Etiology of Weight Change, Type 2 Diabetes, and Mortality in Adult Chinese Singaporeans: The Singapore Chinese Health Study

A DISSERTATION
SUBMITTED TO THE FACULTY OF THE GRADUATE SCHOOL
OF THE UNIVERSITY OF MINNESOTA
BY

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IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

Dr. Mark A. Pereira, Advisor

July 2009

Acknowledgements

The process of this research was supported by grants for the Singapore Chinese Health Study administered by Mimi Yu and through a training grant in Cardiovascular disease Epidemiology and Prevention from the National Heart Lung and Blood institute administered by Dr. Aaron Folsom.

I want to thank and acknowledge Mark Pereira for his guidance, thoughts and mentoring throughout the steps of graduate school. There is not enough space on this page to thoroughly sum up his contributions to my experience as a graduate student. Mimi Yu was central to my involvement with the study at focus. Her mentoring and patience as I cut my teeth over the last couple years on the Singapore study has been gracious, supportive and provided means for my education as well as to travel and attend conferences. I've been afforded a tremendous opportunity to work on the study. I want to thank my other dissertation committee members, Sue Duval and Myron Gross, for providing helpful advice and commentary. Lastly, I want to thank Sarah, my family, friends and Rika for everything they've provided through school and this dissertation.

Abstract

Background: Diet and lifestyle are the primary channels in prevention of weight gain and type 2 diabetes, as well as being implicitly involved with body mass index (BMI). The literature on dietary factors related to obesity and type 2 diabetes has continued to expand, but little research has focused on Asian populations. Furthermore, debate over the optimal BMI range in Asians has become an important public health question in need of more thorough investigation. The objective of this dissertation is to investigate the associations between dietary patterns, weight gain and risk of obesity, dietary patterns and risk of type 2 diabetes, and BMI and all-cause mortality in 61,000+ middle aged Chinese men and women in the Singapore Chinese Health Study (SCHS).

Methods: This dissertation includes three separate research projects aiming to investigate how dietary patterns associate with weight gain and risk of obesity (1), type 2 diabetes incidence (2), and how BMI is associated with all-cause mortality (3). In the first and second projects dietary patterns were derived using principal components analysis. The first project examined how these patterns along with a western fast food index associate with weight gain and risk of future obesity. The second project examined how the dietary patterns were associated with incident type 2 diabetes. Proportional hazards regression was used to characterize the prospective associations with incident obese status and type 2 diabetes. The last project also utilized proportional hazards regression along with a non-parametric trend graph analysis to investigate the association between BMI and all-cause mortality.

Results: Results for the three projects were as follows: (1 and 2) two main dietary patterns were identified. A pattern characterized by high consumption of vegetables, fruit, and soy foods with some fish and seafood was termed vegetable, fruit and soy rich (VFS). The other dietary pattern was characterized by high consumption of dim sum, fresh and processed meats, higher relative intake of noodles and rice dishes, and some sweetened and deep fried foods and was termed dim sum and meat rich (DSM). 1) An increasing VFS dietary pattern score was associated with lower levels of weight gain and an increasing DSM pattern score was associated with increasing weight gain and risk of future obesity, relative risk (RR) of obesity for 4th and 5th vs. 1st quintile of DSM pattern score (1.59 and 1.62). Additionally, each increase in frequency of western fast food consumption was associated with a mean increase in weight gain. 2) Compared to the lowest quintile of VFS dietary pattern score an inverse association with type 2 diabetes was observed in quintiles 2-5, (RR= 0.80, 0.83, 0.75, 0.81). In the main models for the DSM pattern the RR increased similarly in quintiles 2-4 and was further heightened in quintile 5 compared to the 1st quintile (RR= 1.21, 1.17, 1.27, 1.55). The associations persisted after adjustment for all potential confounders including BMI and were limited to non-smokers. 3) In an optimal model of disease-free non-smokers excluding early deaths (< 5 years follow up time) there was a U-shaped association between BMI and all-cause mortality. Compared to the BMI referent group with the lowest mortality rate (18.5-20 kg/m^2) persons with a BMI < 18.5 were at increased risk of premature death (RR=1.41; 95% CI 1.12-1.76), as well as persons with a BMI 26.0-27.4 (RR=1.31; 95% CI 1.05-1.63) and BMI ≥ 27.5, (RR=1.49; 95% CI=1.22-1.83). Further analyses suggest

that the association observed at the low end of the BMI spectrum was driven by persons > 65 years of age with BMI < 17.0.

Conclusions: These results indicate that higher intake of a dietary pattern rich in vegetables, fruits, soy and some fish and seafood is beneficial for weight maintenance and a decreased risk of future type 2 diabetes. On the other hand, higher intake of a dietary pattern rich in consumption of dim sum, meat, sweetened and deep fried foods was associated with increased weight gain, along with increased risks of future obesity and type 2 diabetes. Consideration of the association of BMI with all-cause mortality found a U-shaped association, with BMI from the normal range through the middle range of overweight status (18.5-26) not associated with risk of premature all-cause mortality. As obesity and diabetes become more prevalent in Asia, it is important that future research continues to address and provide data with which Asian populations can identify, in regards to diet and lifestyle. Continued and further sound methodological research is needed that assesses how direct and indirect measures of adiposity associate with chronic disease, mortality, and cause-specific mortality in order to make appropriate public health recommendations in relation to what an optimal weight range may be in Asians.

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The natural history of type 2 diabetes beginning with normal glucose tolerance and progressing through insulin resistance, compensatory hyperinsulinemia, to a state of impaired glucose tolerance and finally to overt diabetes mellitus is a complex interplay of many environmental and genetic factors that influence metabolic processes and ultimately leads to a level of elevated blood glucose resulting from defects in insulin secretion, insulin action or both. Ultimately, overt diabetes mellitus results when the production of insulin is insufficient to overcome the underlying abnormality of increased resistance to its action. Any review of the natural history should begin with the mechanisms involved in maintenance of normal glucose homeostasis.

NORMAL GLUCOSE HOMEOSTASIS

The majority of the body glucose disposal takes place in insulin independent tissues: 50% in brain, 25% in splanchnic area (liver and gastrointestinal tissues) and the remaining 25% in insulin-dependent tissues, mainly muscle tissue and a small amount in adipose tissue.[1] The body also produces glucose. 85% of endogenous glucose production is derived from the liver and 15% from the kidney through glycogenolysis and gluconeogenesis to match basal glucose use.[2] After glucose ingestion and absorption, the increase in plasma glucose concentration stimulates insulin release and the combination of hyperinsulinemia and hyperglycemia stimulates glucose uptake by splanchnic (liver and gut tissues) and peripheral tissues (primarily muscle) while suppressing endogenous glucose production.[2]

The majority of glucose uptake by the peripheral tissues occurs in muscle (~80-85%), and a small amount is metabolized by adipocytes.[2] While fat tissue has a small role in glucose disposal it plays a central role in maintenance of total glucose homeostasis by regulating the release of free fatty acids (FFA) from stored triglycerides and through the production of adipocytokines that influence insulin sensitivity in muscle and liver tissue.[1, 3-6] Increases in plasma insulin concentration inhibit lipolysis leading to a decrease in plasma FFA. This decline strengthens muscle glucose uptake and is a factor in inhibiting hepatic glucose production.[3-6]

Glucagon is also an important component of glucose regulation in post-meal conditions.[7] Glucagon is inhibited by hyperinsulinemia after carbohydrate consumption, which inhibits hepatic glucose output, thus contributing to fuel storage rather than oxidation and a return to glucose homeostasis following the postprandial period.[2]

In short, normal glucose homeostasis is a state of equilibrium between the release and uptake of glucose from the bloodstream into the various tissues. Glycemic control is highly regulated in healthy animals through multiple mechanisms under hormonal control. As a result, in the non-diabetic animal, blood glucose concentration fluctuates within a relatively tight range, rising following carbohydrate ingestion and rapidly returning to near-homeostatic levels typically after one to two hours following ingestion, depending on the amount of carbohydrate ingested.

INSULIN SECRETION AND RESISTANCE

Pancreatic beta cells secrete insulin, which is highly regulated by glucose absorption from the gut as well as feedback from the liver and peripheral tissues. Early in the natural history of type 2 diabetes peripheral resistance to insulin-stimulated glucose uptake by skeletal muscle, liver, and adipose is typically well established. However, fasting glucose concentration, and postprandial glucose tolerance, typically defined as the area under the two-hour glucose concentration curve following ingestion, often remain normal because the beta cells are able to compensate for the peripheral insulin resistance by secreting more insulin. An increase in fasting and postprandial plasma insulin levels can be interpreted as an adaptive response of the pancreas to counter the resistance in the tissues and preserve normal glucose concentrations.[2] Although the precise biochemical pathology leading to insulin resistance is still not clear, it appears to result from gene x environment interactions. Some of the hallmark phenotypical characteristics of the insulin resistant individual include obesity, particularly central obesity in the visceral cavity, and also excess fatty infiltration of skeletal muscle and liver tissue. It is thought that excess visceral fat depots are particularly pernicious, relative to subcutaneous fat depots, because the visceral depots drain directly into the liver. The excess circulating FFAs appear to interfere with the action of insulin on the hepatic insulin receptors. Thus, more insulin is required to overcome this resistant state if hepatic glucose output is to be inhibited by insulin. Excess fatty acids in skeletal muscle probably also interferes with insulin action in muscle tissue, an important site for glucose disposal. As mentioned earlier, excess circulating FFA in the obese state may also contribute to insulin resistance in the adipose tissue, leading to a viscous cycle of a relative decrease in FFA uptake and further exacerbation of insulin resistance. Ultimately, in some individuals with severe insulin resistance, as well as significant compromise of beta cell mass and/or function, insulin secretion is no longer sufficient to overcome the resistance in the peripheral tissues. It is also at this point that hepatic glucose production, the main determinant of fasting plasma glucose levels, begins to rise abnormally.[2] The beta cell continues to respond to the elevated plasma glucose which is now further exacerbated by the increase in hepatic glucose output, but if the insulin resistance is not ameliorated by environmental conditions or therapy the blood glucose concentrations in the fasted and/or postprandial state will begin to increase beyond the normal range.

In the progression from normal to abnormally elevated blood glucose concentration, fasting and glucose-stimulated plasma insulin levels remain high due to the insulin resistant state.[2] This intermediate state between normoglycemia and frank diabetes can be defined by a fasting blood glucose concentration of 100 to 125 mg/dL, referred to as "impaired fasting glucose" (IFG). Alternatively, blood glucose concentrations of 140 to 199 mg/dL 2-hours post ingestion of 75 grams of glucose in solution is referred to as "impaired glucose tolerance" (IGT). In the progression from IFG or IGT to type 2 diabetes the beta cell loses its ability to maintain its previously high rate of insulin secretion in response to glucose without some level of deterioration of tissue sensitivity to insulin.[2] Insulin secretion begins to decline as a function of beta cell apoptosis / decreased beta cell mass and/or beta cell dysfunction leading to decreased insulin output. This significant beta-cell compromise is an essential feature in type 2 diabetes pathology. It is at this point in time that blood glucose concentration increases further into the diabetic ranges of ≥126 mg/dL fasting, or ≥200 mg/dL 2-hr following a 75 gram glucose load. Many insulin resistant individuals with IFG or IGT never precede on to frank type 2 diabetes because their beta cells are able to maintain the hyperinsulinemia indefinitely. It is therefore not surprising that recent genetic studies are discovering polymorphisms relating to beta cell function that may differentiate those with type 2 diabetes from their non-diabetic peers.

In summary, the earliest detectable abnormality in type 2 diabetes pathophysiology is decreased insulin sensitivity (insulin resistance) in the peripheral tissues; there is a compensatory increase in fasting and glucose-stimulated plasma insulin secretion. Impaired fasting glucose and impaired glucose tolerance may follow due to continued exacerbation of insulin resistance for which beta cell insulin output cannot entirely compensate.[2] In essence, hyperinsulinemia precedes the development of type 2 diabetes and is a strong predictor of IGT and type 2 diabetes. However, it is only when beta cell mass or function is compromised and insulin levels therefore decline that diabetic onset occurs.

Hypoinsulinemia and Type 2 Diabetes

Insulin deficiency alone, without tissue insulin resistance, can also lead to type 2 diabetes. When insulin secretion is impaired this can lead to high plasma glucose levels. Type 2 diabetes can manifest with this state even in the absence of insulin resistance. While there is some evidence that points to a specific genetic defect, the specific cause is unknown.[2] This state is differentiated from type 1 diabetes because it tends to happen later in life and there is gradual beta cell compromise rather than abrupt loss of all beta cells early in life that is type 1 diabetes.

Causes of Impaired Insulin Secretion in Type 2 Diabetes

Multiple irregularities have been shown to contribute to impaired insulin secretion from the beta cells. There is evidence from twin studies,[8-11] as well as recent genome-wide association studies,[12-14] of a strong genetic basis for beta cell dysfunction. Glucotoxicity, where the beta cell is exposed to chronic high glucose concentrations has been shown to lead to decreased insulin synthesis and secretion.[15] Lipotoxicity has also been implicated. Short term exposure to increased circulating free fatty acids (FFA) stimulates insulin secretion, but chronic exposure to elevated FFA (typically in the obese insulin resistant phenotype) can set off a chain of pathways that involve inflammation and oxidative stress, impairing beta cell function and promoting apoptosis.[2] Other pathogenic factors potentially involved include resistance to incretins (gut hormones that trigger insulin secretion) and amylin deposits in beta cells,.[2]

INSULIN RESISTANCE AND TYPE 2 DIABETES

Multiple lines of evidence support that the progression from normal to impaired fasting glucose or impaired glucose tolerance is associated with the development of insulin resistance. In this state plasma insulin concentrations are increased regardless of fasting or post meal states, the absolute insulin secretory rate is increased and beta cell sensitivity to glucose is reduced in lean and obese individuals.[2] Additionally, the ability of glucose to stimulate its own uptake is also impaired.[16]

Insulin resistance occurs because there is not a normal insulin secretory response and normal tissue sensitivity to hyperinsulinemia and hyperglycemia.[2, 17] Insulin and hyperglycemia promote glucose disposal through three tightly coupled mechanisms: 1) suppression of endogenous (mostly hepatic) glucose production; 2) stimulation of glucose uptake by the splanchnic (hepatic + GI) tissues; and 3) stimulation of glucose uptake by peripheral tissues- primarily muscle.

The liver produces glucose at a steady state.[2] This is essential to meet the needs of the brain which uses glucose at a steady state, and accounts for 50-60% of all glucose disposal.[1] When carbohydrate is ingested, glucose is absorbed into the blood stream and insulin is secreted into the portal vein where it is taken up by the liver and suppresses glucose output. If the liver does not utilize the insulin properly it will continue to produce glucose, so there will be two sources of glucose into the body, thus creating an excessive fasting plasma glucose state.

The splanchnic tissues are largely insensitive to insulin in the basal state.[2] However, after glucose ingestion hyperglycemia should enhance splanchnic glucose uptake but diminished uptake has been shown to contribute to IGT.[2] On the other hand muscle is the major site of insulin-stimulated glucose disposal and approximately 80% of total body glucose insulin-dependent uptake occurs in skeletal muscle.[18] In summary, insulin resistance in muscle and liver is a characteristic feature of type 2 diabetes mellitus. Overproduction of hepatic glucose is the primary determinant of elevated FPG while the efficiency of glucose uptake in muscles is diminished.

On the cellular level it is known that post binding defects in insulin action are centrally responsible for insulin resistance.[2] Generally, FFA/lipid oxidation levels are increased when defects are observed and impaired glycogen synthesis appears to represent the major pathway responsible for insulin resistance and is present early in the natural history of the disease.[2]

RELATIONSHIP OF INSULIN SENSITIVITY AND SECRETION

Even in an insulin resistant state the majority of individuals will have normal glucose tolerance because their pancreatic beta cells are able to compensate and increase their insulin secretory rate.[2] However, what usually triggers type 2 diabetes is the imbalance between insulin secretion and the severity of insulin resistance in the liver and muscle resulting in fasting hyperglycemia and significant glucose intolerance. Essentially, in the progression to type 2 diabetes from IGT there is a decrease in insulin secretion without any worsening of insulin resistance. There appears to be some beta-cell fatigue but not to the extent of diabetes onset.

In synopsis, insulin resistance usually occurs early and is prominently involved in the natural history of type 2 diabetes. Diabetes manifests when the beta cells are unable to appropriately increase secretion of insulin to compensate for the insulin resistance, or when insulin secretion is critically impaired and even those with normal insulin sensitivity may develop type 2 diabetes.

