

School of Public Health

**A Case-Control Study of Risk Factors for Type 2 Diabetes Mellitus in
Vietnam**

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Declaration

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgement has been made. This thesis contains no material, which has been accepted for the award of any other degree or diploma in any university.

Signature

(Signed)

Date: September 23, 2016

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Abstract

Introduction

Type 2 diabetes mellitus (T2DM) has reached epidemic proportions worldwide. The burden of T2DM in both developed and developing countries has warranted much attention and strong actions to mitigate this disease. In the past few decades, the global prevalence of T2DM has dramatically increased. According to the World Health Organisation (WHO), about 346 million people in the world have diabetes, in which T2DM accounts for 90%. It is projected that deaths from T2DM will double from 2005 to 2030, and 80% of the mortality will occur in low and middle-income countries.

While T2DM is the fastest growing chronic disease, Asia has the largest number of cases, and the prevalence of T2DM in Vietnam has increased twofold from 2.7% in 2002 to 5.4% in 2012. Therefore, it is important to investigate whether physical activity and certain components of the traditional Vietnamese diet can offer some protection against this disease. Epidemiologic research on protective factors, together with understanding the disease mechanism, will provide an opportunity for early detection, management, control and treatment by implementing effective interventions based on the identified factors in a timely manner. However, little information is currently available on the protective and modifiable lifestyle factors in Vietnam. A case-control study was conducted to investigate the risk factors of T2DM; especially, the relationship between physical activity, tea and coffee consumption, and the risk of T2DM for the Vietnamese population. These three protective factors are modifiable and can be promoted to the population for better T2DM prevention and control. The present study represents the first analytical assessment of these three factors with regard to T2DM in Vietnam. The findings provide epidemiological evidence for better understanding, control and prevention of T2DM in this developing country.

Methods

Recruitment of participants took place at one hospital in Hanoi located in northern Vietnam. A total of 600 incident T2DM patients and 600 hospital-based controls were recruited during 18 months of data collection at the tertiary hospital. Frequency matching on age and gender between case and control groups was applied during subject recruitment, upon satisfying the prescribed selection criteria. The WHO diagnostic criteria of 2006 for T2DM were used to confirm the disease status. Face-to-face interviews were conducted using a validated and standardised questionnaire, specifically a food frequency questionnaire (FFQ) developed for the Vietnamese population. Detailed information was sought on demographic characteristics, dietary habits and lifestyle including alcohol drinking, tobacco smoking and habitual physical activity. The reference period of the FFQ was set before the first diagnoses of T2DM for cases and excluding subjects who had changed dietary habits. Descriptive statistics, logistic regression analyses were conducted to assess the associations between exposure variables of interest, namely, tea and coffee consumption, physical activity, and the T2DM risk. Plausible confounding factors including age (years), sex (female, male), education level (\leq secondary school, $>$ secondary school), occupation (physically heavy job, physically light job), family history of diabetes in first-degree relatives (yes, no), alcohol consumption (yes, no), smoking status (never, former, current), body mass index (BMI) (kg/m^2), waist-hip ratio (high WHR: males ≥ 0.9 , females ≥ 0.85 , low WHR: males < 0.9 , females < 0.85) hypertension (yes, no), total cholesterol (mmol/l), and total energy intake (kcal). Both crude and adjusted odds ratios (ORs), together with their 95% confidence intervals (CI) and corresponding test of linear trend, were examined to ascertain the apparent relationships.

Results

A total of 1198 eligible participants (599 cases and 599 controls) were available for analysis. The average age of participants was 58.4 years (SD 6.6) and 46% were men. The mean age was 58.1 (SD 6.6) for men and 58.7 (SD 6.5) for women.

Tea consumption: In univariate analysis, tea consumers had a significantly lower risk of T2DM than non-consumers (OR 0.76, 95%CI 0.60 to 0.96). Adjustment for potential confounders including demographics, clinical variables, biomarkers, and anthropometrics did not alter the result much (OR 0.75, 95%CI 0.57 to 0.99). Similarly, compared to non-consumers, individuals consuming >4 cups of tea per day was associated with T2DM (OR 0.67, 95%CI 0.48 to 0.93). The inverse association remained significant after accounting for plausible confounding variables (OR 0.59, 95%CI 0.40 to 0.87). Participants with cumulative exposure >40 cup-years or >10 years of tea consumption had significantly lower risks of T2DM when compared to their counterparts at the same consumption level, the respective OR (95% CI) being 0.65 (0.47 to 0.91, P for trend 0.013) and 0.66 (0.47 to 0.92, P for trend = 0.015). These results indicated that regular green tea consumption was associated with a decreased risk of T2DM.

Coffee consumption: Overall, participants who consumed 1-3 cups of coffee per day were associated with a lower risk of T2DM than non-consumers (OR 0.55, 95%CI 0.34 to 0.88, P for trend <0.05) after adjusting for confounders. Women consuming 1-3 cups of any type of coffee daily were associated with a reduced odds (OR 0.25, 95%CI 0.11 to 0.55, P for trend <0.001) relative to non-consumers. A similar relationship was also observed for men, albeit statistically non-significant (OR 0.94, 95%CI 0.50 to 1.79, P for trend 0.525).

Physical activity: The control subjects reported significantly longer duration of moderate activity and physically more active in daily life than their diabetic counterparts. Increased engagements in such leisure time activities were associated with reduced T2DM risk after adjustment for confounding factors. A significant inverse dose–response relationship was also evident for total physical activity exposure, with adjusted OR 0.66 (95%CI 0.48 to 0.91) for engaging in 26 or more metabolic equivalent tasks (MET)-hours per week, relative to those with less than 13 MET-hours per week.

Conclusions

The findings of this case-control study suggested inverse associations between regular and long-term tea and coffee consumption and the risk of T2DM among Vietnamese adults. The study also provided epidemiological evidence that habitual physical activity could reduce the risk of T2DM, which is important for the promotion and encouragement of leisure time exercise activities to prevent the onset of this chronic disease.

Abbreviations

2h-OGTT	2 hours-oral glucose tolerance test
ADA	American Diabetes Association
BIA	Bioelectrical impedance analysis
BMI	Body mass index
CI	Confidence interval
CVD	Cardiovascular diseases
EGCG	Epigallocatechin-3-gallate
EPIC	European Prospective Investigation into Cancer and Nutrition
FFQ	Food frequency questionnaire
GDM	Gestational diabetes mellitus
HDLC	High density lipoprotein cholesterol
IDF	International Diabetes Federation
IPAQ-SF	International physical activity questionnaire-short form
IR	Insulin receptor
IRS	Insulin receptor substrate
JNK	c-Jun N-terminal kinase
LDLC	Low density lipoprotein cholesterol
MEC	Multiethnic Cohort
MET	Metabolic equivalent tasks
NEFA	Non-esterified fatty acids
OR	Odds ratio
PI3KAkt	Phosphatidyl inositol 3 kinase
PKC	Protein kinase C
ROS	Reactive oxygen species
RR	Relative risk
SD	Standard deviation
T2DM	Type 2 diabetes mellitus
WC	Waist circumference
WHO	World Health Organisation
WHR	Waist-hip ratio

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CHAPTER 1: INTRODUCTION

This chapter provides an overview of the epidemiology of type 2 diabetes mellitus (T2DM) and systematically reviews the associated factors of T2DM in Vietnam. Particularly, a case-control study design including location, objectives, and its significance will be presented. The chapter will also briefly describe the scope and contents of next chapters.

1.1 Background

T2DM has reached epidemic proportion as a non-communicable disease (Zimmet, Alberti, and Shaw 2001). The burden of T2DM in both developed and developing countries has warranted attention and urgent actions to mitigate the effect of this disease. Its high prevalence has raised a concern on the global burden of T2DM (Hu 2011). According to the WHO (2011), about 346 million people in the world have diabetes, in which T2DM accounts for 90%. It is projected that deaths from diabetes will double from 2005 to 2030. In 2004, it was estimated that about 3.4 million people worldwide died from consequences of high blood sugar, and 80% of deaths occurred in low and middle-income countries (WHO 2011).

Vietnam is a developing country facing the emerging burden of T2DM because the nutritional transition and lifestyle have been changing fast for the last two decades (Bassett 2005, Khan and Khoi 2008) from the traditional Vietnamese diet to Westernised diet and become more sedentary. Epidemiology and risk factors of T2DM in Vietnam is little known, despite several cross-sectional studies have been conducted in the past decades. Therefore, the epidemiology of T2DM including its prevalence and associated risk factors are systematically reviewed to demonstrate the high demand for analytical studies.

According to the 2012 national diabetes report (National Hospital of Endocrinology 2012), the occurrence of T2DM was estimated to be 5.4% overall in Vietnam but varied between rural (5.2%) and urban (6.7%) areas (Pham and Eggleston 2016). It was anticipated that the prevalence of T2DM would continue to rise due to changes in the dietary pattern of healthy foods and lifestyle and no effective action being taken (National Hospital of Endocrinology 2012). It is important to investigate whether physical activity and certain components of the traditional Vietnamese diet can offer protection against this chronic disease. Among protective factors for T2DM, physical activity is one of modifiable factors for an effective intervention to reduce the incidence of T2DM. For example, in the general population, walking 2.5 hours a week is associated with a 63% reduction in developing T2DM compared to walking less than one hour a week (Jeon et al. 2007). Recently, the beneficial roles of tea and coffee consumption in regard to reduced risk of T2DM have been suggested in several populations, but inconsistent findings remained. Vietnam is one of the Asian countries that have the traditional culture of daily green tea consumption. Coffee is widely produced in Vietnam. Although it is perceived that a low proportion of coffee drinkers, the increasing trend of consumption has been shown recently. Therefore, tea, coffee consumption and physical activity are given a priority to investigation related to T2DM risk. This type of research may offer opportunities to develop population-based strategies for T2DM prevention. In view of the rising prevalence of T2DM, a hospital-based case-control study was conducted to investigate the association between modifiable risk factors namely; tea and coffee consumption, physical activity and T2DM risk among Vietnamese adults. The hospital setting was chosen to recruit newly diagnosed cases of T2DM based on their blood testing results, which would be difficult to implement in community based-clinics.

1.2 Study location

Hanoi city is the capital of Vietnam located in the North region with approximately 3.4 thousand km² (Figure 1). According to the 2009 Vietnam Population and Housing Census, the population of Hanoi was 6.5 million in which about 1.6 million aged 40-65 years. Residents lived in urban area accounting for 40%.

1.3 Study design

A case-control study was conducted to determine the risk factors of T2DM. Recruitment of participants took place at one hospital located in Hanoi, Vietnam. A total of about 600 newly diagnosed T2DM cases and 600 hospital-based controls (free of T2DM) were recruited during the period of data collection, 2013-2015. Frequency matching on age and gender between case and control groups was implemented, during the recruitment of participants. The WHO diagnostic criteria of 2006 for T2DM were used to confirm the disease. Face-to-face interviews were conducted by using a questionnaire, which has been validated and standardised for the Vietnamese population. The survey included demographic, lifestyle and food frequency questionnaire. Adjusted odds ratios were calculated to assess the associations between exposure variables of interest, namely tea and coffee consumption, and physical activity, and T2DM risk.

1.4 Objectives of the study

The primary aim was to ascertain the protective factors of T2DM in Vietnam. Specifically, the roles of tea and coffee consumption and physical activity on the T2DM prevalence were investigated. The particular objectives of the study were as follows:

1. To systematically review the prevalence of, and risk factors for, T2DM in Vietnam;
2. To evaluate the association between tea consumption and the risk of T2DM;

3. To assess the association between coffee consumption and the risk of T2DM;
4. To examine the relationship between habitual physical activity and the risk of T2DM.

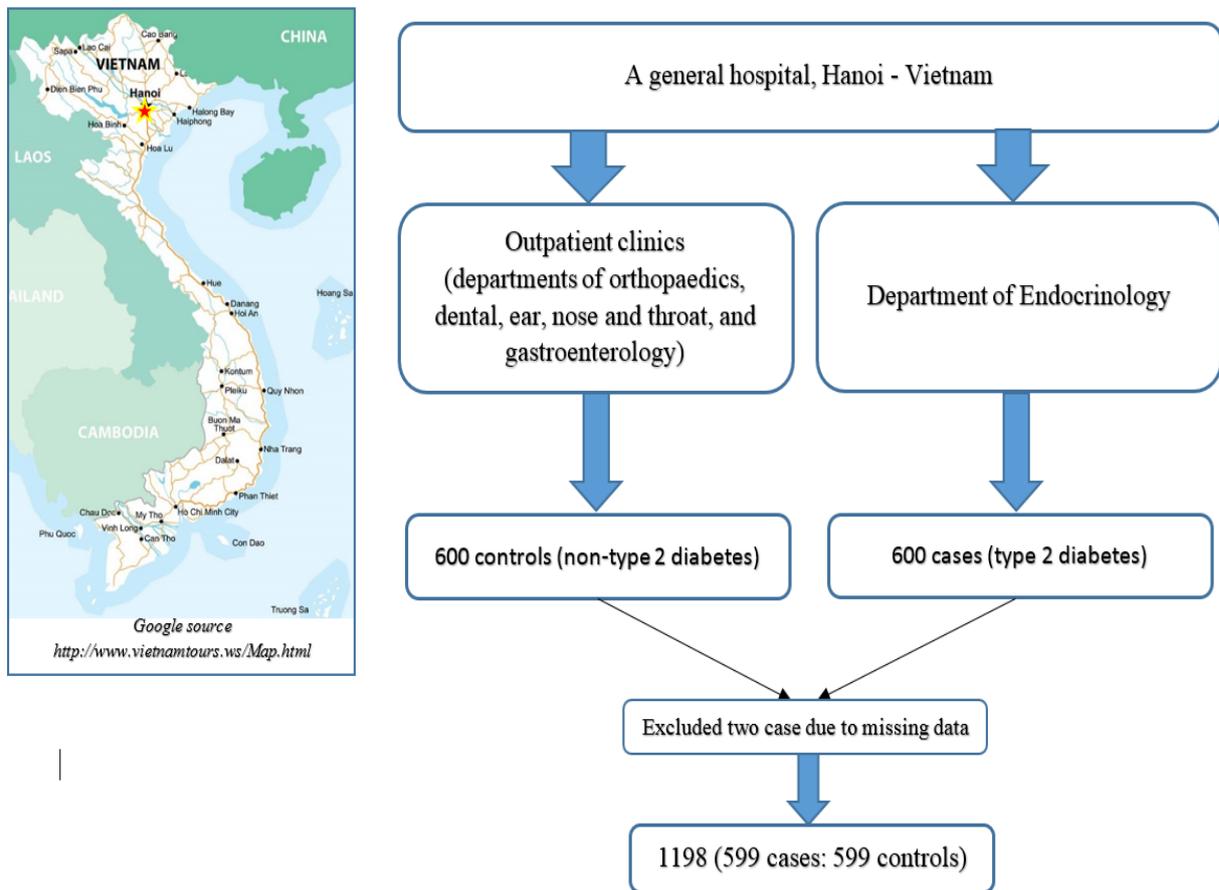


Figure 1: Study location (Hanoi city) and data collection procedure

1.5 Significance of the Study

The proposed study presents the first attempt to investigate the role of tea and coffee beverages and physical activity on the T2DM prevalence in Vietnam. Although little is known about T2DM in Vietnam, an upward trend in prevalence has been evident in recent years; probably due to rapid economic development, dietary changes and sedentary behaviours influenced by the transition to modern lifestyle during the past decade. Therefore, it is important to conduct an epidemiological study to provide information on associated factors with T2DM pertinent for the Vietnamese people. In particular, this study aims to assess the strength of associations

between tea and coffee consumption and the risk of T2DM. Furthermore, we also assess the relationship between physical activity and the risk of T2DM among Vietnamese adults. While existing evidence for their effect appears to be inconsistent across different populations, the present case-control study will address the gap in the literature, especially since tea and coffee are the daily consumed beverages in Vietnam. From the perspective of public health, findings of the present study have important implications for primary prevention of this emerging chronic disease through modifying behaviour and lifestyle.

1.6 Scope of the study

A hospital-based case-control study was implemented at Thanh Nhan Hospital, which is located in the catchment covering both rural areas and urban areas of Hanoi. The hospital is a general hospital of Hanoi consisting of 600 beds, 39 departments and 853 staff. According to an annual report, there were more than 300,000 patients, of whom half were inpatients, treated in this hospital in 2009. About 5,000 diabetic patients were treated, monitored, and managed by the hospital in 2012. It was estimated that on average 30-40 cases of T2DM patients are newly diagnosed per month, which met the sample size requirement of this study design within the data collection time frame.

1.7 Outline of the thesis

This thesis consists of six chapters. Chapter one provides a brief introduction of T2DM and an overview of the study location. The first chapter also includes the study design, objectives, significance and scope of the study.

Chapter two reviews the pertinent literature on the topic of the study. It provides a review of T2DM epidemiology and associated factors with T2DM in Vietnam. The risk or protective

factors related to T2DM will also be elaborated and briefly discussed in various sections of the second chapter.

Chapter three presents the methodology used in the study, which includes the issues on study instruments, ethical considerations, sample size calculation, the procedures of data collection and management, data cleaning, and statistical analysis.

Chapter four provides the detailed results of the study. It also encompasses some comparisons and sensitivity analyses of subgroups of interest.

Chapter five gives discussions of the results, particularly on the findings from the study in relation to the literature and previous studies. The chapter also summarises the limitation of the study.

Chapter six provides the conclusion and makes recommendations for future research and T2DM prevention programmes.

Ethics approval letters, information sheet, consent form, questionnaires, publications and other relevant documents are enclosed in the Appendices.

To summarise, along with rapid economic growth and urbanisation, Vietnam is one of the Asian developing countries that has experienced lifestyle and dietary changes towards unhealthy foods, including increasing fat and meat consumption (Khan and Khoi 2008). There are also concerns about increasing physical inactivity (Ta 2008, Ta et al. 2010, Le et al. 2004), tobacco smoking (WHO 2010a), and alcohol overuse (Giang et al. 2008) among Vietnamese

adults. Increased life expectancy (Hoi et al. 2009) has resulted in a rapid growth in the number of older persons, partly contributing to a high prevalence of T2DM. However, no analytical studies have been conducted to provide evidence of the role of regular tea and coffee consumption and habitual physical activity on T2DM in Vietnam. Therefore, this case-control study serves as the first analytical epidemiologic study to investigate the associations between these factors and T2DM risk among Vietnamese adults. Its findings may contribute to the development of national policy on the prevention and control of T2DM in Vietnam.

CHAPTER 2: LITERATURE REVIEW

This chapter describes the general epidemiology of T2DM and examines the associations between tea and coffee consumption, and physical activity and the risk of T2DM. Some materials presented in this chapter have been published in the journal article (Nguyen et al. 2015).

2.1 Global trend and burden

The prevalence of T2DM is increasing dramatically in the world, especially in low and middle-income countries. According to the recent review conducted by Bruno and Landi (2011), it is predicted that China and India will have the greatest numbers of people affected by this disease. In developed countries, the upward trend of T2DM is more noticeable than that of developing countries. However, the trend may be mainly explained by the prolonged survival of patients and the increase in life expectancy of the population. In other words, T2DM is more likely to occur amongst elderly people in Western developed countries.

Studies have indicated that onset at the younger age is becoming a tendency (Alberti et al. 2004). Therefore, T2DM will impose its burden not only on individuals but also on the health care systems in many societies (Bruno and Landi 2011). Unlike developed countries, T2DM has become a new epidemic and a major public health problem in low and middle-income countries. The prevalence of T2DM is increasing in both urban and rural areas but tends to be higher in urban areas. This tendency may reflect a difference in the pace of urbanisation and industrialisation between urban and rural areas (Ramachandran, Ma, and Snehalatha 2010).

Furthermore, differences in lifestyle and dietary patterns may also explain the lower number of patients in rural areas compared to that of urban areas (Pham and Eggleston 2016). For instance, in a systematic literature review of South Asian countries, Gupta and Kumar (2008) showed that current prevalence rates were 5-16% in urban areas and 2-8% in rural areas. A population-based survey with 4,757 participants aged over 20 years in Bangladesh in 2006 showed that prevalence of T2DM in rural areas was 6.8% compared to 2.3% in an earlier survey ($P < 0.05$) (Rahim et al. 2007).

Regardless of the increasing number of new cases of T2DM, those who suffered from the disease faced its complications, reduced quality of life, increased health care–related costs, and risk of other chronic diseases (Tan 2004, Benhalima et al. 2011). Unlike infectious diseases which usually have specific biological agents such as viruses, microbacteria, fungi, and protozoa, T2DM is a non-communicable disease with its onset depending much on genetic, anthropometric, and environmental factors. For public health practice, modifiable factors such as dietary factors and lifestyle can be changed to prevent, manage, and control T2DM.

Furthermore, recent studies showed that the epidemiological features of T2DM can vary amongst countries significantly, especially in low and middle-income countries. This characteristic may offer many opportunities for investigating T2DM worldwide. For example, the most commonly used predictor for the development of T2DM is overweight and obesity. However, the use of BMI cut-points for Caucasians to classify overweight and obesity may not be appropriate to Asians (WHO 2000). Therefore, the WHO has advised using BMI more flexibly in different populations (WHO 2004).

Although there are reliable estimates of the global or national prevalence of T2DM, these estimates are local and incomparable across the world. Many factors affecting the estimation of prevalence have been noted, such as place of residence, country of residence, ethnicity, lifestyle, obesity, socio-economic status, race, gender, age and so on (Jain and Saraf 2010). None of the studies so far have all such information to estimate the T2DM prevalence. However, the upward trend of T2DM in almost all countries has been identified and warranted further public health actions to prevent and control this epidemic effectively. Besides, many studies revealed that rural areas are less affected by T2DM when compared with urban areas. However, high undiagnosed T2DM in rural areas were problematic in many developing countries, which may underestimate its T2DM prevalence compared to its urban counterpart (Dong et al. 2005).

Premature morbidity and mortality are often used as indicators to assess the burden of a disease. Annually, there are about 4 million deaths worldwide due to T2DM, which is almost the same as the number of deaths attributed to smoking (The Lancet Editorial 2009). Patients with T2DM tend to have co-morbidity such as cardiovascular diseases (CVD) (Huxley et al. 2015). This co-morbidity not only affects diabetic patients but also has a large impact on the health care system. For example, Mody and colleagues (2006) assessed the effects of cardiovascular co-morbidity on total and diabetes-related healthcare costs in the year 2002 in the United States. The result indicated that T2DM patients with cardiovascular co-morbidity had significantly higher total healthcare cost compared to those who had no co-morbidity.

