851)	43 (1253)	40 (1411)	55 (867)	36 (4101)
Missing	1.2 (1996)	2 (634)	2 (65)	2 (71)	1.4 (22)	1.4 (156)
Household income						
<$20k	16 (26304)	20 (6525)	24 (695)	23 (806)	18 (293)	16 (1875)
$20K-<40K	17 (27847)	17 (5648)	15 (430)	15 (533)	12 (185)	14 (1643)
$40K-<70K	19 (31265)	17 (5528)	17 (511)	19 (662)	16 (254)	18 (2128)
>=$70K	27 (43344)	24 (7827)	19 (558)	20 (690)	34 (542)	32 (3678)
Missing	21 (33400)	23 (7493)	25 (741)	24 (834)	20 (312)	19 (2204)
Location of residence						
Major Cities	39 (63745)	54 (17685)	92 (2692)	83 (2926)	82 (1303)	65 (7474)
Inner Regional	38 (61047)	34 (11141)	6 (177)	12 (424)	13 (213)	25 (2924)
Remote/very remote	23 (37330)	13 (4188)	2 (65)	5 (175)	4 (69)	10 (1126)
Private health insurance						
No health insurance	31 (50800)	40 (13254)	35 (1013)	39 (4477)	36 (577)	45 (1573)
Health Insurance	69 (111356)	60 (19766)	65 (1922)	61 (7051)	64 (1009)	55 (1952)
Smoking status						
Current Smoker	8 (12288)	8 (2615)	5 (138)	6 (213)	4 (67)	9 (991)
Ex Smoker	33 (54043)	42 (13866)	14 (423)	17 (601)	21 (329)	36 (4134)
Never Smoker	59 (95342)	50 (16439)	80 (2355)	77 (2702)	75 (1187)	55 (6369)

Table 1 (continued)

	Australia	Europe	Northeast Asia	Southeast Asia	South & Central Asia	Other
	N=162152 (n)	N=33018 (n)	N=2934 (n)	N=3525 (n)	N=1586 (n)	N=11528 (n)
Alcoholic drinks/week						
0	30 (48897)	28 (9158)	66 (1925)	66 (2325)	50 (792)	33 (3841)
1-14	53 (86172)	56 (18617)	27 (794)	24 (858)	39 (616)	53 (6108)
15 or more	15 (29816)	15 (24620)	14 (4503)	2 (69)	3 (90)	6 (94)
Missing	2 (2471)	2 (743)	5 (147)	7 (252)	5 (84)	3 (343)
Physical activity						
<150min/week	42 (73413)	42 (13104)	62 (1694)	53 (1855)	48 (704)	42 (4981)
≥150min/week	54 (94019)	53 (16536)	32 (874)	40 (1400)	46 (674)	53 (6285)
Missing	4 (6966)	5 (1560)	6 (164)	7 (245)	6 (88)	5 (593)
BMI						
15-<18	2 (3624)	3 (908)	8 (238)	5 (175)	3 (53)	3 (342)
18-<23	13 (21156)	14 (4628)	33 (978)	26 (914)	17 (268)	15 (1698)
23-<25	19 (30433)	21 (6926)	28 (829)	28 (911)	28 (440)	20 (2336)
25-<30	37 (59354)	38 (12554)	28 (640)	28 (985)	35 (562)	36 (4191)
30-<50	22 (15927)	18 (6066)	4 (106)	7 (218)	11 (187)	19 (2142)
Missing	8 (12377)	6 (1933)	4 (131)	7 (235)	6 (102)	7 (803)
Self reported diabetes						
No	93 (150673)	92 (30325)	92 (2705)	89 (3125)	82 (1308)	92 (10616)
Yes	7 (11487)	8 (2696)	8 (230)	11 (400)	18 (278)	8 (912)
Treated for hypertension						
No	78 (127142)	79 (26064)	85 (2487)	79 (2801)	80 (1262)	83 (9567)
Yes	22 (35018)	21 (6957)	15 (448)	21 (724)	20 (324)	17 (1961)
Treated for high cholesterol						
No	88 (142120)	87 (28632)	91 (2661)	85 (2986)	85 (1348)	89 (10204)
Yes	12 (20040)	13 (4389)	9 (274)	15 (539)	15 (238)	11 (1324)

Statistical analysis

Excluding 376 (0.14%) participants with invalid age and/or date of recruitment, questionnaire data from 266,777 study participants were linked to data on hospital admissions and deaths. Participants with confirmed linkage errors (n=22; 0.01%), with missing data on country of birth, age, or sex (n=2341; 0.9%) were excluded from analysis.

Previous CVD was defined as either self-reported heart disease, stroke or blood clot on the baseline questionnaire or a hospital admission in the 6 years prior to entering the study, with ICD-10-AM diagnosis codes I20-I28, I30-I52, I60-I82, G45, G46 (major CVD) in any of the 55 diagnostic fields, or Australian Health Intervention

Classification or CVD-related procedure codes (coronary artery bypass angioplasty/stent: 35310, 38306, 35304-00, 30305-00, 38300-00, 38303-00; coronary artery bypass graft: 38497, 38500, 38503, 90201; coronary revascularisation procedures: 38497, 38500, 38503, 90201, 35310, 38306, 35304-00, 30305-00, 38300-00, 38303-00) in any of the 50 procedure code fields (11). Data from participants with previous CVD conditions (n=49,671; 18.6%) were exclude from this study. We only present data from participants without previous CVD (n=214,743) in this study.

Frequency tables and cross tabulations were used to describe baseline characteristics in the 45 and Up Study participants according to region of birth. Estimates of sex-specific incident CVD hospitalisation rates since baseline were calculated for each region of birth group, age-standardized to the 2006 NSW population, using the direct method.

Hazard ratios (HRs) with 95% confidence intervals (95% CIs) for combined major CVD outcomes, specific CVD outcomes, and all-cause mortality, according to region of birth overall and separately for men and women (using Australian-born participants as the reference group), were estimated using Cox regression modeling, using age as the underlying time variable and adjusting for other socio-demographic factors (education, income, private health insurance and location of residence). Although some social habits and customs may also vary according to the country of origin, risk factors such as smoking and alcohol consumption were not adjusted because they are on the causal pathway to CVD. Missing values for covariates were included in the models as separate categories. To investigate whether the association between region of birth and CVD varied according to degree of acculturation, adjusted hazard ratios (HRs) according to duration of residence and age at migration to Australia were estimated for each immigrant sub-group.

The proportionality assumption was verified by plotting the Schoenfeld residuals against the time variable in each model; a stratified form of the model was used where covariates displayed non-proportionality of hazards.

Results

A total of 214,743 participants were included in the analyses, of whom 52,591 (24.5%) were born outside of Australia (2,934 from Northeast Asia, 3,525 from Southeast Asia, 1,586 from South and Central Asia, 33,018 from Europe, 11,528 from other regions).

Compared to Australian-born participants, immigrants tended to live in major cities. Individuals from Asia were younger and more likely than others to have a university degree and more likely than others to report a lower household income (Table 1). Asian-born participants had a lower average BMI than Australian-born and European-born individuals and were more likely to be non-drinkers and to have never smoked.

Incident CVD hospitalisation and All-cause Mortality by Region of Birth

The median follow-up time in the total study population was 3.4 years. We observed 24,640 incident hospital admissions related to major CVD outcomes during 1,077,170 person-years of follow up. A total of 12,283 deaths were observed during 1,116,752 person-years of follow up.

There was considerable variation in the incidence of CVD-related hospitalisation and mortality across different immigrant subgroups (Figure 1). The rates and adjusted hazard ratios for incident hospitalisation for IHD and major CVD were lower for participants born in Northeast Asia (adjusted HR for IHD: 0.50, 0.35-0.71); adjusted HR for major CVD: 0.56, 0.45-0.70) and Southeast Asia (adjusted HR for IHD: 0.70, 0.53-0.94); adjusted HR for major CVD: 0.68, 0.56-0.82), compared to Australian-born participants. However, IHD incidence was higher in South and Central Asian-born participants compared to Australian-born participants (adjusted HR: 1.35, 1.01-1.80) (Figure 2). The incidence of hospitalisation for cerebrovascular disease did not differ significantly between any of the immigrant sub-groups and Australian-born individuals. Compared to those born in Australia, all-cause mortality was significantly lower for Southeast Asian-born (adjusted HR: 0.75, 0.58-0.97) and South & Central Asian-born (adjusted HR: 0.51, 0.34-0.78), but not for Northeast Asian-born participants (adjusted HR: 0.79, 0.61-1.03) (Figure 2). The age-standardised incidence of hospitalisation for major CVD and IHD, and all-cause mortality, were higher in men than in women for Australian-born and European-born participants (Figure 1).