Diagnosis of Type 2 Diabetes

Diagnosis of diabetes mellitus is largely performed through clinical practice and relies mainly on measurement of blood glucose levels (whole blood or plasma). Given that diabetes is a heterogeneous metabolic disease by nature, diagnosis may be made when one presents with hyperglycemic symptoms or without the presence of symptoms, similar to the case with hypertension. Unfortunately, since the early stages of the disease are often symptom-free with insidious onset, approximately 1/3 of existing cases are thought to go undetected. Therefore, screening high risk individuals is an ongoing public health challenge. The gold standard for diagnosis is using a random or 2 hour post glucose load (75 gm ingested in solution) cutoff of ≥11.1 mmol/L (200 mg/dL) as diagnostic criteria.[19] Although glycemic control is on a continuum, this cutoff is used diagnostically because of pathophysiological significance as diabetic retinopathy was found in patients with plasma glucose levels above this point.[20, 21] This cutoff is also thought to be the level at which insulin secretion from pancreatic beta cells starts to decline.[22] A fasting plasma glucose test uses a cutoff value of ≥7.0 mmol/L (126 mg/DL). To confirm diagnosis the test is repeated on a different day unless there is unequivocal hyperglycemia with acute metabolic decompensation or other obvious symptoms.[22] The utilization of oral glucose tolerance tests (OGTT) is controversial as they have been shown to have poor reproducibility in some instances,[23, 24] along with inconvenience and cost to the patient.[22] However, the same cut off levels of plasma glucose are still applicable. Use of glycated hemoglobin levels (HbA1c) have been suggested as only proper for screening purposes for diabetes.[25] HbA1c tests are less sensitive than OGTT, have a higher cost and the standardization of lab techniques are still developing.[22] However, there has been much scientific and technological progress in this area and HbA1c tests may be used for diagnosing diabetes in the future.

Management and Treatment of Type 2 Diabetes

The impact of type 2 diabetes economically and on morbidity and mortality is enormous. In the United States alone, estimates from 2002 put the costs at approximately 132 billion dollars in direct medical costs and indirect costs related to disability and mortality.[26] In theory, primary prevention should be the first goal for dealing with diabetes given that it is highly preventable. Then again, this is easier said than done and there is no cure for the disease, so effective treatment methods through established avenues of diet, exercise, energy balance and drug treatment are the current practice when individuals develop type 2 diabetes or are at very high risk for developing the disease.

Dietary Management

Central to or accompanying the vast majority of treatment programs is dietary modification. A large body of evidence suggests individuals with type 2 diabetes who adopt a prudent diet in line with the best advice will show improvement in the many major metabolic abnormalities that present with the condition. Some experience a large enough improvement in glycemic control that they no longer need drug therapy or insulin. The role of diet in managing diabetes generally has a few goals and the major principles of the recommendations fall in line with general dietary recommendations for health and for entire populations at higher risk of cardiovascular disease.[27] The first aim is to minimize short term glycemic fluctuation, the second is to reduce the risk of long term complications by achieving optimal glycemic control and levels of blood lipids and the third is to prevent weight gain and if necessary lose a moderate amount of weight.

Highlights of specific recommendations from the most recent American Diabetes Association nutrition guidelines includes[28]:

- In the short-term (up to 1 year), either low-carbohydrate or low-fat, energy-restricted diets may be effective for weight loss
- Patients receiving low-carbohydrate diets should undergo monitoring of lipid profiles, renal function, and protein intake (in patients with nephropathy), and have adjustment of hypoglycemic therapy as needed
- Primary prevention for individuals at high risk of developing type 2 diabetes should include structured programs targeting lifestyle changes, with dietary strategies of decreasing energy and dietary fat intakes. Goals should include moderate weight loss (7% body weight), regular physical activity (150 minutes/week), dietary fiber intake of 14 g/1000 kcal, and whole grains comprising half of total grain intake
- Intake of low-glycemic index foods that are rich in fiber and other vital nutrients should be encouraged, both for the general population and for those with diabetes
- Secondary prevention, or controlling diabetes, should include a healthy dietary pattern emphasizing carbohydrate from fruits, vegetables, whole grains, legumes, and low-fat milk
- A key strategy for achieving glycemic control is to monitor carbohydrate by counting, exchanges, or experienced-based estimation
- Use of glycemic index and load may be modestly beneficial vs. considering only total carbohydrate

- Saturated fat should be limited to less than 7% of total energy, and *trans* fat should be minimized
- Protein should not be used to treat acute or prevent nighttime hypoglycemia and high-protein diets are not recommended for weight loss
- If adults with diabetes choose to use alcohol, intake should be restricted to 1 drink per day or less for women and 2 drinks per day or less for men and consumed with food

Specific discussion of dietary factors and patterns in relation to type 2 diabetes is found in a following section. Diet is of vital importance in management and achieving dietary goals usually requires intensive education and motivation of the diabetic patient.

Exercise

Exercise may be of high benefit to the diabetic patient by improving overall glycemic control which would reduce risk of complications and mortality.[29] Exercise exerts its potential benefits through multiple physiological pathways. The fundamental mechanism is an improvement in insulin sensitivity.[27] Further gains in reducing body fat levels,[30, 31] blood pressure,[31, 32] and hypertriglyceridemia [31, 32] add to risk reduction of complications and mortality. Most types of physical activity, including leisure time activities; recreational games; and high-performance, competitive sports are appropriate for individuals with diabetes.[33] Improved insulin sensitivity lasts 24-72 hours after each bout of activity.[33] Thus, for optimal benefits and glucose regulation, activity should occur regularly throughout the week. This improvement in insulin sensitivity is accompanied by relief of overloaded beta cells and diminished plasma insulin levels.[34] Overall, exercise appears to stimulate hepatic glucose production, and a decrease in plasma insulin concentration is essential since this glucose production varies with the changes in insulin levels. During exercise glucose uptake in the muscle varies inversely with the rate of secretion and concentration of plasma insulin.[34] Even non-exhaustive non-endurance activities enhance insulin action and this increase is incrementally seen all the way through daily endurance activity.[34] The enhanced insulin secretion seen in acute exercise is predominantly located in the recruited muscles, however, in chronic training exercise may also improve insulin action in extramuscular tissues by increasing hepatic glucose storage capacity.[34] Furthermore, a minimal level of physical activity is necessary to maintain glucose homeostasis; adaptations in insulin secretion/action develop rapidly with habitual physical activity, but disappear in less than two weeks if activity levels are not upheld.[34] Additionally, though it is beyond the scope of this thesis, consideration and discussion of the multiple complications, special precautions and other conditions that may accompany exercise in diabetics is necessary and done on an individual basis with the treating physician.

Energy Balance/Weight Management

In overweight type 2 diabetics some prescription of decreased energy intake and increased physical activity is usually advised. Clinically significant weight reduction should reduce insulin resistance and improve other abnormalities as well.[35] Ideally the individual will reduce their weight to the point considered desirable and reasonable in discussion with the healthcare provider. However, this is a well established challenge regardless of one’s disease state. Therefore, the approach taken should depend upon the requirements and characteristics of the patient.[27] Obesity is the strongest modifiable risk factor for developing diabetes and for those who have the disease for prevention of morbidity and mortality. In diabetics a highly individualized approach should be taken considering current medications and insulin, which can actually lead to weight gain, to manage and lose weight.[27]

Drugs

Evidence suggests that type 2 diabetes is largely preventable through diet and lifestyle approaches. Yet, drug treatment will be necessary for many that develop the disease in addition to intense dietary and exercise intervention or because the intervention was insufficient in achieving its goals. There are currently a variety of drugs widely used on the market that work to counteract the metabolic disturbances of diabetes and reduce risk for micro and macrovascular complications. Individual discussion of the recommended usage, effects, side effects and cost effectiveness is beyond the scope of this dissertation; however a brief discussion of the major drug classes follows.

Drugs that sensitize the body to insulin and/or control hepatic glucose production include thiazolidinediones and biguanides. Drugs classes that stimulate insulin production in the pancreatic beta cells include sulfonylureas and meglitinides. Drugs that slow the absorption of starches include alpha-glucosidase inhibitors. These are prescribed separately and in combination therapy depending on the patient's needs.[27]

Complications

Micro and macrovascular complications are the chief causes of morbidity and mortality in diabetic patients. Evidence suggests that chronic hyperglycemia is the root cause of diabetic complications, especially of the microvascular nature, although the exact mechanism is unknown.[36] Diabetes is the leading cause of microvascular complications such as retinopathy that may lead to blindness, nephropathy that may lead to end-stage renal disease, and neuropathy (along with peripheral vascular disease) that may lead to non-traumatic amputation in developed countries.[36] Cardiovascular disease is the most common macrovascular complication followed by cerebro-vascular and peripheral vascular disease in diabetics. Diabetes is an established independent risk factor for development of atherosclerosis.[37] However, the causal link between cardiovascular disease and hyperglycemia is not as strong relative to microvascular disease, likely due to the multifactorial nature of the disease.[36] Nonetheless, rigid glycemic monitoring, management and control through diet, physical activity, weight control and medication may significantly reduce one’s risk of serious complications.

Epidemiology of Type 2 diabetes

Type 2 diabetes is an epidemic of the late 20th and early 21st centuries that promises to challenge health-care systems as rates across the globe continue to increase. In 2003 the International Diabetes Federation estimated 194 million people had diabetes globally and by 2025 approximately 333 million will have the disease.[38] Prevalence rates vary by region according to genetic factors, lifestyle, affluence, urbanization and mechanization. Data from the DECODE study show that the prevalence in Europe is generally lower than other regions of the world as European rates are less than 10% in people younger than 60 years of age and between 10-20% at 60-79 years of age.[39] Comparatively, the most recent prevalence rates from 2005 in the United States estimate approximately 10% of people 20 and older have diabetes and approximately 21% of people 60 and older have diabetes.[40] There is some difference by sex and race/ethnicity as 10.5% of men over 20 versus 8.8% of women have the disease in the U.S. and Hispanic/Latino Americans are 1.7 times more likely, non-Hispanic Blacks are 1.8 times more likely, and American Indians/Alaska Natives are 2.2 times more likely to have diabetes compared to non-Hispanic Whites.[40] Elsewhere in North America the most recent available data from Mexico estimate that over 30% of the population over 60 years of age has diabetes and over 9% in the age range 20 -59 have the disease.[41] Additionally, the disease is more prevalent in Mexican women where it is also the primary cause of death in the country and the 2nd principal cause of death in men.[42] In South America recent estimates from Brazil put the overall prevalence slightly over 12%.[43]

Type 2 Diabetes in Asia and the Asian Paradox

The increases observed in prevalence rates in Asia are troubling as this is the most populous area in the world, an area increasing in development and affluence, and has already undergone vast changes demographically, epidemiologically and socioeconomically.[44] The diabetes epidemic is a major risk to drain the finite health care resources in the region as public health measures have been slow to enact.[45] Additionally, the increases in rates in Asia are dramatic. In the US it has been suggested that the prevalence of type 2 diabetes mellitus has doubled from 4 to 8% over the last 40 years.[46] By contrast, the prevalence rates in China, India, Korea, Indonesia and Thailand have all increased three to five fold over the past 30 years.[47-53] In Singapore the prevalence in ethnic Chinese nearly doubled from 1984 (4.7%) to 1998 (8.0%) despite low rates of obesity.[54] There is evidence this increase is occurring much quicker in areas of China and India and in younger age groups.[48-50] These increases observed in Asians signify a major public health issue.

Asians appear to be more susceptible to the disease and develop it at a lower body mass index (BMI) and younger age when compared to western populations.[44] a troubling sign given the increase in rates of obesity in many parts of Asia[44]. Clinically, this may be explained by the relatively high proportion of body fat and abdominal fat in Asians compared to white populations.[55-57] This characteristic may make Asians more inclined to develop insulin resistance.[55] Another troubling factor more pronounced in Asians relates to insulin secretion dysfunctions.[58, 59] In part due to the accumulating clinical and mechanistic evidence for differences in body composition between Southeast Asians and other groups, as well as epidemiologic data suggesting that Southeast Asians have a steep increase in risk of diabetes at relatively low levels of adiposity based on measurement of the body mass index or waist circumference, the World Health Organization has recommended lower thresholds of BMI in Asians in order to identify those who may be at high risk.[60] However, the scientific basis for setting separate thresholds for disease risk across race-ethnicity, based on body mass index and waist circumferences, continues to be a matter of scientific debate.[50, 61, 62] Certainly data from the Singapore Chinese Health Study has a strong potential to contribute to our understanding of this topic.

Risk Factors

The rapid increase of type 2 diabetes rates in recent decades has led researchers to believe that environmental factors, rather than genetics, are responsible for the epidemic. Risk factors for the development of insulin resistance and pancreatic beta cell dysfunction include many lifestyle factors such as physical inactivity and a multitude of dietary factors. Exercise and diet are known to have important direct effects on insulin sensitivity and insulin secretion, as well as having indirect effects through body composition, weight gain, and obesity. Multi-factorial intervention trials have shown that diabetes is preventable. On the other hand, numerous epidemiologic studies have contributed to the understanding of risk factors and have helped discern multiple individual factors. The following is a brief summary of prospective epidemiologic data and the main intervention trials on the topic.

Obesity is considered the strongest, modifiable risk factor for diabetes.[63] This topic has received thorough investigation to the point where meta-analyses summarizing the topic across study design and ethnicity have been performed.[64] Some of the prominent and recent results related to the topic have been found in the Nurses' Health Study where the relative risks for women in the second class of obesity (BMI $\geq$ 35.0

kg/m^2) were 38.8 (95% CI, 31.9-47.2) compared to those with a of BMI < 23.0 kg/m^2.[63] This study also found that 61% (95% CI, 58%-64%) of type 2 diabetes cases were attributed to overweight or obesity when using BMI ≥ 25.0 kg/m^2.[63] In our preliminary studies of the Singapore Chinese Health Study a similar and strong pattern was found as risk increased as BMI increased in a dose response pattern and risk started increasing at BMI's considered lean and normal when using WHO guidelines for Asians for overweight and obesity. In this study, participants in the 2nd decile of BMI (18.8-20.2 kg/m^2), mean 19.6 kg/m^2 had a hazard ratio (HR) of 1.70 (95% CI = 1.20-2.42) compared to participants in the first decile of BMI (<18.8 kg/m^2).

Central adiposity or abdominal obesity assessed indirectly by waist circumference and waist-to-hip ratio has been observed to portend increased risk of type 2 diabetes independent of BMI in numerous studies.[65-68] Weight gain is also associated with a substantial increased risk of incident type 2 diabetes, even at moderate levels, as found in two cohorts in the United States.[69, 70]

Physical activity is another risk factor with established, strong evidence for its role in relation to type 2 diabetes. Physical activity is thought to be beneficial because of its clear role in weight maintenance and studies suggesting that even moderate physical activity improves insulin sensitivity.[71] The direct effects were discussed earlier and its important to note that physical activity may have effects indirectly through changes in body composition and obesity.[34] Extensive evidence from prospective epidemiological studies has shown that increased walking, moderate and strenuous physical activity is associated with reduced risk of developing type 2 diabetes independent of relative body weight.[63, 71-76] Similar associations have been observed in the Singapore Chinese cohort in men but not women. However, overall levels of reported physical activity are very low in the cohort, especially in women.

The literature on dietary factors and their association with type 2 diabetes is extensive and includes multiple well established risk factors along with multiple newer potential risk factors and some prospective data on specific nutrients. An extensive review is beyond the scope of this thesis, so a focus on selected, large, methodologically strong, prospective cohort studies makes up the extent of this review.

Dietary fat as a risk factor has received serious research efforts through investigation in animal studies, clinical feeding studies and epidemiological studies. Dietary fat is of particular interest as it may act through the development of obesity if consumed at high levels, as it is energetically dense, or through promoting insulin resistance through direct pathways. However, recent prospective studies have found no association between total dietary fat intake and risk of type 2 diabetes.[77-81] Moreover, specific types of dietary fat appear to be much more important than the total fat. High polyunsaturated fat intake was found to be inversely associated with diabetes risk in three large studies.[77, 80, 81] Conversely, a positive association between trans-fat and diabetes risk was observed in the Nurses' Health Study, [80] but not in the Iowa Women's Health Study[77] or Health Professionals Follow-Up Study.[81]

High fiber diets have been studied as a preventative risk factor for type 2 diabetes across multiple prospective studies. In four large prospective cohorts a significant inverse association between high intake of dietary fiber and incident type 2 diabetes was found.[78, 79, 82, 83] These studies also found that cereal (grain) fiber displayed a stronger association than fruit and vegetable fiber. A related topic of research has been the role of whole grains in relation to type 2 diabetes risk. Meyer et al. [82] reported an inverse association with high levels of whole grain intake and type 2 diabetes risk as have three other recent large prospective studies.[84-86]

Carbohydrate quality defined by glycemic index or load; a measure of glycemic response due to the amount and type of carbohydrate ingested has recently been investigated as a potential risk factor in large epidemiologic studies. The findings of glycemic load in relation to type 2 diabetes are mixed to date, with two studies finding an increased risk of type 2 diabetes in the highest quantile vs. lowest quantile of glycemic load, [78, 79] and two studies finding null associations. [82, 83]

Currently, there is developing literature on coffee consumption, sugar sweetened beverages, meat and processed meat consumption among other individual foods. A meta-analysis and systematic review of epidemiological evidence provides support of an inverse association of higher levels of coffee drinking with type 2 diabetes risk. [87] Findings from the Singapore Chinese Health Study were very similar to the results of this systematic review. Additionally, results from the Singapore Chinese Health study also indicate an increased risk of diabetes with relative higher levels of soft drink consumption, in line with the Nurses' Health Study.[88] Additional well done prospective epidemiological and clinical studies are needed to continue to understand how dietary factors relate to type 2 diabetes risk.