Increasing mortality in T2DM is associated with multiple risk factors. A systematic review and meta-analysis showed that approximately a two-fold increase in the mortality risks in T2DM when compared with the general human population (Nwaneri, Cooper, and Bowen-Jones

2013). A ten-year cohort study conducted in New Zealand indicated that glycaemic parameters were more strongly associated with the mortality rate for ten years of follow-up than six months of follow-up (Florkowski et al. 2001). An intervention study aimed to avert complications related to glycaemic control, involving management of hypertension and dyslipidaemia, in order to reduce the mortality of T2DM in Denmark. After six years of follow-up, the intervention altered the risk of T2DM related complications but could not reduce the mortality rate (Gagliardino 2002).

In contrast, a study of Japanese–American men and women found that T2DM was a strong independent risk factor for cardiovascular mortality (Imazu et al. 2002). The major causes of increased mortality amongst T2DM patients include cardiovascular diseases and infection-related complications. Cardoso and Salles (2007) concluded that there was a six-fold excess infection-related mortality amongst T2DM patients when compared to the general Brazilian population. Micro-and macro-vascular complications such as diabetic retinopathy and blindness were identified as the main risk factors for the increased mortality in T2DM patients (Adler et al. 2000, Holman et al. 2008).

Costs of diagnoses, treatment, and care for T2DM have large economic impacts on patients, families, and health care systems in many countries. The WHO (2005) estimated that China would spend about \$558 billion in fixed national income for heart diseases, stroke, and diabetes alone in the period 2006-2015. Rodbard and co-workers (2010) conducted a study of 3,551 participants in the United States and concluded that out-of-pocket expenses for both annual medical cost (\$1,158) and monthly prescription cost (\$144) of T2DM patients were significantly higher than those of the non-diabetic group. A large survey in China in which direct medical costs of T2DM with or without complications were evaluated, indicated that the

high economic burden placed a challenge to the health care system. Furthermore, that study also reported that the annual direct medical expense of T2DM patients with complications (\$1,080) including micro-and macro-vascular diseases was significantly higher than that of patients without complications (\$514) (Wang et al. 2009). The United Nations and the WHO predicted that in 2030, about \$490 billion would be spent on diabetes globally. In addition, about \$1,330 per person was anticipated to spend on diabetes in 2010 (Zhang 2010).

According to the International Diabetes Federation (IDF) (2015), the T2DM epidemic influences about 387 million people worldwide in 2014, approximately 46% of those affected aged from 40 to 59 years. The total number of people with diabetes will rise steeply to 642 million by 2040 if no prevention and control strategies are implemented. In 2006, the IDF estimated that Eastern Mediterranean and the Middle East were regions with high rates of affected people in the world with 9.2% and then followed by North America with 8.4%. However, the largest numbers were found in the Western Pacific region, with 67 million patients with T2DM, followed by Europe with 53 million diagnosed patients. With respect to country, India still leads the global top ten of the highest number of diabetic people with 40.9 million, followed by China with 39.8 million.

T2DM is a chronic disease and as it progresses, it introduces multi-system complications for patients. These complications of the disease produce a tremendous impact on patients and the health care system as well. The quality of life is severely reduced when people have T2DM accompanied with complications. Both tangible and intangible costs for these patients are predicaments not only to families but also to the society. The often seen complications are micro-vascular endpoints such as retinopathy, neuropathy and macro-vascular endpoints including ischaemic heart disease, stroke, and peripheral vascular illnesses. People with T2DM

are vulnerable to other diseases. In particular, patients with T2DM are about four times more likely to develop CVD than the general population (Barr 2007) and have a five-fold greater risk of dying from these conditions (IDF 2015). Apparently, complications of T2DM not only add to the overall burden but also increase the mortality rate of this disease.

2.2 Vietnam

2.2.1 Epidemiology

Once T2DM was considered as a disease of affluent countries, but now it has also become a public health priority for developing countries. The prevalence rate of T2DM in Asia has increased rapidly in the past decade, characterised by young age of onset and low BMI (Chan et al. 2009). It was estimated that 387 million people suffering from this disease worldwide in 2014, of which 213 million reside in Asia (75 million in South East Asia and 138 million in Western Pacific). Furthermore, about 3.6 million patients died annually from diabetes related causes in this region (IDF 2015).

In Vietnam, epidemiological characteristics of T2DM are little known compared to other countries in the Asian region. A recent national survey reported that an overall prevalence rate of T2DM in the Vietnamese population was 5.4% in 2012 (National Hospital of Endocrinology 2012). However, this prevalence is more likely to be underestimated because of the use of fasting blood glucose for testing (Wahl et al. 1998). Understanding the risk factors is critical for effective prevention and control strategies for T2DM. The etiology of T2DM is characterised by the interaction between environmental and genetic factors. While the association between T2DM and genetic factors is strong (Hara et al. 2014), other modifiable risk factors including diet and lifestyle play an important role in the occurrence of T2DM (Chan

et al. 2009). Unhealthy diets (Ley et al. 2014), physical inactivity (Schellenberg et al. 2013), passive and active smoking (Zhu et al. 2014, Willi et al. 2007), and excessive alcohol intake (Wei et al. 2000) are common modifiable risk factors for T2DM.

Along with rapid economic growth and urbanisation, Vietnam is one of the Asian countries that has experienced dietary changes, including increasing fat and meat intakes (Khan and Khoi 2008). There are also concerns about increasing body size (Ta 2008, Ta et al. 2010, Le et al. 2005), physical inactivity (Ta 2008, Ta et al. 2010, Le et al. 2004), tobacco smoking (WHO 2008b), and alcohol overuse (Giang et al. 2008) among Vietnamese adults. Meanwhile, increased life expectancy (Hoi et al. 2009) has resulted in a rapid growth in the number of older persons, and low health care expenditure (Palmer 2014) are also contributing to a high prevalence of T2DM. These changes are all potentially contributing to the accelerating prevalence of T2DM in Vietnam. During the past two decades, in this country, a number of epidemiological studies on T2DM have been undertaken at both national (National Hospital of Endocrinology 2012, Ta 2008, National Hospital of Endocrinology 2002) and regional levels (Ta et al. 2010, Quoc et al. 1994, Tran et al. 2012, Pham and Eggleston 2015). Synthesis of these epidemiological data can provide a better understanding of the prevalence and trends, and suggest solutions to addressing the problem. Therefore, a systematic review of epidemiological studies in Vietnam on T2DM was performed to address secular prevalence trend and its risk factors.

We performed a systematic literature search through PubMed, Web of Science, Wiley Online Library, and Scopus databases in 2 steps. First, we identified relevant publications using the key words: diabetes, diabetes mellitus, type 2 diabetes, type 2 diabetes mellitus,

hyperglycaemia, Vietnam without any restriction on the type, year, and language of publication. Second, we eliminated duplicated articles retrieved from the aforementioned databases. In the next stage, we checked the titles and abstracts of each identified article for eligibility based on the following selection criteria:

Inclusion criteria

- Primary data, population-based epidemiological studies
- Hospital-based studies

Exclusion criteria

- Gestational diabetes
- Type 1 diabetes
- Latent autoimmune diabetes in adults
- Letters, commentaries, and editorials

We extended our search to published reports from Web sites of the WHO and IDF. We also searched the reference lists of selected articles and recruited relevant articles and national reports in Vietnamese, then contacted authors or co-authors to obtain full-text records. Finally, the full text of eligible articles and reports were evaluated and synthesized in this review. This systematic review was conducted according to the PRISMA guidelines (Moher et al. 2009).

2.2.2 Trend in the prevalence

Selection procedure

Figure 2 shows the PRISMA flow diagram of the systematic search. From the total 329 publications identified and retrieved from the databases and other sources, 86 articles were

found to be associated with diabetes in Vietnam after initial screening and excluding duplicates. These articles were manually checked by title and abstract, and accordingly 58 articles were found irrelevant to the inclusion criteria. Of the 18 remaining articles that met the selection criteria, we excluded one research letter, one editorial, and 6 non-full text articles. Finally, 10 original full text articles were included for this review.

Characteristics of included studies

Three studies estimated only the prevalence of T2DM (National Hospital of Endocrinology 2012, 2002, Do and Le 2008), two investigated risk factors (Le et al. 2005, Tran, Phuong, et al. 2013), and five addressed both prevalence data and risk factors (Ta 2008, Ta et al. 2010, Le et al. 2004, Quoc et al. 1994, Tran et al. 2012). The sample sizes varied from 144 to 11,191 subjects. The eight studies that estimated the prevalence all used the 1998 WHO diagnostic criteria (Alberti and Zimmet 1998), except for one that used the 1985 WHO criteria (WHO 2008b). One study (Le et al. 2004) recruited subjects aged over 15 years and the remainders selected adults aged 30 years and above (National Hospital of Endocrinology 2012, Ta 2008, Ta et al. 2010, National Hospital of Endocrinology 2002, Quoc et al. 1994, Tran et al. 2012, Do and Le 2008) (Table 1). Risk factors and their odds ratios (ORs) with 95% confidence interval (95% CI) for T2DM are presented in Table 2. All selected studies meet the level III of evidence which is recommended by the National Health and Medical Research Council of Australia (2009).

Prevalence of T2DM

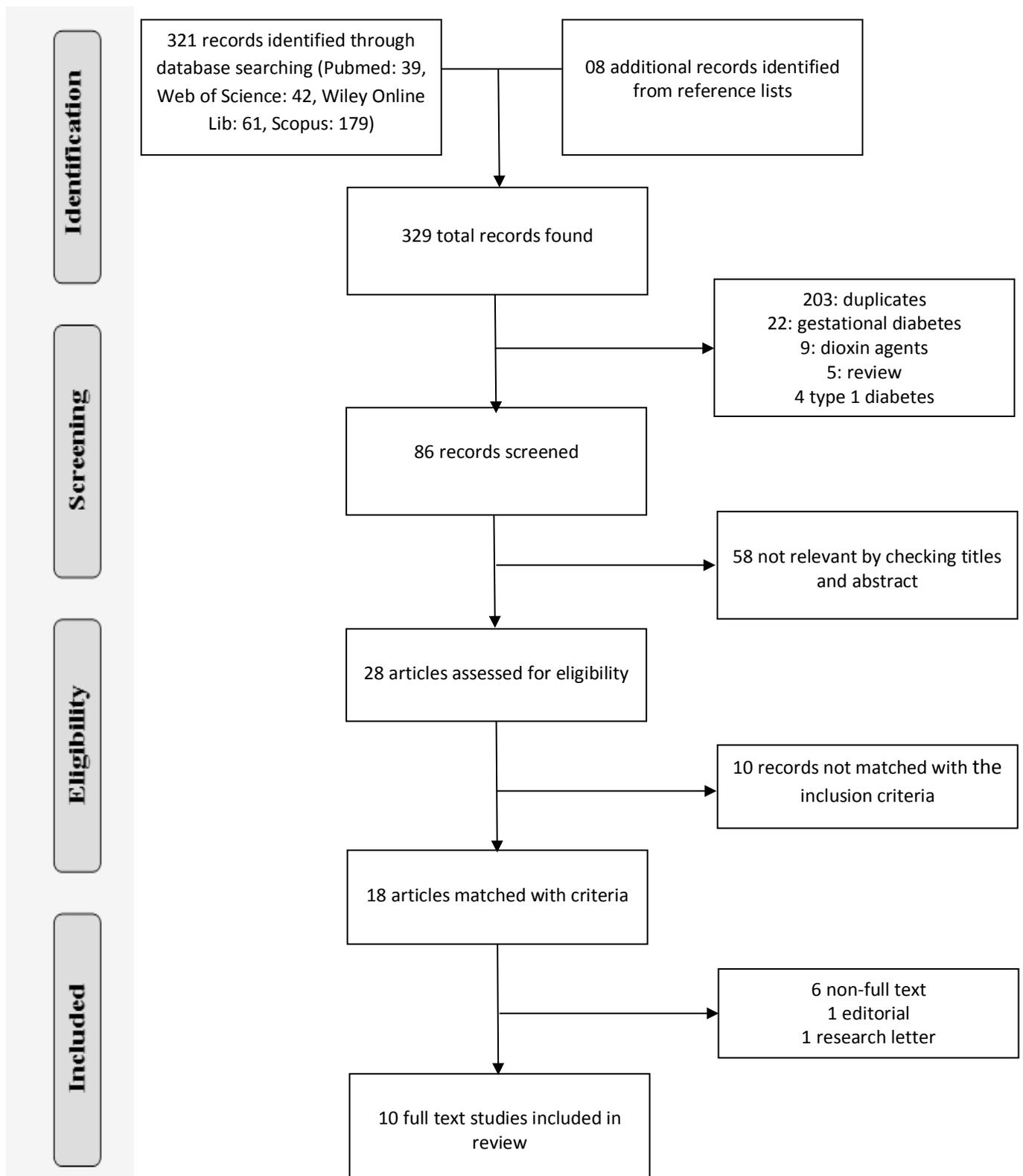


Figure 2: PRISMA flow diagram for study selection in the systematic review on trends in prevalence and risk factors of T2DM in Vietnam (1994-2012)

The prevalence of T2DM was estimated regionally and nationally between 1994 and 2012 (Table 1). Data derived from two national surveys which used the same 1998 WHO criteria showed that aged-standardised prevalence rates were 2.7% in 2002 (National Hospital of Endocrinology 2002) and 5.4% in 2012 (National Hospital of Endocrinology 2012). The prevalence rates of T2DM in the northern region were 1.4% in 1994 (Quoc et al. 1994) and 3.7% in 2012 (Tran et al. 2012); the corresponding rates in the southern region were 3.8% in 2004 (Le et al.), 7.0% in 2008 (Do and Le), and 12.4% in 2010 (Ta et al.).

2.2.3 Risk factors

Demographic factors

T2DM is a chronic disease that is accelerated by the ageing population. A range of evidence showed that increasing prevalence and incidence of T2DM are associated with advancing age (WHO 2010b). In Vietnam, the prevalence of T2DM increased with age and the highest prevalence was found in subjects of over 65 years old (Le et al. 2004). The association between age and T2DM prevalence was examined in two studies (Ta 2008, Le et al. 2004), showing that increasing age was positively associated with higher prevalence of T2DM; the OR (95% CI) among subjects aged ≥ 45 relative to under 45 year-old group was 3.5 (2.1 to 5.8) (Ta 2008), and the correspondent values among those aged ≥ 40 versus under 40 year-old group was 3.3 (1.9 to 5.5) (Le et al. 2004). There was no measurable difference in prevalence of T2DM between men and women as reported by the two national surveys (National Hospital of Endocrinology 2012, 2002). However, two regional studies revealed that women were more likely to have T2DM than men; ORs (95%CI) were 2.3 (1.3 to 4.1) in an earlier study (Quoc et al. 1994) and 1.8 (1.2 to 2.8) in a more recent one (Le et al. 2004).

Table 1: Prevalence of T2DM in Vietnam: a systematic review 1994-2014

Source	Region (City/province)	Age	Study design	Sample size	% T2DM (95% CI)	Diagnostic criteria
Quoc, Chartles et al. 1994 (Quoc et al. 1994)	North (Hanoi City)	30-64	Cross-sectional	4,912	1.4 (0.9 to 1.8) (adjusted, M/F: 0.7/1.8)	WHO1985: 2h-OGTT \geq 11.1 mmol/l OR Fasting capillary blood glucose \geq 6.7 mmol/l (whole blood) OR self-report
National Hospital of Endocrinology 2002 (National Hospital of Endocrinology 2002)*	Nationwide	30-64	Survey	9,122	2.7 (2.4 to 3.1) (adjusted [†])	WHO1998: Fasting plasma glucose \geq 7mmol OR 2h-OGTT \geq 11.1mmol/l
Le et al.2004 (Le et al. 2004)	South (Ho Chi Minh City)	>15	Cross-sectional	2932	3.8 (3.5 to 4.1) (adjusted [†])	WHO1998/ADA1997: Fasting plasma glucose \geq 7mmol/l OR using hypoglycaemic treatment OR self-report
Do and Le 2008 (Do and Le 2008) *	South (Ho Chi Minh City)	30-69	Cross-sectional	1,456	7.0 (5.7 to 8.4) (crude, M/F: 8.2/5.5)	WHO1998: Fasting plasma glucose \geq 7mmol OR 2h-OGTT \geq 11.1mmol/l OR self-report
Ta 2008 (Ta 2008)*	4 major cities (Hanoi, Ho Chi Minh, Haiphong, Danang)	30-64	Cross-sectional	2,394	4.0 (3.3 to 4.9) (adjusted, M/F: 6.0/5.2)	WHO1998: Fasting plasma glucose \geq 7mmol OR 2h-OGTT \geq 11.1mmol/l
Ta, Nguyen et al. 2010 (Ta et al. 2010)	South (Ho Chi Minh City)	30-72	Cross-sectional	2,142	12.4 (11.0 to 13.8) (crude, M/F: 10.8/11.7)	WHO1998: Fasting plasma glucose \geq 7mmol OR 2h-OGTT \geq 11.1mmol/l
Tran, Phuong et al. 2012 (Tran et al. 2012)	North (Hanam province)	40-64	Cross-sectional	2,710	3.7 (2.7 to 4.7) (adjusted, M/F: 4.6/2.9)	WHO1998: Fasting plasma glucose \geq 7mmol OR 2h-OGTT \geq 11.1mmol/l OR self-report
National Hospital of Endocrinology 2012 (National Hospital of Endocrinology 2012)*	Nationwide	30-69	Survey	11,191	5.4 (4.8 to 6.0) (adjusted, M/F: 6.0/5.4)	WHO1998: Fasting plasma glucose \geq 7mmol OR 2h-OGTT \geq 11.1mmol/l

*Articles are in Vietnamese.

[†] No sex-specific prevalence rate.

ADA: American Diabetes Association. M: male. F: female. 2h-OGTT: 2 hours-Oral Glucose Tolerance Test.

In addition, the present review indicated that urban residents were more likely to have T2DM than their rural counterparts; OR (95%CI) for T2DM were 1.3 (1.0 to 3.2) (Quoc et al. 1994) and the prevalence of T2DM in urban and rural populations were 4.4% and 2.3%, respectively (National Hospital of Endocrinology 2002).

Anthropometric parameters

Anthropometric features of T2DM vary between countries and races. Anthropometric factors reviewed in this chapter are BMI and waist-hip ratio (WHR). Amongst the five articles retrieved for Vietnam, there was only one article mentioning central obesity (Ta et al. 2010). The authors stated that the risk of having T2DM was increased by 6.4-fold (95%CI 3.2 to 13.0) in males and 4.1-fold (95%CI 2.2 to 7.6) in females when comparing between central obesity group and non-central obesity group. They also reported that higher WHR and hypertension were independently associated with elevated risk of T2DM. Another study similarly indicated that lower BMI values should be used for classifying overweight and obesity to evaluate the risk of T2DM in Vietnam (Duc et al. 2005).

BMI is commonly used to identify and classify overweight and obesity in epidemiological studies. However, the index may not be appropriate to all races in the world to study T2DM risk. Western and Asian people do not share the same cut-off values of BMI in the classification of overweight and obesity (Barba 2004). The WHO (2004) has approved new criteria for classifying overweight and obesity applicable to Asians. BMI cut-off values for Asians were lower than those of Caucasians in evaluating T2DM risk. For instance, a review of anthropometric characteristics in Vietnam suggested that lower cut-off values of BMI and WHR (0.90 for males and 0.85 for females) should be applied to T2DM related studies in Vietnam because BMI was similar between T2DM case and control groups (Duc et al. 2005).

In addition, this study also indicated that central obesity and percent body fat of Vietnamese people seemed to be higher than Caucasians. If these results are reliable, the new cut-off value of BMI will have significant implications for primary prevention and future interventions in Vietnam. A recent extensive study in China showed that even amongst the T2DM group, their mean BMI was observed to be lower than 18. Namely, there was a T2DM prevalence of 4.5% in Chinese people with a BMI of less than 18 kg/m² (Cheng 2010), which raises concerns about the effectiveness of the use of BMI values in the classification of overweight and obesity. Although BMI is a practical measure, being a crude measure, it could not distinguish between fat mass and lean mass and may underestimate T2DM risk among Asian people. A recent study suggested that a percent body fat >30 in men or percent body fat >40 in women should be used as diagnostic criteria for obesity in Vietnamese adults (Ho-Pham et al. 2015).

Indicators of abdominal adiposity such as waist circumference, WHR and waist-height ratio, are alternatives to BMI to predict the risk of CVD and T2DM (WHO 2008a). These measurements aim to reflect visceral adipose tissue associated with a range of metabolic disorders that increase the risk of T2DM. A range of evidence in the last three decades has indicated a positive association between obesity and the risk of developing T2DM based on both cross-sectional studies (Hartz et al. 1983, Skarfors, Selinus, and Lithell 1991, Shaten et al. 1993) and cohort studies (Ohlson et al. 1985, Cassano et al. 1992).

In our systematic review (Table 3), two studies showed a significantly higher odds of T2DM among overweight subjects compared with their normal-weight counterparts; ORs (95% CI) were 2.6 (1.6 to 4.0) (Ta 2008) and 1.6 (1.1 to 2.0) (Le et al. 2004) using a cut-off point of ≥ 23 and ≥ 25 (kg/m²), respectively. Of four studies presenting WHR, three reported a positive association between this parameter and T2DM prevalence, though the remainder did not. Two

studies found a significantly positive association between percent body fat determined by the bioelectrical impedance analysis (BIA) and T2DM prevalence; ORs (95%CI) per one unit increase in body fat were 1.0 (1.0 to 1.1) (Tran et al. 2012) and 1.5 (1.2 to 1.7) (Le et al. 2005). The prevalence of T2DM also increased as abdominal fat increased; ORs (95%CI) per 1 standard deviation increment (4 kg) in abdominal fat among men and women were 1.7 (1.3 to 2.2) and 1.5 (1.3 to 1.8) (Ta et al. 2010), respectively, see [Table 2](#).

These studies also suggested the consistency of relationship across the adulthood populations, in spite of differences in measurement methods of fatness and diagnostic criteria for T2DM, which reflects the strength of the association. Obviously, the risk factor of T2DM increases with increasing obesity. Many analyses of this association between obesity and onset of T2DM in adults have confirmed that abdominal obesity is an important risk for T2DM after controlling for age, smoking, and family history of diabetes. Since BMI correlates less closely with abdominal adipose tissue than waist circumference, indicators such as waist circumference and WHR have been the topic of T2DM study for the last 30 years.