Figure 1: Age standardised incidence rates per 1000 person-years of major CVD hospitalisation and of all-cause mortality by region of birth and sex, directly age-adjusted to the 2006 New South Wales population

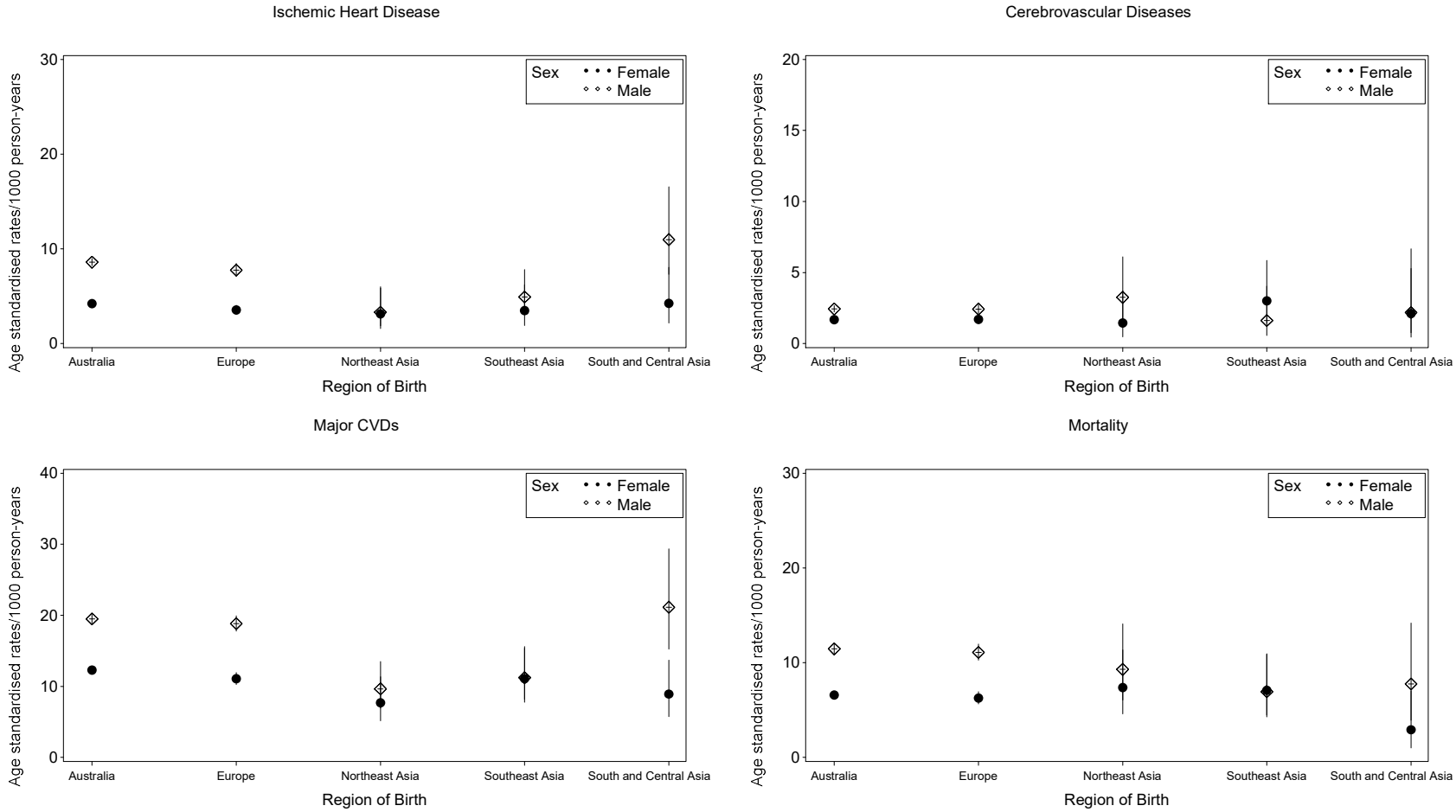
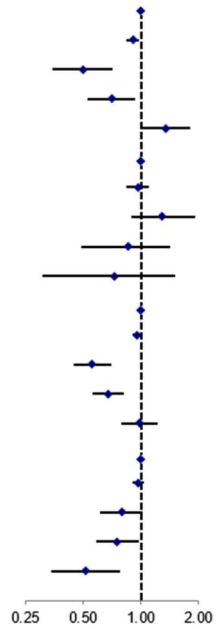


Figure 2: Hazard ratios (95%CI) for CVD hospitalisation and all-cause mortality according to region of birth

CVD Outcomes	Region of Birth	Events/pys	HR^1	HR^2	(95% CI)
IHD					
	Australia	3922 /690248	1.00	1.00	
	Europe	840 /140826	0.91	0.91	(0.84 - 0.98)
	Northeast Asia	30 /12412	0.49	0.50	(0.35 - 0.71)
	Southeast Asia	48 /14898	0.68	0.70	(0.53 - 0.94)
	South and Central Asia	47 /6711	1.29	1.35	(1.01 - 1.80)
Cereberovascular disease					
	Australia	1142 /697351	1.00	1.00	
	Europe	301 /142185	1.03	1.01	(0.88 - 1.15)
	Northeast Asia	21 /12449	1.20	1.14	(0.73 - 1.76)
	Southeast Asia	20 /14967	1.06	1.01	(0.65 - 1.58)
	South and Central Asia	10 /6792	0.92	0.91	(0.48 - 1.69)
Major CVD					
	Australia	9038 /677557	1.00	1.00	
	Europe	2093 /137601	0.96	0.96	(0.91 - 1.00)
	Northeast Asia	80 /12282	0.56	0.56	(0.45 - 0.70)
	Southeast Asia	108 /14761	0.67	0.68	(0.56 - 0.82)
	South and Central Asia	82 /6620	0.96	0.98	(0.79 - 1.22)
Mortality					
	Australia	4418 /691108	1.00	1.00	
	Europe	1185 /140574	1.00	0.97	(0.91 - 1.03)
	Northeast Asia	59 /12367	0.84	0.79	(0.61 - 1.03)
	Southeast Asia	61 /14897	0.83	0.75	(0.58 - 0.97)
	South and Central Asia	23 /6765	0.53	0.51	(0.34 - 0.78)



Australian-born group is used as the reference group

HR^1:hazard ratio, adjusted for age

HR^2:hazard ratio, adjusted for age, education, annual income, private health insurance and location of residence

The forest plot shows HR^2 (95%CI)

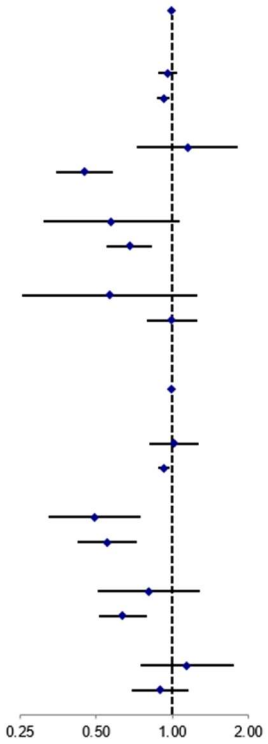
There was no statistically significant variation in the relationship of region of birth to CVD incidence according to sex (p(interaction)=0.44)(Figure 2).

Incident Major CVD Hospitalisation and Acculturation Indicators

Compared to Australian-born individuals, the risk of hospitalisation for a major CVD was substantially lower in Northeast Asian-born participants who migrated at age ≥20 years (HR: 0.45, 0.35-0.59) than for those who migrated at less than 20 years old (HR: 1.15, 0.72-1.82) (Figure 3). There was no significant relationship of duration or residence or age at migration on the incidence of hospitalisation for major CVD for other immigrant groups or outcomes (Figure 3). The results on acculturation and major CVD hospitalisations have to be interpreted with caution due to the small number of events.