Smoking and alcohol consumption are general risk factors with essentially all chronic diseases, however their association with type 2 diabetes generally does not receive the same attention as the aforementioned risk factors and dietary risk factors even though strong and consistent evidence is present in the literature. A recent meta-analysis of active smoking and type 2 diabetes risk of 25 different prospective cohort studies found that former smokers, low to moderate smokers and active smokers all had significantly increased risk of type 2 diabetes in a dose-response manner.[89] An abundance of prospective cohort studies have also found an U-shaped association with moderate alcohol consumption as 1-3 drinks a day has been consistently associated with lower incidence of diabetes compared with abstinence or occasional alcohol consumption.[63, 90]

Intervention Studies

The preventability of type 2 diabetes by lifestyle changes has been demonstrated in three different randomized controlled trials as well as a feasibility/demonstration project. As mentioned earlier, lifestyle change is central to the management of diabetes once diagnosed and also focuses on key physiologic components of the disease such as insulin sensitivity and weight loss. Additionally, diabetes usually has a pre-diabetic stage that is extended and identifiable by simple diagnostic tests making safe, lifestyle interventions a practical approach.

In a feasibility study in Malmo, Sweden [91] of 415 men between ages 47-49 who had progressed to different stages in the natural history of diabetes were non-randomly assigned to lifestyle intervention or usual care groups. The lifestyle intervention focused on weight control through prudent dietary advice and increased physical activity levels. In men with impaired glucose tolerance, 10.6% in the lifestyle intervention group developed type 2 diabetes vs. 28.6% in the usual care group after six years of follow up.

The Da Qing prevention trial of 577 individuals with impaired glucose tolerance in the industrial city of Da Qing in northern China [92] randomized participants to a control group or one of three intervention groups (diet, physical activity, diet + physical activity) by clinic. The dietary group was prescribed and made goals to limit caloric intake based on BMI (kg/m^2) as well as specific consumption goals of cereal fiber, vegetables, meat, dairy and oil intake. The exercise group was encouraged to increase their leisure time physical activity. Participants received individual counseling from physicians and sessions in small groups. All three intervention groups significantly decreased the progression to diabetes, as the control group had 68% of its members develop incident diabetes. The intervention groups all reduced risk by 31% (diet) to 42% (diet + exercise) and 46% (exercise) although there was no significant difference between the intervention groups.

In the Finnish Diabetes Prevention Study [93] 522 participants with impaired glucose tolerance were randomized to either a control group of usual care or a lifestyle intervention focusing on advice on reducing weight, increasing exercise and a diet of whole grains, fruit and vegetables, low fat dairy and meat products and beneficial fatty acids. This trial was stopped early as the results showed that after a mean 3.2 years of follow up the intervention group had a 58% lower incidence of diabetes compared to the control group.

The largest prevention trial is the Diabetes Prevention Program (DPP), [94] which enrolled 3,234 participants with impaired glucose tolerance in the United States and randomized them to either intensive lifestyle modification, metformin therapy with standard care in respect to lifestyle advice, troglitazone with standard care in respect to lifestyle advice and placebo with standard care in respect to lifestyle advice. The intensive lifestyle group had a 58% lower incidence of diabetes compared to the control group and was more effective than the metformin group. The troglitazone group was discontinued due to safety concerns.

As demonstrated in these studies, prevention is key and attainable in populations and individuals. Also important is that these studies also demonstrated improvement of cardiovascular risk factors, a major cause of morbidity and mortality in diabetics. Lastly, analyses from the DPP trial found that the lifestyle intervention was more cost effective in the short and long term perspective compared to drug treatment.[94] This may be especially important to developing Asian countries where diabetes incidence and prevalence is increasing in line with economic development and the developing epidemic may likely hinder this development in the future.

Chapter 2: Etiology of Obesity and Weight Change

Fundamentally and simply put, obesity is thought to stem from an imbalance in energy; that is energy intake exceeds energy expenditure. Further developing this idea is that obesity is a physiological response, especially by genetically susceptible individuals, to an environment that supports sedentary lifestyles and promotes overconsumption of poor quality food. In an obese state an individual is at a significantly increased risk for multiple chronic diseases.[95] This is especially true for type 2 diabetes where obesity is the strongest modifiable risk factor.[63] Weight gain and obesity occur in this state. Central to understanding weight change and obesity are the components of energy balance in humans. What follows is a succinct overview of the components of energy balance and mainly of energy expenditure.

Components of Energy Expenditure

Energy expenditure is divided into a few different components. This division is important as abnormal energy expenditure can then be ascribed to a combination of subcomponents.[96] Resting metabolic rate is the rate of energy expenditure under standardized conditions; at complete rest, in the morning, after sleep in a post absorptive state, essentially in comfortable environmental conditions.[97] This rate includes the functioning of organs, skeletal muscle, adipose tissue.[96] This represents 60-75% of total energy expenditure, declines with age, and is lower in women.[96] A central component of the basal metabolic rate is determined by the level of fat-free mass.[96, 98] Furthermore, exercise can maintain and potentially raise the basal metabolic rate.[96, 99] Body size explains the majority of the variation in energy in low physical activity states as the amount of lean body mass is the main source of variability.[96]

Another sub-component of energy expenditure is physical activity. This encompasses planned activity and non-planned activity as well as non-exercise activity thermogenesis (NEAT).[100] Physical activity accounts for 5-40% of total energy expenditure depending on actual activity level and is the largest source of variability in energy balance.[96, 97] Thermogenic effect of food and adaptive thermogenesis comprise the last sub-component of energy expenditure. Thermogenic effect of food is the metabolic cost of digestion, absorption and storage of food, varies to an extent with the source of energy and is about 8-10% of energy.[101] Adaptive thermogenesis has different meanings to different researchers but is generally thought of as the ability of an individual to conserve or expend energy in response to variable intake of food or temperature.[98]

Implications of a positive energy balance leading to weight gain and obesity in Asians have gained notice and importance as an obesity and diabetes epidemic occurs in this ethnic group.[44] Typically obesity has been measured using body mass index but research has shown that applying standards developed in European/White populations is likely not appropriate for Asian populations as they develop diabetes and cardiovascular diseases at much lower levels of BMI compared to Whites.[56, 57, 102] Therefore, measures of adiposity such as waist circumference and lipid profiles and glucose should be monitored closely and may better represent Asians for risk of chronic diseases related to obesity.[103]

Literature Review of Asian Studies

Asians constitute the largest percentage of the global population. From a public health standpoint obesity is a current topic of importance as populous nations such as China and India, as well as elsewhere in the continent, are experiencing rapid social and economic changes leading to changes in diet and physical activity. This is of concern as this transition is leading to a higher prevalence of overweight and obesity which is a major risk factor for many of the chronic diseases that manifest downstream. There is a scarce amount of research published to date on the predictors, risk factors and etiology of weight change in an Asian population. What follows is a review of relevant literature.

Bell et al.[104] studied and described the 8 year weight change, especially gain, and baseline characteristics of a cohort of 2,488 Chinese adults, aged 20-45 from seven provinces in the Chinese Health and Nutrition Survey. Participants were selected using a multi-stage, random cluster sampling process and the overall response rate was 59%. All data were collected by health workers administering surveys and height and weight were measured using a standardized protocol. Dietary data were collected using 24 hour recalls over three consecutive days. BMI (kg/m^2) was calculated from the measured weights and heights in 1989 and 1997. Participants who did not have height and weight data from these two points were excluded.

The investigators stratified by gender, chi square tests were used to compare weight change from baseline and eight years later and linear regression was used to model exposures (dietary, physical activity, work activity, lifestyle, etc.) in the prediction of weight change as a continuous variable. Four exclusive weight change categories were formed based on weight change: Loss (mean -4.8 kg), stable (mean 0.1 kg), moderate gain (mean 3.6 kg) and large gain (mean 8.5 kg). Relative risks were calculated using multiple logistic regression to determine which variables were important predictors of weight loss, moderate and large weight gain using the referent category as weight stable.

Main results included that the mean BMI increased from 21.5 kg/m^2 to 22.4 kg/m^2, and men who were taller, were not as active and more educated were predictive of weight gain over eight years. A similar pattern was observed in women except the higher educated group was predictive of weight loss. Little to no activity at work was also predictive of subsequent weight gain. Alcohol consumption as a behavior was also a risk factor for weight gain in men. Strengths of this study include the standardized measures of weight and height over time and detailed collection of other important data. Limitations include the moderate sample size and the investigators found they had collected a somewhat biased sample. Additionally, they did not assess chronic diseases, so they did not control for them in the analysis. This is potentially highly problematic given the pathogenesis of many chronic diseases and aging. Furthermore, the use of three, 24 hour dietary recalls on consecutive days is a strength in collecting enough dietary data, however there are multiple weaknesses potentially involved with different biases of using this method and the use of consecutive days.[98]

In another prospective study utilizing the same national study as above changes in diet and physical activity were examined in relation to body mass index in Chinese adults.[105] This study assessed 3,484 Chinese adults from 2,050 households, aged 20-45 at baseline using data from the first and second China Health and Nutrition Study conducted in 1989 and 1991. Dietary data were collected using 3 consecutive 24 hour recalls. Anthropometric data were collected by measurements and physical activity data were collected on occupation activity level, whereas no leisure or sport activity data were assessed. The investigators make the strong but questionable assumption that work activity level was an adequate proxy for leisure and sport activity.

The investigators were largely interested in how dietary fat may affect BMI, and they partitioned energy intake into fat/non-fat categories in multivariable analyses. To look a the cross-sectional relationship between baseline BMI and dietary intake multiple regression analysis was used adjusting for biological and socioeconomic factors for the whole study and stratified by sex. The prospective analysis of diet and BMI used a fixed effects model that focuses on the change in the dependent variable (BMI) in relation to the changes in explanatory variables (diet and physical activity).

This study found that women, urban residents, non-smokers, and those with sedentary activity levels generally had a higher BMI than the rest of the sample. In the cross-sectional analysis total energy intake was associated with higher BMI and total fat intake was associated with higher BMI's in men. Additionally, an urban residence, age and significant household assets were also associated positively with higher BMI's. Household assets were defined as electrical appliances, livestock, farming equipment, etc. Education level was inversely associated with BMI, as was a higher level of physical activity. The longitudinal analysis found that increasing physical activity levels were associated with a lowering of BMI and sedentary activity levels were associated with a higher BMI. The multiple regression model found no association between any dietary factors and change in BMI while the fixed effects model found that change in fat intake in men was significant, albeit the mean change was miniscule (mean 0.2 kg/m^2, SD 1.6) and insignificant using the prior mentioned analysis method. The authors focused on the contribution of fat intake in relation to change in BMI and went to great lengths to validate this assertion in their discussion and in their presentation of the results. The conclusions by the authors are strong and overstated in some instances given the methods of data collection of dietary intake and the assumption regarding physical activity along with the short time span and the very slight mean changes in all variables of interest. Thus, there are some major limitations which the authors do address such as how multiple dietary assessments improve the within-person error and give a better estimate. Consideration of a cross-sectional assessment and temporality was also given, as well as incomplete physical activity data. A point that would contribute to the interpretability and discussion of this paper would be the inclusion of the actual other dietary components as these were not named. Indeed, fat intake is correlated with many other food groups, fiber, carbohydrate and total energy.

One other prospective study examining the etiology of obesity in an Asian population was conducted by Hodge et al.[106] In Mauritius, an island country of mainly Indian peoples (70 %), Chinese (2.1%) and mixed ancestry (27.9%) a national survey of non-communicable diseases was administered in 1987 and then followed up in 1992. The aim of the study was to assess prevalence of overweight, obesity and abdominal obesity and examine the incidence of obesity and the factors associated with weight gain in those who participated in both surveys (n=3,667). Height, weight, waist and hip circumferences were measured in each survey using standardized methods. Statistical analyses looking at changes in BMI, WHR with physiological, behavioral and socioeconomic factors used one-way and multivariate ANOVA. For incidence of overweight, baseline BMI was divided into categories of < 22, 22-25 and > 25 kg/m^2.

Additionally, WHO guidelines of overweight (BMI > 25 < 30 kg/m^2) and obesity (BMI > 30 kg/m^2) were used to define overweight and obesity.

The investigators observed a significant change in levels of overweight and obesity as they increased from 26.2% to 35.7% in men and from 37.9% to 47.7% in women. In univariate and multivariate analyses, being younger with a lower BMI was a strong predictor of the largest weight gain and incident "overweight" or "obesity". Glucose tolerance status, as determined by an oral glucose tolerance test (OGTT), strongly predicted changes also. Diabetics at baseline lost the most weight and non-diabetics gained the most weight. The association of income and education were inconsistent with no statistically significant trends across groups. Multivariate analyses displayed similar trends to the univariate analyses. Overall, women showed greater weight gain than men. Strengths of the study include the standardized measures and assessment of diabetes and glucose levels as well as the high level of follow up (73%). Investigators were able to successfully track trends in abdominal and overall obesity and gain insight into the etiology of weight gain in relation to quitting smoking and becoming diabetic. They were able to parse out, because of these specific measurements, that most of the weight loss in participants with diabetes was due to poor glycemic control rather than successful interventions. Additionally, this also allowed them to determine the majority of participants who gained weight remained non-diabetic or developed diabetes during follow up. Limitations include the lack of description on how leisure time physical activity was assessed along with level of work activity. Also, age showed highly significant trends but little description of factors by age group was included.

Given the sparse amount of prospective data relating to Asians, any published cross-sectional data, even with its inherent weaknesses may be informative on this topic. What follows is a discussion of the couple of studies in this category. Hu et al. [107] looked at urban Chinese adults in the Tianjin project, a project of prevention and control of chronic diseases with participants assessed with two independent cross-sectional surveys in 1989 and 1992 of 2,631 participants ages 25-64 and selected by random stratified cluster sampling. Participants had dietary habits surveyed by 3 day food records with weighing at home of all food materials and then estimating portion sizes considering number of people in the household and dish sizes. Height and weight were measured using a standardized procedure and physical activity was assessed through a questionnaire that included occupational, commuting and leisure time physical activity. ANOVA with adjustments was used to determine differences between dietary factors in overweight vs. normal weight participants. The association between weight and risk factors, dietary and non-dietary were calculated using logistic regression. The surveys were combined because the investigators did not find any significant differences between main measures of diet, activity or demographic variables.

The study found that the overweight group (BMI>25, n=888) were older, reported less commuting activity, less education and higher income and marriage levels. They also consumed significantly more energy and subcomponents (carbohydrate, fat) than the normal weight group (BMI<25, n=1,743). In the logistic regression models the authors found that for every 100/kcal increase in energy consumption the odds ratio of being overweight was 1.04; 95% CI = 1.02, 1.06 compared to normal weight after adjustment for age, demographic and time variables. Non-dietary factors related to overweight included being married, OR=3.70: 95% CI = 2.23, 6.12 compared to non-married participants after full adjustment for potential confounders. Smoking was associated inversely with overweight. Commuting for greater than 30 minutes by foot or 15 minutes by bicycle to work was inversely associated with overweight in both men and women (OR=0.48; 95% CI 0.31, 0.76 in men). Leisure time activity was not associated with overweight status nor was income or education. Strengths of this study include the measurement of height and weight and sophisticated attempt at collecting dietary data. It also appears to be one of the first studies to address this question in an urban Asian population. There are also limits in respect to dietary collection in respect to the biases related to food records and the estimation methods that required major assumptions to be met for validity. Additionally, similar results to the 100/kcal energy were reported for fat and carbohydrate and arbitrary increases in each were chosen and found to be similar in their association with overweight. However, these variables are likely highly correlated with energy and disentangling what these results mean in this smallish sample of a cross-sectional nature, without actual correlation coefficients reported is nearly impossible.

Another cross sectional study utilizing more advanced dietary data collection methods, body composition assessment and physical activity was completed in 130 urban residing, Chinese men and women aged 35-49.[108] Participants were selected for enrollment in the study from a screening interview assessing, medical history, eating habits and activity related to work, transportation, household items and leisure time. Participants who were in the upper and lower thirds of estimated activity and estimated dietary fat intake were eligible and were chosen in this manner to broaden the range of intakes. Approximately more than half of the participants used doubly labeled water for the study to look at energy expenditure. Physical activity was measured by an activity monitor and motion detector on their bike. Dietary data was collected on 3 different days (1 weekend day). Participants were instructed to maintain normal diet and weigh foods whenever possible at home and when away from home estimate the size of the food eaten if they did not have their scale to weigh it. Detailed methods of weighing and recording food occurred. The study utilized the Chinese food composition table of nutrient contents of prepared dishes. Body composition was determined by the 3 compartment model. In the analyses differences between sexes were examined using independent sample t tests. Stepwise multiple regression with general linear model analysis of variance was performed to examine the associations of physical activity and dietary variables.

The main findings were that dietary variety and frequency of eating at restaurants were positively associated with body fatness. Dietary fat and energy density were not associated with body fatness. Strengths of the study include the validated and more precise methods of assessment of diet and activity along with energy expenditure and body composition. Limits include the generalizability to the regular Chinese population as the characteristics of the study population were not alike in fat intakes and were selected non-randomly. Additionally, there was no way to assess long time exposure as the study was cross-sectional.