A recent review revealed that anthropometric measures such as BMI, waist circumference, WHR and waist-height ratio were similar for predicting the risk of T2DM (Qiao and Nyamdorj 2010). However, most of these studies mentioned above employed a cross-sectional design and suggested that waist circumference and WHR may be more effective predictors than BMI. Although the evidence is neither totally convincing nor generalisable, these measures are still potentially useful towards estimating the risk of T2DM.

The main methodological issues that influence the ability to draw clear conclusions by anthropometric-related studies were addressed by Qiao & Nyamdorj (2010). Most research

studies utilised the sensitivity and specificity approach to determine the optimal cut-off values for anthropometric-related measures. However, the selection of these cut-off values appears to be arbitrary, because there is a trade-off between sensitivity and specificity. In reality, the high sensitivity of waist circumference measurement may be preferred in health promotion for the purpose of raising awareness of the public; whereas the high specificity of waist circumference is expected in diagnosing T2DM in clinical practice. Thus, the role of waist circumference as an initial diagnostic tool of T2DM is still unclear (Zimmet, Alberti, and Shaw 2001). Further cohort studies with incident cases of T2DM are required to make clearer recommendations for the use of waist circumference.

The review by Qiao & Nyamdorj (2010) suggested that the optimal cut-off points for obesity and waist circumference vary across different populations and countries. Waist circumference, WHR, and BMI cut-off values should be flexibly applied to various populations. According to the WHO (2008a), a wide range of associations were apparent between anthropometric measures and risk of T2DM; hence, it would be difficult to conclude that measures of abdominal adipose obesity are always superior to BMI in predicting the risk of T2DM.

Table 2: IDF criteria for ethnic or country-specific values for waist circumference

Country or ethnic group	Sex	Waist circumference (cm)
European	Men	>94
	Women	>80
South Asian, Chinese, Japanese	Men	>90
	Women	>80

Source: Adapted from Zimmet and Alberti (2006)

Table 3: Risk factors of T2DM in Vietnam

Source	Study design	Sample size	Year(locations)	Risk factors
Tran, Phuong et al.2013 (Tran, Phuong, et al. 2013)	Case-control study	349	2013 (Hanam province)	FTO-rs9939609polymorphism:adjustedOR=1.92(95%CI1.09 to 3.19)(perAallele)
Tran, Phuong et al.2012 (Tran et al. 2012)	Cross-sectional	2,710	2012 (Hanam province)	WHR: adjusted OR=1.5(95%CI1.2 to 1.9) Percent body fat: adjusted OR=1.0(95%CI1.0 to 1.1) Family history: adjusted OR=4.4(95%CI2.2 to 8.7) Hypertension: adjusted OR=1.7(95%CI1.1 to 2.7)
Ta, Nguyen et al. 2010(Ta et al. 2010)	Cross-sectional study	2,142	2010 (Ho Chi Minh City)	WHR (per0.07increase): adjusted OR=2.5(95%CI1.8 to 3.5) in women and 1.7(95%CI1.4 to 2.0) in men. Central adiposity (per4kgincrease): OR=1.7(95%CI1.3 to 2.2) in men and 1.5(95%CI1.3 to 1.8) in women Systolic blood pressure (per20mmHgincrease): OR=1.4(95%CI1.1 to 1.7) inmenand1.5 (95%CI1.2 to 1.5) in women.
Ta2008(Ta 2008)	Cross-sectional	2,394	2008 (Hanoi, Ho Chi Minh, Danang and Haiphong)	Age≥45:OR=3.5(95%CI2.1 to 5.8) BMI≥23:OR=2.6(95%CI1.6 to 4.0) Family history: OR=3.5(95%CI2.0 to 5.6) Hypertension: OR=2.0(95%CI1.3 to 3.0) Light physical activity (moderate and vigorous PA as reference):OR=1.6(95%CI1.0 to 2.5)
Le, Hanhetal. 2005(Le et al. 2005)	Case-control study	144	2005 (Ho Chi Minh City)	WHR: adjusted OR=1.0(95%CI0.8 to 1.5) Percent body fat: adjusted OR=1.5(95%CI1.2 to 1.7) Animal protein intake: adjusted OR=1.2(95%CI1.1 to 1.3)
Leetal.2004 (Le et al. 2004)	Cross-sectional	2,932	2004 (Ho Chi Minh City)	Age≥40:OR=3.3(95%CI1.9 to 5.5) Sex (male as reference):OR=1.8(95%CI1.2 to 2.8) WHR (normal WHR as reference):OR=2.6(95%CI1.9 to 3.6) Overweight (BMI≥25):OR=1.5(95%CI1.1 to 2.0) Having a large for gestational age baby: OR=2.7(95%CI1.6 to 4.4) Light physical activity (heavy PA as reference):OR=2.2(95%CI1.2 to 4.2) Sedentary behaviour: OR=2.1(95%CI1.2 to 4.1)
Quoc, Charlesetal.1994(Quoc et al. 1994)	Cross-sectional	4,912	1994 (Hanoi City)	Sex (male as reference): RR=2.3(95%CI1.3 to 4.1) Locality (rural as reference): RR=1.3(95%CI1.0 to 3.2)

Family history

It is well known that T2DM is in part, inherited. Many studies have confirmed that people whose first-degree relatives have T2DM were approximately three times more likely to develop the disease than those without any family history (Florez, Hirschhorn, and Altshuler 2003, Gloyn 2003, Hansen 2003). Some twin studies also found that concordance rates for monozygotic twins are considerably higher than those among dizygotic twins (Gale et al. 2001). Therefore, there is a strong association between the genetic factor and T2DM risk.

Based on the epidemiological evidence of genetic-related T2DM, one approach is to identify candidate genes (Barroso et al. 2003, Stumvoll 2004). Candidate genes are selected mostly based on the relationship between pancreatic functions and metabolic disorders. About 50 candidate genes are being studied in various populations. However, research findings remain conflicting. Amongst these genes, some promising candidates are PPAR γ (RR, 1 to 3), ABCC8 (RR, 2 to 4), KCNJ11 (RR, 1 to 2), and CALPN10 (RR, 1 to 4). Small sample sizes, different susceptibility across ethnic populations, variation in environmental exposures, and gene-environmental interactions are the possible explanations for the discrepancies. Our systematic review found cross-sectional studies in Vietnam also indicated that family history of diabetes (Ta et al. 2010) and genetic factor (FTO-rs9939609 polymorphism) (Tran et al. 2012) were related to an increased likelihood of T2DM.

Gestational diabetes mellitus

According to the WHO (2011), gestational diabetes mellitus (GDM) refers to a hyperglycaemia with onset or first recognition during pregnancy. GDM is most often diagnosed through prenatal screening. A review study (Bellamy et al. 2009) concluded that women with gestational diabetes during their pregnancy had an increased risk of developing T2DM

compared with those who had a normoglycaemic pregnancy (RR 7.4, 95% CI 4.7 to 11.5). Lauenborg et al. (2009) concluded that GDM and T2DM were positively associated.

In Vietnam, little is known about the association between GDM and risk of T2DM. However, a study carried out in Australia (Henry et al. 1993) on Vietnam-born women found that their incidence of T2DM (7.8%) was higher than those of Australian with GDM (4.3%), which deserves further investigation on GDM and T2DM risk in the future.

Dietary factors

Diet plays a vital role in human health. However, over-consumption of food may lead to excessive energy intake and result in overweight and obesity (Allison and Mattes 2009), which is closely associated with the onset of T2DM (Smyth and Heron 2006). Furthermore, high dense energy foods or beverages with high sugar content are known to increase the risk of T2DM and CVD (Ventura, Davis, and Goran 2011, Imamura et al. 2015). Fast foods and processed foods have been increasingly consumed worldwide. Low and middle-income countries usually have traditional dietary patterns that provide healthy foods for people, but now they are facing the nutritional transition and changes of food choices (Hu 2011).

People living in urban areas tend to consume more fast foods because of convenience and time saving. Vietnam is a low and middle-income country experiencing a nutrition transition (Khan and Khoi 2008). The dietary pattern has been also changed from healthy traditional pattern to an unhealthy pattern. It could be associated with the higher T2DM prevalence, which has been reported recently in the central cities. In a systematic review found a small case-control study (n=144) conducted in southern Vietnam reported that animal protein intake was positively associated with the risk of T2DM (Le et al. 2005). For low-resource countries,

investigation of traditional dietary factors, which may be protective factors for T2DM is essential.

Consumption of single dietary components such as nutrients or foods has been shown favorably associated with prevention of T2DM. For example, fruit and vegetables, cereal fiber, moderate alcohol, tea, coffee, low-fat dairy may reduce the risk of developing T2DM in human (Jiang, Zhang, and Jiang 2014, Mamluk et al. 2016, Yang, Wang, et al. 2014, Kastorini and Panagiotakos 2009). Selected nutrients contained in dietary or food components have been observed related to T2DM because they may affect glucose and insulin metabolism (Bantle et al. 2008). However, little convincing data documents their roles in the development of T2DM. Therefore, dietary-patterning analysis has been used as an alternative method to single nutrient approach because it can evaluate cumulative effects of the overall diet.

Hypertension

Hypertension and diabetes are the leading risk factors for atherosclerosis, heart attacks, and strokes. Their etiology and disease mechanisms may have shared characteristics. In the US population, hypertension presents in about 30% of type 1 diabetic patients and in 50% to 80% of type 2 diabetic patients (Landsberg and Molitch 2004). Another prospective cohort study in the United States claimed that T2DM was almost 2.5 times as likely to develop in hypertensive subjects as in subjects with normal blood pressure (Gress et al. 2000). In the Hong Kong Cardiovascular Risk Factor Prevalence Study, only 56% of people with hypertension had normal glucose tolerance and only 42% of people with diabetes had normal blood pressure (Cheung 2010). Hypertension and diabetes are found in the same individual more often than would occur by chance (Cheung et al. 2008). This may suggest that either shared genetic or environmental factors in the etiology (Cheung 2010).

Studies (Everett, Frithsen, and Player 2011, Sheng and Sun 2011) have indicated that the use of anti-hypertension medication may increase the risk of T2DM. However, others claimed that the risk of T2DM is not significantly different between the used and the non-used (Gress et al. 2000). For instance, treatment of thiazide did not increase the risk of T2DM. After controlling for confounders including age, sex, race, and use of other antihypertensive medications, hypertensive patients who were taking thiazide diuretics were not at a higher risk of developing T2DM than those not taking the medicine (relative hazard 0.91, 95% CI 0.7 to 1.1) (Gress et al. 2000). Gress et al. (2000) also observed that subjects who took angiotensin-converting–enzyme inhibitors and calcium-channel antagonists were not at higher risk than others in the placebo group. On the contrary, hypertensive subjects who took beta-blockers had a 28% increased risk of subsequent T2DM (Gress et al. 2000).

Cohort and randomised controlled trials have suggested that T2DM incidence is unchanged or increased by thiazide diuretics and beta blockers (Padwal and Laupacis 2004). In addition, ACE inhibitors, calcium channel blockers and angiotensin receptor blockers seem not to affect the T2DM incidence (Padwal and Laupacis 2004). The findings of recent studies are still inconsistent regarding antihypertensive medications and risk of T2DM (Helgeland 1980, Neaton et al. 1993, Berglund, Andersson, and Widgren 1986). Ta et al showed that elevated systolic blood pressure (OR 1.4, 95% CI 1.1 to 1.7) (Ta et al. 2010) and hypertension (OR 2.0, 95% CI 1.3 to 3.0) (Ta 2008) were positively associated with T2DM prevalence in Vietnam.

Cigarette smoking

Cigarette smoking has been established as an independent risk factor for developing T2DM. A prospective cohort study of 7,124 men with no history of diabetes, coronary heart disease, or stroke at the baseline, found that cigarette smoking was associated with a significant increase

in T2DM risk, after adjustment for age, BMI, and other potential confounding factors. The benefit of giving up smoking was apparent after five years of smoking cessation, and risk reverted to that of never-smokers only after 20 years. The risk of T2DM amongst those who switched from smoking cigarettes to pipe or cigars remained similar to the risk of continuing cigarette smokers. Men who quit smoking during the first five years of follow-up showed significant weight gain and subsequently higher risk of T2DM than continuing smokers (Wannamethee, Shaper, and Perry 2001). Recent meta-analyses revealed an increased risk in new quitters when compared with never smokers; however, the risk reduced substantially after five and ten years since quitting (Pham et al. 2015, Pan et al. 2015).

Another prospective cohort study conducted on Japanese males from 1984 to 1992 found that the risk of developing T2DM increased three times among those who smoked 16-25 cigarettes a day than those who never smoked, after controlling for other risk factors such as alcohol consumption and obesity (Kawakami et al. 1997). Furthermore, the study also indicated that the risk was considerably higher among those who started smoking at the age of 18, or before, in comparison to never-smokers after controlling for age. Another follow-up study on Japanese males (n=1,266) between 1994 and 1999 estimated that the level of consumption and the number of years of smoking were positively correlated with the development of T2DM as well as impaired fasting glucose (Nakanishi et al. 2000). A study of male physicians in the USA (n=21,068) also established that cigarette smoking was an independent risk factor for developing T2DM. Current smokers who smoked 20 cigarettes a day showed an RR of 1.7 (95%CI 1.3 to 2.3) when compared with those who never smoked, after controlling BMI, physical activity, and other confounding factors such as medical history and alcohol consumption. Similarly, current smokers of over 20 cigarettes per day (RR 1.5, 95%CI 1.0 to 2.2) and past smokers (RR 1.1, 95%CI 1.0 to 1.4) also had increased risks of developing T2DM

when compared to never-smokers, though elevated risk was not as high as the heavy smokers (Manson et al. 2000). A 17-year prospective cohort study conducted in the UK (n=7,735) found cigarette smoking was significantly associated with the risk of T2DM independent of age, BMI, and other confounding factors. Furthermore, this study also indicated that cigarette smoking was an independent risk factor for T2DM among light smokers (less than 20 cigarettes per day) as well as heavy smokers (20 or more cigarettes per day). However, a dose-dependent association was not established (Wannamethee, Shaper, and Perry 2001).

More recent studies have found a dose-response relationship between T2DM and cigarette smoking. A meta-analysis of 25 studies reported that when compared to never-smokers, the RR of T2DM was greatest for current heavy smokers (RR 1.61, 95% CI 1.43 to 1.80), followed by current light smokers (RR 1.29, 95% CI 1.13 to 1.48), with the least risk in the former smoker group (RR 1.23, 95% CI 1.14 to 1.33) (Willi et al. 2007). However, the authors concluded that a causal relationship between smoking and the development of T2DM still could not be established, because the influence of mediating factors such as stress levels, diet, and physical activity levels are not yet fully understood (Tonstad 2009). No information on the association between cigarettes smoking and T2DM risk was found in a recent systematic review in Vietnam.

2.3 Popular beverages

2.3.1 Tea consumption

Tea is the second most commonly consumed beverage in the world, after water. Tea, including green tea, black tea and oolong tea, is derived from the leaves of the plant called *Camellia sinensis* (Graham 1992), of which green tea is the dominant type in Asian countries including Vietnam (Sun et al. 2007). Tea, particularly green tea, is rich in polyphenolic compounds

(Zaveri 2006) as principal active ingredients to protect against oxidative damage and increase insulin sensitivity (Brown et al. 2009, Pham et al. 2014), suggesting a beneficial role of tea consumption against T2DM. Experimental studies in animals have demonstrated reduction of oxidative stress and the anti-diabetic activity of green tea extracts (Sabu and Kuttan 2002, Hininger-Favier et al. 2009). The predominant active component is likely to be epigallocatechin gallate (EGCG) in green tea extracts, which increased uptake of blood glucose by rat adipocytes regardless of the presence or absence of added insulin (Anderson and Polansky 2002).

Several epidemiological studies have been undertaken to examine the association between habitual tea consumption and T2DM (Greenberg et al. 2005a, Song et al. 2005, Odegaard et al. 2008, van Dieren et al. 2009, Iso et al. 2006), but their results are not entirely consistent (Oba et al. 2010, Panagiotakos et al. 2009). A large prospective cohort study of 1,440 adults in Japan showed an inverse association between green tea consumption and T2DM risk (Pham et al. 2014) whereas another study in Singapore found no association (Odegaard et al. 2008). The follow-up of the Singaporean study was less than six years, which may underestimate the association between green tea and risk of T2DM. In addition, only 12% of participants reported that they drank at least one cup of black or green tea per day while 71% of participants reported drinking coffee more than one cup per day. Therefore, the coffee was commonly consumed but not green tea in this study. A recent meta-analysis (Yang, Mao, et al. 2014) confirmed that drinking ≥ 3 cups of tea daily was associated with reduced risk of T2DM, 16% reduction for Asian people, but only 3% for Europeans. The meta-analysis study also provided a systematic review of current cohort studies related to tea consumption and T2DM risk, but it was unable to conduct stratified analysis for different tea types, and most of the included studies did not adjust for coffee intake which may confound the association. Albeit epidemiological studies

have provided evidence for the protective role of tea consumption against T2DM in Asian people, few studies have addressed the role of tea in T2DM in this region, particularly green tea (Sun et al. 2007, Iso et al. 2006). A clinical trial observed that tea intake was associated with lower blood glucose levels (Hosoda et al. 2003), but the hypoglycaemic effect of green tea on diabetic patients was not consistent with another study (MacKenzie, Leary, and Brooks 2007). The inconsistency may be explained by the short duration of trials, different doses of tea consumption and various types of tea. Green tea has been incorporated in functional foods, which are conceivably preferable to drugs for prevention and control of T2DM in Asia. However, to promote tea consumption for people as a beneficial beverage against T2DM needs more reliable evidence from future studies.

Given the increasing prevalence of T2DM in Vietnam, it is imperative to elucidate whether green tea consumption as a daily beverage may offer some protection against this disease. The present case-control study aimed to investigate the association between habitual green tea consumption and T2DM risk among Vietnamese adults.

2.3.2 Coffee consumption

Similar to tea, coffee is one of the most common beverages in the world, particularly in the Western population. A prospective cohort study (n=17,111) reported that coffee consumption may be associated with a reduced risk of T2DM (van Dam and Feskens 2002). This finding was supported by a similar cohort study in Japan (n=1,916 men and 2,704 women) (Isogawa et al. 2003), whereas no protective effect was seen in one cohort study among the Finnish people (n=19,518 men and women) (Reunanen, Heliövaara, and Aho 2003) and one American study (n=2,680) (Saremi, Tulloch-Reid, and Knowler 2003). Whether coffee consumption is associated with a reduced risk of T2DM thus seems to be unclear. A systematic review of

"adding number of included studies" prospective studies conducted in mainly Western countries between 1966 and 2009 stated that every additional cup of coffee consumed daily was associated with a 7% decrease in the risk of T2DM (RR 0.93, 95%CI 0.91 to 0.95) after controlling for potential confounders (Huxley et al. 2009). This review also reported that only 20% of the studies were conducted in non-white populations, which fairly restricted the findings to mainly Western populations.

Components in coffee that may have beneficial effects on glucose tolerance have been indicated recently. For example, magnesium and chlorogenic acid may improve on insulin sensitivity (Salmeron et al. 1997, Khan et al. 1998) and caffeine may be beneficial with regard to beta-cell function (Shi 1997). In addition, magnesium may also improve b-cell function (Paolisso et al. 1992). Moreover, studies on caffeine have shown that this compound can improve insulin sensitivity (Reunanen, Heliövaara, and Aho 2003), but its opposite action has also been reported (Keijzers et al. 2002).

Little information has been found in the literature with regard to the association between coffee consumption and T2DM in Vietnam, the second largest coffee beans exporting country in the world (Food and Agricultural Organisation 2016). To our best of knowledge, none of the observational studies were conducted to investigate the association between coffee consumption and T2DM in Vietnam. Therefore, to mitigate the negative effect of the T2DM epidemic, protective dietary factors should be investigated particularly daily beverages such as tea and coffee.

2.4 Physical activity

Physical activity plays a significant role in the aetiology of several metabolic diseases, including T2DM. It is well known that the intensity of physical activity is more important than having exercise. The intensity of activities is assigned an intensity level based on the rate of energy expenditure expressed as metabolic equivalent tasks (METs). According to the updated Compendium of Physical Activities (Ainsworth et al. 2000), there are 21 major headings including 605 specific physical activities assigned to different levels of intensity. In observational epidemiologic studies, the classification for physical activity by three levels, namely, light (<3 METs), moderate (3-6 METs), and vigorous activity (>6 METs) has been commonly used. Moderate to vigorous physical activity have been reported to delay or reduce the onset of T2DM (Hayes and Kriska 2008) whilst light physical activity appears to have little effect (Zhang et al. 2010). In addition, a review of 10 cohort studies, including more than 300,000 participants and 9,367 incident T2DM cases, indicated that the average RR of T2DM was 0.69 (95%CI 0.58 to 0.83) for regular physical activity of moderate intensity when compared to being sedentary (Jeon et al. 2007). Regular physical activity with moderate or vigorous intensity is likely to be protective against T2DM (Blair 2009). The findings of our systematic review indicated that there was a cross-sectional study conducted in Ho Chi Minh city reporting that light physical activity and sedentary behaviour were positively associated with T2DM prevalence in Vietnam (Le et al. 2004). A recent national estimate for physical activity level in Vietnam reported that around seven-in-ten Vietnamese people aged 25–64 years met the WHO recommendations for total physical activity, which was mainly derived from work activities and higher in rural areas (Van Bui et al. 2015). Despite the emerging evidence of physical activity for T2DM, little information has been available from Vietnam where the trend in prevalence of this disease has increased sustainably in the last two decades.

From the public health point of view, exploring the association between physical activity and T2DM risk is important for the control and prevention of T2DM.

2.5 Summary of literature review

In this literature review, epidemiological characteristics of T2DM are presented, mainly focusing on the prevalence of T2DM and its associated factors in Vietnam. Evidence in the few observational studies suggested that older age, urban residence, overweight, increased central adiposity, and physical inactivity are probably responsible for the epidemic. In addition, the study showed that family history of diabetes, genetic factors, hypertension, and high intake of animal protein may contribute to the accelerated T2DM prevalence. Investigation of dietary factors and lifestyle is vital for T2DM prevention, especially since the prevalence of T2DM has increased two-fold from 2.7% in 2002 to 5.4% in 2012 (Nguyen et al. 2015). The traditional beverage, green tea, may offer protection against T2DM, as about 70% of the population consume green tea daily. Furthermore, coffee, increasingly consumed in Vietnam, deserves an examination with regard to its role for T2DM development. Habitual physical activity is also an interesting factor need to be investigated for T2DM risk among Vietnamese adults. Protective factors of T2DM, such as tea and coffee consumption and physical activity, which are modifiable, can be promoted to the population for better T2DM prevention and control. Therefore, we conducted a case-control study in order to investigate the role of these factors for T2DM in Vietnam.