Figure 3: Hazard ratios for Major CVD Hospitalisation by Region of Birth, Age of Migration and Duration of residence in Australia

Region of Birth	Acculturation Indicators	Events/pys	HR#	(95% CI)
	Age of migration			
Australia		9038 /677557	1.00	
Europe	<20 yrs	605 /54569	0.96	(0.88 - 1.04)
	≥20 yrs	1371 /77559	0.92	(0.87 - 0.98)
North East Asia	<20 yrs	18 /1234	1.15	(0.72 - 1.82)
	≥20 yrs	58 /10765	0.45	(0.35 - 0.59)
South East Asia	<20 yrs	10 /1998	0.57	(0.31 - 1.07)
	≥20 yrs	92 /12320	0.68	(0.55 - 0.83)
South and Central Asia	<20 yrs	6 /1047	0.56	(0.25 - 1.26)
	≥20 yrs	73 /5392	0.99	(0.79 - 1.25)
	Duration of residence			
Australia		9038 /677557	1.00	
Europe	<20 yrs	80 /7310	1.02	(0.81 - 1.27)
	≥20 yrs	1878 /124279	0.93	(0.88 - 0.98)
North East Asia	<20 yrs	22 /3662	0.49	(0.32 - 0.75)
	≥20 yrs	54 /8280	0.55	(0.42 - 0.72)
South East Asia	<20 yrs	18 /2429	0.81	(0.51 - 1.29)
	≥20 yrs	83 /11839	0.64	(0.51 - 0.79)
South and Central Asia	<20 yrs	22 /1741	1.14	(0.75 - 1.74)
	≥20 yrs	58 /4696	0.90	(0.69 - 1.16)



Australian-born group is used as the reference group

HR#:hazard ratio, adjusted for age, education, annual income, private health insurance and location of residence

The forest plot shows HR# (95%CI)

Discussion

The main findings of this study were that the incidence of hospitalisation for major CVD and IHD was significantly lower in individuals born in Northeast Asia and Southeast Asia compared to Australian-born participants, and higher in South & Central Asian-born participants. There was no significant difference in the rate of hospitalisation for incident cerebrovascular disease in any immigrant sub-group compared to the Australian-born. A reduced risk of major CVD was observed in Northeast Asian-born individuals who migrated at ≥20 years of age compared to Australian-born, but not in those who migrated before 20 years old. This trend was not found for other immigrant groups and when duration of residence was used as an acculturation indicator.

To our knowledge, this is the first study to compare the rates of major cardiovascular conditions as a combined outcome in overseas-born compared to host populations. Previous studies have consistently reported that IHD incidence is lower in Northeast and Southeast Asian-born immigrants, compared to immigrants from other countries as well as the host country population. For example, in a study conducted in Victoria, Australia, the rates of acute myocardial infarction hospitalisation were lower in Northeast Asian-born (HR: 0.46, 0.34-0.60) and Southeast Asian-born immigrants (HR: 0.68, 0.58-0.79) but higher in those born in Southern Asia (HR: 1.46, 1.26-1.68) compared to the Australian-born participant group (8). Similar variation in both IHD incidence and mortality among these Asian immigrant sub-groups has also been shown in several studies in Europe (12, 13).

Previous studies have reported inconsistent findings in relation to variation in incident cerebrovascular disease across immigrant subgroups and in comparison to those born in the host country. For example, although one study in Australia reported a lower risk of stroke in Northeast Asian-born individuals (8), studies from Europe and North America have shown a higher incidence of stroke in some Asian immigrant groups (i.e. Chinese, Vietnamese and South Asian immigrants) (14, 15). In this study, there was no significant variation in stroke risk between immigrant sub-groups and the Australian-born group.

Paradoxically, despite the much lower IHD hospitalisation, all-cause mortality was not significantly lower for Northeast Asian-born participants, compared to those born in Australia (adjusted HR: 0.79, 0.61-1.03). A recent meta-analysis reported that western-dwelling Chinese immigrants had lower incidence of IHD but potentially worse survival outcomes once diagnosed (16). The potential explanation for this finding was that lower CHD hospitalisation among Asian immigrants may be related to poorer health care utilisation due to language barriers, poor health literacy, and lack of trust in Western medicine and health care systems. Some of these issues, such as poorer language proficiency, are used as an indicator of lower acculturation level, and are more common among the immigrant groups that maintain the value and customs of their countries of origin.

Duration of residence in the host country and age at migration are both indicators commonly used to measure acculturation. There is considerable evidence that, for some immigrant groups, a greater degree of acculturation is associated with higher prevalence of CVD risk factors such as obesity and hypertension (17). The evidence is much less consistent for the association between indicators of acculturation and CVD morbidity and mortality. An Australian study reported decreasing CVD mortality with increasing duration of residence in Australia in immigrants from some European countries and South Asia, which was not observed in East Asian immigrants (5). In contrast, another study reported increasing HRs for IHD within only five years after migration to Denmark from Southeast and East Asia (6). We found no evidence of an effect of duration of residence, for incidence of hospitalisation for major CVD in any of the immigrant groups. Migration at early age from a country with higher IHD incidence (i.e. Finland) to one with lower incidence (i.e. Sweden) has been associated with a reduced risk of subclinical atherosclerosis (18). Consistent with this, we found that older age at migration was associated with a reduced incidence of hospitalisation for major CVD in immigrants from Northeast Asia (an area of low CVD prevalence/incidence) to Australia (comparatively high CVD incidence) compared to the Australia-born population.

It seems likely that the association between indicators of acculturation and CVD outcomes varies according to the relative burden of CVD risk factors and CVD in the home versus the host country and possibly also different processes of acculturation across immigrant sub-groups. Our study suggested age at migration might play a role in the susceptibility to the risk factors in the host country. Thus, age at migration is possibly a more sensitive acculturation indicator than duration of residence to measure the association between acculturation level and CVD outcomes.

Strength and Limitations

The large sample size and prospective design of the 45 and Up Study has allowed us to investigate the variation of rates in incident hospitalisation for a range of CVD outcomes in overseas-born populations according to heterogeneous regions of birth. We had comprehensive individual-level hospitalisation data on CVD from administrative databases, allowing objective and complete ascertainment of the

outcomes of interest. Prior work has demonstrated the validity of administrative coding for CVD outcomes (19, 20). Our study used hospitalisation data up to the year 2011, which may better reflect the pattern of CVD morbidity in recently arrived immigrant groups than some older studies.

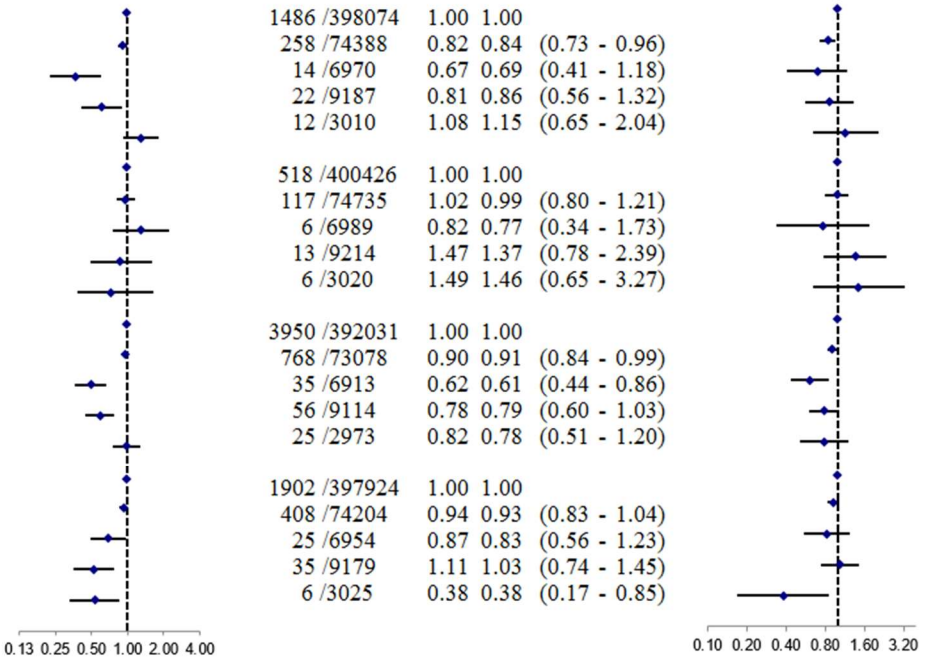
There are however some limitations to this analysis. First, there was a relatively short follow-up time, which led to small numbers of events for some CVD outcomes and limited ability to draw firm conclusions, e.g. for women in the sex-specific analyses (Figure 4). This also meant that we were unable to use finer categories of acculturation indicators or examine the association between acculturation and specific CVD outcomes (i.e. IHD and stroke). Secondly, the 45 and Up Study questionnaire was available only in English. Non-English speaking immigrants with limited English skills were thus less likely to be involved in this study. Reduced participation of less acculturated and more disadvantaged immigrants may lead to more conservative estimates for differences in CVD risks. Thirdly, the duration of residence was calculated based on the date of first arrival in Australia. For those who return periodically to their country of origin, this may not reflect the actual duration of residence in Australia. Finally, cause of death information was not available at the time of this analysis.