No studies on Asian populations and only a few previous studies have examined the association between dietary patterns and a measure of weight change.[109-112] In a smaller population from the Baltimore longitudinal study of aging with a wide age range a dietary pattern rich in lower fat dairy and high fiber foods was associated with a smaller gains in BMI and waist circumference and a diet rich in sweets, fast food, vegetables and dairy was associated with an increased gain of waist circumference.[109] Using an alternative approach to defining the dietary patterns produced a similar association in the same cohort.[110] This study used 7 day food records and then grouped foods before deriving the dietary patterns. Further, this study was small (n=459) and many food group variables were factorially complex, that is, multiple variables loaded strongly on different factors making interpretation of that factor and variable less clear. In a study of Danish citizens aged 30-60 a 26 item FFQ was used to assess diet and factors were derived by sex. No prospective association was found between the factors and BMI or weight.[111] Discussion and interpretation of this study is limited by the apparent underlying inability of this study to adequately assess diet with the short FFQ. The Nurses' Health Study similarly examined this question and is the largest study to date and also was able to account for changes in dietary pattern over time.[112] The prudent pattern in this study was similarly high to the VFS dietary pattern in vegetables, fruit and fish, but also was high in whole grains, an aspect lacking in the Singapore Chinese Health study. This dietary pattern may be the best for weight maintenance as well. The western dietary pattern, which was rich in meats, refined grains, desserts and soft drinks, appeared to contribute to long term weight gain. This pattern had some similarities to the DSM pattern in predicting greater weight gain and that it was rich in energy dense foods, meats, refined grains, and lower in fiber and whole grains. We are not aware of other studies investigating dietary patterns and risk of future obesity.

Only a few other studies have examined the association between fast food and weight gain in adults.[113-115] After adjustment for many potential confounders Pereira et al. found a significant and direct association with increase in body weight and increasing fast food consumption in the CARDIA study focusing on young adults.[113] Using the same base study and comparing restaurant and fast food intake Duffey et al. found a significant and slight increase in BMI with higher consumption of fast food.[114] In another cohort based in Spain of more middle aged participants, increased consumption of hamburgers, pizza and sausages was associated with a significant but slight increase in the odds of becoming overweight over time.[115] We observed similar results to these studies as with each increase in frequency of fast food we observed an increase in mean weight gain over time after adjustment for numerous potential demographic, lifestyle and dietary confounders. We also found that soft drinks appear to increase weight gain beyond the consumption of fast food. There are many different variables- physiological, behavioral, contextual and metabolic that should be considered in interpretation of this further weight gain potentially due to soft drinks. Indeed, evidence is continuing to build on this topic.[116, 117]

Excess weight is now generally considered a major risk factor for a range of chronic diseases. Prevalence of overweight and obesity continue to rise in Asia and the chronic diseases that seem to follow have increased rates also. Understanding the specific variables and factors that are strongly predictive of weight gain in this population will help to develop more efficient public health approaches as the East continues to adapt "Western" habits. Indeed, the literature on Asians and weight change suggests that dietary habits that lend themselves to increased energy intake and physical activity habits of less activity tend to predict weight gain. The Singapore Chinese Health Study has the potential to provide data above and beyond the current literature related to Asians as our study on dietary patterns, western fast food, weight gain and obesity may provide a more complete picture of diet populations can identify with, as well as touching on western fast food, a topic of potential importance and easily transferable to a simple public health message.

Chapter 3: Dietary Patterns and Risk of Type 2 diabetes

The majority of dietary research in relation to development of type 2 diabetes, and other chronic diseases, has focused on individual nutrients or food items. However, this approach has a number of weaknesses if not interpreted in the scheme of all related research on the specific topic.[118] People eat combinations of foods rather than single foods or nutrients in isolation.[119, 120] Given the lack of precision of how nutrients are calculated from observational studies,[98] as well as that we still have much to learn on the actual role of many individual foods and the nutrients within them, this approach may be confounded by the effects of dietary patterns.[119] Since people consume a mixed diet, with mixed meals having potential for interactions between foods and nutrients, the effect of the overall diet on health outcomes may best be studied with dietary pattern analyses that take into account the entire spectrum of food intake and therefore may begin to identify possible synergistic effects among foods and nutrients on health outcomes.

Analysis of dietary patterns is becoming more common for studying dietary associations with health.[121] Approaches used include factor analysis, cluster analysis, reduced rank regression and creating dietary indices. Factor and cluster analysis are a posteriori methods driven by the data at hand. Reduced rank regression is a mix of a priori and a posteriori where a linear combination of predictor variables (diet) accounts for as much variation in response variables (intermediate biomarkers) as possible. The pattern developed in RRR is then analyzed in relation to the endpoint. Creation of a dietary index is generally used to describe an ideal diet for disease prevention based on available evidence.

Review of specific studies

Van Dam et al.[122] looked at dietary patterns in the Health Professionals Follow up Study of 51,529 male health professionals (dentists, veterinarians, pharmacists, optometrists, osteopathic physicians and podiatrists) from all 50 states. Diet was assessed by a 131 item FFQ using frequencies of intake from never to 6+ a day and commonly used unit and portion size with intakes averaged over time. Thirty-seven predefined food groups were developed using similar nutrient profiles and culinary use as criteria. Exclusions for the analysis included baseline chronic disease, as these diagnoses may affect diet or reporting of diet, as well as excluding those who did not fully report diet. The final sample was 42,504 men followed for 12 years. The data were analyzed using principal components analysis (factor analysis) using SAS with varimax (orthogonal) rotation. They retained two factors based upon eigenvalues, scree test and the interpretability of the derived factors and named them "prudent" pattern and "western" pattern. However, the exact eigenvalues of the factors and scree test parameters as well as "interpretability" were not defined in the paper.

The authors reported calculating each factor score by summing the standardized intake of foods using servings/day as the standardized measure. The patterns were divided into quintiles. The validity of the patterns was assessed by examining a subgroup of 127 participants and the Pearson correlation coefficient was found to be 0.52 for the prudent pattern and 0.74 for the western pattern. The investigators used pooled logistic regression analyses with 2 year intervals, a technique similar to Cox proportional hazards analyses. Models included the covariates BMI, age, time period, total energy intake physical activity, smoking, alcohol, ancestry, hypercholesterolemia, hypertension, and family history of type 2 diabetes. Energy adjustment was done to further reduce extraneous variation or confounding due to variation in body size, physical activity, metabolic efficiency, or over/under reporting, and used the residual method of energy adjustment.[88] The prudent pattern was characterized by high consumption of vegetables, fruit, whole grains, fish and poultry, and the western pattern was characterized by high consumption of red meat, refined grains, French fries, high fat dairy products, sweets and desserts, high sugar drinks and eggs.

The results did not specify the total amount of variance explained by both patterns and nonspecific parameters for retaining the factors were also not given. Furthermore the investigators report the prudent pattern as being modestly associated with reduced risk in the 5th vs. 1st quintile RR=0.84, 95% CI; 0.70-1.00, however the p value for trend was 0.2 and the only quintile that was significant (CI without 1.0 in it) was the 2nd quintile, a group with the lowest score on this pattern. RR=0.77, 0.65-0.92. The western pattern was significantly associated with increased risk across quintiles and became more strongly associated when stratified on the basis of low activity and obesity. The authors did complete multiple sensitivity analyses in regard to diabetes status and choices in retaining factors. They found similar patterns when using individual foods rather than groups and by retaining three factors instead of two, also using an oblique instead of orthogonal rotation.

Fung et al.[123] examined the association of dietary patterns with the incidence of type 2 diabetes in the Nurses' Health Study. The original sample for this study was

116,000 women nurses in 11 states starting in 1976. Dietary assessment began in 1980 and occurred in 1984, 1986, 1990 and 1994. The 1984 FFQ was considered baseline as it was a more extensive version. Anyone with a baseline chronic disease was excluded as were those who did not adequately fill out the FFQ. Follow up included 69,554 women up to 14 years (1998). Cumulative averages over time were used in calculating intakes. Foods from the 116 item FFQ were classified into 36-38 food groups based on nutrient profiles and culinary usage. Foods that did not fit into any of the groups or may have represented distinct patterns were left as individual categories. Vitamins and minerals were adjusted for in the analysis but were not included in the development of food groups. Diabetes was validated by a questionnaire on symptoms, diagnostic tests and treatments.

Dietary patterns were generated by factor analysis and orthogonally rotated. Eigenvalues > 1.0 were used to retain patterns along with a scree plot test for interpretability. The factor scores were calculated by summing intakes of food groups giving each participant a factor score. Cox proportional hazards models were used to examine the association between major dietary patterns and diabetes risk. Adjustments for age, family history of diabetes, history of hypercholesterolemia, smoking, hormone therapy, energy intake, hypertension, physical activity, alcohol, and BMI occurred.

The investigators characterized two patterns- a prudent pattern characterized by higher intake of fruits, vegetables, whole grains, fish and poultry and low fat dairy products and a western pattern characterized by higher intakes of red and processed meats, refined grains, sweets and desserts and high fat dairy products. Patterns were derived from the standard of each food group as servings/day. No beverages loaded or potentially were not reported in the loading of individual components of each pattern, although it was noted they were included as individual food groups.

The results showed increasing risks across quintiles of the “western” pattern and a decreasing risk in the 3rd quintile of the “prudent” pattern compared to the first quintile and non-significant but suggestive inverse risks in the 4th and 5th quintiles. The only significant data for the prudent pattern was found in a sensitivity analysis of only symptomatic cases. Strengths of the study include the use of repeated assessments of exposure over time, an attribute that separates it from essentially all other large, prospective cohorts. The homogeneous population by work status would seem to make the results generalizable to women with similar educations, but limited otherwise. Limitations include the lack of reporting of total amount of variation explained by these two factors along with some other steps in the decision process of illuminating these factors. For example, we do not know if they attempted sensitivity analyses on the number of factors or the extent of which other factors may be involved in this population. Additionally, the authors may have overstated the benefits they believe to be found from a “prudent” dietary pattern in relation to incident type 2 diabetes as some of their results are suggestive but there is no consistency or trend across the prudent pattern of reduced risk until a sensitivity analysis of symptomatic cases is considered. However, the results for the western pattern do not materially change in this analysis.

Montonen et al.[124] examined dietary patterns and risk of incident type 2 diabetes in 4,304 Finnish participants, aged 40-69, free of diabetes between 1967 and 1972 who participated in the Finnish Mobile Clinic Health Examination Survey. Dietary and lifestyle habits were surveyed at baseline. A glucose tolerance test was administered at baseline to determine prevalent cases. Habitual diet over the previous year was measured using a 100 item questionnaire of foods and mixed dishes common to the Finnish diet. Foods were grouped into 23 groups based on nutrient profile and culinary use of item. These categories were summed as grams/day.

The analysis method for generating the dietary patterns was principal components analysis. Only factors with eigenvalues >2.5 were included (2 total). Patterns with an eigenvalue < 1.5 were excluded using a scree test and interpretability of the factors. In 23 years of follow up 383 participants developed diabetes. Incident cases were identified by the nationwide social insurance registry and those who received reimbursement for diabetes drugs were considered a case. Each participant has one ID code and was linked to the registry. The investigators found two patterns and named them prudent and conservative. The analyses were energy adjusted using the residual method as described by Willett.[98]

The prudent pattern was characterized by high loadings of vegetables and fruit, poultry, eggs, red meat, regular dairy products and berries, whereas the conservative pattern was characterized by butter, potatoes, whole milk, red meat, jams and sugar rich condiments, processed meat, smoked/salted fish and regular fish and eggs. After adjustment for demographic variables, body mass index, energy intake, smoking, history of diabetes, cholesterol and hypertension, comparing the highest quartile to lowest for the "prudent" pattern found a HR of 0.72, 95% CI (0.53, 0.97) p *trend* =0.03, and the corresponding finding for the "conservative pattern" was 1.49 (1.11, 2.00), p *trend* =0.01. Further analyses were done on cross tabulations of the two patterns and found no significant findings except persons with a high conservative score and low prudent score had an increased risk of diabetes. Sensitivity analyses including nutrients, dietary components such as fiber, and socio-demographic factors such as education, job status attenuated the results. No significant interactions were found by age, sex, body mass index or smoking. One concern was the apparent lack of measurement of physical activity, and thus the lack of inclusion of activity in the analysis.

The authors rationalize that even though whole grain products were found in the "conservative" pattern that the high usage of spreads and butters in this population would diminish any contribution these food products would contribute to an overall risk.

In relation to previous similar studies this study explained more of their methodological choices as they gave specific eigenvalues and how they interpreted the data. However, they did not note how much variation either dietary pattern explained. Other strengths include a thorough investigation of potential effect modification, and this appears to be the only study to date that has done any cross tabulation of patterns, an innovative approach. There were also a number of limitations. First, alcohol consumption and physical activity were not measured or included in the study. This is troubling on both ends, but especially physical activity, a major component of lifestyle related to type 2 diabetes. Another concern was the lack of inclusion of non-caloric beverages such as coffee in the dietary patterns. Finland has been noted to have some of the highest coffee intake in the world,[125] which has been shown across many studies to be inversely associated with diabetes risk. This was likely due to the food groups being included as grams/day instead of servings/day, or another numerator/denominator combination that would allow them to be included. The determination of cases in the manner noted also contributes to the interpretability of the study as lifestyle and dietary changes would have been missed, as would have cases that did not look for reimbursement of any diabetes related drugs. This could potentially affect the power of the study.

Dietary patterns and their association with incident type 2 diabetes have also been investigated in the Melbourne Collaborative Cohort Study of 41,258 men and women aged 27-75 (99.3% were 40-69).[126] 5,425 participants were migrants from Italy and 4,535 were from Greece. Baseline measures were completed in 1990-1994. Exclusions were self reported baseline diabetes or diabetic plasma glucose as measured at baseline and those missing relevant risk factors measured at baseline, leaving 36,787 participants. Dietary information was collected using a 121 item FFQ, self administered developed for the study. Incident cases were self reported on a follow-up questionnaire mailed approximately 4 years after baseline. Confirmation of cases was done by participant reference of a physician, who was then contacted. Factor analysis was performed on the 121 items, oils and alcohol from wine. For the 121 items intake was measured as daily equivalent frequency, oils were measured in mL/week and alcohol as grams/day. The question that arises from the usage of the foods in what appears to be non-standardized units is what effect does this have, if any, on the results and interpretation? Orthogonal rotation was used in interpretation of factors and to ensure they were not correlated. Factors with eigenvalues > 2.0 were retained. Variables with a factor loading of > 0.3 were used in interpreting factors. Factors were not derived by sex as there was no apparent difference. However, linear regression was used to calculate how much variance in factor scores was associated with country of birth and other potential confounders. After exclusions, 365 cases and 31,276 non cases were analyzed. 4 factors were derived and the final models included the four dietary pattern scores as well as adjustment for age, birth country, and energy intake, family history of type 2 diabetes, BMI and WHR-- possible intermediates in the pathway.

The four factors explained 68% of the variance in dietary intake. Factor 1, which explained 27.9% of variance, had high loadings of olive oil, vegetables, legumes and avoidance (negative loadings) of biscuits, cakes, margarines and teas. Factor 2 had high loadings of vegetables and salads, and Factor 3 had high loadings of meat, pastries, fried eggs and fish and potatoes, while factor 4 had high loadings of fruit. Patterns were associated with country of birth but were not a substitute. Participants native to Australia and the United Kingdom scored higher on factor 2. Those from Greece and Italy higher on factor 1 and those from Greece on factor 3. Factor 2 had an inverse association with type 2 diabetes until adjustment for BMI and WHR. Factor 3 had a positive association with type 2 diabetes increasing across quintiles. Factors 1 and 4 were not associated with diabetes risk.

Strengths of this study include the thorough reporting of methodological steps and an objective approach to naming the factors. A difference between this analysis and other prospective analyses is that foods were not grouped before the factor analysis, avoiding the assumptions of what should be put together and how. Additionally, a glucose test at baseline and validation of most, but not all cases, demonstrates a level of validity. Limitations include the short follow up time, potentially, not allowing for many cases lessening power, or for analyses accounting for follow up time such as a Cox proportional hazards analysis. Furthermore, the study did nothing to categorize migrants beyond looking at variation explained through linear regression. Considering that approximately ¼ of the population were Italian immigrants and ¼ were Greek immigrants, the dietary patterns seemed somewhat distinct, a stratified analysis may have been informational regarding a look at maintenance of diets typical to these areas instead of what is typically consumed in Australia, which appears to be higher in meat and white bread to an extent in this study. Overall, this study was more thorough than all previous studies, potentially due to awareness and evolution of the analysis to being less subjective and more objective as possible.

The only study that was multi-ethnic was an investigation in the MESA study of dietary patterns and type 2 diabetes in 5,011 participants, including 2,634 men and 2,377 women (2,177 white, 1,205 black, 1,016 Hispanic, and 613 Chinese).[127] Four different dietary patterns dietary patterns were identified: 1) Fats and processed meats, 2) vegetables and fish, 3) Beans, tomatoes and refined grains, 4) Whole grains and fruit. This study employed a sound methodological approach to deriving the patterns. The results from the study found a positive association with incident diabetes with a 1 SD increase in Beans, tomatoes and refined grains pattern score and an inverse association with the Whole grains and fruit dietary pattern. The vegetables and fish and fats and processed meats were both similar in structure and factor loading to the aforementioned “prudent” and “western” dietary patterns yet were null in association. Important to note in this finding is that the factors were somewhat factorially complex, that is, multiple food groups loaded significantly on multiple dietary patterns, potentially clouding the interpretation of the results.