CHAPTER 3: METHODS

3.1 Introduction

Lifestyle and diet are important determinants of T2DM. It has been suggested that tea and coffee consumption, and physical activity are beneficial to health. Their impact on the development of T2DM can be evaluated using clinical and epidemiological approaches. Randomised controlled trials are the most rigorous design, but would be ethically impossible; prospective cohort studies are ranked highest in the hierarchy of epidemiological evidence despite being expensive, time-consuming, and less powerful for populations with low prevalence of the disease. In resource-limited settings, case-control studies are considered an appropriate design. The present hospital-based case-control study was used to investigate the association between tea and coffee consumption, and physical activity and T2DM risk among adults in Vietnam. Some materials presented in this chapter have been published in the journal article (Nguyen et al. 2016).

3.2 Methodology

3.2.1 Study design

This study included T2DM cases frequency matched to controls by age and sex on a 1:1 ratio in a hospital in northern Vietnam. Data were obtained by interviewing patients with and without T2DM. Medical records of eligible cases and controls were searched for laboratory test results and medical history information.

3.2.2 Setting and location

The case-control study was undertaken in Thanh Nhan Hospital located in the catchment covering both rural and urban areas of Hanoi City, Vietnam. The period of the study was from 8/2013 to 10/2015. This is a general hospital comprising 600 beds, 39 departments/units, and 853 employees. In 2009, there were 317,343 individuals seeking medical care in this hospital, with nearly 50% being inpatients. In addition, about 5,000 diabetic patients are being monitored and managed in their outpatient department. On average, 30-40 cases of T2DM patients are newly diagnosed every month, which would allow recruiting adequate sample size for this study within the target time frame.

3.2.3 Sample size calculation

Our primary objective was to test for the association between green tea consumption, a favourite beverage in Vietnam, and the risk of T2DM, and therefore, we used this exposure to estimate the required sample size. We implemented frequency-matched sets of cases and controls with one matched control per case. Available data indicated that the proportion of individuals consuming 1-4 cups of green tea per week (1 cup ~ 200 mL) among controls is 0.7 (unpublished data). We postulated that the odds ratio for T2DM in subjects drinking 1-6 cups of green tea per week relative to non-consumers would be 0.66 (Iso et al. 2006). We need to recruit 544 T2DM patients and 544 non-T2DM patients to be able to reject the null hypothesis (OR=1.0) with a statistical power of 90% at 5% level of significance (Lwanga SK 1991). In practice, to further account for potential refusal and withdrawal, 1200 subjects (600 cases and 600 controls) were recruited.

3.2.4 Outcome and exposure measures

Selection of cases

T2DM cases were identified by searching the medical records of the Department of Endocrinology. The hospital uses the 2006 WHO diagnostic criteria for T2DM (WHO 2006). We interviewed participants from consecutive patients when they came for treatment. Potential participants were asked to take part in the study if they could voluntarily provide informed consent. An appointment was arranged for personal interview to obtain information if the patient met the selection criteria and agreed to participate.

Inclusion and exclusion criteria

Eligibility: Age: 40-65 years

Matching: cases and controls were frequency matched by age group and gender.

Inclusion criteria for cases

- Patients with T2DM diagnosed within 4 weeks before the interview;
- Diagnoses were based on levels of fasting plasma glucose and/or 2h-OGTT by WHO criteria 2006; and
- Being able to undertake a 40-minute face-to-face interview including measurements.

Exclusion criteria for cases

- Patients deemed too ill to participate;
- Diagnosed with T2DM more than 4 weeks before the interview;
- In long-term modification of diet due to any reason; and
- Non-residents.

Selection of controls

Controls were selected from individuals seeking medical care in an outpatient department of the hospital. A control, being frequency-matched to a case on sex and age (± 3 years) was

recruited on the same day using the cumulative distributions of age and gender variables of the case and control groups. Diabetic-free status among controls was verified by checking results of plasma glucose in medical records. The overnight fasting blood test was routinely conducted in the morning at the hospital. If an eligible control consented to participate in the study, s/he was then interviewed using the same questionnaire as the cases.

Inclusion criteria for controls

- Individuals who attend the hospital outpatient clinics due to minor health problems;
- Plasma glucose levels in medical records at the normal range based on the WHO diagnostic criteria 2006; and
- At the same age group as cases (± 3 years).

Exclusion criteria for controls

- Non-diabetic patients with malignant cancers;
- Outside the desired age range;
- In long term modification of diet due to any reason;
- Non-residents, tourists or foreigners; and
- Deemed too ill to participate as determined by their medical doctors.

Data collection tools

A structured questionnaire was used for the face-to-face interview, see Appendix B. This questionnaire comprised two sections related to lifestyle information and dietary intake. Questions about lifestyle factors, including physical activity, smoking and alcohol drinking, were developed in reference to the literature. Habitual physical activity was adapted from a validated International Physical Activity Questionnaire-Short Form (IPAQ-SF) for Vietnamese adults (Tran, Lee, et al. 2013), while the questions on smoking and alcohol drinking were based on the WHO STEPwise approach to non-communicable disease risk factor surveillance

(STEPS) (WHO 2008b). Dietary intake was assessed using a validated food frequency questionnaire for Vietnamese adults (Tran, Van Hoang, et al. 2013). Clinical and biochemical outcomes such as blood pressure, pulse rate, triglycerides, low density lipoprotein cholesterol (LDLC) and high density lipoprotein cholesterol (HDLC) and total cholesterol, were abstracted from medical records. Anthropometric measurements, including height, body weight, waist and hip circumferences, were measured using a standard protocol through the instruments, including a digital electronic weighing scale (Tanita BC-601), a plastic tape measure, and a height stadiometer bar. The percent body fat and adiposity levels were measured by BIA (Kyle et al. 2004).

Description of variables

The outcome variable is dichotomous, i.e., presence or absence of T2DM. Major exposures are green tea and coffee consumption, and physical activity. In addition, dietary energy intake (kcal per day) and lifestyle factors (smoking, alcohol drinking) are also examined. Additional confounding variables and measurement taken included in this study such as demographic information (age, sex, marital status, occupation, and education level), clinical data (systolic and diastolic blood pressure, pulse rate), biomarkers (fasting plasma glucose, 2h-OGTT, lipid profile, plasma uric acid), and anthropometrics (height, weight, waist, hip circumference).

Assessment of physical activity

Sedentary time was defined as time spent in sitting at home (using computers, watching TV, eating meals, and reading newspapers/books), travelling (sitting on motorbikes, in vehicles or trains), and sitting in the workplace. Habitual physical activities before the onset of T2DM including strenuous sports, vigorous activity, and moderate activity were documented. The intensity of each type of physical activity was determined in terms of MET value (Ainsworth

et al. 2000) and expressed as a sum of MET multiplied by time (hour) spent in each activity per week. Lifelong physical activity involvement was defined as doing active sports or vigorous exercise or work long enough to get sweaty, at least twice a week. We categorised lifelong activity into 3 levels; “never been much involved in physical activity”, “intermittently active”, and “always been involved”.

Other lifestyle factors

Alcohol consumers were defined as those who consumed alcoholic beverages at least once per week over a period of one year or longer; with former alcohol consumers being separated from lifelong abstainers. Smokers were defined as those who have ever smoke one or more cigarettes per day for at least one year or longer, with past smokers being differentiated from life-long non-smokers. Past and current smokers were asked to report their average number of cigarettes smoked per day or per week and total months or years of smoking. For never smokers, passive smoking information was sought whether they were often exposed to smokers at work, public places or at home, and if exposed, the frequency of exposure was inquired. Information about sleeping duration per day was also collected. Because most Vietnamese habitually take a nap after lunch, this was also recorded and daily sleeping hours was calculating by averaging weekdays and weekends.

Dietary assessment

Dietary habits over the three preceding years were ascertained using a 128-item semi-quantitative FFQ (Tran, Van Hoang, et al. 2013). This FFQ records the intake of commonly consumed food items in Vietnam, which are classified into 15 major food groups (soybean products, tomato products, vegetables, fresh fruits, cereal, meat, seafood, egg, cooking oil, seasoning, milk, alcohol, tea, coffee, and juice). The frequency of food consumption was

ascertained according to month, week, or day. A portion size (small, standard, or large) was estimated using the picture book developed in a previous study (Kusama et al. 2005). Dietary intake of 128 food and beverage items, energy intake, and selected nutrients were computed using an *ad hoc* computer algorithm developed for the FFQ, analysis with reference to the standard table of food compositions in Vietnam (National Institute of Nutrition 2007).

Abstraction of clinical data

Clinical data including fasting plasma glucose and 2-h OGTT, lipid profile (triglycerides, LDLC, HDLC, and total cholesterol) were retrieved from medical records. Comorbidities were inquired by interviewers and verified by searching medical records or medical log books. The first degree-relative family history of diabetes was determined via interviews, to clarify whether subjects' parents, sisters/brothers and their offspring have diabetes. The type of diabetes (type 1 or type 2 diabetes) was recorded if applicable.

Measurements and data collection

A single interviewer was trained by the candidate in interview technique and research procedure. The interviewer was a research assistant who had a bachelor degree in public health. On a typical day, the interviewer was present at the study site when patient registration began in the early morning. Patients who had agreed to participate in the study, would be referred by physicians to the interviewer. After explaining the study's purpose, the interviewer asked the patient to sign an informed consent form, see Appendix A. One-to-one interviews and measurements were scheduled and arranged to obtain information. Cases were selected first, and the investigator continuously updated the distribution of sex and age of accumulating cases. Selection of controls was made by frequency-matched to cases on a 1:1 ratio for sex and age (± 3 years). Participants were requested to respond to a brief questionnaire comprising socio-

demographic, lifestyle questions, and an FFQ. Clinical and laboratory data as well as medical history were obtained from both medical records and the personal interview. Anthropometric measurements (weight, height, waist and hip circumference) were taken by the investigator.

Body weight was measured with subjects wearing light clothing and no shoes on a digital electronic weighing scale (Tanita BC-601, range 0.1 to 150 kg) and recorded to the nearest 100 g. Standing height was measured using a stadiometer bar, without shoes, with shoulders in a relaxed position and arms hanging freely, and recorded to the nearest 0.1 cm. BMI was calculated as weight in kilograms divided by height in metres squared. Waist circumference (WC) was measured as the minimal abdominal circumference between the lower edge of the subcostal ridge and the iliac crests using the plastic measure tape. Hip circumference was determined as the broadest buttock circumference. The waist-hip ratio was calculated as WC (cm) divided by the hip circumference (cm). Body fat percentage and central adiposity level were determined by BIA (BC-601; Tanita Corporation, Tokyo, Japan). Both systolic and diastolic blood pressure were measured twice in a sitting position after participant's rest for at least 5 minutes. All equipment had been calibrated.

The transcribed forms were checked by the investigator for completion. Missing, inconsistent, or illogical information were clarified with notes and subsequently rectified. Only the principal investigator was allowed to correct the information in the forms. An audit trail of data was kept of all data collection and data rectification.

Data management

Hard copy forms of the collected data were temporarily stored in an office accessible to the investigator only. Data were entered into Epi-data (Lauritsen JM and Bruus M. 2004), in which

logical errors, missing information, or incorrect coding could be automatically checked. Although basic data cleaning was largely handled by the Epi-data, data entry errors remained to be verified. Therefore, range checking, detection and handling of missing data and outliers were performed on a daily basis to maximize the completeness of data (WHO 2008b). Outliers were examined using Tukey's method (boxplot), diagnostic graphs, standard deviation (SD) method (values exceeding mean \pm 2 SD), and residual statistics (Studentised residuals, Cook's D and leverage measures) (Osborne 2010). Once data entry had been completed, the resulting electronic dataset was securely stored in a password-protected computer at the National Institute of Hygiene and Epidemiology, Vietnam.

3.2.5 Statistical analysis

Data from Epi-data were exported to Stata for further cleaning and analyses. Frequency distributions were created, and graphs were depicted, to check for outliers and missing values. In all analyses, potential confounding variables and effect modifiers were considered. Descriptive statistical analyses were initially performed, followed by multivariate regression analysis. Specifically, characteristics of variables of interest between cases and controls were compared using two-sample t-test and Wilcoxon rank-sum test for normally and non-normally distributed continuous variables, respectively, and the Chi-square test for categorical variables. Variables related to physical activity, alcohol drinking, smoking, and sleeping duration were analysed by employing appropriate statistical methods to ascertain their association with T2DM. The association between each exposure of interest and risk of T2DM was investigated using unconditional logistic regression models. An OR and 95% CI for T2DM risk according to the exposure was presented. Potential confounding factors were considered based on prior knowledge, literature review, causal diagram, and change-in-estimate strategies (Greenland and Pearce 2015, Greenland 1989). Age and sex were also adjusted for in the multivariable

models. Interaction of potential effect modifiers on the association between an exposure of interest and T2DM was examined using the likelihood ratio test. A test for linear trend across categories of an exposure of interest in relation to T2DM was ascertained treating the median value for each category of exposure under study as a continuous variable. A two-sided P values <0.05 was considered statistically significant. All statistical analyses were performed using the Stata 12 (StataCorp LP, College Station, TX, USA).

3.2.6 Ethical considerations

An information sheet was given to each participant with verbal briefing and explanation. All participants provided written informed consent before the conduct of interview and having their medical records examined. Ethical approval of this protocol was obtained from the Human Research Ethics Committee of Curtin University with the approval number of HR105/2013.

CHAPTER 4: RESULTS

4.1 Overview

This chapter presents results of the study. Section 4.1 overviews the chapter structure. In section 4.2, demographic characteristics and other variables are compared between case and control groups. In section 4.3, univariate analyses of the association between tea consumption and T2DM risk are described. The findings of multivariate regression models are then presented for habitual tea consumption in this section. Similarly, results of coffee consumption and habitual physical activity are presented, respectively in section 4.4 and 4.5.

4.2 Comparison between case and control groups

4.2.1 Demographic characteristics

A total of 1280 (630 cases and 650 controls) were approached and invited for participation. From the 1200 study subjects recruited (participation rate 94%), a total of 1198 eligible participants (599 cases and 599 controls) were available for analysis due to missing data on anthropometric measures on two participants. Complete data were available for all participants (n= 1198). The general demographic characteristics of cases and controls were compared in Table 4.

As expected from the frequency matched case-control study design, there were no significant differences between case and control groups on age, whose average age was about 58.4 years (SD 6.6). The mean age was 58.1 (SD 6.6) for men and 58.7 (SD 6.5) for women. Among participants, there were 46% men. There were significant differences between case and control groups in educational levels, family history of diabetes and occupation (physically light job).

Table 4: Demographic characteristics of participants (n=1198)

Characteristic	Cases	Controls	p-value
No. of participants	599	599	
Age in years, mean (SD)	58.6 (6.5)	58.3 (6.6)	>0.05
Female, n (%)	324 (54.0)	324 (54.0)	>0.05
Secondary school completion*, n (%)	283(47.2)	169 (28.2)	<0.001
Physically light job**, n (%)	326 (54.4)	375 (62.6)	0.004
Family history of diabetes, n (%)	158 (26.4)	56 (9.3)	<0.001
Married, n (%)	587 (97.8)	578 (96.3)	0.123
Retired, n (%)	474 (79.0)	438 (73.0)	0.015

P-value for differences between cases and controls; t-test for continuous variables and chi-square test for categorical variables.

** Participants who completed secondary school (year 9) according to the Vietnam Education System.*

*** Physically light job refers to office clerk, teacher, and house worker.*

4.2.2 Lifestyle, anthropometric and other characteristics

There were significant differences between case and control groups in BMI, WHR, hypertension, total cholesterol, and total energy intake. However, alcohol consumption and smoking status were not statistically significant as compared between case and control groups; see Table 5.

4.3 Tea consumption

Tea consumption accounted for 59% (707/1198) among participants. As can be seen in Table 6, the average amount of tea consumption per day was about 317 ml for cases and 392 ml for controls. Overall, the control group consumed more tea than the case group. There was a statistically significant difference regarding total amount of tea consumption per day between case and control groups.

Table 5: Comparison of variables between case and control groups

Characteristics	Cases	Controls	p-value
No. of participants	599	599	
Alcohol consumption, n (%)	275 (45.9)	253 (42.2)	0.20
Smoking status, n (%)			0.051
Never	408 (68.1)	444 (74.1)	
Former	100 (16.7)	88 (14.7)	
Current	91 (15.2)	67 (11.2)	
BMI, kg/m ² , mean (SD)	23.5 (3.2)	22.7 (2.9)	<0.001
High waist-hip ratio, n (%)	424 (70.7)	383 (63.9)	0.012
Hypertension, n (%)	121 (20.2)	90 (15.0)	0.019
Total cholesterol, mmol/l, mean (SD)	5.5 (1.2)	5.2 (1.6)	0.002
Total energy intake, kcal, mean (SD)	1532 (565)	1330 (474)	<0.001
HDL cholesterol, mmol/l, mean (SD)	1.3 (0.4)	1.1 (0.4)	<0.001
Triglyceride, mmol/l, mean (SD)	2.2 (1.8)	2.5 (2.2)	0.001

P-value for differences between cases and controls; t-test for continuous variables and chi-square test for categorical variables.

Control participants consumed more fresh green tea leaves than their case counterparts, but case participants consumed more dried green tea than controls; see Table 6. However, few participants habitually drank black tea and/or oolong tea.

Table 6 showed that the proportion of controls who daily consume tea was higher than that of cases for both 2-4 cups per day and for more than 4 cups per day (range 1-6 cups). However, tea consumption at the lower of fewer than 2 cups per day was similar between cases and controls. Among participants who did not drink tea (non-drinkers), the percentage of T2DM patients was higher than that of control patients. Cumulative exposure including years (range 1-50) and cup-years of tea consumption (range 1-90) of the control group was also significantly higher than that of the case group.

**Table 6: Comparison of habitual tea consumption between case and control groups
over the 3 years prior to interview**

	Cases (n=334)	Controls (n=373)	p-value
Amount of tea consumption, ml/day, mean (SD)	317 (233)	392 (355)	0.001
Type of tea, n (%)			
Dried green tea	270 (55.6)	216 (44.4)	0.001
Fresh green tea leaves	171 (39.6)	261 (60.4)	<0.001
Black tea	2 (25)	6 (75)	
Oolong tea	1 (10)	9 (90)	
Type of tea, ml/day, mean (SD)			
Dried green tea	217 (173)	181 (195)	0.03
Fresh leave green tea	274 (211)	401 (242)	<0.001
Black tea	-	-	
Oolong tea	-	-	
Number of cups per day, n (%)			0.065
<2	153 (25.5)	152 (25.3)	
2-4	91 (15.1)	107 (17.8)	
>4	90 (15.0)	114 (19.0)	
Duration of tea drinking (years)	13.6 (29.8)	15.5 (11.7)	<0.05
Cumulative tea consumption (cup-years)	28.8 (29.8)	41.3 (55.6)	< 0.01

**P-value for differences between cases and controls; t-test for continuous variables and chi-square test for categorical variables.*

In Table 7, univariate logistic regression analysis showed that participants who habitually consumed tea had lower odds of T2DM (OR 0.76, 95%CI 0.60 to 0.96) than non-drinkers. Compared with the non-drinkers, high level of tea consumption (>4 cups per day) was associated with lower odds of T2DM (OR 0.67, 95% CI 0.48 to 0.93). Furthermore, high cup-years (>40) and long exposure (>10 years) to tea drinking were associated with lower odds of T2DM in the present study. Overall, a consistent trend in tea consumption being associated with lower odds of T2DM was found, with P value for trend<0.01.

Multivariate logistic regression analyses found an inverse association between habitual tea consumption and T2DM risk, as shown in Table 8. After adjusting for confounders, the association becomes weaker with OR 0.75 (95%CI 0.57 to 1.00), not statistically significant (P=0.051). However, the higher level of tea consumption >4 cups per day, was significantly associated with reduced odds of T2DM compared to non-drinkers (OR 0.59, 95%CI 0.40 to 0.87, P trend= 0.005). Cup-years (>40) and years of tea consumption (>10) also exhibited an inverse association with T2DM risk when compared to the reference non-drinkers; adjusted ORs were 0.65 (95%CI 0.47 to 0.91, P trend = 0.013) and 0.66 (95%CI 0.47 to 0.92, P trend =0.015), respectively.