Conclusion

Our study demonstrates considerable differences in the incidence of hospitalisation and mortality for major CVD and IHD, but not for cerebrovascular disease, in Asian immigrant sub-groups compared to an Australian-born population. The risk for major CVD hospitalisation was low in Northeast Asian-born and Southeast Asian-born participants, but those migrated at a young age (<20 years) were at similar risk for hospitalisation due to CVD as Australian-born individuals. Additionally, all-cause mortality was significantly lower in Southeast, South & Central Asian born participants than that in Australian-born participants, but such phenomenon was not observed in Northeast Asian-born population. Our results suggest that the effect of location of birth and age at migration varies across different types of CVD and is likely to be determined by a complex interaction of factors related to both the host country and the country of origin.

Figure 4: Hazard Ratios for CVD hospitalisation and all-cause mortality by Region of Birth and Sex

		Male				Female			
CVD Outcomes	Region of Birth	Events/pys	HR[1]	HR[2]	(95% CI)	Events/pys	HR[1]	HR[2]	(95% CI)
IHD									
	Australia	2436 /292174	1.00	1.00		1486 /398074	1.00	1.00	
	Europe	582 /66438	0.91	0.91	(0.83 - 1.00)	258 /74388	0.82	0.84	(0.73 - 0.96)
	Northeast Asia	16 /5442	0.38	0.37	(0.23 - 0.61)	14 /6970	0.67	0.69	(0.41 - 1.18)
	Southeast Asia	26 /5711	0.62	0.61	(0.41 - 0.90)	22 /9187	0.81	0.86	(0.56 - 1.32)
	South and Central Asia	35 /3701	1.23	1.29	(0.92 - 1.81)	12 /3010	1.08	1.15	(0.65 - 2.04)
Cereberovascular disease									
	Australia	624 /296925	1.00	1.00		518 /400426	1.00	1.00	
	Europe	184 /67450	1.00	0.99	(0.83 - 1.17)	117 /74735	1.02	0.99	(0.80 - 1.21)
	Northeast Asia	15 /5461	1.40	1.32	(0.78 - 2.22)	6 /6989	0.82	0.77	(0.34 - 1.73)
	Southeast Asia	7 /5753	0.70	0.67	(0.32 - 1.43)	13 /9214	1.47	1.37	(0.78 - 2.39)
	South and Central Asia	4 /3772	0.55	0.55	(0.20 - 1.48)	6 /3020	1.49	1.46	(0.65 - 3.27)
Major CVD									
	Australia	5088 /285526	1.00	1.00		3950 /392031	1.00	1.00	
	Europe	1325 /64523	0.96	0.96	(0.90 - 1.02)	768 /73078	0.90	0.91	(0.84 - 0.99)
	Northeast Asia	45 /5369	0.50	0.49	(0.37 - 0.66)	35 /6913	0.62	0.61	(0.44 - 0.86)
	Southeast Asia	52 /5647	0.60	0.59	(0.45 - 0.78)	56 /9114	0.78	0.79	(0.60 - 1.03)
	South and Central Asia	57 /3647	0.95	0.98	(0.76 - 1.28)	25 /2973	0.82	0.78	(0.51 - 1.20)
Mortality									
	Australia	2516 /293184	1.00	1.00		1902 /397924	1.00	1.00	
	Europe	777 /66371	0.97	0.92	(0.85 - 1.00)	408 /74204	0.94	0.93	(0.83 - 1.04)
	Northeast Asia	34 /5413	0.77	0.69	(0.49 - 0.98)	25 /6954	0.87	0.83	(0.56 - 1.23)
	Southeast Asia	26 /5719	0.61	0.53	(0.36 - 0.78)	35 /9179	1.11	1.03	(0.74 - 1.45)
	South and Central Asia	17 /3740	0.55	0.53	(0.33 - 0.86)	6 /3025	0.38	0.38	(0.17 - 0.85)



Australian-born group is used as the reference group

HR[1]:hazard ratio, adjusted for age

HR[2]:hazard ratio, adjusted for age, education, annual income, private health insurance and location of residence

The forest plot shows HR[2] (95%CI)

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Chapter 8

Discussion and Conclusions

Cardiovascular disease (CVD) is the leading cause of death in Australia and accounts for the second-highest disease burden in DALYs (1, 2). In 2011-12, 22% of Australians aged 18 and over (3.7 million people) reported that they had at least one type of CVD, including heart disease, stroke, or heart failure (2). This included an estimated 590,000 (3% of Australians 18+ years) who reported IHD and 377,000 (2%) who had had a previous stroke. According to a recent report 28.1% (i.e. 6.6 million people) of the estimated resident population was born overseas. This is the highest proportion of immigrants in the past 120 years (3). Moreover, immigration to Australia has already played a major role in the growth of the population with immigrants contributing more than 50% to the population growth in Australia since 2005-06.Of the top ten countries of birth of these immigrants, four are in the East- and Southeast-Asian region, namely China, Philippines, Vietnam, and Malaysia.

Patterns of CVD risk, incidence, and mortality vary significantly across different ethnic population groups (1, 2, 4). This means that the demographic change in the Australian population due to overseas immigration is likely to alter patterns of CVD in terms of incidence, prevalence, and mortality in both the short and long term. Furthermore, these changes in the pattern of CVD as a result of overseas immigration may challenge existing health policies, modes of service, and guidelines for prevention and care in Australia. Therefore, it is now important to understand the risk for major CVD and risk factor profiles in immigrants compared to the Australian-born population, and how these factors change according to acculturation. This thesis has presented six studies that have addressed the following research questions:

1. Does the profile of CVD risk factors change as migrants become acculturated to the host country?
    - 1.1 Does the prevalence of smoking change in relation to indicators of acculturation in Asian populations living in western countries?
    - 1.2 What are the factors related to vitamin D deficiency (a possible CVD risk factor) in Northeast Asians living in Australia and is there an association between vitamin D status and level of acculturation?
    - 1.3 Are models used to predict vitamin D status (for example, for use in population-based studies investigating vitamin D deficiency as a risk factor for CVD) valid?

1.4 Does the CVD risk factor profile differ in East-Asian immigrants compared to the Australian-born population and in relation to time indicators of acculturation?

2. Does the risk of CVD change as East-Asian immigrants become acculturated to the host country?
   2.1 Does the incidence of major CVD-related hospitalisation and all-cause mortality differ in East-Asian immigrants compared to the Australian-born population?
   2.2 Does the incidence of major CVD-related hospitalisation and all-cause mortality differ in relation to time indicators of acculturation in East-Asian immigrants to Australia?

These research questions address gaps in the literature and have important policy and future research implications.

This chapter presents the key findings and conclusions of the six research papers in the context of the two main research questions of the thesis. The public health implications and further investigative opportunities suggested by the studies' findings for each of the research questions are also discussed.

Acculturation and CVD risk factors

Understanding the profile of CVD risk factors in East-Asian migrants provides an evidence-base to guide development of prevention programs targeted to multicultural communities.

Table 1 summarises studies published during 1990-2015 on the prevalence of CVD risk factors in East-Asian populations living in Australia and the association with acculturation. A total of eleven publications reported the prevalence of a selection of CVD risk factors in East-Asian immigrant populations living in Australia. Seven of these publications also reported the association between an acculturation indicator and CVD risk factors; time indicators were most commonly used in these publications (in five publications). However, six out of the eleven studies were published more than ten years ago and the CVD risk factor profiles have not been investigated systematically with recent data.

To fill this identified information gap, this thesis systematically examined the prevalence of CVD risk factors in East-Asian immigrants compared to Australian-born populations and how these varied according to indicators of acculturation. Overall, the thesis added evidence that significant variation in the risk factor profiles exists across immigrant subgroups. CVD risk factor profiles of Asian immigrants tended to approximate those of Australian-born people with increasing acculturation, in both favourable and unfavourable directions. A number of key conclusions were drawn regarding different acculturation indicators and CVD risk factors. These are discussed below.

Acculturation and smoking prevalence

The research question 'does the prevalence of smoking change in relation to indicators of acculturation in Asian populations living in western countries?' was addressed by the two studies presented in Chapters 4 and 6. These studies added new information to the body of knowledge on the association between acculturation indicators and smoking prevalence in East-Asian immigrant subgroups.

Chapter 4 presented a meta-analysis on the association of acculturation and smoking prevalence and quit ratio in East-Asian immigrants living in a selection of Western countries including Australia. This study provided results stratified by different indicators of acculturation, thus providing an accurate and robust estimation of the size of the effect of acculturation on smoking. This systematic review and meta-analysis found that men were more likely to be current-smokers than women amongst Asian immigrants to the USA, Canada, and Australia. Current-smoking prevalence decreased in relation to acculturation indicators in Asian men, but increased in Asian women.