While seemingly similar to the other patterns in the same study and the aforementioned prudent dietary patterns, a potential explanation for the null results is this study is comparatively heterogeneous in ethnic makeup, and the dietary assessment tools in this study was not ethnic-specific, even though valid, potentially adding further noise than usual to a risk estimate as the complete diet may not have been assessed or reported. Moreover, the racial, cultural and geographical differences in this study highlight important dietary similarities and differences, and point to the complicated and heterogeneous nature of the diet-diabetes association

A nested case control of participants in the European Prospective Investigation into Cancer and Nutrition- Potsdam Study has also investigated dietary patterns and risk of diabetes.[128] It consisted of 27,548 individuals aged 35-65. Enrollment occurred in 1994-98 with follow up every 2-3 years assessing baseline measurements and updating disease status. This study considered participants with follow up who were diabetes free at baseline and may have developed diabetes through November 2001 192 individuals who had a valid case status along with no missing exposure variables and 382 controls matched on age and sex were considered. The study's aim was to cross-sectionally identify a dietary pattern associated with plasma concentrations of HbA1c, HDL cholesterol, C - reactive protein and adiponectin in reduced rank regression (RRR) and then to investigate whether the pattern obtained is prospectively associated with type 2 diabetes.

Diet was assessed through a FFQ asking for frequency and portion size of 148 foods consumed during the previous year. Frequencies ranged from never to 5 times a day or more and portion sizes were estimated using photographs. The amount of food in grams/day was calculated. 48 food groups were created. Additional measurements used in the analysis included body weight, height, hip and waist circumferences using standardized measures and protocol. The author's used reduced rank regression as an analysis technique and chose four markers measured at baseline, HbA1C, HDL cholesterol, C-reactive protein and adiponectin for intermediates between diet and type 2 diabetes. RRR determines linear combinations of predictor variables by accounting for as much of the variation in response variables (intermediates) as possible. If there is only one response variable RRR is identical to multiple linear regression.

In RRR the number of extracted scores can only equal the number of selected responses; four in this case were selected. The authors chose to only include one pattern as they noted this explained much more variance (7.4%) in the biomarkers than any other pattern. Food groups were considered to significantly contribute to the pattern if they had a factor loading >0.2. Adjustments were made for cholesterol medications, lipid lowering drugs, anti-inflammatory drugs as well as age, sex, leisure time activity, smoking status, educational level, and total energy intake and with and without BMI and WHR. Odds ratios with 95% CI were calculated using conditional logistic regression.

Diabetics had higher mean values of BMI and WHR and were lesser educated. Activity, energy intake, and percentage of smokers did not differ between groups. The first score obtained explained 7.4% of the total variation in the four selected biomarkers compared to 3.6, 1.9 and 1.5% of the following three patterns. Individual variation explained in each biomarker was 9.4% of HDL cholesterol, 10.2% of adiponectin, 9.1% of HbA1C, and 1.1% of CRP of the selected food pattern. The investigators found a significant inverse association with type 2 diabetes in each increasing quintile of pattern score. This pattern score was directly associated with fruit and inversely associated with high intake of soft drinks, beer, red meat, processed meat, poultry, legumes and white bread. This pattern was also cross-sectionally associated with higher HDL cholesterol, adiponectin and lower HbA1C and CRP. In the fully adjusted model for the 5th vs. 1st quintile an OR (95% CI) of 0.27 (0.13-0.64) was found. A more precise CI was found in the 4th quartile.

The strengths of this study include the prospective nature even though a nested case control design was employed. The diabetics were medically confirmed however, they excluded approximately 200 incident cases that they could not directly confirm. A number of concerns also arise after reading the study. First, to employ RRR, using a small sample is likely required due to the cost of lab analysis. However, the follow up time was short, potentially less than three years for some participants. Indeed, matching was done on age and sex, but it may have been prudent to match on year of enrollment and follow up time. Furthermore, there were highly significant differences in obesity between the cases and controls at baseline- overall (BMI) and abdominally (WHR). This is troubling given the results because the biomarkers chosen are all highly associated with obesity and this may explain their significance cross-sectionally, at baseline as much as diet, and especially the increased risk of diabetes. Additionally, in a sensitivity analysis that excluded HbA1C there was significance in the trend across the dietary pattern quintiles, however individually no one level was significantly associated with decreased risk except the 4th quintile. Given the small sample size and case control nature of the study, concerns arise over whether this is artifactual. Also, analysis of this study as a prospective cohort may be a better approach to studying this question rather than a nested case control. Indeed, there are inherent biases in a prospective study of diet and disease related to selection into the study, reporting of diet among others, but these, as well as the different types of selection bias in a nested case control, especially given how the matching was conducted in this study, provide another level of bias to consider in interpretability. Concern over the highly significant difference in education level between cases and controls is also a concern as disease free subjects had higher levels of education. The investigators also could have applied this dietary pattern analysis to the whole cohort to see if a similar pattern was observed using factor or cluster analysis.

In a further analysis of the Nurses' Health Study, Schulze et al.[129] conducted a nested case control study to examine markers of inflammation mediated by a dietary pattern through reduced rank regression. They identified a pattern high in sugar sweetened beverages, refined grains, diet soft drinks, processed meat, and low in wine, coffee and vegetables. In the nested case control study this pattern was strongly associated with increased risk of incident type 2 diabetes with increasing strength across quintiles.

The investigators then utilized the same dietary pattern to look at a full analysis of NHS I and NHS II as a validation effort and to investigate the pattern over the whole cohort. To determine the dietary pattern they used stepwise linear regression on all the loading factors in the nested case control pattern and developed a dietary pattern nearly exact to the case control, with a correlation coefficient of 0.75. The results they found were very similar to those found in the nested case control with a dose response association across increasing quintiles of intake in this pattern with similar relative risks.

Given the high level of similarity in results between the pattern derived from the reduced rank regression analysis and driven by a defined biological pathway of inflammation, the similar pattern applied to the full cohorts and the pattern earlier derived by Fung et al through principal component analysis and termed "Western", I wonder if there are truly important subtle differences in dietary patterns that influence different pathological processes or if dietary patterns of this nature influence multiple pathways? If the latter is true, what information are we gaining with methods like RRR?

The only published study to date looking at dietary patterns and glucose disorders in an Asian population was a cross sectional study of 2,106 Japanese men aged 47-59 who participated in a pre-retirement health checkup and underwent an oral glucose tolerance test and filled out questionnaires on diet, activity, lifestyle and demographic related items.[130] Diet was assessed using an FFQ designed to assess the average intake of 74 foods, food groups and food preparation over the previous year. The questionnaire was derived from a similar questionnaire used on this population. The original FFQ was validated, but not the expanded one utilized in this study. The investigators analyzed the food as frequency of intake per week for everything except, green tea, coffee and rice bowls, which were included as servings/day. Factor analysis was used to derive dietary patterns and the number of retained factors was considered by examining at the scree plot and interpretability which was undefined.

Three dietary patterns were derived, one high in dairy, high starch foods and breads, fruits and vegetables and low in alcohol, a second high in animal foods (meats, poultry, fish, processed meats and fish), and a third that was a more traditional Japanese pattern (high in soybean products, vegetables, seaweed, green tea). The factors explained 24% of the variance in the diet. The relative risks for glucose abnormalities (IFG, IGT, T2D) were determined by multiple logistic regression. The first pattern loading high in dairy, starches, fruits and vegetables was consistently associated with reduced risk of all abnormalities. The pattern high in animal foods showed no associations, and the Japanese pattern was positively associated with abnormalities.

There were multiple minor limitations in the approach in this study, but the major, overarching limitation that prohibits interpretation in this author's view is the cross-sectional nature. These participants, due to their employment, received thorough medical workups and attention and, like all people who undergo regular physical exams, those with glucose abnormalities or frank diabetes may have been recommended to change their diet as a way to counteract the current or potential health issue. Thus, there was likely mixing of dietary patterns by health status. Indeed, the protective dietary pattern was similar to that of the DASH diet, so there may be some biological relevance there, but disentangling the effects of any of these diets is purely speculative due to lack of temporality and the possible diagnoses/intervention bias on self-reported dietary intake.

Table 3.1: Summary of prospective cohort studies using principal components analysis to examine dietary patterns and incident type 2 diabetes.

Study	Population and Dietary Assessment	Methods	Dietary Patterns	Results
Health Professionals Follow up Study Van Dam et al	-42,504 male health professionals, aged 40-75 in 1986 -131 item FFQ with repeated measurements; 37 food groups analyzed	-Principal Components Analysis (factor analysis) with orthogonal rotation, -Pooled logistic regression analysis - Diabetes self reported and validated through questionnaire on symptoms, diagnostic tests and treatments and medical record sub-sample (n=71)	-"Prudent" characterized by high consumption of vegetables, fruit, whole grains, fish and poultry -"Western" characterized by high consumption of red meat, refined grains, French fries, high fat dairy products, sweets and desserts, high sugar drinks and eggs	-No association with prudent pattern and increasing risk across increasing quintiles of western pattern -Amount of variation in cohort not reported
Nurses' Health Study, Fung et al	-69,554 female nurses aged 38-63 in 1984 -116 item FFQ with repeated measurements	-Principal Components factor analysis and orthogonal rotation -Cox Regression Analysis - Diabetes self reported and validated through questionnaire on symptoms, diagnostic tests and treatments and medical record sub-sample (n=62)	- "Prudent" pattern characterized by higher intake of fruits, vegetables, whole grains, fish and poultry and low fat dairy products -"Western" pattern characterized by red and processed meat, refined grains, sweets and desserts and high fat dairy products	-Suggestive inverse association with prudent pattern and increasing risk across quintiles of western pattern -Amount of variation in cohort not reported
Finnish Mobile Clinic Health Examination Study, Montonen et al.	-4,304 men and women aged 40-69 -100 item FFQ of foods/dishes common to Finnish diet at baseline	-Principal components analysis and orthogonal rotation. -Cox Regression Analysis -Diabetes determined through nationwide index of drug reimbursement	-"Prudent" pattern characterized by high loadings of vegetables and fruit, poultry, eggs, red meat, regular dairy products and berries -"Conservative" pattern characterized by butter, potatoes, whole milk, red meat, jams and sugar rich condiments, processed meat, smoked/salted fish and regular fish and eggs	-Significant inverse association across increasing quartiles of the "prudent" pattern and significant positive association across increasing quartiles of "conservative" pattern -Amount of variation in cohort not reported
Melbourne Collaborative Cohort Study, Hodge et al	-31,641 men and women aged ~40-69. Of the original 41,528 participants 5,425 were migrants from Italy and 4,535 were migrants from Greece	-Principal components analysis and orthogonal rotation -Logistic regression analysis	-Factor 1: olive oil, vegetables, legumes and avoidance of biscuits, cakes, margarines and teas. -Factor 2: vegetables	-Factor 2 had an inverse association with type 2 diabetes until adjustment for

	-121 item FFQ of foods and dishes specifically developed for the study	-Diabetes self reported on follow up questionnaire 4 years after baseline and confirmed by physician	and salads -Factor 3: meat, pastries, fried eggs and fish and potatoes -Factor 4: fruit.	BMI and WHR. -Factor 3 had a positive association with type 2 diabetes increasing across quintiles. -Factors 1 and 4 were not associated with diabetes risk -68% of dietary variance explained by patterns
MESA, Nettleton et al	5,011 participants, including 2,634 men and 2,377 women (2,177 white, 1,205 black, 1,016 Hispanic, and 613 Chinese)	-Principal components analysis and orthogonal rotation. -Cox Regression Analysis -Self-reported type 2 diabetes, fasting glucose ≥ 126 mg/dl at any exam, or use of diabetes medication	-Fats and processed meats -Vegetables and fish -Beans, tomatoes, and refined grains -Whole grains and fruit	-Beans, tomatoes, and refined grains positive association with 1 SD increase -Whole grains and fruit inverse association

Chapter 4: Background on BMI and All Cause Mortality

The prevalence of obesity has started to increase to epidemic levels in developed and developing Asian nations and the levels of chronic disease have mirrored this trend.[44] Because of the trends in obesity across the globe, especially in the recent past, the interest in the effect of body weight on mortality has received heightened interest and importance. Indeed, this interest has spurned much research, mostly on western populations, with divergent results. Some studies suggest that BMI acts in a near dose-response fashion with mortality, some indicate a U-shaped or J-shaped curve, and finally some suggest BMI may have little or no impact on longevity.[131] The investigation into BMI and mortality in Asians presents an intriguing study as they have a larger proportion of the population with low BMI's, despite some parts of Asia having very high rates of type 2 diabetes, and research on Asian populations is comparatively sparse. There is debate on what is an optimal weight in an Asian population separate from the debate in Western populations.

There are multiple methodological issues and considerations in the study of body weight and mortality. The majority of them have to do with the best approach of analyzing data from a prospective cohort study. One consideration is adequate control for cigarette smoking. Smoking is more prevalent among lean individuals, perhaps primarily due to its known anorectic effects, and is a strong independent risk factor for cancer and cardiovascular diseases, as well as type 2 diabetes. Failure or inadequate control for smoking in analyses of body weight and mortality may therefore bias the association between body weight and mortality towards the null or alternative hypothesis.[132] Manson et al [132] believe studies of non-smokers provide the best data in the relationship between body weight and mortality. Conversely, Fontaine and Allison [131] summarized evidence that smoking may not be as strong a confounder as believed in the association as the U/J shape curve remained in the majority of studies regardless of how smoking was treated in the analysis. In the studies that did account for smoking the relative risks were attenuated but the shape of the risk curves remained.

Reverse causation is another concern, as low weight status may be a product of preexisting disease states. For example, lean people may be a mix of those who are healthy, and those who are ill and lost weight, or have a pre-existing, underlying diseases causing weight loss. This is a particular concern in aging cohorts, as an elderly population is more likely to have these underlying and preexisting chronic diseases. Indeed, Flegal et al.,[133, 134] have clearly demonstrated in analyses of NHANES data an important interaction between age and BMI on mortality risk. The relative risk between obesity and mortality is considerably attenuated with advancing age. Because mortality rates increase with age, prior studies estimating the number of deaths in the population attributed to obesity produce gross exaggerations due to failure to consider the important age – BMI interaction.[135] Thus the effects of BMI on mortality may be biased by the mixing of different health and diseased groups, as well as failure to stratify by age groups.[131, 132] Generally, an approach taken to account for these biases is to limit the analyses to only those who appear healthy at baseline, to those who die after the first few years of follow-up, to exclude smokers or stratify on smoking status, and to stratify on age group. Allison et al examined the approach of excluding those who die in the first few years of follow-up using analytic methods, simulations and meta analysis.[136-138] Their results suggest that excluding participants in this type of study does not necessarily reduce the bias of undetected disease, however in some cases it may be highly effective at reducing the bias. At the core of this idea is that there is truly bias there in the first place. The meta-analysis [137] showed that exclusion of these early deaths does slightly change the shape of the association and this very slight change is statistically significant, but it may or may not be meaningful depending on the population and other aspects of the study and data analysis.

Another issue noted by Manson et al. [132] is that some studies have inappropriately controlled for biological consequences of obesity such as hypertension, dyslipidemia and hyperglycemia, which eliminates pathophysiological pathways through which obesity may be operating. A further consideration is that of physical inactivity, activity and fitness level. The fit vs. fat debate is beyond the scope of this chapter, but a sedentary lifestyle even among thin persons, may be responsible for increased mortality in a low BMI range.[139] Indeed this is an important consideration in the Singapore Chinese Health Study. The issue of dietary patterns that are associated with obesity and have independent causal effects on morbidity and mortality also needs to be considered in analogous ways as the fitness/fatness problem.

BMI as a marker for adiposity is an overarching factor in the relationship between relative weight and mortality. Important aspects to note include that body mass is composed of fat free mass and fat mass, which poses an important limitation in using the BMI to delineating the true relationship between body composition and mortality. Fontaine aptly stated that risk of death may increase with increasing fat mass and decrease with increasing fat free mass,[131] yet this question has only been addressed in a handful of studies and the results suggest that adiposity is driving the association.[140-144] Related to this question is the point in life that BMI was measured. As one ages BMI is a less reliable marker of adiposity due to differential loss of muscle and lean body mass.[132] This observation must contribute to the phenomenon of weaker relative risk between elevated BMI and mortality with advancing age, as discussed above. Furthermore, it is also possible that if BMI is only measured later in life many of the susceptible (i.e. obese) participants may have already died of obesity related outcomes. However, this is unlikely as most deaths in the population occur later in life. Indeed there are multiple considerations in examining the BMI-mortality association, yet attention to these confounders and modifiers may be helpful in determining what an optimum relative weight may be.

Literature Review of Studies in Asian Populations

Gu et al. [145] examined the question of body mass index and all cause mortality in a nationally representative sample of 154,736 Chinese men and women aged 40 years or older in 1991. At a single baseline visit, height and weight were measured using a standardized protocol. Other demographic and lifestyle variables were also assessed. Work-related physical activity was assessed because leisure time physical activity was rare. Follow up was conducted in 1999-2000. BMI was divided into the following categories (<18.5, 18.5-19.9, 20-20.9, 21-21.9, 22-22.9, 23-23.9, 24-24.9, 25-26.9, 27-29.9, ≥ 30). Cox proportional hazards regression models were used for analysis. Adjustments for baseline age, sex, cigarette smoking, alcohol, work related physical activity, education, geography, urbanization were done. The referent group was

BMI=24.0-24.9 because this group had the lowest mortality. In mean 8.3 years of follow up 17,687 deaths were documented. A statistically significant U-shaped association was observed in all analyses and sub-group and sensitivity analyses between BMI and all-cause mortality. This included checks by age, sex and disease status. A sensitivity analysis that excluded deaths within the first 3 years of follow up observed a similar pattern of relative risks. A similar pattern was observed in a cause specific analysis in both cardiovascular disease and cancer and was also consistent among men and women.