Table 7: Univariate analysis of tea consumption and T2DM risk

	Cases/controls	Crude OR (95% CI)
Tea drinking		
No	265/226	Reference
Yes	335/373	0.76 (0.60 to 0.96)
Cups per day (1cup=100ml)		
Never or seldom	265/226	Reference
1-2	95/87	0.93 (0.66 to 1.30)
>2-4	149/172	0.73 (0.55 to 0.97)
>4	90/114	0.67 (0.48 to 0.93)
<i>P for trend</i> [†]		0.006
Cup-years		
Non-drinkers	265/226	Reference
≤40	185/186	0.84 (0.64 to 1.11)
>40	149/187	0.67 (0.51 to 0.89)
<i>P for trend</i> [†]		0.007
Duration of tea consumption (years)		
Non-drinkers	265/226	Reference
≤10	173/183	0.80 (0.61 to 1.05)
>10	161/190	0.72 (0.54 to 0.95)
<i>P for trend</i> [†]		0.018

[†]Based on unconditional logistic regression models

Table 8: Multivariate analysis of tea consumption and T2DM risk

	Cases/controls	Adjusted OR^a (95% CI)
Tea drinking		
No	265/226	Reference
Yes	335/373	0.75 (0.57 to 1.00)
Cups per day (1cup=100ml)		
Never or seldom	265/226	Reference
1-2	95/87	1.00 (0.67 to 1.48)
>2-4	149/172	0.76 (0.55 to 1.05)
>4	90/114	0.59 (0.40 to 0.87)
<i>P for trend[†]</i>		0.005
Cup-years		
Non-drinkers	265/226	Reference
≤40	185/186	0.86 (0.63 to 1.19)
>40	149/187	0.65 (0.47 to 0.91)
<i>P for trend[†]</i>		0.013
Duration of consumption (years)		
Non-drinkers	265/226	Reference
≤10	173/183	0.85 (0.62 to 1.17)
>10	161/190	0.66 (0.47 to 0.92)
<i>P for trend[†]</i>		0.015

^aAdjusted for age (years), sex (female, male), education level (≤secondary school, >secondary school), family history of diabetes in first-degree relatives (yes, no), habitual physical activity (irregularly, regularly), alcohol consumption (yes, no), smoking status (never, former, current), BMI (kg/m²), Waist-hip ratio (high WHR: males ≥ 0.9, females ≥ 0.85, low WHR: males < 0.9, females < 0.85) hypertension (yes, no), total cholesterol (mmol/l), coffee consumption (yes, no), total energy intake (kcal per day)

[†]Based on unconditional logistic regression models

Table 9: Subgroup analysis by gender for tea consumption and T2DM risk

	Men		Women	
	Cases/controls	OR ^b (95%CI)	Cases/controls	OR ^b (95%CI)
Tea drinking				
No	90/61	Reference	175/165	Reference
Yes	185/214	0.48 (0.31 to 0.76)	149/159	0.94 (0.66 to 1.35)
Cups per day (1cup=100ml)				
Never or seldom	90/61	Reference	175/165	Reference
1-2	65/50	0.84 (0.47 to 1.48)	30/37	0.88 (0.48 to 1.63)
>2-4	63/113	0.31 (0.18 to 0.53)	86/59	1.57 (0.99 to 2.46)
>4	57/51	0.57 (0.31 to 1.05)	33/63	0.45 (0.26 to 0.78)
<i>P for trend[†]</i>		0.001		0.240
Cup-years				
Non-drinkers	90/61	Reference	175/165	Reference
≤40	94/110	0.51 (0.30 to 0.84)	91/76	1.23 (0.80 to 1.91)
>40	91/104	0.48 (0.28 to 0.80)	58/83	0.70 (0.44 to 1.11)
<i>P for trend[†]</i>		0.007		0.247
Duration of consumption (year)				
Non-drinkers	90/61	Reference	175/165	Reference
≤10	75/93	0.46 (0.27 to 0.79)	98/90	1.19 (0.79 to 1.80)
>10	110/121	0.51 (0.31 to 0.84)	51/69	0.66 (0.40 to 1.08)
<i>P for trend[†]</i>		0.015		0.232

^b Adjusted for age (years), education level (≤secondary school, >secondary school), family history of diabetes in first-degree relatives (yes, no), habitual physical activity (irregularly, regularly), alcohol consumption (yes, no), smoking status (never, former, current), BMI (kg/m²), Waist-hip ratio (high WHR: males ≥ 0.9, females ≥ 0.85, low WHR: males < 0.9, females < 0.85) hypertension (yes, no), total cholesterol (mmol/l), coffee consumption (yes, no), total energy intake (kcal per day).

[†]Based on unconditional logistic regression models

We conducted a subgroup analysis by sex (Table 9), which showed a statistically significant reduction in T2DM risk for men (adjusted OR 0.48, 95%CI 0.31 to 0.76, P trend = 0.002).

However, the result for women was not significant (adjusted OR 0.94, 95%CI 0.66 to 1.35, P trend = 0.80). For the full model, the consumption level of 2-4 cups per day was significantly associated with reduced odds of T2DM compared with non-drinkers (OR 0.31, 95%CI 0.18 to 0.53, P trend= 0.005) for men. For women, the high level of tea consumption (>4 cups per day) was associated with lower odds of T2DM, yet not significant (OR 0.45, 95%CI 0.26 to 0.78, P trend= 0.24). Similarly, men who maintained tea consumption habits for >40 cup-years and >10 years, the reduced odds of T2DM was observed; OR=0.48 (95%CI 0.28 to 0.80) and OR=0.51 (95%CI 0.31 to 0.84), respectively. At this same level of exposures as men, women had lower odds of T2DM, but their reductions in risk were not statistically significant. The interaction term between tea consumption and sex was further analysed in the full model to investigate effect modification; however, the interaction term was not significant (P value=0.16).

4.4 Coffee consumption

Among control participants, 28% of them consumed coffee daily and their mean consumption was about 66 ml per day, which was higher than the case group; see Table 10. Brewed coffee, including black coffee and milk coffee (defined as black coffee mixed with milk, contributed 79.2% of total coffee consumption, followed by instant coffee with added sugar (20.8%). Data in Table 10 also showed that the number of cups of coffee drinking among controls was higher than that among cases. The percentage of control participants who drank 1-3 cups of coffee per day was higher than that of case participants; 60.0% versus 40.0%. Similarly, for those who drank less than 1 cup of coffee per day, the percentage of control participants was also higher than their case counterparts; 55.6 versus 44.4%. In addition, years of coffee consumption was significant different between case and control groups; the average of more than 12 years for

controls while only 10.4 years for cases. In contrast, no difference in terms of cup-years was found between case and controls group, with $P>0.05$.

Table 10: Comparison of coffee consumption between case and control groups over the 3 years prior to interview

	Cases (n=145)	Controls (n=192)	p-value
Coffee consumption, ml/day, mean (SD)	63.6 (83.3)	67.5 (77.5)	0.65
Type of coffee, n (%)			
Black coffee	81 (54.7)	67 (45.3)	0.21
Instant coffee	24 (31.6)	52 (68.4)	0.001
Milk coffee	54 (38.0)	88 (62.0)	0.002
Type of coffee, ml/day, mean (SD)			
Black coffee	75.9 (95.5)	79.5 (64.8)	0.79
Instant coffee	55.4 (58.7)	62.5 (96.0)	0.73
Milk coffee	32.3 (43.4)	49.0 (60.4)	0.06
Number of cups per day, n (%)			
<1	103 (44.4)	129 (55.6)	0.008
1-3	42 (40.0)	63 (60.0)	
Years of consumption, mean (SD)	10.4 (4.2)	12.2 (8.5)	0.018
Cup-years, mean (SD)	6.5 ± 8.6	8.8 ± 13.4	0.07

P-value for differences between cases and controls; T-test for continuous variables and Chi-square test for categorical variables.

In univariate analysis, coffee consumption was associated with reduced odds of T2DM, see Table 11. Our results found that an additional cup of coffee per day conferred a 25% risk reduction (crude OR 0.75, 95%CI 0.63 to 0.90) while drinking 1-3 cups per day had a 41% reduced odds (crude OR 0.59, 95%CI 0.39 to 0.90). The higher exposure in terms of cup-years (>20) and duration (>10 years) also showed significantly T2DM risk reduction, without accounting for the effect of confounding variables.

Table 11: Univariate analysis of coffee consumption and T2DM risk

	Cases/controls	Crude OR (95%CI)
Coffee drinking		
No	454/407	Reference
Yes	145/192	0.67 (0.52 to 0.87)
Frequency of coffee consumption (cup/day)		
Never or seldom	454/407	Reference
<1	103/129	0.71 (0.53 to 0.95)
1-3	42/63	0.59 (0.39 to 0.90)
<i>P for trend</i> †		0.002
Cup-years		
Non-drinkers	454/407	Reference
<20	68/93	0.65 (0.46 to 0.92)
≥20	77/99	0.69 (0.50 to 0.96)
<i>P for trend</i> †		0.007
Years of consumption		
Non-drinkers	454/407	Reference
≤10	106/121	0.78 (0.58 to 1.05)
>10	39/71	0.49 (0.32 to 0.74)
<i>P for trend</i> †		<0.001

†Based on unconditional logistic regression models

In the multivariate models, coffee consumption was associated with reduced odds of T2DM. Each additional cup of coffee per day may offer a 27% risk reduction (OR 0.73, 95%CI 0.59 to 0.90) and coffee drinkers of 1-3 cups per day had a 45% reduced odds (OR 0.55, 95%CI 0.34 to 0.88). Cup-years (≥20) and duration (>10 years) also demonstrated an inverse association with T2DM risk when compared to the reference non-drinkers; adjusted ORs were 0.67

(95%CI 0.46 to 0.98, P trend= 0.013) and 0.41 (95%CI 0.25 to 0.67, P trend= 0.001), respectively.

Table 12: Multivariate analysis of coffee consumption and T2DM risk

	Cases/controls	Adjusted OR ^a (95% CI)
Coffee drinking		
No	454/407	Reference
Yes	145/192	0.66 (0.49 to 0.88)
Frequency of coffee consumption (cup/day)		
Never or seldom	454/407	Reference
<1	103/129	0.71 (0.51 to 1.00)
1-3	42/63	0.55 (0.34 to 0.88)
<i>P for trend</i> †		0.004
Cup-years		
Non-drinkers	454/407	Reference
<20	68/93	0.64 (0.43 to 0.96)
≥20	77/99	0.67 (0.46 to 0.98)
<i>P for trend</i> †		0.013
Duration of consumption (years)		
Non-drinkers	454/407	Reference
≤10	106/121	0.81 (0.58 to 1.13)
>10	39/71	0.41 (0.25 to 0.67)
<i>P for trend</i> †		0.001

^a Adjusted for age (years), sex (female, male), education level (≤secondary school, >secondary school), occupation (physically heavy job, physically light job), family history of diabetes in first-degree relatives (yes, no), habitual physical activity (irregularly, regularly), alcohol consumption (yes, no), smoking status (never, former, current), BMI (kg/m²), waist-hip ratio (high WHR: males ≥ 0.9, females ≥ 0.85, low WHR: males < 0.9, females < 0.85) hypertension (yes, no), total cholesterol (mmol/l), tea consumption (yes, no), total energy intake (kcal).

SD: standard deviation.

†Based on unconditional logistic regression models

Table 13 shows that the risk of T2DM associated with total coffee consumption. The interaction term between total coffee consumption and sex was significant in the full model (P=0.04).

Women drinking 1-3 cups of coffee daily had a significantly lower risk (OR 0.25, 95% CI 0.11

to 0.55, P trend<0.001) than others reporting non-drinking whereas the relationship in men was not significant (OR 0.94, 95% CI 0.50 to 1.79, P trend=0.525).

Table 13: Subgroup analysis by gender for coffee consumption and T2DM risk

	Men		Women	
	Cases/controls	OR ^b (95%CI)	Cases/controls	OR ^b (95%CI)
Coffee drinking				
No	189/179	Reference	265/228	Reference
Yes	86/96	0.81 (0.53 to 1.23)	59/96	0.49 (0.32 to 0.77)
Frequency of coffee consumption (cup/day)				
Non-drinkers	189/179	Reference	265/228	Reference
<1	57/66	0.75 (0.46 to 1.22)	46/63	0.64 (0.39 to 1.05)
1-3	29/30	0.94 (0.50 to 1.79)	13/33	0.25 (0.11 to 0.55)
<i>P for trend</i> [†]		0.525		<0.001
Cup-years				
Non-drinkers	189/179	Reference	265/228	Reference
<20	35/50	0.56 (0.31 to 1.00)	33/43	0.69 (0.39 to 1.21)
≥20	51/46	1.08 (0.64 to 1.82)	26/53	0.36 (0.20 to 0.64)
<i>P for trend</i> [†]		0.816		<0.001
Years of consumption				
Non-drinkers	189/179	Reference	265/228	Reference
≤10	63/66	0.89 (0.55 to 1.42)	43/55	0.70 (0.42 to 1.15)
>10	23/30	0.64 (0.32 to 1.27)	16/41	0.23 (0.11 to 0.49)
<i>P for trend</i> [†]		0.222		<0.001

^b Adjusted for age (years), education level (≤secondary school, >secondary school), occupation (physically heavy job, physically light job), family history of diabetes in first-degree relatives (yes, no), habitual physical activity (irregularly, regularly), alcohol consumption (yes, no), smoking status (never, former, current), BMI (kg/m²), waist-hip ratio (high WHR: males ≥ 0.9, females ≥ 0.85, low WHR: males < 0.9, females < 0.85) hypertension (yes, no), total cholesterol (mmol/l), tea consumption (yes, no), total energy intake (kcal).

[†] Based on unconditional logistic regression models

4.5 Physical activity

Table 14 shows that only 9.7% of cases (n=58) reported their participation in strenuous physical activity as a habit, compared to 7.7% (n=46) for non-T2DM patients. There was no significant difference ($P>0.05$) between case and control groups for the strenuous sports in our study but when combining strenuous and vigorous activities the case group had significantly higher ($P=0.03$) participant rate (12.5%) than the control group (8.3%). Similarly, participants who had a habit of doing vigorous activity were fewer; 3.0% (n=17) of cases and 0.7% (n=4) of controls. However, the study participants tended to engage more time in moderate activity than strenuous sports and vigorous activity. The average hours per week spent on moderate activity were 3.6 (SD=3.0) for cases and 4.6 (SD=3.4) for controls, their difference being statistically significant with $P<0.01$. Overall, total physical activity was 17.0 MET-hours per week for cases versus 21.4 MET-hours per week for controls ($P<0.001$).

Table 14: Comparison of physical activity and sitting duration between case and control groups

Activity	Cases n=599	Controls n=599	p-value
Habitual physical activity			
Strenuous sports, n (%)	58 (9.7)	46 (7.7)	0.21
Vigorous activity, n (%)	17 (2.8)	4 (0.7)	-
Moderate activity, hours/week, mean (SD)	3.6 (3.0)	4.6 (3.4)	<0.001
Total physical activity, MET-hours/week, mean (SD)	17.0 (13.9)	21.4 (15.2)	<0.001
Lifelong physical activity			<0.001
Never been much involved, n (%)	276 (46.1)	189 (31.5)	
Intermittently active, n (%)	87 (14.5)	93 (15.5)	
Always been involved, n (%)	236 (39.4)	317 (53.0)	
Total sitting duration, hours/week, mean (SD)	38.5 (21.7)	30.2 (17.6)	<0.001

T-test for comparing two means, Chi-squared test for comparing category variables.

Concerning lifelong physical activity, the present study showed that the control group had a higher prevalence than the case group for actively involving and doing physical activity (53.0% versus 39.4%). In addition, total average sitting hours per week was also significantly higher in the case group when compared to their control counterparts (38.5 versus 30.2), $P < 0.001$.

Table 15: Univariate analysis of physical activity and T2DM risk

	Cases, n (%)	Controls, n (%)	Crude OR (95% CI)
Habitual physical activity			
Moderate activity (hours/week)			
<3	254 (42.4)	216 (36.1)	Reference
3-5	169 (28.2)	176 (29.4)	0.81 (0.61 to 1.07)
>5	176 (29.4)	207 (34.5)	0.72 (0.55 to 0.94)
Total activity (MET-hours/week)*			
<13	229 (38.2)	188 (31.4)	Reference
13-26	202 (33.7)	216 (36.0)	0.76 (0.58 to 1.00)
>26	168 (28.1)	195 (32.6)	0.70 (0.53 to 0.93)
Lifelong physical activity			
Never been much involved	276 (46.1)	189 (31.5)	Reference
Intermittently active	87 (14.5)	93 (15.5)	0.64 (0.45 to 0.90)
Always been involved	236 (39.4)	317 (53.0)	0.50 (0.39 to 0.65)
Total sitting duration (hours/week)			
<20	117 (19.5)	170 (28.4)	Reference
20-35	207 (34.5)	239 (39.9)	1.25 (0.93 to 1.69)
>35	275 (46.0)	190 (31.7)	2.10 (1.55 to 2.83)

* Included strenuous and vigorous activities

Univariate analysis showed that the controls engaged in longer duration and participated in more moderate activity than the cases ($P < 0.05$). The average weekly time spent at least 5 hours on moderate activities was 29.4% for cases and 34.5% for controls, see Table 15. Because the

great majority of subjects did not participate in any strenuous and vigorous activities, the effect of these activities on T2DM risk cannot be separately analysed in the present study.

Table 16: Multivariate analysis of physical activity and T2DM risk

	Cases n (%)	Controls n (%)	Adjusted OR ^a (95% CI)	Adjusted OR ^b (95% CI)	p for trend ^c
Habitual physical activity					
Moderate activity (hours/week)					<0.001
<3	254 (42.4)	216 (36.1)	Reference	Reference	
3-5	169 (28.2)	176 (29.4)	0.77 (0.58 to 1.02)	0.79 (0.58 to 1.08)	
>5	176 (29.4)	207 (34.5)	0.71 (0.54 to 0.94)	0.68 (0.51 to 0.93)	
Total activity (MET-hours/week)*					
<13	229 (38.2)	188 (31.4)	Reference	Reference	<0.001
13-26	202 (33.7)	216 (36.0)	0.72 (0.55 to 0.95)	0.75 (0.55 to 1.01)	
>26	168 (28.1)	195 (32.6)	0.69 (0.52 to 0.92)	0.66 (0.48 to 0.91)	
Lifelong physical activity					
Never been much involved	276 (46.1)	189 (31.5)	Reference	Reference	<0.001
Intermittently active	87 (14.5)	93 (15.5)	0.59 (0.42 to 0.85)	0.54 (0.36 to 0.80)	
Always been involved	236 (39.4)	317 (53.0)	0.48 (0.37 to 0.62)	0.46 (0.35 to 0.62)	
Total sitting duration (hours/week)					
<20	117 (19.5)	170 (28.4)	Reference	Reference	<0.001
20-35	207 (34.5)	239 (39.9)	1.24 (0.92 to 1.68)	1.24 (0.89 to 1.73)	
>35	275 (46.0)	190 (31.7)	2.15 (1.57 to 2.95)	2.32 (1.64 to 3.29)	

^a Adjusted for age (years), sex (female, male), BMI (kg/m²).

^b Adjusted for age (years), sex (female, male), education level (\leq secondary school, >secondary school), occupation (physically heavy job, physically light job), family history of diabetes in first-degree relatives (yes, no), alcohol consumption (yes, no), smoking status (never, former, current), hypertension (yes, no), total cholesterol (mmol/l), BMI (kg/m²), total energy intake (kcal).

^c Separated unconditional logistic models. * Included strenuous and vigorous activities

In terms of total physical activity, an inverse association with T2DM risk was found for the high level of >26 MET-hours per week compared to <13 MET-hours per week (OR0.70, 95%

CI 0.53 to 0.93), see Table 15. In addition, a two-fold increase in risk of T2DM was seen for participants who spent more than 35 hours sitting per week compared to <20 hours sitting per week.

Table 16 presented the multivariate logistic regression results. The reasons of presenting two adjusted OR models were to assess the additional effects of other confounding variables apart from age, gender and BMI. Significant inverse association with T2DM risk was evident for moderate activity. For total physical activity exposure, the T2DM risk decreased by 34% for engaging in 26 or more MET-hours per week relative to less than 13 MET-hours per week. The corresponding dose–response relationship was also significant with P for trend <0.001. In terms of lifelong physical activity, there was a consistent reduced odds of T2DM for participants who actively involved in physical activity compared with those less involved. The multivariate results also ascertained that the increase in T2DM risk for a longer sitting duration of 35 or more hours per week relative to less than 20 hours per week. No interaction between sex and moderate physical activity (P=0.3), total MET (P =0.2), and sitting duration (P =0.85) was found.

Table 17 showed that subgroup analysis by gender investigating the association between physical activity and T2DM risk. Although men tended to have more benefit by doing physical activities than women, no significant differences between men and women in all categories of physical activities with respect to T2DM risk was evident. However, we found the significant dose-response relationship between total physical activity and T2DM risk for both men and women with P<0.01. For each additional MET-hour per week of total physical activity exposure, a consistent risk reduction of T2DM in both men (0.97, 95%CI 0.96 to 0.98) and women (0.98, 95% CI 0.97 to 0.99) was showed in the present study.

Table 17: Adjusted ORs of T2DM for habitual physical activity in men and women

	Men, n=550		Women, n=648	
	Cases/ controls	Adjusted OR ^c (95% CI)	Cases/ controls	Adjusted OR ^c (95% CI)
Habitual physical activity				
Moderate activity (hours/week)				
<3	116/99	Reference	138/117	Reference
3-5	78/80	0.82 (0.51 to 1.32)	91/96	0.76 (0.50 to 1.16)
>5	81/96	0.68 (0.43 to 1.08)	95/111	0.71 (0.47 to 1.07)
<i>P for trend</i>		<0.001		<0.001
Total activity (MET-hours/week)*				
<13	102/85	Reference	127/103	Reference
13-26	95/100	0.75 (0.47 to 1.19)	107/116	0.75 (0.50 to 1.14)
>26	78/90	0.67 (0.41 to 1.08)	90/105	0.69 (0.45 to 1.06)
<i>P for trend</i>		<0.001		<0.001
<i>1 SD increment</i>		0.97 (0.96 to 0.98)		0.98 (0.97 to 0.99)
Lifelong physical activity				
Never been much involved	130/71	Reference	146/118	Reference
Intermittently active	35/34	0.38 (0.20 to 0.74)	52/59	0.64 (0.39 to 1.06)
Always been involved	110/170	0.31 (0.20 to 0.48)	123/147	0.65 (0.45 to 0.96)
<i>P for trend</i>		<0.001		<0.001
Total sitting duration (hours/week)				
<20	49/69	Reference	68/101	Reference
20-35	87/112	1.11 (0.65 to 1.88)	120/127	1.39 (0.90 to 2.16)
>35	139/94	2.22 (1.29 to 3.83)	96/136	2.50 (1.57 to 3.97)
<i>P for trend</i>		<0.001		<0.001

^cAdjusted for age (years), education level (\leq secondary school, $>$ secondary school), occupation (physically heavy job, physically light job), family history of diabetes in first-degree relatives (yes, no), alcohol consumption (yes, no), smoking status (never, former, current), hypertension (yes, no), total cholesterol (mmol/l), BMI (kg/m²), total energy intake (kcal).

* Included strenuous and vigorous activities

SD: standard deviation

The present study found that BMI was a significant predictor of T2DM. Total physical activity was inversely associated with T2DM risk for participants who had BMI < 25 kg/m². However, the association was weaker and non-significant for those with BMI ≥ 25 kg/m² (overweight or obesity).

CHAPTER 5: DISCUSSION

In this chapter, the results presented in the chapter 4 are discussed in relation to the main aims of the study, which were to investigate the association between the tea, coffee consumption, physical activity and T2DM risk in Hanoi city, Vietnam. In relation to each specific objective, comparisons between the main findings in the present study and those in the literature are also reported, together with description of the plausible underlying mechanisms. Strength and limitations of the study will then be discussed.

5.1 Tea consumption and T2DM risk

Our study found that about 73% men and 48% women in Hanoi city, Vietnam, drink tea. The majority of participants reported green tea consumption. In the present study, higher tea consumption was associated with significantly reduced odds of T2DM (OR=0.59, 95%CI, 0.40 to 0.87). The association with the decreased T2DM risk appeared to be similar for both men and women, but more consistent among men. To our knowledge, this is first observational study in Vietnam investigating the association between habitual tea consumption and T2DM risk.