Chapter 6 examined the association between two time indicators of acculturation (i.e. duration of residence in Australia and age at migration) and smoking prevalence using baseline data from the large New South Wales 45 and Up Cohort Study. There was a much lower prevalence of current-smoking among Asian-born women in comparison to Asian-born men and Australian-born individuals. The prevalence of smoking increased in association with longer duration of residence in these women. This finding is consistent with other studies from the United States, Canada, and Australia

and also the findings in Chapter 4. In addition, this study also found that smoking prevalence was higher with older age of arrival in Australia, and longer duration of residence in East-Asian-born men, which is consistent with other recent research (5), but at odds with the results from the systematic review presented in Chapter 4.

One possible explanation for the inconsistency in these findings is that Chapter 6 focused on older immigrants, aged 45 years or older, while Chapter 4 included all adult immigrants. In addition, most studies included in Chapter 4 were conducted in North America, and this may not reflect the pattern of smoking behaviour among immigrants in Australia. The only Australian study (6), conducted in 1993, suggested a similar trend in smoking prevalence in association with duration of residence in Australia as was found in the meta-analysis in Chapter 4. However, these results are from over 20 years ago, during which time smoking prevalence has greatly reduced in Australia and the results may not be relevant to the current situation.

Consistent with the findings of this thesis, a meta-analysis of studies examining smoking in Asian immigrants to the United States also found higher levels of smoking with increasing acculturation in Asian women (7). One possible explanation is that there are different social norms regarding gender and smoking in Asian and Western countries. Smoking is commonly viewed as a masculine behaviour in many Asian countries, not acceptable for women, whereas smoking is no longer the symbol of women's freedom and independence in Western countries, and the negative health effects arising from smoking have been made known. Social norms around smoking may change as migrants adopt the host culture (8, 9).

There is also a need to acknowledge the potential for both selection bias and confounding in these findings, which may also contribute to the inconsistencies in the findings within this thesis. The 45 and Up Study questionnaire was available only in English. Non-English speaking immigrants with limited English skills were thus less likely to be involved in this study. Reduced participation of less acculturated and more disadvantaged migrants may lead to more conservative estimates as a result of this type of selection bias (10).

Future studies using more culturally sensitive tools may be more informative and provide more accurate data on the prevalence of smoking in different Asian immigrant populations at different stages of acculturation. Such data will be required to further our understanding of the role of acculturation in the smoking behaviour of East-Asian immigrants to Australia, to guide health care provision to these groups.

Vitamin D deficiency as a risk factor for CVD

Cross-sectional studies have identified an association between vitamin D deficiency and increased risk of CVD including hypertension, and IHD (11-13). Also, emerging evidence from observational studies suggests that Asian-born immigrants are at higher risk of vitamin D deficiency than Australian-born people (14-16). Elucidating the determinants of vitamin D deficiency and the association between vitamin D deficiency and acculturation in East-Asian-born populations is a first step to evaluating vitamin D deficiency-related CVD risk in this population.

Issues in estimating vitamin D status

Vitamin D testing is expensive and may not be feasible in large epidemiological studies. To overcome this problem, some studies have used prediction models to produce a vitamin D "score" based on parameters derived from questionnaire data (16). Inaccuracies and imprecision in the calculated vitamin D score can lead to incorrect results and inconsistencies and confusion in the evidence.

The research question, 'Are models used to predict vitamin D status (for example, for use in population-based studies investigating vitamin D deficiency as a risk factor for CVD) valid?' was addressed in three studies included in Chapter 5. This chapter identified three potential problems that may introduce both bias and confounding when using predicted vitamin D scores in population based studies: 1) misclassification of predictors; 2) using invalid instrumental variables and 3) prediction inaccuracy. The misclassification of predictors was discussed in the Asian Australian Health Study. The issues of invalid instrumental variables and prediction inaccuracy were explored in two validation studies included in Chapter 5.

Skin melanin density and sun sensitivity are important determinants of 25(OH)D level. However, in the Asian Australian Health Study, Northeast-Asian participants

tended to underestimate the darkness of their skin compared to an objective measure. Other studies have shown that self-reported Fitzpatrick skin phototype (FST) does not accurately reflect melanin density as measured by reflectance spectrometry in ethnically diverse participants. Both self-reported skin colour and race are not adequate predictors of sun sensitivity (17, 18). The tendency for East-Asian immigrants to systematically underestimate the darkness of their skin is important, reported in Chapter 5 for the first time, as it suggests that better instruments need to be developed to measure skin colour (relevant to sun sensitivity and vitamin D production) in ethnically diverse populations. Importantly, skin colour that is self-reported by an ethnically diverse study sample may not be validly comparable within the sample.

The first validation study found that there was considerable risk of bias in the estimates of effect, when predicted vitamin D scores are used in large-scale epidemiological studies seeking to clarify links between vitamin D status and disease risks. This study indicated that incorrect specification of instrumental variables resulted in bias and that this could alter the results and therefore the interpretation of the findings of the study. The risk and magnitude of this possible bias should be fully considered and the possible effects on the results discussed in studies using this methodology. The second validation study found that using the support vector regression method improved prediction accuracy in a validation sample compared to multiple linear regression modelling.

Overall, in Chapter 5 I showed that prediction models were unlikely to accurately and precisely estimate vitamin D status for consideration of the relationship to CVD risk. This was due to a lack of well-validated algorithms for estimating 25(OH)D levels, and limited accuracy of the underlying predictors, such as skin type. The role of vitamin D deficiency as a risk factor for CVD in East-Asian immigrants remains unclear.

Vitamin D status and acculturation

The second research question ‘What are the determinants of vitamin D status in the Northeast-Asian-born population living in Australia and what is the association with acculturation?’ was addressed by the study presented in the first part of Chapter 5.

This study found that greater acculturation was associated with lower risk of vitamin D deficiency. This finding is consistent with the findings from previous studies (17).

One community-based study conducted in Sydney investigated generational status and the association with serum 25(OH)D level in elderly Vietnamese immigrants. There was a nearly three-fold increase in the odds of vitamin D deficiency (25(OH)D<37nmol/L, AOR=2.8 (1.4 -5.9)) in study participants born in Vietnam compared to those born in Australia (15). In another cross-sectional study of Chinese and Korean women in Sydney, greater acculturation was associated with higher vitamin D status (18).

Chapter 5 also explored potential mediators of this association and found that the association between acculturation and vitamin D deficiency was mediated by physical activity and time outdoors. Chapter 6 suggested that the prevalence of physical inactivity decreased as Asian immigrants adopted an Australian lifestyle. The increased physical activity seems likely to contribute to the improved vitamin D status observed in the more acculturated participants of the Asian Australian Health Study.

Besides increased physical activity, increased sun exposure may also contribute to the improvement of vitamin D status. Asian cultures typically appreciate lighter skin colour, while Western cultures value a 'tanned appearance' (14). One study conducted in California investigated the change in attitudes and behaviours toward sun exposure as Asian-Americans adopt Western culture (19). This study found that sun exposure increased in relation to acculturation. Similarly, immigrant generational status, location raised and self-rated acculturation were associated with the attitude that a tan is attractive ($p<0.001$). But only generational status was significantly related to time spent in the sun on a typical weekend ($p=0.009$). Among more westernised Asian-Americans, the practice of deliberate sunbathing was widespread (60%-58%) (19).

Vitamin D status and CVD risk

The paper presented in Chapter 5 showed a lower risk of hypercholesterolemia, but not other markers of cardio-metabolic ill-health, associated with higher 25(OH)D levels. This association has not been consistently found in other studies, and trials of

vitamin D supplementation do not indicate a convincing beneficial effect for CVD outcomes (19, 20).

One limitation of the study reported in Chapter 5 was that the Asian Australian Health Study was a cross-sectional study of a community-based volunteer sample and the sample size was relatively small. In this type of study it is not possible to investigate the temporal relationship between 25(OH)D and hypercholesterolaemia and there is a risk that the results are due to residual confounding, for example by physical activity (21).

Acculturation and CVD risk factors other than smoking

Chapter 6 addressed the research question, 'is there an association between time indicators of acculturation and CVD risk factor profiles in the East Asians living in Australia?'

One of the major findings of Chapter 6 is that CVD risk factor profiles of East-Asian immigrants tended to approximate those of Australian-born people with increasing levels of acculturation.

Body mass index (BMI)

In the analysis of results from the 45 and Up Study, this thesis showed that higher acculturation level was associated with higher BMI and greater prevalence of overweight/obesity (6). Similar results have been reported by two other studies (22, 23) in Asian and sub-region groups: Chinese and Korean populations.

Physical activity

Most studies suggest that both men and women from East Asia are at higher risk of physical inactivity compared to the host Western population (24). Most studies show that acculturation is associated with greater leisure-time physical activity (4, 6, 25).