The data show the range of BMI where it is not associated with increased risk of mortality was 24-26.9 overall. Essentially, being underweight, normal weight, and obese by BMI measures is associated with an increased risk of death in this study since the only non-increased risk is in the overweight range in the study. The authors concluded that their data do not support different or lower BMI cut points for obesity in this population. They note the increased risk of BMI's > 27 and BMI's < 18.5 but do not address the significant increase in risk of early all cause mortality in the BMI range of 18.5-24 in the overall cohort as well as "healthy" participants, which are not clearly defined. A question remains whether the associations observed in the low end and in normal weight individuals are an artifact of the high level of smoking in the leaner individuals of this population, or likewise, residual confounding by not stratifying or excluding these participants.

Jee et al. [146] examined the question of body mass index and mortality in 1,213,829 Korean men and women between 30 and 95 years of age who had undergone a biennial medical exam between 1992 and 1995 for the national health insurance corporation. All persons were free of atherosclerotic disease, cancer, liver disease, diabetes or respiratory illness before the initial study visit, and participants missing any relevant information or a BMI < 16.0 kg/m^2 were also excluded. An attempt to minimize the effect of underlying conditions was also done by excluding those with an event within the first two years of follow up. Height and weight were directly measured and data was collected on other lifestyle and demographic factors. Participants were followed up for death through December 31, 2004. BMI was categorized as < 18.5, 18.5-19.9, 20.0-21.4, 21.5-22.9, 23.0-24.9, 25.0-26.4, 26.5-27.9, 28.0-29.9, 30.0-31.9 and >32.0. Model covariates included age at enrollment (continuous), alcohol intake (g/day), participation in regular physical activity (y/n), and smoking status. The mean BMI of the study population was 23.2 for both sexes and mean age was 45 for men and 49 for women. A total of 82,372 deaths were recorded. The referent category was 23.0-24.9 as this had the lowest risk of death from any cause. A J-shaped association was observed for all cause mortality regardless of smoking status. Specifically, men with a BMI <18.5 who did not smoke had an elevated risk of death (HR=1.29, 95% CI 1.15-1.44) and those with a BMI >30 had an elevated risk of death also (HR=1.71, 95% CI 1.44-2.03). Similar, but not as strong associations were observed in smokers and in women. No association was found in BMI levels between 18.5 and 30 for all cause mortality. For participants greater than 64 years of age at baseline there was no association between BMI and mortality. Related to this, it is important to keep in mind when interpreting the data that this study included persons aged 30-95, a wider age range than any other study with BMI having divergent meanings and reflecting different aspects throughout this age range. Otherwise, this study was executed with appropriate methods and the cause-specific results further add to the literature, but are beyond the scope of this discussion and study.

Song et al. [147] also investigated the relationship between BMI and all cause mortality in women in the same Korean cohort utilizing a national insurance corporation similar to Jee et al.[146] The study comprised 338,320 women aged 40-64 who had all relevant measures and were free of cancer at baseline and did not die during the baseline examination period (1993-94). In the appropriate adjustment model for all-cause mortality that also excluded early deaths, a U-shaped association was observed with increased risk of mortality in BMI < 21 and BMI ≥ 27.0 compared to the referent group of BMI=21-22. They also stated the association did not differ when excluding smokers.

A couple points that stuck with this author after reading the paper were why no consideration of effect modification by age was considered. An attempt to stratify by menopausal status was attempted and this was arbitrarily set at age 55 even though no data were collected on menopausal status and no follow up data on change in menopausal status was included.

Tsugane et al. [148] examined the association of relative body weight and mortality in a Japanese population of 40,815 men and women aged 40-59 years who self reported height and weight and were free of cancer, cerebrovascular disease, history of myocardial infarction, or chronic liver disease at baseline as well as having a BMI between 14.0 and 40.0. Cox proportional hazards was used to analyze the data and sex stratified models adjusting for age (continuous), smoking status, alcohol consumption, education, sports and physical exercise, geographic area of Japan and weight change since 20 years old. BMI was divided into the following categories: 14.0-18.9, 19.0-20.9, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-29.9, ≥ 30.0. The BMI range of 23.0-24.9 (middle BMI category) was chosen as the referent category; however the rationale for the decision was not reported. A U-shaped association was observed for all-cause mortality in men with increased risk in BMI's < 23 and > 27. Estimates excluding early deaths showed an increased risk only in BMI < 23 and of never-smokers in BMI < 19. However, interpretation of these findings should be cautious because of the potential instability of the estimates due to small numbers. Women with a BMI < 19.0 and >30.0 also were at increased risk of all cause mortality and the association was maintained in never-smokers. Similar to the SCHS, a disproportionate amount of men smoked vs. women. This study may have increased their power of examining the never-smokers if they would have stratified on smoking status, rather than sex, and then looked at sex differences.

Yuan et al. [149] analyzed the association in the Shanghai cohort study of 18,244 Chinese men aged 45-64 years in Shanghai, China. BMI was determined by self-reported height and weight and numerous other lifestyle and demographic factors were gathered at baseline. Cox proportional hazards regression methods were used to analyze the data with adjustments for age (< 54, 55-59, 60-64, 65+), education level, alcohol consumption, smoking status and specific number of cigarettes a day if a current smoker as well as age started. The referent BMI category chosen was 21-23.5 as this was determined to be the most healthful range by metropolitan insurance tables according to the authors. Of lifetime never-smokers those with BMI's < 18.5 and > 26.0 had an increased risk of mortality. Of ever-smokers and current smokers there was no association. A limit in interpretation of the results is that there did not appear to be any adjustment for physical activity levels related to work, leisure time or general lifestyle. Overall, our results are very similar when looking at the range of BMI of no increased risk of death.

Recently the Shanghai Women Health study evaluated the relationship between BMI and mortality and potential methodological biases.[150] This study began with 74,896 women with BMI, waist and hips measured at baseline (1996-2000) from age 40-70 and followed up through April 2007. Participants were also asked to recall weights from age 20 and age 50 if over age 50 at baseline. From the original study population, 62,779 participants were never smokers without a history of previous disease, did not die during the first 3 years of follow up, and reported not having lost 10% of their body weight since age 50, thus making this the relevant population for study. The mean age of the cohort was 52 years and mean baseline BMI was 24.0 with mean follow up of 7.4 years. In an age adjusted cubic spline Cox regression analysis of the 62,779 participants using the median BMI as a referent point, a dose-response type of association of increased risk above BMI of ~ 25.0 was observed. Fully adjusted models were not presented. The rest of the presented analysis focused on small sub-groups of quartiles of BMI using the lowest quartile as the referent group and showing increased risk at each increasing quartile beginning at a BMI > 24.4. Appropriate adjustments were made in these models but the overall interpretation of this study and its role in the literature is not clear because of decisions to not present the full set of data, as well as not present any data on waist circumference which may add to understanding the data. Furthermore, results from this study are not directly comparable due to participants being grouped into BMI's encompassing wider groups in the BMI spectrum.

In summary, the studies to date looking at BMI and all-cause mortality in Asian populations have not been uniform in methodological approach. Comparing data from the Shanghai cohort study is difficult because of the approach taken to analyzing the data.

Gu et al found a U-shaped association with the only range of non-increased risk of mortality was in BMI's 24-26.9. However, in the main analyses smoking was only adjusted for and it wasn't clear in sensitivity analyses if smokers were actually excluded, thus this may have affected the results. In a study of Korean national health insurance participants utilizing a sound methodological approach, with the referent (23-24.9) being the lowest risk, a J-shaped association was observed with risk increasing in BMI's < 18.5 and > 30, however this study had a wide age range of study (30-95). Utilizing a national sample of Korean woman a U-shaped association between BMI and all-cause mortality was also observed when applying appropriate methods with increased risk in BMI's < 21 and ≥ 27.0. In the Japanese study of disease free men and women, including smokers, men with a BMI of 23-27 were not at increased risk for premature mortality and women, who smoked much less, had no increase in risk between BMI's of 19-30 after adjustment and exclusion of smokers. Because of approach taken, the results beyond the noted are not interpretable or potentially applicable. In population similar to the SCHS, of Shanghai men, a U-shaped association was observed with risk increasing at BMI < 18.5 and > 26.0.

Indeed recommendations for BMI cut points for overweight and obesity are related to mortality, and some researchers believe that alternative cut points for Asians are not needed [151] Continued evaluation of the effect of BMI on mortality is needed in Asian populations as well as studies on outcomes thought to be related to weight to give a thorough view of what an optimum weight range may be. Furthermore, studies accounting for years of functional and high quality life may be of better focus for this topic, yet have none or little data published to date.

Chapter 5: The Singapore Chinese Health Study

The Singapore Chinese Health Study is a prospective cohort study initiated to identify dietary associations with cancer risk and other health outcomes. The cohort is made up of permanent residents or citizens of Singapore who resided in government-built housing estates, where ~86% of residents reside. Chinese men and women of Hokkien descent, who originated from southern Fujian Province and Cantonese descent, who came from central Guangdong Province aged 45-74 years between April 1993 and December 1993 enrolled in the study. Both provinces are in southeastern China. The study aimed to enroll 60,000 participants with four equal dialect-gender subgroups. When enrollment closed in December 1993 63,257 subjects had been recruited. Recruitment occurred by an initial letter informing potential participants of the study and inviting them to participate. Approximately five to seven days later, a door-to-door invitation was given. Approximately 85% of eligible subjects who were invited responded positively. At recruitment a face-to-face interview was conducted in the subject's home by a trained interviewer using a structured, scanner-readable questionnaire which requested information on demographics, height, weight, use of tobacco, usual physical activity, menstrual and reproductive history (women only), medical history, family history of cancer and a 165-item food frequency section assessing current dietary intake pattern. A follow-up telephone interview took place between 1999 and 2004 for 52,325 cohort members (83% of recruited cohort), and questions were asked to update tobacco and alcohol use, medical history, height and weight and menopausal status of women.

A feature of the Singapore Chinese health study making it unique among Asian cohorts and cohorts of western populations is the food frequency questionnaire employed to assess usual dietary intake at the baseline interview. The development of the questionnaire stemmed from 400 person-days of food intake among an equal sample of Cantonese and Hokkien permanent residents of Singapore in a pilot study. Information was collected by interview in the home of the participant using a standardized protocol and trained interviewers. Measurements were made of common measures of consumption units, e.g. Chinese spoon and rice bowl as well as consideration of cooking methods, food preparation and types of oil used. The majority of Chinese foods are prepared as mixed dishes of meats and vegetables and many have standard recipes. A set of rules were developed to estimate the quantity of spices, oils, seasonings and sauces used in food preparation. For all mixed dishes in the cohort questionnaire this information was used to construct prototype recipes for dishes.

Another main component of the Singaporean Chinese diet is the consumption of hawker foods, which are ubiquitous in the country. These are purchased at hawker centers which resemble fast food courts in U.S. shopping malls. Generally the dishes from these foods are noodle/rice based. Hawker food recipes were developed from purchasing samples from hawker centers and directly weighing the ingredients. Five representative samples were purchased from different hawker stalls and ingredients were measured, and then used to transcribe the amounts in the pilot studies and recipes to a food matrix table. Related, unknown or doubtful measurements obtained from the multitude of hawker food sources were directly sought out and weighed. For example, data on chickens were not directly available, so a variety were purchased, cooked, deboned, weighed, and transcribed for the data.

The actual structured FFQ for the study utilized data from a pilot study and includes 165 food and beverage items individual in nature, as dishes and as food in categories based on content. The FFQ was administered during the baseline interview and the scale of responses was eight different frequency levels for foods ranging from never or hardly ever to two or more times a day and nine frequency levels for beverages. The food items also included three different portion sizes and most items utilized color photographs roughly representing the 15th, 50th, and 85th percentile of food reported in pilot data. Same size plates were also utilized to enable a sense of scale in the interview.

The food composition database for the study includes raw and cooked foods and utilizes data from the cancer research center of Hawaii as well as composition tables from China, Malaysia and Taiwan. Items not available from other sources had their composition determined using developed item specific formulas adjusting raw foods to cooked foods. A total of 849 items are in the database and of this total 359 are mixed dishes in 52 categories.

Validation of the FFQ was done by administering two 24 hour dietary recalls on two separate occasions covering a weekday and a weekend day approximately two months apart in 1994-1997. 852 randomly selected participants took part. Another 164 participants completed the first interview. Approximately two months after the second 24 hour recall the original FFQ was re-administered. Correlation coefficients and linear regression slopes were calculated between the FFQ and 24 hour recall intakes for subjects by sex and dialect. Checks were done to ensure that nutrients and foods did not differ by sex, dialect, education, age or BMI. A range of correlation coefficients from 0.24-0.79 was observed of energy/nutrients by the two different methods. Furthermore, the distribution for energy and nutrients was similar between the 24 hour recalls and the FFQs. Indeed, the validation study provides calibration results allowing for correction of measurement errors given the assumption that 24 hour recalls are a "gold standard" method of measuring diet.

Assessment of diabetes

Self-reported diabetes as diagnosed by a physician was evaluated at baseline. Diabetes status was assessed again by the following question asked during the follow-up telephone interview: "Have you been told by a doctor that you have diabetes (high blood sugar)?" If yes: "Please also tell me the age at which you were first diagnosed?" Participants were classified as having incident diabetes if they reported developing diabetes anytime between the initial enrollment interview and the follow up telephone interview that occurred between July 1999 and October 2004.

A validation study of the incident diabetes mellitus cases used two different methods.[152] First, cases were ascertained through linkage with hospital records in a nationwide hospital-based discharge summary database, an administrative database in the Singapore Ministry of Health. If subjects in the study had been admitted to hospitals for diagnoses carrying diabetes-related ICD codes (250.00-250.92) after recruitment into the cohort, they were considered a valid case. A total of 949 cases were validated through the linkage. Cases that did not have hospitalization records available with diabetes-related diagnoses were contacted to answer a supplementary questionnaire regarding symptoms, diagnostic tests and hypoglycemic therapy during a telephone interview. A total of 1,321 subjects who reported incident diabetes but had no relevant hospitalization records were contacted. 619 participants refused or were not available for further interview while 702 (53%) agreed, of which 682 (97%) were considered valid cases.

Assessment of Mortality

Information on date and cause of death is obtained through linkage with the Singapore government's Vital Statistics Office. This is done through sharing of the participants NRIC number (national registration identity card number) with the study. The exact date of death as well as primary cause, secondary cause and underlying causes are noted for each death. ICD-9 codes specifying cause(s) are decided by the coder at the Ministry of Home Affairs and come from the person's death certificate. Up to six causes may be given.

Chapter 6: Manuscript 1: Dietary patterns, western fast food, weight gain and risk of obesity: The Singapore Chinese Health Study

Introduction

Increased relative weight and weight gain are significant risk factors for a number of chronic diseases and health conditions.[95] The rapidly increasing prevalence of obesity in the United States is widely cited and noted.[95] Asians constitute the largest percentage of the global population, and from a public health standpoint obesity is a current topic of importance, as populations in Asia are experiencing rapid social and economic changes leading to changes in diet and lifestyle. Indeed, the prevalence of obesity has been increasing in developing and developed regions of Asia.[44] However, there is scant research published on the predictors, risk factors and etiology of weight change in an Asian population.

Dietary intake is one part of the energy balance equation. Significant research has been devoted to studying the role of macronutrients and individual dietary components in clinical and epidemiological studies of relative weight and weight change in populations. An alternative approach that considers the whole dietary pattern has been increasingly employed in population research.[121] The overall eating pattern may be an important guide in understanding weight change in populations with little research to guide weight maintenance strategies. As well, an overall pattern may resonate more with the public and is less prone to confounding that is a significant concern when investigating single foods or beverages in consideration of long term energy balance. However, few studies have prospectively examined the association between dietary patterns and changes in weight.[109-112]

Another aspect of dietary intake that may add to understanding weight change and supply a simple target message in weight management and obesity prevention is the intake of western fast food. Western fast food is convenience food purchased in self-service or carry out eating venues without wait service.[113] This food is typically energy dense, nutritionally poor, low in fiber, and high in glycemic load with excessive portions.[113] The increase of western fast food consumption is not limited to westernized countries as the increase of this industry and food is occurring globally.[153] While hawker centers are central to the food history and culture of Singapore and could be described as the source of traditional fast food in the country; western fast food is different culinary wise and culturally. Research on the role of fast food in weight change is sparse.[153] Therefore research investigating how western fast food is associated with weight change in developing regions of the world may be particularly informative

The Singapore Chinese Health Study (SCHS) is a population-based prospective cohort investigation of over 63,000 Chinese men and women in Singapore. The aim of this paper was to derive dietary patterns and examine their association with weight gain and risk of obesity in this cohort, as well as to investigate the association of western fast food intake with weight gain and risk of obesity.

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Subjects and Methods

Study Population

The design of the Singapore Chinese Health Study has been previously described.[154] Briefly, the cohort was drawn from men and women, aged 45 to 74, who belonged to one of the major dialect groups (Hokkien or Cantonese) of Chinese in Singapore. Between April 1993 and December 1998, 63,257 individuals completed an in-person interview that included questions on demographics, height, weight, use of tobacco, usual physical activity, menstrual and reproductive history (women only), medical history, family history of cancer and a 165-item food frequency section assessing usual dietary intake of the previous year. A follow-up telephone interview took place between 1999 and 2004 for 52,325 cohort members (83% of recruited cohort), and questions were asked to update tobacco and alcohol use, medical history, and menopausal status of women. The institutional review boards at the National University of Singapore and the University of Minnesota approved this study.