The inverse association between tea consumption and T2DM has also been observed in cohort studies. Namely, a study in US (n=7006; 8.4 years of follow-up) showed that about 23% reduced risk of T2DM for persons aged 60 years or less who had regular tea drinking; HR 0.77, 95% CI 0.59 to 1.00; P <0.05 (Greenberg et al. 2005b). A similar reduction in T2DM risk was found in the present study after adjustment of confounders; OR 0.75, 95% CI 0.57 to 1.00. Despite of consistent findings were showed in both studies the study designs are different

(prospective cohort study design versus case-control study design). In terms of cups of tea per day, our findings suggested that drinking tea regularly 2-4 cups per day (100ml per cup) was inversely associated with T2DM risk (reduction of 24%). At high level of consumption (>2 cups per day), T2DM risk was reduced by over 60% (HR 0.37, 95% CI 0.16 to 0.85, P<0.05) for the US study. Besides, regular tea consumption in the US study was unclear whether black tea, green tea or oolong tea was consumed, and the quantity of containers (cup) was not presented. In our study, the majority of participants drank green tea. Due to few case-control studies on tea consumption and T2DM risk, comparison of the current study findings with previous cohort studies are necessary. In a large study of 17,413 middle aged Japanese men and women, Iso et al.(Iso et al. 2006) observed that green tea consumption of 1 - 6 cups per week was associated with 34% reduction in T2DM risk after a 5-year follow up and adjusting for confounders. The inverse association between tea consumption and T2DM risk was also ascertained in a Mediterranean study (n=1040; 2 years of follow-up) (Panagiotakos et al. 2009).

However, the findings on the relationship between tea consumption and T2DM risk were not always consistent. A prospective cohort study in Singapore conducted on 36,908 participants (5 years of follow-up) suggested that participants reporting ≥ 1 cup of black tea per day had a 14% reduction in T2DM risk (RR 0.86, 95% CI 0.74 to 1.00) compared to participants who were non-drinkers, but no such inverse association for green tea consumption (Odegaard et al. 2008). The difference may be explained their qualitative assessment the levels of green tea consumption such as never or monthly, weekly or daily, but could not quantity consumption in terms of number of cups per time unit.

In addition, our findings cohere with a recent meta-analysis of cohort studies showing that the reduced risk of T2DM among individuals with higher tea consumption (≥ 3 cups per day)

compared to those who were non-drinkers (Yang, Mao, et al. 2014). A subgroup analysis of the meta-analysis also found a significant association between tea consumption and decreased T2DM risk in the Asian population (RR 0.84, 95%CI 0.71 to 1.00), but not in the American and European populations (RR 1.00, 95%CI 0.97 to 1.04). The different types of tea consumed in different regions may offer an explanation. It is well known that black tea is commonly consumed in the USA and European countries, whereas green tea is preferred in Asian countries (Yang, Mao, et al. 2014). However, no comparison between the types of tea (black tea, green tea, oolong tea) and T2DM risk was performed in this meta-analysis.

We examined the association between frequency intensity of cups consumed per day and T2DM risk. The lower levels of tea consumption (1-2 or 2-4 cups per days) were not significantly associated with the T2DM risk. However, a significant association with the decreased risk of T2DM by about 40% was evident at the higher consumption level (>4 cups per day); adjusted OR 0.59, 95%CI 0.40 to 0.87. Our findings were slightly different from previous meta-analysis studies. For example, Jing et al (Jing et al. 2009) showed that ≥ 4 cups per day of tea consumption was associated with reduced risk of T2DM by 20% (RR 0.80, 95%CI 0.70 to 0.93) while a meta-analysis conducted by Huxley et al (Huxley et al. 2009) showed that daily tea consumption (3–4 cups per day) was associated with a lower T2DM risk by approximately 15%.

To verify the effect of cumulative tea consumption on the risk of T2DM, we investigated cup-years and year of tea consumption. The results suggested that both cup-years (>40) and tea consumption duration (>10 years) were significantly associated with reduced odds of T2DM, (P<0.05). The odds of T2DM was reduced by 35% for participants who had more than 40 cup-

years of cumulative tea consumption and 34% for those who drank tea for more than 10 years, relative to non-drinkers.

Some observational studies have found the inverse association between green tea consumption and T2DM risk (Yang, Mao, et al. 2014). However, the effects of green tea consumption on blood glucose control and insulin sensitivity are inconsistent in many interventions. Fukino et al (Fukino et al. 2005) conducted a randomised controlled trial (66 patients aged 32-73 years; 53 males and 13 females with borderline diabetes or diabetes) to evaluate the effect of green tea polyphenol intake on insulin resistance. The trial revealed that the daily supplementary intake of 500 mg of green tea polyphenols did not have clear effects on blood glucose level, HbA1c level and insulin resistance. However, recent trials showed that green tea supplementation might increase insulin activity (Mirzaei et al. 2015, Hsu et al. 2011, Bogdanski et al. 2012, Wu, Juan, Ho, et al. 2004). For example, Wu et al (2004) found that green tea polyphenols increased glucose uptake of adipocytes and suggested that polyphenols in green tea might be responsible for increasing insulin activity. A recent meta-analysis of 17 randomised controlled trials conducted from 1980 to 2013 in human found that green tea significantly lowered fasting glucose, HbA1c concentrations, and may also reduce fasting insulin concentrations (Liu et al. 2013).

Although observational studies have found a beneficial role of tea consumption against T2DM, the apparent mechanism by which tea can protect against the development of T2DM remains controversial. The first possible mechanism is through ameliorating insulin resistance (Wu, Juan, Hwang, et al. 2004). It is well known that insulin resistance is one of the biomarkers of T2DM progression. T2DM is defined as a progressive condition in which the body becomes resistant to the normal effects of insulin and/or gradually loses the capacity to produce enough

insulin in the pancreas. Therefore, improving the insulin resistance or increasing insulin activity may be useful for T2DM prevention. Moreover, polyphenol is one of the chemical components found in green tea. Intakes of green tea and black tea extracts have been found to be associated with lower blood glucose in streptozotocin-induced diabetic rats (Gomes et al. 1995). In addition, Deng et al. (Zeyuan et al. 1998) found that serum glucose and triglyceride levels in rats decreased after green tea supplementation. Another study (Wu, Juan, Ho, et al. 2004) showed that plasma insulin levels in the green tea group were lower than their comparison group after 12 weeks of supplementation. In other words, the insulin sensitivity of the rats improved as a result of green tea supplementation. Higher glucose uptake activity was evident in the green tea group than the control group, indicating that the effect of green tea on improving insulin sensitivity. The green tea extracts helped adipocytes to increase their glucose uptake, consequently increasing insulin sensitivity.

Another mechanism is the tea polyphenol (–)-epigallocatechin-3-gallate (EGCG), which exhibits some antidiabetic effects (Lin and Lin 2008). Potential mechanism concerns high glucose induced insulin signalling blockade in HepG2 cells. High glucose condition generates intracellular reactive oxygen species (ROS), which are accumulated within the HepG2 cells. The high glucose-induced oxidative stress triggers serine kinase cascades by activating protein kinase C (PKC) and c-Jun N-terminal kinase (JNK). Accordingly, it induces Ser307 phosphorylation of critical insulin receptor substrate sites (IRS-1), reducing IRS-1 tyrosine phosphorylation, and thereby inhibiting IRS-1 binding to insulin receptor (IR)(Lin and Lin 2008). These results down regulate phosphatidylinositol 3 kinase (PI3K/Akt) signalling pathway and decrease insulin-stimulated glucose uptake and glycogen synthesis. However, IRS-1 tyrosine phosphorylation has been demonstrated to be positively regulated by 5'-AMP-activated protein kinase (AMPK) activation. EGCG was shown to both reduce PKC/JNK

activation and activate AMPK activity leading to block IRS-1 serine phosphorylation and attenuate high glucose-induced insulin signalling blockade (Li et al. 2011).

A study found that black tea extracts possess curative effect on streptozotocin-induced diabetes in mice (Manikandan et al. 2009). The findings confirmed that the number of β cells increased in the islets of the diabetic mice fed with black-tea extract. Also, an increase in secretory granules in the cells indicates that the cells have been stimulated for hormone synthesis. However, little information is available in green tea extract. Green tea is more effective as a preventive agent via improved insulin sensitivity whereas black tea extract appears to be more effective as a curative. In the present study, the inverse association between habitual green tea consumption and T2DM risk may be explained by the preventive role of green tea constituents, especially polyphenols.

Subgroup analysis on sex showed a difference between men and women in accordance to habitual green tea consumption and the risk of T2DM. We found that the inverse association between tea consumption and T2DM risk is consistent with a recent meta-analysis (Yang, Mao, et al. 2014). Besides, a Japanese study observed an inverse relationship between tea consumption and T2DM in women, but not in men (Iso et al. 2006). Although we observed the reduced odds of T2DM in both men and women, there is a significant association among women at the high level of tea consumption (>4 cups per day), but not significant among men at the same consumption level. One possible explanation for the sex difference is the lower prevalence of drinking tea among women than men; 48% versus 73%, respectively. In addition, the average duration of tea consumption among women (13.1 years, SD=10.9) was also shorter than that of men (15.8 years, SD=9.5). Another possible biological explanation for the sex difference is that high testosterone level is associated with the higher risk of T2DM in women

but the lower T2DM risk in men (Grossmann 2011, Ding et al. 2006). In an animal study, tea intake increases total testosterone levels in male rats (Sato et al. 2002). Therefore, tea consumption may elevate testosterone level in men and in turn decrease the T2DM risk.

5.2 Coffee consumption and T2DM risk

The current study has found that habitual coffee consumption was associated with lower odds of T2DM prevalence. This association was significant for the increasing frequency of drinking (number of cups per day) with P trend value <0.01. After adjusting for confounders, participants who maintained a habit of coffee consumption 1-3 cups every day had a lower risk of T2DM than non-drinkers. Besides, the findings also showed that higher cumulative exposure in terms of cup-years (≥ 20) and years of coffee drinking (>10 years) appeared to be negatively associated with the lower odds of T2DM. In sub-analysis by sex, we found significant inverse association with T2DM risk among women with higher coffee consumption (1-3 cups per day). The highest level of habitual coffee intake was related to a 75% lower T2DM risk in women but only a 6% non-significant reduction of risk in men. It should be remarked that the substantially higher levels of coffee consumption in other studies than our participants. In summary, habitual coffee consumption was found to be linked to a lower risk of T2DM among Vietnamese women.

Consistent with previous studies, coffee consumption was associated with a reduced risk of T2DM (Van Dam and Hu 2005, Muley, Muley, and Shah 2012, Huxley et al. 2009). Meta-analyses indicated a weak dose-response relationship between coffee and T2DM, but several individual studies reported more of a threshold effect with a substantial risk reduction (20–45%) already at consumption levels of around three cups per day (Rosengren et al. 2004,

Tuomilehto et al. 2004, Carlsson et al. 2004, van Dam et al. 2006). Consistent with two meta-analyses that found inverse association with T2DM risk (Huxley et al. 2009, Van Dam and Hu 2005), we found a 27% reduced risk in consumers of 1–3 cups per day. The first meta-analysis included 9 prospective cohorts with about 190,000 participants in America and Europe and reported that habitual coffee consumption of 4–6 and 6–7 cups per day reduced risk by 28% and 35%, respectively (Van Dam and Hu 2005). The second meta-analysis recently summarized 18 cohort studies including 457,922 subjects with more than 21,000 incident cases of T2DM; and concluded that each additional cup of coffee contributed to a 5% to 10% lower risk (Huxley et al. 2009). This review also reported a reduced T2DM risk for those who drank 3–4 cups of decaffeinated coffee per day (HR 0.64, 95% CI 0.54 to 0.77) (Huxley et al. 2009). After these meta-analyses had published, four new cohort studies published their findings, which are also in agreement (Oba et al. 2010, Boggs et al. 2010, Floegel et al. 2012, Doo et al. 2014).

Among the four new cohort studies regarding coffee consumption and T2DM risk, the first study was the Hawaii component of the Multiethnic Cohort (MEC) (Doo et al. 2014). It was conducted on a multiethnic population. The highest category of regular coffee consumption was related to a 34% lower T2DM risk in women but only a borderline 14% reduction of risk in men. The benefit of coffee consumption was found in women of all 3 ethnic groups: Caucasians, Japanese Americans, and Native Hawaiians. The interaction term with ethnicity was not significant despite some variations in effect size. It concluded that regular, but not decaffeinated, coffee intake was more protective against T2DM in women of all ethnic groups than in men.

The second was the European Prospective Investigation into Cancer and Nutrition (EPIC)-Germany study conducted in 10 European countries (Floegel et al. 2012). The study investigated the association between coffee consumption and the risk of chronic diseases prospectively, including T2DM, myocardial infarction, stroke, and cancer. With more than 42,000 participants prospectively observed over 8.9 years, 1,432 incident cases of T2DM occurred. Coffee consumption was assessed by a self-administered food frequency questionnaire. No association between high coffee consumption (≥ 4 cups per day) with the overall risk of chronic diseases was observed when compared to less than one cup per day. However, it reported a 23% lower incidence of T2DM for caffeinated intakes of ≥ 4 cups per day (one cup was defined as 150 mL). Similar to the MEC study, the findings of the EPIC supported the beneficial role of coffee consumption and T2DM risk at the population level. Although the EPIC study did not test for the interaction term between sex and coffee consumption, the interaction term between smoking and caffeinated coffee consumption was analysed. Among non-smokers, an inverse association was found between caffeinated coffee consumption and risk of T2DM; among current smokers, such dose-dependent inverse association was not observed. Because smoking is an established risk factor for T2DM, the adverse effects of smoking may cancel out the potential benefits of coffee consumption on T2DM risk. Thus, the EPIC study concluded that smokers might not benefit from coffee consumption with respect to the T2DM risk.

Thirdly, the Black Women's Health study (Boggs et al. 2010) included 46,906 African American women aged 30–69 years at baseline in 1995. Dietary intake was assessed in 1995 and 2001 by using a validated FFQ. During 12 years of follow-up, there were 3,671 incident cases of T2DM. The study findings supported that moderate consumption of caffeinated coffee (2-3 cups per day) could reduce the risk of T2DM in African American women. Similarly, the

present study also found the inverse association between coffee consumption and the risk of T2DM for Vietnamese women. About 24% of Vietnamese women drinks coffee while a lower percentage was observed among African American women (14% for both caffeinated and decaffeinated coffee). Decaffeinated coffee drinkers reported healthier lifestyles in terms of physical activity, weight, and diet, but adjustment for these factors did not appear to attenuate the association between decaffeinated coffee intake and T2DM risk. The lack of significance for decaffeinated coffee may be due to confounding. Since caffeine is regarded as an “unhealthy” substance by some, individuals diagnosed with hypertension or heart disease might have switched to decaffeinated coffee after early signs of illness were noted (Doo et al. 2014, Shlonsky, Klatsky, and Armstrong 2003). In our study, because of the low prevalence of drinking decaffeinated coffee among Vietnamese adults, no such information was collected.

Fourthly, a Japanese cohort study (Oba et al. 2010) reported a lower risk of T2DM for regular coffee consumption, but not caffeinated. The association between estimated total caffeine intake and risk of T2DM was non-significant both among men and among women. The results imply that coffee consumption could reduce the risk of developing T2DM, whose protective effect may exist independent of the influence of caffeine intake.

Adjusted and unadjusted models in the present analytical observational study suggested that the inverse association for coffee consumption is stronger for women than for men. Two other observational studies (Kato et al. 2009, Bidel et al. 2008) showed similar results. A Japanese cohort study found an 18% lower risk in men but 60% lower risk in women who drank ≥ 5 cups per day (Kato et al. 2009). A study in Finland reported a 29% lower risk in men and a 53% lower risk in women (Bidel et al. 2008). However, two studies observed that T2DM risk among men was lower among men than women when drank 4 or more cups of coffee per day (Paynter

et al. 2006, Salazar-Martinez et al. 2004) while the protective effects were similar across sex in two other studies (Oba et al. 2010, Iso et al. 2006). Hormonal mechanisms for a sex-differential aetiology have been proposed (Tuomilehto et al. 2004), but appear unlikely given the relative consistency of effect sizes in meta-analyses (van Dam 2008, Natella and Scaccini 2012).

Another plausible explanation is reporting of coffee consumption being less accurate by men relative to women, which led to reduced risk estimates. The original calibration study provides some evidence for lower correlations among Caucasian men than women (Stram et al. 2000). Finally, our results could be a chance finding. Only a few of the studies have provided information by ethnicity. Four studies in Asia have been conducted (Oba et al. 2010, Kato et al. 2009, Iso et al. 2006, Odegaard et al. 2008), but none specifically analysed Vietnamese. Two studies on Native Americans (Zhang et al. 2011, Saremi, Tulloch-Reid, and Knowler 2003), one on African-American women (Boggs et al. 2010), and another study on Puerto Ricans (Fuhrman et al. 2008) agreed that coffee is associated with a lower risk of T2DM. Results from these 8 studies are consistent with our study findings, in particular in regard to the stronger association among women.

Our study results were in agreement with the beneficial role of total coffee consumption for T2DM development in women, but not observed in men. Similarly, the prolonged duration of coffee consumption (including cup-years and years of consumption) was analysed by sex. The interaction term between sex and total coffee consumption was marginally significant with $P = 0.046$. In Vietnam, more than 60% of male adults currently or used to smoke whereas females are almost non-cigarette smokers. Participants who were male smokers accounted for more

than 61% whereas only 1% of women reported currently smoke cigarettes or used to smoke cigarettes.

We also noted that Vietnam ranked the second largest exporter of coffee beans in the world, with coffee production accounted for 13% of total world coffee production in 2010 (Food and Agricultural Organisation 2016). However, the annual per capita consumption was 0.7 kg, compared with the average of 1.3 kg in the world , though the trend for Vietnamese consumption has increased dramatically over time (Jolliffe and Bui 2006). In comparison with the US standard cup of coffee, Vietnamese drinks coffee using a smaller cup, about 150ml. Nevertheless, it is conceived that Vietnamese coffee is more condensed in concentration than other cultures.

Prior to exploring the biological mechanism of coffee in relation to T2DM, a brief review of coffee components is of value. Coffee beans contain many constituents, including lipids, proteins, carbohydrates, vitamins, and minerals. Consequently, isolating specific compounds responsible for the protective effects of coffee against T2DM is difficult. To date, the majority of research on the biological activity of coffee has mainly focused on caffeine. More recently, the acknowledgment that coffee and caffeine are not physiologically equivalent has led to the exploration of other coffee constituents (Farah et al. 2006, Johnston, Clifford, and Morgan 2003, McCarty 2005, Nunes and Coimbra 2007, Shearer et al. 2003). It is evident that the contribution of coffee to the daily recommended intake of both macro- and micronutrients is minimal (Tunnicliffe and Shearer 2008). Despite this, its potential contribution cannot be entirely discounted.

Previous studies had investigated a potential underlying mechanism regarding the beneficial effect of coffee consumption on insulin sensitivity (van Dam et al. 2004, Agardh et al. 2004).

Coffee is a major source of chlorogenic acid and lignans, antioxidants that have beneficial effects on insulin sensitivity and glucose metabolism (van Dam 2006, Tunnicliffe and Shearer 2008). Indeed, two studies have shown an association between coffee consumption and increased insulin sensitivity (Agardh et al. 2004, Ärnlov, Vessby, and Risérus 2004). In another cross-sectional study, after adjustment for T2DM risk factors, coffee consumption was associated with significantly lower fasting plasma glucose concentrations (Bidel et al. 2006). These are in contrast with results from randomized controlled trials (van Dam, Pasman, and Verhoef 2004, Wedick et al. 2011, Ohnaka et al. 2012), where no indication of improvement of insulin sensitivity or secretion has been seen. The this discrepancy could be attributed to the short-term effects of coffee, which may even imply detrimental effects on insulin sensitivity (Keijzers et al. 2002) as different from long-term effects. There are, however, other possible pathways linking coffee to improved glucose tolerance. For example, Wedick et al. found indications of improved adipocyte and liver function following exposure to coffee (Wedick et al. 2011). The protective effect may also be attributed to the antioxidative properties of coffee. Indeed, data from an in vitro study suggested that caffeic acid, one of the major components of coffee, might protect against pancreatic islet destruction attributable to oxidative stress (Cheng et al. 2011). Therefore, mechanisms other than glucose metabolism and insulin resistance may play a role in how coffee drinking reduces diabetes risk.

In addition, inflammatory markers and lipids may be involved apart from the insulin sensitivity related-mechanism. A recent intervention trial showed favourable effects of coffee on inflammatory markers and lipids but not on glucose metabolism (Kempf et al. 2010). Beneficial effects of coffee on T2DM risk could also be mediated by attenuation of subclinical inflammation, through decreased levels of interleukin-18 and up-regulation of adiponectin, as shown by Kempf et al. (Kempf et al. 2010). Caffeine did not appear to exert any protective

effect against T2DM, but a reduced risk of T2DM has been linked to decaffeinated coffee intake (van Dam et al. 2006, Salazar-Martinez et al. 2004). With regard to coffee type, protective effects have been reported for both filtered and instant coffee (van Dam et al. 2006, Hjellvik, Tverdal, and Strom 2011). In Vietnam, filtered coffee is by far the most common type, contributing more than 79% of the total coffee consumption among our study participants, while decaffeinated coffee consumption is uncommon.

5.3 Physical activity and T2DM risk

Our study found that habitual physical activity was inversely associated with the T2DM risk. After adjusting for confounders, the inverse association appeared to be more prominent for participants whose moderate physical activity (either occupational or leisure-time activity) exceed 5 hours per week relative to those with 3 hours or less per week. Further analysis showed that total physical activity was inversely associated with the odds of T2DM, particularly for participants with more than 26 MET-hours per week compared to those with less than 13 MET-hours per week. Total physical activity was computed by summing activities with different intensities such as strenuous, vigorous and moderate activities. Of note, the majority of total physical activities were derived from moderate intensity activities. Both occupational and leisure time activity levels were measured using a validated and reliable instrument (Tran, Van Hoang, et al. 2013).

Lifelong physical activity can offer a long-term assessment of physical activity on the development of T2DM. We categorised lifelong activity into 3 levels; “never been much involved in physical activity”, “intermittently active”, and “always been involved in physical activity”. In comparison to the “never been involved in physical activity”, apparent inverse associations with T2DM risk were found among individuals who were “intermittently active”

and “always been involved in physical activity”. Our findings were consistent with previous studies which supported the beneficial role of lifelong activity to prevent T2DM (Warburton, Nicol, and Bredin 2006).