Biomedical risk factors

The effect of acculturation on CVD-related health states such as hypertension, diabetes and atherosclerosis is unclear (25). Only one community-based study in

Sydney showed that the risk for dyslipidaemia and insulin resistance increased in relation to duration of residence in Australia (26).

These findings suggested that retaining the healthy facets of the traditional lifestyle (e.g. retaining a normal BMI, maintaining low smoking prevalence in women) and adopting healthy aspects of the host country lifestyle (e.g. increasing physical activity) may help to minimise CVD risk in immigrant populations.

Acculturation and incidence of CVD related hospitalisation and deaths

A recent review of the published literature identified a lack of prospective studies on adverse CVD outcomes in international immigrant groups (27). The research question, 'is there an association between time indicators of acculturation and incidence of major CVD-related hospitalisations and all-cause mortality in the East Asians living in Australia' was addressed in Chapter 7.

The findings in Chapter 7 add to the body of knowledge by investigating CVD-related hospitalisations over five years of follow up. The results presented in Chapter 7, from a prospective cohort study, showed that there was significantly lower incidence of major CVDs, IHD hospitalisation, and all-cause mortality in Northeast-Asian-born and Southeast-Asian-born men compared to their Australian-born counterparts, whereas Asian-born women did not differ markedly. Reduced risk for major CVDs was observed in Northeast-Asian-born individuals who migrated at an older age compared to Australian-born, but not in those who migrated before 20 years old.

In Chapter 7, we found that the risk of major CVD hospitalisation was low in Northeast-Asian-born and Southeast-Asian-born participants, but this finding did not apply to those who migrated at less than 20 years of age. This group had a similar risk for hospitalisation to Australian-born individuals. The findings further suggested that the effect of region of birth and age at migration varies across different types of CVDs and is likely to be determined by a complex interaction of factors (e.g. socio-demographic factors, and lifestyle factors) related to both the host country and the country of origin.

Only one population-based study conducted in Australia has investigated the relative risk (RR) of CVD mortality in relation to duration of residence in Australia, based on individual death records for the period 1998-2002 (28). For East-Asian immigrants, the adjusted RR (adjusted for age, sex and year of death) did not vary according to duration of residence in Australia. These findings are consistent with our findings but differ from previous studies conducted in the United States and United Kingdom (29, 30). The difference in findings might be explained by the fact that Australia is one of the most multicultural societies in the world, with a unique social environment where maintenance of cultural traditions is actively promoted. Family-centred community and cultural clusters may encourage the continuation of the original lifestyle and retention of traditional healthy habits. These factors may lead to protective effects and less CVD in immigrants living in Australia, particularly among older immigrants. Younger immigrants who are immersed in the Australian culture through school and childhood activities may be more like their Australian counterparts and less tightly integrated with the traditional community.

Strength and limitations of data sources

This thesis used various data sources to examine the research questions. These data sources complement each other and each has its own strengths and limitations.

In Chapter 4, I used data from a variety of published studies on the prevalence of smoking and quit rates in East Asian migrants to western countries. The data derive mainly from the USA with only a few studies from Australia, Canada and the UK. Many of these studies use only very simple measures of acculturation; the resulting meta-analysis thus also uses only a simple conceptualisation of acculturation using a linear model. Furthermore, some of the studies do not clearly separate different East Asian population groups, thus limiting the level of specificity of the findings to a single East Asian population, and many of the studies are community- rather than population-based, making it difficult to be confident that the estimate of prevalence is valid for the population of interest.

In Chapter 5, I first used published data from the NHANES Study and from the Ausimmune Study to examine issues in using predictive models for vitamin D status.

The study populations are primarily Caucasian. Nevertheless, the general conclusions around the threats to validity of the effect estimates should also be relevant for East Asian populations.

I then developed and ran the Asian Australian Health Study to derive more detailed data on vitamin D deficiency in East Asian immigrants. This small community-based cross-sectional study allowed an in-depth exploration of different measures of acculturation in the more homogeneous Northeast Asian population. A major strength of this study was that culturally sensitive instruments were used and questionnaires were available in English, Chinese, Korean and Japanese. The major limitation of this study was that it used a volunteer sample with a relatively small sample size.

In order to look at CVD risk both cross-sectionally and prospectively, I then turned to data already collected as part of the large population-based 45 and Up cohort study. This allowed the comparison of a range of CVD risk factors and outcomes between East Asian immigrants and both Australian-born and other immigrant groups. The comprehensive individual-level hospital data on CVD from administrative databases was linked to baseline data allowing objective and complete ascertainment of the outcomes of interest. However, the study of the effects of acculturation was limited by the use of an English-only questionnaire that potentially reduced participation of less acculturated and more disadvantaged immigrants. In addition, only time and language indicators were available as measures of acculturation, limiting the conceptualisations of acculturation that could be examined.

It is the complementarity of these datasets that allowed the depth of exploration possible in this thesis. Limitations within one data source in measures of acculturation were countered by richness of outcome data and large sample size; while richness of the acculturation measures was achieved in the smaller Asian Australian Health Study. Data from published studies or administrative data from the NHANES Study were able to be used to address specific research questions for which exposure and outcome data were available. Using already collected data in this way, supplemented by a small detailed study, proved an efficient and cost-efficient way in which to test the overall hypothesis of this thesis and to answer the research questions.

Effect of different acculturation measurements on estimations

This thesis used different methods to measure acculturation. A multi-item scale and time indicators for acculturation were used in the Asian Australian Health Study (Chapter 5) and the 45 and Up Study (Chapters 6 and 7) respectively. The systematic review and meta-analysis (Chapter 4) explored the potential impact of using different acculturation measures on the estimated association between acculturation and smoking prevalence. This thesis found that the magnitude of this association in men varied according to the indicator that was used to measure acculturation. Specifically, using time indicators resulted in more conservative estimates.

The impact of using different acculturation tools, in relation to estimating the association between acculturation and CVD risks, is unclear. This thesis suggests that the heterogeneity of the acculturation tools may contribute to the inconsistency in the findings from different studies (e.g. smoking prevalence in men) and also the inconsistent conclusions from previous studies. Significant changes in fundamental values and attitudes occurring as a result of acculturation are likely to be challenging to measure and to change. Public health researchers and practitioners work to identify and ameliorate health disparities from a social determinants of health framework. Acculturation can influence the relationship between some determinants of health and health outcomes as either a mediator (a variable that accounts for the relationship between the independent and dependent variables) or a moderator (a variable that affects the direction or strength of the relationship between the independent and dependent variables) (31). Thus, it is important for public health researchers to understand how the process of acculturation may be influencing health outcomes of individuals and their communities.

Recommendations for policy

The findings from the various studies in this thesis are directly or indirectly relevant to policy and policy implementation. For example, guidelines for the assessment and management of absolute CVD risk issued by the Heart Foundation and the National Stroke Foundation should include strategies to prevent an increase in smoking uptake

by Asian women, and strategies encouraging Asian men to quit smoking. The findings about the pattern of CVD risk factor profiles and CVD hospitalisation associated with immigration and acculturation provide an evidence-base for future health promotion programs in multicultural communities and identify several at-risk groups that should be targeted in such programs. The findings can also be used to guide public health strategies aimed at reducing cost and minimising disease burdens.
For Asian-born immigrants, future guidelines to assess and manage CVD risk should encourage East-Asian immigrants to identify and retain healthy facets of their traditional lifestyles such as a normal body mass index, and relatively low blood cholesterol, by continuing to eat Asian-style diets. Equally, ethnicity-specific guidelines should encourage East-Asian immigrants to recognise unhealthy low physical activity levels in less-acculturated people and encourage adoption of the host country's more active lifestyles. In the long term, such targeted health promotion messages around CVD risk may reduce the risk of hospitalisation for CVD, delay the age of first occurrence of CVD, and reduce the burden caused by CVD.

The finding that Northeast-Asian participants tended to underestimate the darkness of their skin may have implications for public health messages about sun protection that provide advice according to skin type. Current sun exposure advice is that fair skinned (i.e. skin type II) people should be able to maintain adequate 25(OH)D levels during summer by walking outside for six-seven minutes during the peak UV period with 15% of the body surface exposed (32). People with darker skin are likely to need "longer" sun exposure time than that recommended for fair-skinned people (33). The findings from the Asian Australian Health Study indicate that East-Asian people may inappropriately classify their skin type as "fair" and thus follow guidelines for fair-skinned people, resulting in being outdoors for a much shorter time than will be required for their vitamin D adequacy. In the study by Jang et al, women born in Northeast Asia reported knowledge of the need for sun protection to reduce the risk of skin cancer, but few of them reported knowledge about the benefits of sun exposure for adequate vitamin D status (14).