Assessment of diet

A semi-quantitative food frequency questionnaire specifically developed for this population assessing 165 commonly consumed food items was administered during the baseline interview. During the interview the respondent referred to accompanying photographs to select from eight food frequency categories (ranging from ‘‘never or hardly ever’’ to ‘‘two or more times a day’’) and three portion sizes. The food frequency questionnaire has subsequently been validated against a series of 24-hour dietary recall interviews in a random sample of 1000+ participants that occurred on one weekday and one weekend day approximately two months apart,[154] as well as selected biomarker studies.[155, 156] A range of 0.24 to 0.79 in correlation coefficients of energy/nutrients was obtained using two methods, and the majority of macro-nutrients and food groups display correlation coefficients in the high end of this reported range.[154]

In conjunction with this cohort, the Singapore Food Composition Table was developed, a food-nutrient database that lists the levels of 96 nutritive/nonnutritive components per 100 g of cooked food and beverages in the diet of the Singaporean Chinese. By combining information obtained from the food frequency questionnaire with nutrient values provided in this food-nutrient database, we were able to compute the mean daily intakes of nutrients for each subject.[154]

Western fast food and soft drinks were assessed with the following questions from the FFQ. Study subjects were asked to report the intake frequency of soft drinks such as coca cola, 7-up etc. from nine predefined categories (never or hardly ever, 1–3 times a month, once a week, 2–3 times a week, 4–6 times a week, once a day, 2–3 times a day, 4–5 times a day and 6 or more times a day). The standard serving size for these beverages referenced during the interview was "1 glass or hawker portion". One glass was assigned a value of 237 mL, or approximately 1 cup. However, there is likely heterogeneity in serving size and the analysis is focused on frequency. Additionally, individual questions were asked relating to the frequency for each of the following foods: Hamburger or cheeseburger, French fries, pizza, ham and other sandwiches, deep fried chicken and hot dogs.

Assessment of non dietary exposures

Self reported height and weight were collected at baseline and during the follow up telephone interview. Validity of self reported height and weight has been shown to be highly reliable in other adult cohort studies.[157, 158] Physical activity was assessed by asking participants the average time each day they spent doing sitting activities such as sitting in a car or bus, sitting at work, watching TV, sitting at meals or other sitting activities such as reading, playing cards, sewing, etc in seven continuous categories ranging from never, less than 1 hour, 1-2 hrs, 3-4 hrs, 5-6 hrs, 7-10 hrs, to 11 hrs or more. They were also asked the average time in a week using eight continuous categories ranging from never to 31 hours or more they spent doing strenuous sports (e.g. jogging, bicycling on hills, tennis, squash, swimming laps or aerobics); vigorous work (e.g. moving heavy furniture, loading or unloading trucks, shoveling or equivalent manual labor); and moderate activities (e.g. brisk walking, bowling, bicycling on level ground, tai chi and chi kung). At the baseline examination, usual sleep duration was assessed by asking participants the following question: "On the average, during the last year, how many hours in a day did you sleep?", with the following response categories: 5 hours or less, 6 hours, 7 hours, 8 hours, 9 hours, and 10 hours or more. The physical activity questionnaire was modeled after and had similar questions as the questionnaire used in the EPIC Study of lifestyle and cancer, which has been shown to have good validity and high repeatability, with a weighted kappa statistic of 0.6 ($p < 0.0001$) and $r = 0.73$.[159, 160]

Assessment of outcome

Participants reported their body weight and height at the baseline and follow up interviews. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m). Weight change for each participant was calculated by subtracting baseline weight from follow up weight. Obesity was defined as BMI ≥ 27.5 kg/m^2, consistent with the World Health Organization's criterion for this population.

Statistical Analysis

The present analysis included participants from the baseline population of 63,257 persons. Participants were first excluded if they died before the follow up interview (7,722), reported a history of or a diagnosis of diabetes, cardiovascular disease, and cancer except non-melanoma skin cancer (16,398), Parkinson's disease, tuberculosis, malaria, hip fracture, and stomach removal (1,379), or ever smoked (10,078). Participants with a health condition, disease or a history of smoking were excluded as their lifestyle may change upon diagnosis, may change how weight is gained or lost, or are systematically different from those seemingly healthy and included in the analysis. Those missing weight or height at baseline or follow up (6,755) were also excluded. Further exclusions occurred for extreme sex specific energy intakes (<600 or >3,000 kcal women) (<700 or >3,700 kcal men), extreme weight loss or gain (> ± 15 kg) equal to the top and bottom 1/2 % of weight change between baseline and follow up, and any participants with a history of smoking. After these exclusions 20,077 participants remained for the analyses.

Dietary patterns were derived using principal component analysis (PCA) SAS version 9.1 (SAS Institute Inc, Cary, NC). The aim of PCA in nutritional analyses is to account for the maximal variance of dietary intake by combining the many different dietary variables into a smaller number of factors based upon the intercorrelations of these variables. All 165 foods and beverages were first standardized to the same frequency/month unit before the PCA method was applied and factors were extracted.

The factors were rotated orthogonally to maintain an uncorrelated state and improve interpretability, and a two factor solution was retained based upon eigenvalues, scree plot and factor interpretability. The factors loadings presented are highly statistically significant ($p<0.0001$) in consideration of a formula accounting for sample size and the critical value in a table for correlation as suggested by Stevens.[161] For comparability and interpretability of our results we present factor loadings > 0.20 even though values <0.20 are statistically significant due to the larger sample size of the study. Factor scores for each participant were calculated by multiplying the intake of the standardized food item by their respective factor loadings on each pattern. The scores are linear variables and represent the weighted sum of all 165 food items. Participants were divided into quintiles by score to indicate the level their dietary intake corresponded with each pattern, i.e. a higher score corresponds with greater conformity to the derived pattern. Factors were initially extracted by sex and dialect and were highly similar in loading structure and their ability to predict weight change and risk of obesity to the full study population, so the factors derived from the study population were used. The patterns were named vegetable, fruit and soy rich (VFS) and dim sum and meat rich (DSM) as these foods loaded strongest and most frequently on the respective patterns. The sensitivity and reproducibility of the patterns have previously been shown to be strong.[162]

The western fast food index and western fast food index plus soft drink intake were created by summing the reported individual frequencies of intake of hamburgers and cheeseburgers, French fries, pizza, ham and other sandwiches, deep fried chicken, and hot dogs, plus soft drinks in the index accounting for them. The derived western fast food index categories were based on intakes that allowed for logical cut points and provided sufficient participants per category and are as follows: Never or hardly ever (0), 1 time a month, 2-3 times a month, 1 time a week or more. The top category of this index is defined by the median value. The index including soft drinks includes the following categories: Never or hardly ever (0), monthly (1-3 times a month), one time a week, two-three times a week, and four or more times a week.

Baseline and dietary characteristics were calculated for participants across quintiles of each dietary pattern score and the western fast food indexes. Tests for trend across dietary patterns scores and indexes were performed by assigning the median value of the quintile or index to the respective categories and entering this as a continuous variable into the models. Mean weight change between baseline and follow up per quintile of dietary pattern score and level of index score was calculated using general linear modeling (PROC GLM). For the dietary patterns adjustments were made for age (continuous), sex, dialect (Hokkien vs. Cantonese), year of baseline interview (1993-95 vs. 1996-98), time between baseline and follow up interviews, baseline BMI (continuous), education (none, primary, secondary+), hours of moderate and strenuous physical activity per week, average nightly sleeping hours, and amount of television watched on a daily basis. Calculation of mean weight change across the western fast food index adjusted for the same variables plus potential dietary confounders in total intakes (g/day) of dietary fat, fruit and fruit juice, vegetables, dairy, meat, candy and desserts, alcohol, frequency of coffee, black and green tea and frequency of preparing deep fried foods at home. Soft drink intake was adjusted for in the western fast food index not containing the variable. Sensitivity analyses included dietary fiber (g/day) and total energy intake (kcal/day) as mediators were completed. Further analyses for both the dietary patterns and indexes examined if weight change differed by baseline BMI (< 23, ≥ 23), age (<55, 55+), sex, physical activity (never vs. ever), television watching (≤ 2 hrs, 3+ hrs). To examine the mean weight change in persons most prone to gaining weight in this cohort, a sensitivity analysis of 8,639 participants who reported a BMI < 23.0, were ≤ age 54 and reported no physical activity at baseline was carried out adjusting for the same covariates of the main models.

To examine the risk of incident obesity (BMI ≥ 27.5) obese persons at baseline were excluded. Person years for each participant were calculated from the date of recruitment to the date of the follow up interview. Relative risks per quintile of dietary pattern score and per category of western fast food index were estimated by Cox proportional hazards regression models (PROC TPHREG) with simultaneous adjustment for demographic, lifestyle, and dietary variables. All regression analyses were conducted using SAS statistical software version 9.1 (SAS institute, Cary, NC). There was no evidence that proportional hazards assumptions were violated as indicated by the lack of significant interaction between of the predictors and a function of survival time in the model in either dietary pattern. However, there was evidence that the proportional hazards assumption was violated with the western fast food indexes (p=0.0001) so the analysis was stratified on year of recruitment (1993-95 vs. 1996-98). Upon stratification there was a lack of power due to small numbers of incident obese persons in levels of the indexes making interpretation of the results unclear, so the data are not presented.

Three main models were constructed to examine the association between dietary pattern score and risk of incident obesity: Model 1 included baseline age (continuous), sex, dialect (Hokkien vs. Cantonese), year of baseline interview (1993-95 vs. 1996-98), baseline BMI (continuous), and education (none, primary, secondary+). Model 2 included variables in model 1 plus hours of moderate and strenuous physical activity per week, average nightly sleeping hours, and amount (hours) of television watched on a daily basis. Model 3 included those variables in Model 2, plus and total energy intake (kcal/day), which may represent a mediator in this diet-obesity relationship. Analyses testing for interactions of sex, age, physical activity and BMI with the dietary pattern scores as well as stratification were completed. Lastly, sensitivity analyses excluding participants with a baseline BMI ≥ 26.5 and ≥ 26.0 were carried out.

Results

Two main dietary patterns were derived from principal components analysis. The first pattern was named vegetable, fruit and soy rich (VFS) and factor loadings for this pattern are shown in **Table 6.1.** The higher the loading (correlation) between a food and a factor the more that food uniquely contributes to the pattern score. Of 45 foods loading above the noted minimum threshold on this pattern, 23 were vegetables, 5 were fruits and 5 were soy items. Additionally, different types of fresh and preserved seafood loaded highly on this pattern. The dim-sum and meat rich pattern (DSM) **(Table 6.2)** contained 55 items, predominantly dim-sum, a variety of fresh and processed meats and seafood, noodle and rice dishes consumed at levels beyond other dietary patterns, sweetened foods and deep fried foods. Most dim sum foods are savory pastries- steamed or deep fried dumplings, filled buns, noodles, or sweet pastries, meats and some vegetables. Dim sum is usually served in small quantities so a wide variety of foods may be sampled, but is part of small to large meals.

Baseline characteristics by dietary pattern are presented in **Table 6.3.** Participants with a higher score on the VFS pattern were slightly older, more likely to be female, more physically active and had less education. Dietary wise, a higher VFS score was associated with greater dietary fat and protein intake and less carbohydrate intake. Dietary fiber increased significantly and dietary starch decreased significantly with an increasing VFS score. Participants with a higher score on the DSM pattern were younger, less likely to be female, had higher BMI, exercised less and were more educated. With a higher DSM score a similar trend of macronutrient composition of the diet was observed, however there lower fiber intake with higher scores on this pattern and significantly increasing alcohol and soft drink consumption. Energy intake increased across both patterns since a higher factor score represents the weighted sum of all 165 food items, and thus increased and/or more varied intake of the assessed dietary items.

Table 6.4 presents baseline characteristics across categories of increasing western fast food intake. Although the absolute range is narrow, participants reporting higher western fast food frequency were significantly younger, more likely to be male and more educated. Total energy consumption was higher across higher categories of the index, while the percentage of energy from carbohydrates was lower and dietary fats and protein slightly higher. The amount of alcohol, soft drinks and juice were significantly higher with each increasing category. **Table 6.5** presents the same index but includes soft drink consumption as part of the index itself. Similar age, sex and education levels were observed across the index. Significant decreasing amounts of moderate activity were observed with higher index levels. Soft drink intake is greatly increased on average in participants in the highest category of the index because of being part of the index (4 or more times a week).

For this cohort of 20,077 Chinese Singaporean men (n=5,594) and women (n=14,483) non smokers, mean (SD) age 53.3 (6.9) and mean (SD) baseline BMI, 22.9 (3.2) the overall mean (SD) weight change between baseline and follow up was 0.37 (0.03) kg. In **Table 6.6** the mean weight change across dietary pattern score and western fast food index was calculated after adjusting for many potential demographic, lifestyle and dietary confounders. The mean weight gain was significant in each quintile of both dietary pattern scores. However, in the vegetable, fruit and soy rich pattern (VFS) mean weight gain significantly decreased across increasing VFS dietary pattern score, p trend (0.04). Conversely, weight change significantly increased across increasing DSM pattern score, p for trend (0.004). In the western fast food indexes there was a stepwise increase in mean weight gain in each category of increasing intake. In the western fast food index that included soft drinks the mean weight gain was beyond that of the food only index. Including dietary fiber and total energy intake in the models as mediators did not materially alter the nature or magnitude of results. Juice type drinks in this cohort were not associated with any prospective weight change.

Further analyses for both the dietary patterns and indexes examined if weight change differed by baseline BMI (< 23, ≥ 23), age (≤54, 55+), sex, physical activity (never vs. ever), television watching (≤ 2 hrs, 3+ hrs). There was no evidence mean weight change varied by sex or amount of television watching (interactions P > 0.50) and no material differences upon stratification. Interactions between the dietary patterns and indexes with BMI, age and physical activity produced p values between 0.14 and 0.49

suggesting no difference. However, upon stratification by BMI, age and physical activity the nature of weight gain was similar but more pronounced in those who reported BMIs < 23.0 kg/m^2, were of age 54 or less and reported no physical activity at baseline in each pattern and index. The results from the sensitivity analysis of mean weight gain in these 8,639 participants are presented in **Table 6.7.** The trends and nature of weight gain mirror the results in Table 6, but the magnitude of mean weight change was greater.

Sensitivity analyses that included participants with a history of smoking (current and ex smokers) did not appreciably change the nature of mean weight change in the models but increased the standard errors of the estimates and decreased the p values for trend. The interaction between smoking status and the dietary patterns and indexes in the weight gain models produced p values ranging from 0.07- 0.19. Upon stratification the mean weight change in each quintile of dietary pattern and category of western fast food index was null (P> 0.05) in current and ex smokers.

In 18,436 participants at risk of developing a BMI considered obese (≥ 27.5), who accrued 104,110 person years of follow up, 928 persons developed obesity. Relative risks for incident obesity are presented in **Table 6.8** for the two dietary pattern scores. Overall, there was no association with the VFS dietary pattern and risk of developing obesity. Attempts to account for potential confounding through stratification by sex, BMI, age, and physical activity did not change this null finding.

Conversely, there was a significant increased risk for obesity in the 4th and 5th quintile of the DSM dietary pattern score, (HR=1.44; 95% CI 1.16, 1.78, and HR=1.56; 95% CI 1.26, 1.93) in model 1 for the whole cohort. A test for interaction between baseline BMI and the DSM dietary pattern score found statistically suggestive results

(P=0.08), so the cohort was stratified on BMI < 23.0 n=10,855) and BMI ≥ 23.0 (n=7,581). 859 participants with a BMI ≥ 23.0 developed obesity during 43,084 person-years of follow up. There was no association with incident obesity in participants with a baseline BMI < 23.0, so Table 6.8 includes only participants considered overweight at baseline for the DSM dietary pattern score. In model 2, there was a 62% increased risk of obesity in the 5th vs. 1st quintile of DSM dietary pattern score. (HR=1.62; 95% CI 1.29, 2.02). The associations observed in model 2 were slightly attenuated upon adjustment for total energy intake (kcal/day), but still strongly significant (P trend < 0.0001). Sensitivity analyses excluding participants with a baseline BMI ≥ 26.5 and ≥ 26.0 were carried out to explore whether participants at these levels of BMI just below the obesity cut point were driving the observed associations. However, the associations did not materially differ when excluding participants with these baseline BMIs.

Discussion

In this large prospective study of non-smoking, disease free Chinese Singaporeans increasing intake of a dietary pattern characterized by high consumption of vegetables, fruit, and soy products and some fish and seafood termed vegetable, fruit and soy rich was associated with decreasing mean weight gain. The other dietary pattern was characterized by high consumption of dim sum, fresh and processed meats, higher levels of noodles and rice dishes, sweetened foods and deep fried foods and was termed dim sum and meat rich and increasing intake was associated with increasing mean weight gain. Additionally, each increase in frequency of western fast food consumption was associated with a mean increase in weight gain and taking into consideration soft drink intake revealed further increases in mean weight gain. The results from the Cox regression analysis of incident obese status with dietary patterns found no association with risk of becoming obese with the VFS dietary pattern. In contrast, the DSM dietary pattern was associated with a significant increased risk of developing obesity.