In contrast, a sedentary lifestyle is a significant predictor for the development of T2DM. Previous research demonstrated that sedentary lifestyle may increase the risk of metabolic diseases including T2DM (Healy et al. 2008). Our study also found that sitting duration over 35 hours per week versus less than 20 hours per week was associated with increased odds of T2DM after adjusting for confounders.

The observed inverse association between regular moderate physical activity and T2DM risk has been reported in cohort studies of white populations such as USA, Finland, and UK (Weinstein et al. 2004, Hu et al. 2003, Hsia et al. 2005, Hu et al. 2001), but not in an Asian study (Okada et al. 2000). Hu et al. conducted a cohort study aimed to assess the association between physical activity and T2DM risk. Its findings demonstrated that doing physical activity was associated with a significant reduction in the risk of T2DM, whereas a sedentary lifestyle as indicated by television watching hours was directly associated with an elevated risk (Hu et al. 2001). Our findings similarly suggested a possible beneficial effect of moderate intensity activity and the increased odds of a sedentary lifestyle. However, this large prospective study was conducted on American men only whereas our case-control study examined on both men and women. Stratified analysis by sex in the present data indicated that the inverse association with T2DM risk observed in both men and women, but non-significant for the highest category of moderate physical activity. However, no interaction between sex and moderate activity ($P=0.3$) was found in our study.

A recent meta-analysis also confirmed that about 31% reduction of T2DM risk could be achieved by regular participation in moderate intensity activity, as contrasted to being sedentary (Jeon et al. 2007). The meta-analysis included studies derived mostly from white populations while the present study was concerned with the Vietnamese population. We observed a similar result with a reduction of approximately 32% in T2DM risk. Furthermore, an inverse dose–response relationship was also evident in our study; a reduction of 3% and 2% in T2DM risk for each additional MET-hour per week of total physical activity for men and women, respectively.

Physical activity can increase muscle glucose uptake and insulin sensitivity (Goodyear and Kahn 1998). During exercise, the increased need for metabolic fuel is met partially through an increase in the uptake and utilization of glucose. In the 1950s, studies of rats (Goldstein et al. 1953) and perfused dog hind limbs (Huycke and KruhØFfer 1955) confirmed a phenomenon of decreased glucose concentration in the exercising muscle cells, and in the 1960s glucose uptake kinetics were first described using incubated frog sartorius muscles contracted in vitro (Holloszy and Narahara 1965, 1967). Since these early studies, a considerable amount of work has characterized the effects of exercise on glucose uptake in skeletal muscle, and a few reviews have concentrated on this topic (Richter E. A. 1996, Holloszy and Hansen 1996, Goodyear and Kahn 1998). In addition to the acute effects of physical activity to increase muscle glucose uptake, the period after physical activity is characterized by the muscle being more sensitive to the actions of insulin. This was first demonstrated in perfused rat hind limb muscles (Ivy and Holloszy 1981, Richter et al. 1982) and was subsequently shown in studies of human subjects (Xirouchaki et al. 2016, Richter et al. 1982, Iwabe et al. 2014). However, one-legged exercise models in humans have demonstrated that the exercise-induced increase in insulin sensitivity for glucose uptake is a local phenomenon restricted to the exercised muscles (Richter et al.

1984, Richter et al. 1989). Furthermore, elevated capillary proliferation in muscles, increased muscle mass, and a higher proportion of more insulin sensitive types of muscle fibres, may all contribute to the beneficial effects of physical activity on insulin sensitivity (Goodyear and Kahn 1998).

Obesity affects insulin resistance, which in turn leads to T2DM is a well-known mechanism. Obesity is known to increase peripheral insulin resistance (Després and Marette 1999, Boden), whereas physical activity seems to increase insulin sensitivity in skeletal muscles (Goodyear and Kahn 1998). Physical activity has consistently been a major predictor of weight control (Eriksson and Lindgarde 1991). Adipose tissue affects insulin metabolism by releasing free fatty acids and cytokines (Paolisso et al. 1995, Després and Marette 1999). Previous studies have provided evidence that large fat cells and high fasting plasma non-esterified fatty acids (NEFA) concentration are predictors of T2DM development (Paolisso et al. 1995). Studies showed that the predictive value of plasma NEFA on T2DM become non-insignificant after adjusting for acute insulin response, thus suggesting that NEFA may increase the T2DM risk by inhibiting insulin secretion. This hypothesis was supported by recent observations showing that NEFA may inhibit insulin release in vitro (Opara et al. 1994, Zhou and Grill 1994) through such actions has not demonstrated by several previous studies (Crespin, Greenough, and Steinberg 1969, Campillo et al. 1979). Opara et al. (Opara et al. 1994) revealed that a 20-min exposure of islet cells to 5 mmol/l fatty acids resulted in enhancement or decrease of insulin secretions for C16:0 or C18:2 fatty acids, respectively, whereas Zhou and Grill (Zhou and Grill 1994) indicated that long-term exposure to increased NEFA concentration inhibited glucose-induced insulin secretion. An alternative explanation is that the impaired insulin release results in increased lipolysis and thus causes elevated NEFA plasma levels. Lee et al (Lee et al. 1994) reported similar results making a strong case for the role of high plasma NEFA levels in the

pathogenesis of T2DM in obese Zucker diabetic fatty rats, and defined the inhibitory effect of NEFA on beta-cell response to glucose. Besides, circulating NEFA levels can affect liver metabolism. It has been shown that NEFA inhibits insulin receptor binding and tyrosine kinase activity in isolated hepatocytes (Svedberg et al. 1992), and provides energy for gluconeogenesis thus increasing hepatic glucose output (Williamson, Browning, and Scholz 1969, Foley 1992). However, since increased hepatic glucose production is not predictive of the development of T2DM (Lillioja et al. 1993), the impact of NEFA on liver metabolism is unlikely to play an important role in the aetiology of T2DM. Physical activity is one of the effective activities to sustain body weight control, which may, therefore, be a key mechanism to reduce the secretion of fatty acids and cytokines via decreasing adipose tissue volume, which in turn lessens the risk of T2DM.

Another biological mechanism of physical activity was demonstrated to affect glucose metabolism. Such a mechanism has been identified independent of body fatness. Exercise can increase insulin-stimulated glycogen synthesis through a higher rate of insulin-stimulated glucose transport by GLUT4 glucose transporters and increased glycogen synthase activity (Perseghin et al. 1996). It has been demonstrated that an exercise-training program improved whole-body insulin sensitivity by 40% and whole-body nonoxidative glucose metabolism by 60 to 70% in both the adult children of parents with T2DM and normal participants (Perseghin et al. 1996). Similar results in patients with T2DM and glucose tolerance have been shown in the literature (Oshida et al. 1989, Ryan 2000).

5.4 Strength of the study

Some strengths of the present study deserve mention regarding study design, sample size, data collection, and relevant research questions. This study used a hospital-based case-control

design, which was inexpensive and appropriate for a lower-income country like Vietnam. The present study had relatively large number of cases of newly diagnosed T2DM patients. In addition, this design is suitable for the diseases with long latent period, such as cancers and T2D. Age and gender were used as matching criteria to reduce selection bias (Rothman, Greenland, and Lash 2008). The multivariate regression results have been adjusted for a comprehensive set of potential confounders, including socio-demographic factors, lifestyle, dietary, BMI, WHR, clinical and subclinical related factors. A relatively large sample size to assess different exposures, use of validated instruments for diet and lifestyle assessment, ascertainment of exposure variables via structured interviews, and uniform measurements of clinical and biochemical parameters across case and control groups. Special efforts will be made to increase response rates and minimise withdrawal of participants.

5.5 Limitations

Several limitations deserve mention in the present study, which include the use of hospital-based controls, the introduced complexities of frequency matching, and the possible differential reporting of exposures. As a retrospective design in nature, the assessment of tea and coffee drinking habits may pose recall errors. Although we used a validated questionnaire to collect information on the habit of lifestyle and diet by face-to-face interview, inaccurate estimates of the amounts of tea and coffee consumption probably still occurred. Recall bias is a common issue in a case-control study however; this bias is minimized because we recruited non-diabetic patients in the same hospital as the T2DM patients so that they recall in the similar manner unlike healthy community-dwelling adults. Information bias was unlikely because all participants were blinded to the study hypothesis, while the potential protective effects of tea consumption; coffee consumption and physical activity against T2DM have not been established in Vietnam at the time of interview. Nevertheless, we were unable to determine the

concentration of tea, as green tea including dried or fresh leaves is not commonly packaged with detailed content or portion size in Vietnam. Similarly, data on exposure estimates (tea, coffee consumption, and physical activity) for the underlying population are not available to compare with those from our control participants.

Another source of bias could be introduced if individuals with T2DM changed their dietary habit linked to the onset of T2DM symptoms or diagnosis. To avoid reverse causation, incident patients were selected, i.e. newly diagnosed with T2DM within 4 weeks, while the referral period of habitual consumption of tea and coffee and other dietary factors was set at three years before the interview or diagnosis of T2DM. In addition, we excluded patients who had modified their lifestyle and diet due to any reason recently, as part of our selection criteria.

Selection bias may arise if only severely ill patients are recruited and the controls are drawn from a different reference population. For this reason, we selected newly diagnosed (incident) T2DM patients, while non-diabetic controls are recruited from the outpatient clinics of the same hospital, who came from the same catchment areas as the cases but were unlikely to share the same risk profiles.

Despite the low non-responsive rate, selection bias may be unavoidable because all participants were voluntary to participate in the study. In addition, the hospital-based controls were selected from the same hospital as cases instead of randomly selected from the community and the participating hospital serves the entire catchment region. Residual confounding such as healthy lifestyles might still exist despite established and plausible risk factors have been controlled for in the multivariable logistic regression analyses. Further replications of the study are necessary before generalizing the findings to the general and other populations.

CHAPTER 6. CONCLUSION

This is the first case-control study in Vietnam investigating the association between diet (green tea and coffee consumption) and lifestyle (physical activity) and T2DM risk. In addition, the epidemiology of T2DM has been reviewed systematically and its findings suggest an increasing trend in the prevalence of T2DM in Vietnam. Although factors related to the increasing occurrence of T2DM in previous observational studies were also suggested, evidence was inadequate for the formulation of an effective control and prevention strategy of T2DM in Vietnam. Therefore, we reported the first case-control study's findings to ascertain the association with T2DM risk for tea and coffee consumption, and physical activity. All the objectives stated in Chapter 1 have been achieved successfully.

6.1 The epidemiology of T2DM

T2DM is one of the chronic diseases, which has increased dramatically worldwide. Recent evidence indicated that T2DM is now problematic in both developed and developing countries. To systematically review the prevalence rates of T2DM and its risk factors in Vietnam, electronic databases namely PubMed, Web of Science, Wiley Online Library, and Scopus, were searched to identify the relevant literature. The search resulted in 10 studies, including 2 national surveys and 8 regional investigations. National prevalence estimates of T2DM were 2.7% in 2002 and 5.4% in 2012. The estimates for the northern region were 1.4% in 1994 and 3.7% in 2012 and those for the southern region were 3.8% in 2004, 7.0% in 2008, and 12.4% in 2010. The risk factors of T2DM included older age, urban residence, high levels of body and abdominal fat, physical inactivity, sedentary lifestyle, genetic factors, and hypertension. The prevalence rate by gender was variable in both national and regional studies. There was

insufficient information available on some potentially important risk factors such as smoking, dietary intake, income, and educational level. In conclusion, our review indicated a rapidly growing prevalence of T2DM in Vietnam over the past decade and suggested that extra effort will be required for prevention and control.

Dietary and lifestyle factors pertinent to Vietnamese offer an opportunity for protection against this emerging chronic disease. Therefore, a relatively inexpensive hospital-based case-control study was conducted to investigate the association between these abovementioned factors (tea consumption, coffee consumption, and physical activity) and T2DM risk among Vietnamese adults.

6.2 Green tea consumption and T2DM risk

Green tea is the second most common beverage in Vietnam after water. In the literature, green tea consumption has been suggested to be protective against T2DM. A hospital-based case-control study was conducted between 2013 and 2015, involving a total of 1198 participants (599 T2DM cases, 599 controls). Results showed an inverse association between green tea consumption and T2DM risk; a reduced T2DM odds of 41% for those who drank >4 cups per day relative to the reference group of non-drinkers after adjusting for plausible confounders. The dose-response relationship was also significant, with reduced odds of T2DM by increasing the quantity (cups) of green tea consumed per day. In addition, the cumulative exposure to green tea consumption was found to reduce significantly the risk of T2DM among adults. Green tea drinking is not only part of the Vietnamese dietary culture but also other Asian cultures, which have been shown to be a protective factor against T2DM in the literature, consistent with our case-control study. In conclusion, green tea consumption should be extended to non-tea drinkers in our community to take up the tea drinking habit.

6.3 Coffee consumption and T2DM risk

Coffee is one of the most common beverages drunk in Western populations. Although coffee consumption has been shown to be associated with a lower risk of T2DM in Western countries, little is known about coffee drinking pattern and its relationship with T2DM risk among Asian populations. This hospital-based case-control study provides the first such report in Vietnam. Overall, our results support for the beneficial role of habitual coffee consumption in reducing the risk of T2DM after adjustment for plausible confounding factors. We further found that the inverse association with T2DM risk among women was more apparent than men, consistent with previous studies. For those women who drank 1-3 cups per day, a significant reduction of T2DM risk was observed, whereas such inverse association was weaker for men. Indeed, the interaction term between sex and T2DM was statistically significant. Participants who were male smokers accounted for more than 61%, while only 1% of women reported as current or former smokers. It appears that smoking may confound the relationship between coffee drinking and T2DM risk. In conclusion, coffee consumption was associated with a reduced risk of T2DM in Vietnamese women.

6.4 Physical activity and T2DM risk

Physical activity can affect the development of T2DM, where intensity and frequency of physical activity are important aspects. In the present study, the relationship between physical activity and the risk of T2DM among Vietnamese adults was investigated. After adjustment for plausible confounding factors, significant reductions in T2DM risk were observed among participants undertaking moderate intensity activities (both occupational and leisure-time activity) relative to those who did light physical activity. Total physical activity level was computed as the summation of activities with different intensity levels such as strenuous, vigorous, and moderate activities, but mostly was derived from moderate intensity activities.

Our findings showed that total physical activity level was inversely associated with T2DM, with a 31% odds reduction observed among individuals engaging 26 MET-hours per week relative to those with less than 13 MET-hours per week. Data also indicated a significant, inverse trend of association between total physical activity and T2DM; each MET-hour increment per week was associated with a 3% and 2% lower risk of T2DM in men and women, respectively. The data reported here supported the concept that T2DM may be prevented by increasing overall physical activities, particularly moderate activity in leisure time and occupational settings.

6.5 Recommendations

Our case-control study results showed that habitual consumptions of green tea and coffee were inversely associated with the T2DM risk among Vietnamese adults. Besides, maintaining regular moderate intensity activities may provide an apparent benefit to reduce the T2DM risk. The findings are crucial and potentially contribute to the development of evidence-based guidelines for individuals at risk of T2DM to improve their diet and lifestyle, with the ultimate goal to control and prevent this emerging epidemic in Vietnam. The hospital-based case-control design is relatively inexpensive and thus appropriate to facilitate future replications in similar low- and middle-income countries in Asia.

As little information on tea and coffee drinking is available in Vietnam, our study contributes to better understanding the preventive effects of these beverages. However, due to limitations and biases inherent in our retrospective study design (as discussed in the previous chapter), cause-and-effect relationship could not be established. Therefore, it is important to conduct large-scale prospective cohort studies and randomised controlled trials to determine the protective effects of tea and coffee consumption for the development of incident T2DM. This

thesis focused on tea and coffee consumption and physical activity, other modifiable lifestyle (alcohol drinking and cigarette smoking) and plausible dietary factors of T2DM (traditional foods such as fish, fruits, and vegetables as reviewed in Chapter 2) should be investigated in the future. Similarly, it may be worthwhile to examine the rural/urban differences in T2DM incidence and to perform stratified analyses by residential location.

Similarly, physical activity has been suggested as a protective factor for T2DM and other non-communicable diseases. Consistent with the literature, the present study found the similar benefit of moderate physical activity in reducing the risk of T2DM. A recent WHO STEP survey in Vietnam reported that seven-in-ten Vietnamese people aged 25–64 years meet the WHO recommendations for total physical activity. However, total physical activity was mainly derived from work-related activities (Van Bui et al. 2015). Therefore, changes in infrastructure and surroundings in the community are essential to improve the level of exercise among Vietnamese adults. Finally, randomised controlled trials, using objective measurements such as pedometers and/or accelerometers to assess types and intensities of physical activities, should be implemented to evaluate the effectiveness of physical activity to control and manage impaired glucose status. Regular exercise should be promoted and recommended as part of a healthy lifestyle and body weight control for the prevention of T2DM in Vietnam.

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APPENDIX

Appendix A: Information sheet and consent form



Information letter

**School of Public Health
Curtin University
GPO Box U 1987
Perth, WA 6845, Australia**

Project Title: A Case-control Study of Risk Factors for Type 2 Diabetes Mellitus in Vietnam

My name is Nguyen Thanh Chung. I am a medical and public health researcher, and have a medical degree from Vietnam and a Master of Public Health degree from Curtin University, Australia. I am investigating the dietary factors relating to the development of type 2 diabetes in Vietnamese adults. In this project, I will interview people with and without type 2 diabetes. I am interested to find out what you eat and drink as well as your lifestyle habits such as smoking and alcohol consumption. I will also ask you several questions regarding your health status and demographic details. Each face-to-face interview will take about 40 minutes to complete.

Your participation in this research is completely voluntary. You can refuse any specific question that you are uncertain or find it difficult to answer. During the interview, if you decide to withdraw from the study, please feel free to do so because there will be no negative consequences; especially with respect to the treatment you are receiving at this hospital. I can assure you that your treatment or therapy will not be affected at all by participation in this study.

After you have signed the enclosed consent form, I will assume that you have agreed to participate, and you allow me to use your data in this research project. The information you provided will be kept strictly confidential, and your identity will remain anonymous. Only aggregated data from all participants will be analysed and reported.

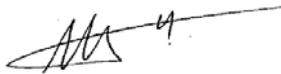
Please be assured that your information will only be accessed by the chief investigator of this project, and not anyone else. In particular, it will not be released to the medical staff and authority of this hospital. Your completed questionnaire and other documents will be kept in a locked cabinet for five years at Curtin University before being destroyed.

If you require further information about this study, please do not hesitate to contact me.

This study has been approved by the Curtin University Human Research Ethics Committee (Approval Number HR105/2013). The Committee is comprised of members of the public, academics, lawyers, doctors and pastoral carers. If needed, verification of approval can be obtained either by writing to the Curtin University Human Research Ethics Committee, Office of Research and Development, Curtin University, GPO Box U1987, Perth, 6845 or by telephoning 9266 2784 or by emailing hrec@curtin.edu.au.

Thank you very much for your participation in this research project. Your contribution is important and greatly appreciated.

Yours sincerely,



Nguyen Thanh Chung
Phone: 0962999628
Email: bsnguyenthanhchung@gmail.com



Professor Andy Lee
Phone: +61-8-92664180
Email: Andy.Lee@curtin.edu.au



Professor Colin Binns
Phone: +61-8-92662952
Email: C.Binns@curtin.edu.au

Consent form

I, _____, have read the information on the attached letter, and have been informed about the purpose of this research project.

I agree to participate in this research, but have the option to change my mind and withdraw at any time.

I agree to take part in an interview where my answers will be transcribed onto a questionnaire.

I understand that all information provided by me will be treated as confidential and that my identity will remain anonymous.

I understand that no individual data will be used except in aggregated form for subsequent reporting purpose.

This study has been approved by the Curtin University Human Research Ethics Committee (Approval Number HR105/2013). The Committee is comprised of members of the public, academics, lawyers, doctors and pastoral carers. If needed, verification of approval can be obtained either by writing to the Curtin University Human Research Ethics Committee, Office of Research and Development, Curtin University, GPO Box U1987, Perth, 6845 or by telephoning 9266 2784 or by emailing hrec@curtin.edu.au.

Name of participant

Signature of participant

Date

Name of witness

Signature of witness

Date

Patient's medical record number:

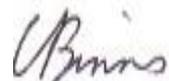
Yours sincerely,



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Appendix B: Research Ethics

To	Professor Andy Lee, Public Health School		
From	Professor Stephan Millett, Chair, Human Research Ethics Committee		
Subject	Protocol Approval ^{TELEPHONE} HR 105/2013		92662784
Date	17 July 2013	FACSIMILE	92663793
Copy	Mr Thanh Chung Nguyen, Public Health Professor Colin Binns, Public Health	EMAIL	hrec@curtin.edu.au

Thank you for providing the additional information for the project titled "A Case-control Study of Risk Factors for Type 2 Diabetes Mellitus in Vietnam". The information you have provided has satisfactorily addressed the queries raised by the Committee. Your application is now approved.

- You have ethics clearance to undertake the research as stated in your proposal.
- The approval number for your project is HR 105/2013. Please quote this number in any future correspondence.
- Approval of this project is for a period of four years 18-07-2013 to 18-07-2017.
- Your approval has the following conditions:
 - i) Annual progress reports on the project must be submitted to the Ethics Office.
- It is your responsibility, as the researcher, to meet the conditions outlined above and to retain the necessary records demonstrating that these have been completed.

Applicants should note the following:

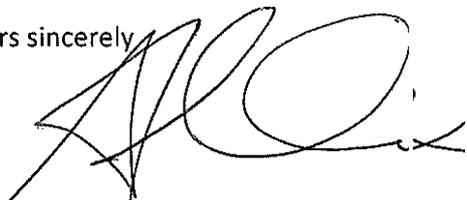
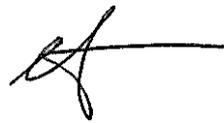
It is the policy of the HREC to conduct random audits on a percentage of approved projects. The audits may be conducted at any time after the project starts. In cases where the HREC considers that there may be a risk of adverse events, or where participants may be especially vulnerable, the HREC may request the chief investigator to provide an outcomes report, including information on follow-up of participants.

The attached Progress Report should be completed and returned to the Secretary, HREC, C/- Office of Research & Development annually.