Outcomes and conclusions

This thesis explored the association between acculturation, putative CVD risk factors, CVD related hospitalisation, and all-cause mortality in East-Asian-born immigrants to western countries, mainly Australia. The thesis applied a variety of research methods to address the specific research questions. According to the conceptual framework of the thesis, behavioural risk factors change gradually as immigrants become acculturated to western society; these changes are evidenced by changes in the prevalence of vitamin D deficiency, as well as gender-specific changes in the prevalence of smoking. The thesis provides evidence of differences in CVD-related hospitalisation and death according to the level of acculturation. It should be noted however that the data available limit the conceptualisation of acculturation that it has been possible to explore. For example, within the smoking meta-analysis reported here, it was possible only to use a linear model, and in the studies based on the 45 & Up Study, only relatively crude time/language measures i.e. duration of residence and age at migration to Australia (which ignore episodes of return to the home country) and language spoken at home, were available. Furthermore, with the available measures of acculturation it was not possible to separate out other possible influences, such as poorer health care utilisation, poorer uptake of health messages because of language barriers, and lack of trust in Western medicine, that could also influence the risk of hospitalisation. In addition, it was not possible to explore factors such as separation, marginalization, integration and assimilation, as drivers of the changing risk exposure and CVD risk.

We have shown that, in the 45 & Up follow-up data, the incidence of CVD hospitalisation is lower in East-Asian immigrant populations than in the Australian-born population. However, our findings of changing risk factor exposure with acculturation suggest that, as East Asian immigrants become acculturated to the Australian way of life, CVD incidence within this population group may increase toward that of the Australian-born population. This thesis has identified that vitamin D deficiency may become less common, probably as immigrants become more physically active, thus reducing CVD risk. At the same time, the prevalence of smoking may increase in women, putting them at greater risk of CVD. The identification of these changing risk factor exposures that occur in association with

acculturation, suggests that there are real opportunities, with targeted, culturally appropriate health promotion materials, to maximise the opportunities within East Asian migrants to make the transition to Australia one that improves, rather than detracts from, their CVD health.

Table 1: Studies on CVD risk factors in East Asian Populations in Australia

Paper	Ethnic Group	Acculturation Measure	Outcome Measure	Conclusion
Rissel et.al, 1993 (34)	Vietnamese	None	Blood pressure, Total Cholesterol, smoking, BMI	• Smoking prevalence: 53% in Vietnamese-born males vs. 24.1% in Australian-born males • High blood pressure: 5.1% in Vietnamese-born vs 11% in Australian-born males and 5% in females • High total cholesterol:21.1% in Vietnamese-born vs 47% in Australian-born males and 39% in females • Overweight: 14.0% in Vietnamese-born vs 49% in Australian-born males and 35% in females
Hsu-Hage et al, 1993 (35)	Chinese	None	Blood pressure, total cholesterol, overweight & obesity, smoking	• Smoking prevalence:26.9% in Chinese-born males vs. 24.1% in Australian-born males • High blood pressure: 5.5% in Chinese-born males and 9.8% in Chinese-born females vs 11% in Australian-born males and 5% in females • High total cholesterol:7.7% in Chinese-born males and 5.2% in Chinese-born females vs 47% in Australian-born males and 39% in females • Overweight:17.7% in Chinese-born males 14.1% in Chinese-born females vs 49% in Australian-born males and 35% in females
Bennet et al, 1993 (6)	Asian	Duration of residence	Cardiovascular risk factors	**Risk factors compared to Australian-born individuals:** • **Smoking:** OR 1.09 (0.76-1.55) in Southeast-Asian-born males compared with Australian-born males; 0.33 (0.20-0.55) in Southeast Asian-born females compared with Australian-born females • **Mean systolic blood pressure (mmHg):** 124.3 and 127.4 in southeast and other Asian-born males vs 131.7 Australian-born males; 116.1 and 121.1 in Southeast and other Asia-born females vs, 124.6 in Australian-born females • **Mean total cholesterol (mmol/L):** 5.45 and 5.48 in Southeast and other Asian-born males vs 5.66 Australian-born males; 5.16 and 5.55 in Southeast and other Asian-born females vs 5.58 in Australian-born females

- **Mean BMI (kg/m^2):** 23.4 and 23.9 in Southeast and other Asian-born males vs 25.4 Australian-born males; 22.3 and 23.0 in Southeast and other Asian-born females vs 24.1 in Australian-born females

Risk factors differential (OR or difference in means) according to duration of residence in Australia

- **Smoking (compared to Australian-born):**
  - OR=1.61 in Asian male immigrants having lived less than fifteen years in Australia; OR=1.12 in Asian male immigrants having lived more than sixteen years in Australia
  - OR=0.51 in Asian female immigrants having lived less than fifteen years in Australia ; OR=0.47 in Asian female immigrants having lived more than sixteen years in Australia
- **Difference in mean systolic blood pressure (mmHg, compared to Australian-born):**
  - -5.1 in Asian male immigrants having lived less than fifteen years in Australia; -4.8 in Asian migrants with more than sixteen years' period of residence in Australia
  - -4.1 in Asian female migrants with less than fifteen years' duration of residence; -1.8 in Asian migrants with more than sixteen years' period of residence in Australia
- **Difference in mean total cholesterol (mmol/L, compared to Australian-born):**
  - -0.01 in Asian male migrants with less than fifteen years' duration of residence; 0.01 in Asian migrants with more than sixteen years' period of residence in Australia
  - -0.11 in Asian female migrants with less than fifteen years' duration of residence; 0.04 in Asian migrants with more than sixteen years' period of residence in Australia
- Mean BMI (kg/m^2):
  - Male: -1.3 in Asian migrants with less than fifteen years' duration of residence vs. -0.4 in Asian migrants with

				more than sixteen years' period of residence in Australia ▪ Female: -0.7 in Asian migrants with less than fifteen years' duration of residence vs. 0.3 in Asian migrants with more than sixteen years' period of residence in Australia
Hong et al, 1996 (36)	Korean students	Duration of residence	Alcohol and cigarette use	Increase of alcohol and cigarette use with longer residence was observed for women only. • Alcohol use is associated with length of residency in Australia (R^2= 0.052) • Cigarette use is associated with length of residency in Australia (R^2=0.120)
Rissel et.al, 2000 (37)	Vietnamese adolescents	Scale designed by authors for immigrant groups in Australia	Tobacco use	Increased smoking risk with greater acculturation disappears with control for contextual factors. • Current and regular tobacco use: 11%, 5%, and 8% in Vietnamese/Southeast Asia ethnic males, females, and total years 10-11 students vs 31%, 24%, and 27% in English ethnic males, females, and total • Current smoking (%) among Year 10 and 11 non-English speaking background Vietnamese/Southeast Asia students and level of acculturation: 1.4% (13/903) in low acculturation group vs 1.9% (17/903) in medium acculturation group vs 2.5% (23/903) in high acculturation group
Singh et al, 2002 (23)	Asian	None	Standardised CVD mortality and hospitalisation, tobacco smoking, alcohol consumption, physical inactivity, overweight and obesity	In comparison with Australian-born people, cardiovascular hospitalisation rates and prevalence of smoking and alcohol consumption were lower in the Asian-born population, despite low levels of exercise. Standardised prevalence relative-ratio (95% CI) • CVD mortality: 0.75 and 0.81 in Asian-born males and females • CVD hospitalisation: 0.75 and 0.76 in Asian-born males and females • Tobacco smoking: 0.87 and 0.27 in Asian-born males and

				females • Alcohol consumption: 0.34 and 0.25 in Asian-born males and females • Physical inactivity: 1.33 and 1.54 in Asian-born males and females • Overweight and obesity: 0.65 and 0.57 in Asian-born males and females
Gray et al, 2007 (28)	East Asian	Duration of residence	CVD and diabetes mortality	CVD and diabetes mortality did not change in relation to duration of residence in migrants from East Asia; decreasing mortality with increasing duration of residence was observed for migrants from South Asia. Relative Risk of circulatory disease and diabetes mortality (95% CI): • Age-adjusted mortality (Australian-born: 1.00): 0.37 (0.30-0.46), 0.41 (0.34-0.48), 0.39 (0.34-0.45) in 45-54, 55-64, all age groups in East-Asian immigrants • Effect of five-year increase in duration of residence on mortality in East-Asian immigrants (1998-2012): 0.99 (0.88-1.12), 1.06 (0.99-1.12), 1.01 (0.98-1.04) in 45-54, 55-64, and all age groups • Effect of duration of residence in broad categories on mortality in East-Asian immigrants (Residence Duration < 17-year: 1.00): 1.52 (0.95-2.42), 0.94 (0.62-1.42), 1.17 (0.86-1.59) in 45-54, 55-64, and all age groups with 17-31 years' residence duration; 1.20 (0.77-1.88) and 1.36 (0.93-1.99) in age 55-64 and all age groups with more than 32 years' residence duration
Weber et al, (2010) (5)	Migrants born in East Asia, Southeast Asia	Age arrived in Australia, Length of residence	Smoking	Compared with Australian-born women, a lower proportion of women from East and Southeast Asia were current smokers • Current smoker prevalence: 8.6% and 8.1% in East- and Southeast-Asian-born males vs 7.4% Australian-born males; 1.8% and 3.5% in East- and Southeast-Asian-born females vs 7.3% Australian-born females

				• Past smoker prevalence: 23.7% and 34% in East- and Southeast-Asian-born males vs 43.6% Australian-born males; 7.7% and 8.9% in East- and Southeast-Asian-born females vs 27.9% Australian-born females • Age, education, income, place of residence adjusted odd-ratio: 0.38 (0.26–0.54) in Southeast-Asian-born females and 0.21 (0.12–0.36) in East-Asian-born females, with 0.06 (0.02–0.26) in China/Taiwan/Hong Kong/Macau -born females. • Effect of "age arrived in Australia" on smoking: The odds of Asian-born women being a smoker decreased by 36% with every 10 year increase in the age they migrated to Australia (0.64, 0.51–0.81, P = 0.0002).
Lee et al, 2011(26)	Chinese	Duration of residence	Insulin resistance, Blood lipids profile	The OR for having a fasting insulin greater than 50pmol/L in Taiwanese women living in Australia for more than 5 years was 6.00 (95%CI 1.33 to 27.9) in comparison with Australians. • Blood insulin and lipid profiles (mean and standard deviation): ▪ Insulin (pmol/L): 51.7±42.2 in Taiwanese-born females vs 45.0±29.0 in Australian-born females ▪ Total cholesterol (mmol/L): 4.7±0.7 in Taiwanese-born females vs 4.7±0.7 in Australian-born females ▪ Low-density lipoprotein cholesterol (mmol/L): 3.0±0.7 in Taiwanese-born females vs 3.0±0.7 Australian-born females ▪ High-density lipoprotein cholesterol (mmol/L): 1.4±0.4 in Taiwanese-born females vs 1.4±0.3 Australian-born females • Effect of length of residence in Australia on blood insulin and lipid profiles in Chinese-born females (mean and standard deviation): ▪ Insulin (pmol/L): 32.4 ±10.5 in length of residence less than 5 years vs 50.0±32.3 in length of residence greater than 5 years ▪ Total cholesterol (mmol/L): 4.6±0.7 in length of residence less than 5 years vs 4.7±0.7 in length of

				residence greater than 5 years ▪ Low-density lipoprotein cholesterol (mmol/L): 2.7±0.7 in length of residence less than 5 years vs 2.9±0.7 in length of residence greater than 5 years ▪ High-density lipoprotein cholesterol (mmol/L): 1.5±0.3 in length of residence less than 5 years vs 1.4±0.3 in length of residence greater than 5 years
Dassanayake et al, 2011 (24)	Migrants born in Southeast Asia, Other Asia	None	Physical activity	• Prevalence of physical inactivity (95% CI): 72.45% (0.63-0.81), 66.67% (0.56-0.76) in southeast and other Asian males vs 61.67% (0.60-0.62) in Australian-born males; 76.04% (0.67-0.84) and 75.45% (0.67-0.83) in Southeast and other Asian-born females vs 72.37% (0.71-0.73) in Australian-born females • Odd-ratio of physical inactivity (95% CI): 2.04 (1.63-2.56) and 1.53 (1.10-2.13) in Southeast and other Asian-born population
Brock et al, 2012 (22)	Chinese and Korean women	Language (use, proficiency), Cultural participation (food and media preference, religious activities), Social relations (support, friends, neighbours)	Vitamin D deficiency, high non-fasting blood glucose, BMI, Waist circumference, blood pressure	40% of these women were vitamin D deficient with odd-ratio 3.1 95% CI: 0.5-18.3. 98% of the population had at least one risk factor for metabolic-syndrome, 85% had two, 55% had three and 8% had four. The finding of the association between low vitamin D status and a higher non-fasting blood glucose in this study is relevant to Asian populations who are known to be at greater risk of diabetes with increased BMI than any other ethnic group.
Tran et.al, 2013 (25)	Vietnamese	Duration of residence, age at migration, level of social interaction, and density of the Vietnam-born population in the local government area (LGA) of residence.	Various food consumption, overweight and obesity, smoking, physical activity, alcohol drinking.	Odd-ratio (95% CI): Physical Activity: • Effect of duration of residence on physical activity: 1.09 (0.71-1.68) in 20-24 years of residence vs 1.16 (0.82-1.66) in more than 25 years of residence • Effect of age of migration on physical activity: 1.38 (0.91-2.08) arrived in Australia at age 30-39 years vs 0.73 (0.51-1.05) arrived in Australia at age less than 30 years BMI: • Effect of duration of residence on BMI: 0.96 (0.63-1.46) in

				20-24 years of residence vs 0.93 (0.67-1.31) in more than 25 years of residence • Effect of age of migration on BMI: 1.19 (0.82-1.74) arrived in Australia at age 30-39 years vs 0.97 (0.68-1.38) arrived in Australia at age less than 30 years Alcohol consumption: • Effect of duration of residence on alcohol consumption: 1.57 (0.81-3.08) in 20-24 years of residence vs 1.26 (0.71-2.28) in more than 25 years of residence • Effect of age of migration on alcohol consumption: 3.11 (1.65-5.91) arrived in Australia at age 30-39 years vs 2.23 (1.21-4.13) arrived in Australia at age less than 30 years. Heart Disease: • Effect of duration of residence on heart disease: 0.41 (0.13-1.26) in 20-24 years of residence vs 1.25 (0.63-2.47) in more than 25 years of residence • Effect of age of migration on heart disease: 0.24 (0.11-0.54) arrived in Australia at age 30-39 years vs 0.17 (0.08-0.38) arrived in Australia at age less than 30 years High Blood Pressure: • Effect of duration of residence on high blood pressure: 0.81 (0.52-1.24) in 20-24 years of residence vs 0.77 (0.54-1.09) in more than 25 years of residence • Effect of age of migration on high blood pressure: 0.61 (0.41-0.88) arrived in Australia at age 30-39 years vs 0.26 (0.18-0.39) arrived in Australia at age less than 30 years.
Singh et al, 2002 (23)	Asian	None	Standardised CVD mortality and hospitalisation,	• Age-standardised CVD mortality ratio: 0.75 and 0.81 in Asian-born males and females. • Age-standardised CVD hospitalisation rate ratio: 0.75 and 0.76 in Asian-born males and females.
Gray et al, 2007 (28)	East Asian	Duration of residence	CVD and diabetes mortality	Relative Risk of circulatory disease and diabetes mortality (95% CI): • Age-adjusted mortality (Australian-born: 1.00): 0.37 (0.30-0.46), 0.41 (0.34-0.48), 0.39 (0.34-0.45) in 45-54, 55-64, all age groups in East-Asian immigrants compared to Australian-

				born individuals Association between 5-year increase in duration of residence and mortality in East-Asian immigrants: RR: 0.99 (0.88-1.12), 1.06 (0.99-1.12), 1.01 (0.98-1.04) in 45-54, 55-64, and all age groups, respectively
Dassanayake et al, 2011 (38)	Migrants born in Southern Asia, Northeast Asia, Southeast Asia	None	Acute myocardial infarction and stroke hospitalisation	• Rate ratio of acute myocardial infarction (95% CI): 0.68 (0.58-0.79) and 0.47 (0.37-0.58) in Southeast-Asian-born males and females Rate ratio of stroke (95% CI): 0.87 (0.74-1.02) and 0.85 (0.72-1.01) in Southeast-Asian-born males and females
Tran et.al, 2013 (25)	Vietnamese	Duration of residence, age at migration, level of social interaction, and density of the Vietnam-born population in the local government area (LGA) of residence.	Heart disease	**Heart Disease:** • **Duration of residence** OR: 0.41 (0.13-1.26) in 20-24 years of residence; OR: 1.25 (0.63-2.47) in more than 25 years of residence compared to Australian-born individuals. • **Age at migration** OR: 0.24 (0.11-0.54) arrived in Australia at age 30-39 years; OR: 0.17 (0.08-0.38) arrived in Australia at age less than 30 years compared to Australian-born individuals.

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