Our website https://research.curtin.edu.au/guides/ethics/non_low_risk_hrec_forms.cfm contains all other relevant forms including:

- Completion Report (to be completed when a project has ceased)
- Amendment Request (to be completed at any time changes/amendments occur)
- Adverse Event Notification Form (if a serious or unexpected adverse event occurs)

Yours sincerely

Professor Stephan Millett

Chair Human Research Ethics Committee

Appendix C: Questionnaire



Questionnaire

Case-Control Study of Risk Factors for Type 2 Diabetes Mellitus in Vietnam

The interviewee is:	<input type="checkbox"/> Case	<input type="checkbox"/> Control
Questionnaire ID:	CA/____/____ <i>Case/"hospital number"/ "case number"</i>	CO/____/____/____ <i>Control/"hospital number"/"control number"</i>
Diagnosis:		
Medical record ID:		
Department :		
Hospital:		
Date of interview:	____/____/____ (dd/mm/yyyy)	
Date of completion:	____/____/____ (dd/mm/yyyy)	
Interviewer ID:		
<p>Structure of the questionnaire:</p> <ul style="list-style-type: none"> A. Demographic information B. Anthropometric measurements (direct measurement) C. Clinical information (extract from medical record) D. Personal and family medical history E. Lifestyle F. Dietary habits – Food frequency questionnaire 		

A. Demographic information			
A1.	Name of interviewee:		
A2.	Address		
	Number:	; Street:	commune/ward:
	District:	; Province:	
A3.	Contact number (home phone/mobile)	[...../.....]	
A4.	Contact phone for next-of-kin	[...../.....]	
A5.	Date of Birth	____/____/____ (dd/mm/yyyy)years	
A6.	Gender	0 [] Male 1 [] Female	
A7.	Marital status	0 [] Never married 1 [] Married/de facto 2 [] Widowers/divorced/separated	
A8.	Age at marriageyears	
A9.	Occupation (before retirement)	0 [] Farmer 1 [] Manual worker 2 [] Office clerk 3 [] Teacher 4 [] House worker 5 [] Other:.....	
A10	Retirement status	0 [] Not retired 1 [] Retired	
A11	What is the highest level of education you have completed?	0 [] No formal education 1 [] Primary school 2 [] Secondary school 3 [] High school 4 [] College/vocational school/University	
B. Anthropometric measurements			
B1.	Blood pressure (I will measure 2 times your arterial blood pressure and your pulse rate at your left arm)		
B2.	Measurement time 1	Systolic Diastolic Pulse rate/minutemmHgmmHg
B3.	Measurement time 2	Systolic Diastolic Pulse rate/minutemmHgmmHg
B4.	Height	____.____	Centimetres
B5.	What is your weight three years ago?	____.____	Kilograms
B6.	Current weight	____.____	Kilograms

B7.	Waist circumference	— — —. —	Centimetres
B8.	Hip circumference	— — —. —	Centimetres

C. Clinical information		
C1.	Diagnosis at hospital:	1 [] Fasting plasma glucose 2 [] 2h OGTT 3 [] other, _____
C2.	Date of diagnosis/...../..... (dd/mm/yyyy)
C3.	Fasting plasma glucosemmol/l
C4.	2h OGTTmmol/l
C5.	HbA1C%
C6.	Triglyceridesmmol/l
C7.	LDL cholesterolmmol/l
C8.	HDL cholesterolmmol/l
C9.	Total cholesterolmmol/l
D. Personal and family medical history		
D1.	Have you been diagnosed of (self-report)?	<u>Year of diagnoses</u> Yes [] No []Hypertension Yes [] No []Coronary heart disease Yes [] No [] Myocardial infraction Yes [] No [] Heart failure Yes [] No []Cardiomyopathy Yes [] No []Cardiac dysrhythmia Yes [] No []Hypertensive heart disease Yes [] No []Inflammatory heart disease Yes [] No []Valvular heart disease Yes [] No []Cerebrovascular disease Yes [] No []Peripheral arterial disease Yes [] No []Congenital heart disease Yes [] No []Hypercholesterol Yes [] No []Hyperlipidemia Yes [] No []Gout Yes [] No []Foot ulcers Yes [] No []Pneumonia Other,
D2.	In your family, is there anyone who has suffered from diabetes?	0 [] No 1 [] Yes => Type 1 [] Type 2 []

D3.	<i>If yes, is the person your?</i>	1 [<input type="checkbox"/>] father 2 [<input type="checkbox"/>] mother 3 [<input type="checkbox"/>] brother 4 [<input type="checkbox"/>] sister
D4.	List of comorbidity (hospital medical records)	1.year [.....] 2.year [.....] 3.year [.....] 4.year [.....] 5.year [.....] 6.year [.....] 7.year [.....] 8.year [.....] 9.year [.....] 10.year [.....] 11.year [.....] 12.year [.....] 13.year [.....] 14.year [.....] 15.year [.....]

E. Lifestyle		
No.	Physical activity	
<i>Before the disease, how long, on the average, in a day (/week) did you spend in the following sitting activities?</i>		
E1.	Sitting in car or bushrs.....mins/day Or :.....hrs.....mins/week
E2.	Riding on motorbikehrs.....mins/day Or :.....hrs.....mins/week
E3.	Sitting at work (e.g. sewing, at office or factory...)hrs.....mins/day Orhrs.....mins/week
E4.	Other sitting activities (e.g. watching TV, eating meals, reading, playing cards, listening radios, computer games...)hrs.....mins/day Orhrs.....mins/week
E5.	Sleeping time (including afternoon naps)hrs.....mins/day Orhrs.....mins/week
<i>Lifelong physical activity involvement was defined as ‘(doing) active sports or vigorous exercise or work long enough to get sweaty, at least twice a week’</i>		
E6.	How would you describe your physical fitness activity over your entire life course?	0 [<input type="checkbox"/>] Never been much involved 1 [<input type="checkbox"/>] Previously active but not any more 2 [<input type="checkbox"/>] Active just recently 3 [<input type="checkbox"/>] Intermittently active 4 [<input type="checkbox"/>] Always been involved
<i>Before the disease, how long, on the average, in a day (/week) did you spend in the following physical activities?</i>		
E7.	Strenuous sports (i.e. jogging, bicycling on hills, tennis, badminton, swimming, aerobics)hrs.....mins/day Orhrs.....mins/week
E8.	Vigorous work (i.e. moving heavy furniture, shovelling, weight lifting, loading/ unloading trucks, or equivalent manual labour)hrs.....mins/day Orhrs.....mins/week

E9.	Moderate activity (i.e. housework, brisk walking, golfing, bowling, bicycling on level ground, gardening, Taichi)hrs.....mins/day Or :.....hrs.....mins/week	
Exposure to cigarette smoking [adopted from(WHO 2008b)]			
E10.	Are you a	0 [] never smoker? 1 [] former smoker? 2 [] current smoker?	<i>If 0, => F13</i>
E11.	On average, how many of the following tobacco products do you smoke per day?	Manufactured cigarettes? Hand-roll cigarettes? Pipes full of tobacco? Cigars, cheroots or cigarillos? Number of water pipe sections? Any others? Specify..... per day per day per day per day per day per day
E12.	How many years have (had) you been smoking? years or since age.....	
E13.	Are your relatives/people living with you smoking at home?	0 [] No 1 [] Yes	

F. Food frequency questionnaire [adopted from (Kusama et al. 2005)] <i>General dietary habit – please recall your habit three years ago</i>		
No	Questions	Answer
F1.	Are you on a special diet listed below now or 3 years ago?	0 [] No 1 [] Vegetarian 2 [] Low fat 3 [] Low salt 4 [] Other:
F2.	Do you have meals regularly (having 3 meals per day)	1 [] Regularly 2 [] Occasionally irregular 3 [] Sometime irregular 4 [] Often irregular
F3.	Your eating habit <i>Eating breakfast:</i> 1 [] everyday 2 [] frequently 3 [] occasionally 4 [] never <i>Eating take-away food or eating out:</i> 1 [] everyday 2 [] frequently 3 [] occasionally 4 [] never <i>Eating snacks (Biscuits, melon seeds):</i> 1 [] everyday 2 [] frequently 3 [] occasionally 4 [] never <i>Eating sweet food (candy, congee...):</i> 1 [] everyday 2 [] frequently 3 [] occasionally 4 [] never	
F4.	Did you or any of your family members feel your food was salty?	0 [] never 1 [] sometimes 2 [] usual

F5.	When you eat meat, did you trim off all the fat?	0 [] never 1 [] sometimes 2 [] usual
F6.	When you ate chicken, did you eat the skin	0 [] never 1 [] sometimes 2 [] usual
F7.	How often do you eat the following types of food? (How many times per Year/Month/Week/Day?) <i>Fried food:</i> <i>Smoked food:</i> <i>Cured food:</i> <i>Grilled food:</i> times/[]Y []M []W []D times/[]Y []M []W []D times/[]Y []M []W []D times/[]Y []M []W []D
F8.	How often do you use vegetable cooking oil? times/[]Y []M []W []D
F9.	How often do you use pork lard? times/[]Y []M []W []D
F10.	When you eat, how often do you use the following seasonings? <i>Fish sauce:</i> <i>Salt:</i> <i>Soybean sauce:</i> <i>Tomato sauce:</i> times/[]Y []M []W []D times/[]Y []M []W []D times/[]Y []M []W []D times/[]Y []M []W []D
F11.	Within the last 3 years, have you changed you diet habit	0 [] No 1 [] Yes
F12.	If yes, please specify: - How you have changed: - The reasons for this change:	

Consumption of beverage: How often/what amount of/ how did you drink the following beverage? – Please tell us about your dietary habits 3 years ago.

No	Beverage	Frequency Per Year/Month/Week/Day	Unit (PS: portion size)	Quantity/ each time (PS)	For how many years?
F13.	Beer	___times/[]Y []M []W []D	300ml cup (A)		
F14.	Home-made rice wine	___times/[]Y []M []W []D	30ml cup (B)		
F15.	Home-made herbal rice wine	___times/[]Y []M []W []D	30ml cup (B)		
F16.	Strong bottled liquor (≥ 39% alcohol; e.g. vodka)	___times/[]Y []M []W []D	30ml cup (B)		

F17.	Light bottled liquor (\leq 29% alcohol; e.g. small bottle vodka)	_____times/[]Y []M []W []D	30ml cup (B)		
F18.	Red wine	_____times/[]Y []M []W []D	100ml cup (C)		
F19.	White wine	_____times/[]Y []M []W []D	100ml cup (C)		
F20.	Within the last 3 years, have you changed your drinking habit for any type of liquor above?			0 [] No 1 [] Yes	
<i>If yes, please tell us the reasons for that change?</i>					
F21.	Green tea (dried)	_____times/[]Y []M []W []D	100ml cup (D)		
F22.	Green tea leave	_____times/[]Y []M []W []D	200ml cup (E)		
F23.	Black tea	_____times/[]Y []M []W []D	100ml cup (D)		
F24.	Oolong tea	_____times/[]Y []M []W []D	100ml cup (D)		
F25.	Within the last five years, have you changed your drinking habit for any type of tea above?			0 [] No 1 [] Yes	
<i>If yes, please tell us the reasons for that change?</i>					
F26.	Black coffee	_____times/[]Y []M []W []D	150ml cup (F)		
F27.	Instant coffee	_____times/[]Y []M []W []D	Bag 5gr spoon (H)bagspoon	
F28.	Milk coffee	_____times/[]Y []M []W []D	150ml cup (G)		
F29.	Within the last 3 years, have you changed your drinking habit for any type of coffee above?			0 [] No 1 [] Yes	
<i>If yes, please tell us the reasons for that change?</i>					
F30.	Water	_____times/day	250ml cup	_____cup	
F31.	Soy milk	_____times/[]Y []M []W []D	250ml cup	_____cup	
F32.	Lemon juice	_____times/[]Y []M []W []D	250ml cup	_____cup	
F33.	Orange juice	_____times/[]Y []M []W []D	250ml cup	_____cup	
F34.	Coconut water	_____times/[]Y []M []W []D	250ml cup	_____cup	
F35.	Fruit shake juice	_____times/[]Y []M []W []D	250ml cup	_____cup	
F36.	What type of fruits did you drink the most?	1 [] mango 2 [] guava 3 [] water melon 4 [] avocado 5 [] custard apple 6 [] paw paw 7 [] Pineapple 8 [] sapodilla 9 [] Other:.....			
F37.	Soft drink (coke, pepsi...)	_____times/[]Y []M []W []D	250ml cup	_____cup	

F38.	<i>What type of soft drinks did you drink the most?</i>	1 [] Coca cola 2 [] Pepsi 3 [] Fanta	4 [] Nestea 5 [] Icetea 6 [] Other canned soft drink
F39.	Did you add sugar into your drinks, such as tea, coffee or orange juice? <i>If yes, how many spoons (5g) did you add?</i>	0 [] No 1 [] Yes,spoons	

Consumption of soy bean products, vegetables and fruits

How often do you eat soy bean products?

No	Food item	Frequency (per month/week/day)	Unit (PS)	Quantity/meal? (½ PS, 1PS, 1.5PS...)
F40.	Fried tofu	___times/[]Y []M []W []D	Piece (I)	___PS
F41.	Raw tofu	___times/[]Y []M []W []D	Piece (I)	___PS
F42.	Soybean curd with sweet syrup	___times/[]Y []M []W []D	Small bowl (J)	___PS

Consumption of vegetables- *How often/what amount of/ how did you eat vegetables?*

F43.	Tomato	___times/[]Y []M []W []D	Whole	___PS
F44.	Bean sprout	___times/[]Y []M []W []D	Small bowl (L)	___PS
F45.	Amaranth, Jute potherb	___times/[]Y []M []W []D	Small bowl (L)	___PS
F46.	Water spinach	___times/[]Y []M []W []D	Small bowl (L)	___PS
F47.	Mustard green, Chinese cabbage	___times/[]Y []M []W []D	Small bowl (L)	___PS
F48.	Malabar nightshade	___times/[]Y []M []W []D	Small bowl (L)	___PS
F49.	Crown-daisy	___times/[]Y []M []W []D	Small bowl (L)	___PS
F50.	Chinese leek	___times/[]Y []M []W []D	Small bowl (L)	___PS
F51.	Cabbage	___times/[]Y []M []W []D	Small bowl (L)	___PS
F52.	French bean	___times/[]Y []M []W []D	Small bowl (L)	___PS
F53.	Pumpkin	___times/[]Y []M []W []D	Small bowl (L)	___PS
F54.	Gourd	___times/[]Y []M []W []D	Small bowl (L)	___PS
F55.	Cucumber	___times/[]Y []M []W []D	Small bowl (L)	___PS
F56.	Broccoli	___times/[]Y []M []W []D	Small bowl (L)	___PS
F57.	Chinese yam (green)	___times/[]Y []M []W []D	Small bowl (L)	___PS
F58.	Chinese yam (white)	___times/[]Y []M []W []D	Small bowl (L)	___PS

F59.	Ash gourd, wax gourd	____times/[]Y []M []W []D	Small bowl (L)	____PS
F60.	Bitter melon	____times/[]Y []M []W []D	Small bowl (M)	____PS
F61.	Capsicum	____times/[]Y []M []W []D	Small bowl (N)	
F62.	Carrot	____times/[]Y []M []W []D	Whole (O)	____PS
F63.	White potato	____times/[]Y []M []W []D	Whole (O)	____PS
F64.	Sweet potato	____times/[]Y []M []W []D	Whole (P)	____PS

Consumption of fruits - How often/what amount of/ how did you eat fruit?

F65.	Dragon fruit	____times/[]Y []M []W []D	Whole	____PS
F66.	Banana	____times/[]Y []M []W []D	Whole	____PS
F67.	Papaya	____times/[]Y []M []W []D	Piece 20x4cm (Q)	____PS
F68.	Pomelo	____times/[]Y []M []W []D	Piece (R)	____PS
F69.	Longan	____times/[]Y []M []W []D	Kg	____kg
F70.	Orange	____times/[]Y []M []W []D	Whole	____PS
F71.	Water melon	____times/[]Y []M []W []D	Piece 100 gr (S)	____PS
F72.	Pear	____times/[]Y []M []W []D	Whole	____PS
F73.	Grape	____times/[]Y []M []W []D	Kg	____kg
F74.	Guava	____times/[]Y []M []W []D	Whole	____PS
F75.	Apple	____times/[]Y []M []W []D	Whole	____PS
F76.	Lychee	____times/[]Y []M []W []D	Kg	____kg
F77.	Mangoes	____times/[]Y []M []W []D	Whole	____PS
F78.	Durian	____times/[]Y []M []W []D	Piece (T)	____PS

Consumption of sweet varieties - How often/what amount of/ how did you eat sweet varieties?

No	Food item	Frequency (per month/week/day)	Unit	Quantity/meal? (½ PS, 1PS, 1.5PS...)
F79.	Sweet soup (made of glutinous rice and bean, corn...)	____times/[]Y []M []W []D	250 ml cup (U)	____PS

F80.	Please choose 3 types that you eat the most?		1 [] Glutinous soup with taro 2 [] Glutinous soup with corn 3 [] Glutinous soup with mung bean 4 [] Glutinous soup with black bean 5 [] Glutinous soup with white bean 6 [] Mix glutinous soup with bean 7 [] Other:.....
F81.	Sweet cakes	____times/[]Y []M []W []D	Piece (V) _____PS
F82.	Biscuits	____times/[]Y []M []W []D	Piece _____PS
Consumption of bread and rice varieties - How often/what amount of/how did you eat the following items?			
F83.	French type bread (either plain or with meat)	____times/[]Y []M []W []D	Load (W) _____PS
F84.	Sliced bread (either plain or with meat)	____times/[]Y []M []W []D	Slice _____PS
F85.	Rice-based noodles	____times/[]Y []M []W []D	Large bowl (X) _____PS
F86.	Wheat-based noodles	____times/[]Y []M []W []D	Large bowl (X) _____PS
F87.	Instant noodle	____times/[]Y []M []W []D	Bag _____PS
F88.	Plain rice (at home)	____times/[]Y []M []W []D	Small bowl _____PS
F89.	Rice comes in a serving (a plate of fried rice, broken rice...) when eating outside	____times/[]Y []M []W []D	Plate _____PS
F90.	Glutinous rice (either plain, with bean, or salted)	____times/[]Y []M []W []D	Small bowl _____PS
F91.	Rice porridge	____times/[]Y []M []W []D	Large bowl (KK) _____PS

Consumption of meat- How often/what amount of/how did you eat?				
No	Food item	Frequency (per month/week/day)	Unit (PS)	Quantity/meal? (½ PS, 1PS, 1.5PS...)
F92.	Pork lean	____times/[]Y []M []W []D	Small piece(Y)	_____PS
F93.	Pork medium fat	____times/[]Y []M []W []D	Small piece(Z)	_____PS
F94.	Pork rib	____times/[]Y []M []W []D	Small piece(AA)	_____PS
F95.	Pork lower leg	____times/[]Y []M []W []D	Small piece(BB)	_____PS
F96.	Pork steak	____times/[]Y []M []W []D	Piece 60g (CC)	_____PS
F97.	Beef	____times/[]Y []M []W []D	Small bowl (DD)	_____PS

F98.	Chicken	____times/[]Y []M []W []D	Small piece(EE)	_____PS
F99.	Pigeon	____times/[]Y []M []W []D	Small piece(FF)	_____PS
F100.	Duck	____times/[]Y []M []W []D	Small piece(FF)	_____PS
F101.	Pork heart	____times/[]Y []M []W []D	gram	_____gr
F102.	Pork liver	____times/[]Y []M []W []D	gram	_____gr
F103.	Pork kidney	____times/[]Y []M []W []D	gram	_____gr
F104.	Chicken heart	____times/[]Y []M []W []D	gram	_____gr
F105.	Chicken liver	____times/[]Y []M []W []D	gram	_____gr
F106.	Chicken kidney	____times/[]Y []M []W []D	gram	_____gr
Consumption of fish, egg and milk- How often/what amount of/how did you eat?				
F107.	Sea fish (Mackerel, tuna...)	____times/[]Y []M []W []D	Piece 70g (GG)	_____PS
F108.	<i>Please check two types of sea fish that you eat the most often?</i>		1 [] Mackerel 2 [] Tuna 3 [] Mullet 4 [] other, specify.....	
F109.	Fresh water fish (Tilapia...)	____times/[]Y []M []W []D	Piece 50g (HH)	_____PS
F110.	<i>Please check two types of fresh water fish that you eat the most often?</i>		1 [] Tilapia 2 [] Snake-head 3 [] Carp 4 [] Chep 5 [] Other, specify.....	
F111.	Shrimp	____times/[]Y []M []W []D	Whole (II)	_____PS
F112.	Squid/octopus	____times/[]Y []M []W []D	Piece (JJ)	_____PS
F113.	Sea shells	____times/[]Y []M []W []D	Small bowl	_____PS
Egg				
F114.	Chicken egg	____times/[]Y []M []W []D	Whole	_____PS
F115.	Duck egg	____times/[]Y []M []W []D	Whole	_____PS
Preserved food				
F116.	Pickle vegetable & garlic	____times/[]Y []M []W []D	gram	_____gr
F117.	Fermented soy product	____times/[]Y []M []W []D	gram	_____gr
F118.	Salted fish	____times/[]Y []M []W []D	gram	_____gr

F119.	Preserved meat (sausage...)	____times/[]Y []M []W []D	gram	gr
Milk				
F120.	Cow whole milk	____times/[]Y []M []W []D	Cup 250ml	____PS
F121.	Soya milk	____times/[]Y []M []W []D	Cup 250ml	____PS
F122.	Milk powder, whole	____times/[]Y []M []W []D	5gr spoon (H)	____PS
F123.	Yogurt	____times/[]Y []M []W []D	Box	____PS
F124.	Condensed milk	____times/[]Y []M []W []D	ml (C)	____PS

Dietary supplements - How often/what amount of/how did you use?

No.	Item	Frequency	Unit	Quantity /time (unit)	Years of use
F125.	Multivitamin	____times/[]Y []M []W []D	Tablet		
F126.	Vitamin A	____times/[]Y []M []W []D	Tablet		
F127.	Vitamin C	____times/[]Y []M []W []D	Tablet		
F128.	Vitamin E	____times/[]Y []M []W []D	Tablet		

Appendix D: Publications

1. Nguyen CT, Pham NM, Lee AH, Binns CW. 2015. "Prevalence of and Risk Factors for Type 2 Diabetes Mellitus in Vietnam: A Systematic Review." *Asia Pac J Public Health*. doi:10.1177/1010539515595860.
2. Nguyen CT, Pham NM, Tran DV., Lee AH, Binns CW. 2016. "Lifestyle and diet in relation to risk of type 2 diabetes in Vietnam: a hospital-based case-control study." *SpringerPlus*. doi: 10.1186/s40064-016-2313-3.