A few previous studies have examined the association between dietary patterns and a measure of weight change.[109-112] In a smaller population from the Baltimore longitudinal study of aging with a wide age range a dietary pattern rich in lower fat dairy and high fiber foods was associated with a smaller gains in BMI and waist circumference and a diet rich in sweets, fast food, vegetables and dairy was associated with an increased gain of waist circumference.[109] Using an alternative approach to defining the dietary patterns produced a similar association in the same cohort.[110] This study used 7 day food records and then grouped foods before deriving the dietary patterns. Further, this study was small (n=459) and many food group variables were factorially complex, that is, multiple variables loaded strongly on different factors making interpretation of that factor and variable less clear. In a study of Danish citizens aged 30-60 a 26 item FFQ was used to assess diet and factors were derived by sex. No prospective association was found between the factors and BMI or weight.[111] Discussion and interpretation of this study is limited by the apparent underlying inability of this study to adequately assess diet with the short FFQ. The Nurses' Health Study similarly examined this question and is the largest study to date and also was able to account for changes in dietary pattern over time.[112] The prudent pattern in this study was similarly high to the VFS dietary pattern in vegetables, fruit and fish, but also was high in whole grains, an aspect lacking in the Singapore Chinese Health study. This dietary pattern may be the best for weight maintenance as well. The western dietary pattern, which was rich in meats, refined grains, desserts and soft drinks, appeared to contribute to long term weight gain. This pattern had some similarities to the DSM pattern in predicting greater weight gain and that it was rich in energy dense foods, meats, refined grains, and lower in fiber and whole grains. We are not aware of other studies investigating dietary patterns and risk of future obesity.

Only a few other studies have examined the association between fast food and weight gain in adults.[113-115] After adjustment for many potential confounders Pereira et al. found a significant and direct association with increase in body weight and increasing fast food consumption in the CARDIA study focusing on young adults.[113] Using the same base study and comparing restaurant and fast food intake Duffey et al. found a significant and slight increase in BMI with higher consumption of fast food.[114] In another cohort based in Spain of more middle aged participants, increased consumption of hamburgers, pizza and sausages was associated with a significant but slight increase in the odds of becoming overweight over time.[115] We observed similar results to these studies as with each increase in frequency of fast food we observed an increase in mean weight gain over time after adjustment for numerous potential demographic, lifestyle and dietary confounders. We also found that soft drinks appear to increase weight gain beyond the consumption of fast food. There are many different variables- physiological, behavioral, contextual and metabolic that should be considered in interpretation of this further weight gain potentially due to soft drinks. Indeed, evidence is continuing to build on this topic.[116, 117]

There are a few different dietary components that appear to be different between the VFS and DSM dietary patterns and may be drivers of the associations observed, although specifically delineating these factors is not possible. First, while the overall macronutrient (carbohydrate, fat, protein) make up of the dietary patterns was similar the DSM pattern reported intake of slightly more energy, although this is measured with error. Thus, the DSM pattern may contribute to increased weight gain and risk of obesity through the consumption of more energy dense foods. Furthermore, dietary fiber is likely important in the regulation of weight change,[163] and intake increases across the VFS yet decreases across the DSM pattern. In addition to the energy density of the food a higher glycemic index may also play a role.[164] We were not able to assess this measure. While the overall composition of the diet contributes to the dietary pattern score it may be worthwhile to point out that energy dense beverages (alcohol and soft drinks) also increased across the DSM pattern score where soft drinks decreased across the VFS pattern and alcohol consumption was not associated with the pattern.

Only a handful of other studies have prospectively investigated the association between dietary patterns, fast food and weight gain and we are not aware of other studies who have examined dietary patterns and risk of obesity. The SCHS is unique in the dietary and lifestyle habits, and ethnic composition of its population. The use of a food frequency questionnaire that was specifically developed and validated in the population and has been shown to be internally consistent and reproducible overall and for dietary patterns is another strength. The prospective nature, high participant response rate detailed collection of data through face to face interview, very low level of participants lost to follow up are other strengths to consider in interpreting the results.

There are a number of limitations to consider as well. This study is an observational study and all heights, weights dietary intake, and lifestyle aspects were self reported. We attempted to check for interaction with and adjust for the numerous other lifestyle characteristics that may confound the relationship between the patterns and fast food intake with weight gain, regardless, residual confounding of these lifestyle characteristics needs to be considered as a possible or contributing explanation. We were also not able to assess potential changes in dietary intake or other lifestyle variables which may have affected weight over time. Misclassification and measurement error in the dietary data also need to be considered as possible explanations, although if non-differential in nature, this would most likely account for a lack of or attenuate the associations we observed. Social and depressive symptoms were also not considered and may contribute to weight change.

In conclusion, after empirically deriving dietary patterns we found a pattern characterized by high vegetables, fruits and soy foods was associated with a decreasing trend of weight gain and not associated with developing obesity, and a pattern characterized by high dim sum, meat and processed meat, sweetened foods and beverages and fried foods was associated with an increasing trend of weight gain and increased risk of obesity in a large cohort of non-smoking Chinese men and women in Singapore. Further, we observed a significant increasing trend of weight gain with each stepwise increase in frequency of western fast food in this cohort. Increased soft drink intake combined with the western fast foods appeared to lead to greater weight gains. In close, dietary patterns are unique to the populations they are derived from, yet consistencies across populations suggest that increased plant food intake such as vegetables, fruits, soy, whole grains and legumes are a central part of a diet conducive to weight maintenance where higher level of meat, processed meat, sweetened foods and beverages and fried foods may lead to increased weight gain over time.

Table 6.1: Factor loadings for foods with vegetable, fruit and soy rich dietary pattern in Singapore Chinese Health Study

Food Item	***Food type***	***Loading***		
Cauliflower	V	0.53		
Green beans/peas	V	0.52		
Yin choi, po choi	V	0.49		
Other tau kwa	O, Pr	0.47		
Other plain tofu	S	0.46		
Carrots	V	0.44		
Head cabbage, wong nga	V	0.44		
Tou gay, tai tau nga	V	0.44		
White potatoes	V	0.42		
Tung goo	O, Pr	0.42		
Gum jum, dried fungus	O, Pr	0.42		
Choi sum	V	0.41		
Broccoli	V	0.40		
Kai lan	V	0.38		
Tomatoes	V	0.38		
Fu kua, mo qua	S	0.37		
Corn	V	0.37		
Pak choy, siew pak choy	V	0.37		
Foojook vegetarian meats	S	0.36		
Other dark green leaves	V	0.34		
Head lettuce, Chinese lettuce	V	0.34		
Fish ball/cake	Fi	0.33		
Other tau pok	S	0.32		
Canned baked beans	L	0.31		
Ikan bilis	Pr, Fi	0.30		
Ung choi	V	0.30		
Watercress	V	0.29		
Cucumber	V	0.29		
Yong tau foo	S	0.29		
Kai choi	V	0.29		
Celery	V	0.29		
Apples	F	0.27		
Boiled/steamed fish	Fi	0.27		
Pan/stir fried fish	Fi	0.26		
Pan/stir fried chicken	P	0.25		
Gee choi	V	0.25		
Bananas	F	0.25		
Onions	V	0.25		
Pears	F	0.23		
Salted leafy vegetables	V, Pr	0.22		
Other dried seafood	Fi, Pr	0.22		
Watermelon	F	0.21		
Papaya	F	0.21		
Canned sardine	Fi	0.21	Dietary variance explained	7.0%
Chinese chives	V, O	0.20		

*Factor loads correspond to Pearson correlation coefficients between the food and the respective dietary pattern.
-Definitions of abbreviations: B-beverage; C-condiment; Da-dairy; DS- dim sum/snack dish;
F-fruit; Fi-fish/shellfish/seafood; L-legumes; M-meat; O-other; P-poultry; Pr- preserved; S-soy food; St-high starch item (e.g. noodle dish, rice dish); Sw-sweet; WG-whole grain

Table 6.2: Factor loadings for foods with dim-sum and meat rich dietary pattern in Singapore Chinese Health Study

Food Item	Food type	Loading	Food Item	Food type	Loading
Siew mai	DS, M	0.41	Chee cheong fun	DS,M	0.23
Chicken rice	P, St	0.41	Salted roots	Pr, V	0.22
Gravy noodle	St, M	0.40	Minced pork	M	0.22
Roasted duck or goose	P	0.39	Red/green bean soups	DS	0.22
Other steamed snack	DS, M	0.39	Hot dogs	Pr, M	0.21
Steamed meat bao	DS, M	0.38	Deep fried fish	Fi	0.20
Chicken, mutton curry	M	0.37	Ice cream/frozen yogurt	Da	0.20
Deep fried chicken	P	0.37	Baked buns with meat	DS, M	0.20
Glutinous rice dumpling	St, M	0.36	Pork spareribs	M	0.20
Other pig organs (intestine)	M	0.36	Fish ball/cake	Fi	0.20
Preserved eggs	O, Pr	0.36			
Coconut rice	St	0.35			
Otar otar	DS	0.35			
Other flavored rice	St, M	0.35			
Belly pork	M	0.35			
Dry noodle dish	St, M	0.34			
Deep-fried snacks	DS	0.34			
Chicken satay	P	0.33			
Ngor hiang	DS, M	0.33			
Roti prata	St	0.33			
Curry rice	St	0.32			
Dry noodle dish	St, M	0.32			
Luncheon meat	M	0.32			
Puffs, curry or bean	DS, V	0.32			
Other fried noodle	St, M, Fi	0.32			
Lup chong	M	0.31			
Popiah	DS, M	0.31			
Chinese rojak	DS, V	0.31			
Coconut desserts	DS, Sw	0.31			
Soft drinks	B, Sw	0.29			
Sweet kuey	DS, Sw	0.28			
Salted fish	Fi, Pr	0.28			
Squid	Fi	0.28			
Salted leafy vegetables	V, Pr	0.27			
Shrimp	Fi	0.27			
Pork liver	M	0.27			
Eggs	O	0.27			
Canned sardine	Fi	0.27			
French fries	St, O	0.27			
Fried rice	St	0.27			
Steamed sweet bao	DS, Sw	0.24			
Other pork	M	0.24			
Western Cakes	DS,Sw	0.23			
Hamburgers	M, St	0.23	Dietary variance explained		6.8%
Other dried seafood	Fi, Pr	0.23			

*Factor loads correspond to Pearson correlation coefficients between the food and the respective dietary pattern.
-*Definitions of abbreviations:* B-beverage; C-condiment; Da-dairy; DS- dim sum/snack dish; F-fruit; Fi-fish/shellfish/seafood; L-legumes; M-meat; O-other; P-poultry; Pr- preserved; S-soy food; St-high starch item (e.g. noodle dish, rice dish); Sw-sweet; WG-whole grain

Table 6.3: Participant characteristics across quintiles of dietary pattern score: SCHS

Characteristic	Vegetable, fruit and soy rich Q1	Vegetable, fruit and soy rich Q3	Vegetable, fruit and soy rich Q5	Dim sum and meat rich Q1	Dim sum and meat rich Q3	Dim sum and meat rich Q5
Age	52.9 (6.9)	53.4 (7.0)	53.5 (7.3)	55.1 (7.3)	53.2 (6.9)	51.7 (6.3)
Female (%)	65.5	73.7	74.0	80.6	74.0	59.4
BMI (kg/m^2)	22.9 (3.2)	23.0 (3.1)	22.8 (3.2)	22.8 (3.2)	23.0 (3.2)	23.1 (3.2)
Weight (kg)	57.7 (9.5)	57.7 (9.2)	57.2 (9.0)	56.2 (9.0)	57.4 (9.3)	59.0 (9.8)
[2]Moderate Activity min/wk	42 (2.2)	57 (2.2)	66 (2.2)	70 (2.2)	52 (2.2)	49 (2.2)
Strenuous Activity (% ever)	9.4	9.1	11.3	9.3	8.8	12.8
Sleep (hr/day)	7.0 (1.1)	7.0 (1.0)	7.0 (1.1)	6.9 (1.1)	7.0 (1.0)	7.1 (1.1)
Education (% secondary)	41.6	36.8	37.3	34.8	35.2	44.5
Dietary Intakes						
Total energy (kcal/day)	1328 (453)	1502 (442)	1860 (497)	1303 (395)	1449 (397)	1989 (515)
Carbohydrate (% energy)	61.0 (7.2)	59.2 (6.6)	55.5 (6.6)	62.5 (6.7)	59.9 (6.4)	54.3 (6.2)
Fat (% energy)	23.9 (5.6)	25.4 (5.0)	28.8 (4.7)	23.4 (5.3)	25.5 (4.9)	29.2 (4.7)
Saturated fat (% energy)	8.8 (2.5)	8.9 (2.4)	9.8 (2.5)	7.8 (2.4)	8.9 (2.2)	10.7 (2.2)
Monounsaturated fat (% energy)	8.1 (2.0)	8.6 (1.9)	9.6 (1.9)	7.7 (1.9)	8.6 (1.8)	10.0 (1.8)
Polyunsaturated (% energy)	4.6 (1.5)	5.3 (1.8)	6.3 (2.2)	5.4 (2.2)	5.3 (1.8)	5.5 (1.6)
Protein (% energy)	14.6 (2.4)	15.3 (2.3)	16.2 (2.4)	14.6 (2.5)	15.4 (2.3)	16.1 (2.2)
Soy protein (% total protein)	7.9 (5.4)	9.7 (5.5)	13.4 (7.5)	11.0 (8.0)	10.0 (5.9)	9.9 (5.2)
Fiber (g/1000 kcal)	7.5 (2.4)	8.7 (2.5)	10.0 (2.4)	10.5 (3.1)	8.5 (2.4)	7.8 (1.9)
Starch (g/1000 kcal)	109.2 (24.8)	103.4 (21.5)	89.7 (19.4)	107.6 (24.8)	103.0 (22.0)	90.9 (18.8)
Alcohol (drinks/month)	3.2 (12.6)	2.4 (13.3)	3.0 (11.9)	1.1 (6.5)	2.3 (10.3)	5.3 (15.9)
Soft drinks (drinks/month)	4.0 (11.6)	2.1 (7.5)	1.9 (6.4)	0.4 (1.9)	1.6 (5.4)	6.3 (14.1)
Juice (drinks/month)	1.5 (4.7)	1.5 (4.2)	2.4 (6.6)	1.3 (3.6)	1.5 (5.2)	2.7 (6.2)
Coffee (drinks/month)	39.4 (35.4)	38.2 (33.2)	36.5 (33.1)	25.2 (26.0)	39.8 (33.3)	47.5 (38.3)
Black tea (drinks/month)	7.6 (17.4)	6.2 (14.5)	7.1 (15.8)	4.6 (12.7)	6.1 (14.4)	9.9 (19.0)
Green tea (drinks/month)	7.2 (20.8)	8.7 (23.0)	11.4 (25.4)	8.5 (23.0)	8.6 (22.5)	9.8 (23.6)

[1]All values mean (standard deviation) except [2]Moderate activity mean (standard error)
SCHS= The Singapore Chinese Health Study N= 4,015 per quintiles 1,3,5; 4,016 per quintiles 2,4

Table 6.4: Participant characteristics according to frequency of western fast food consumption: SCHS

Characteristic	Frequency of Western fast food consumption				
	Never n=8,991	**1x/month n=3,628**	**2-3x/month n=3,796**	**1x +/week n=3,662**	*P*
Age	54.4 (7.2)	53.4 (6.8)	52.5 (6.6)	51.5 (6.3)	<0.0001
Female (%)	73.6	73.2	70.6	69.1	<0.0001
BMI (kg/m^2)	22.9 (3.2)	23.0 (3.2)	23.0 (3.1)	22.9 (3.2)	0.48
Weight (kg)	57.2 (9.3)	57.5 (9.2)	58.0 (9.5)	57.8 (9.3)	<0.0001
[2]Moderate Activity min/wk	56 (2.2)	57 (2.3)	55 (2.3)	51 (2.3)	0.12
Strenuous Activity (% ever)	7.8	8.8	11.4	13.4	<0.0001
Sleep (hr/day)	7.0 (1.1)	7.0 (1.1)	7.0 (1.1)	7.0 (1.1)	0.023
Education (% secondary)	31.6	35.1	40.9	51.1	<0.0001
Dietary Intakes					
Total energy (kcal/day)	1433 (459)	1486 (458)	1599 (483)	1786 (521)	<0.0001
Carbohydrate (% energy)	60.4 (7.0)	59.2 (6.6)	57.5 (6.6)	55.4 (6.4)	<0.0001
Fat (% energy)	24.4 (5.3)	25.5 (5.0)	26.8 (4.9)	28.8 (4.8)	<0.0001
Saturated fat (% energy)	8.4 (2.4)	9.0 (2.3)	9.5 (2.3)	10.3 (2.3)	<0.0001
Monounsaturated fat (% energy)	8.1 (1.9)	8.6 (1.8)	9.1 (1.8)	9.8 (1.8)	<0.0001
Polyunsaturated (% energy)	5.2 (1.9)	5.3 (1.9)	5.4 (1.8)	5.8 (1.8)	<0.0001
Protein (% energy)	15.1 (2.5)	15.2 (2.3)	15.6 (2.3)	15.9 (2.2)	<0.0001
Soy protein (% total protein)	10.4 (6.9)	10.2 (6.0)	9.9 (5.5)	9.9 (5.4)	<0.0001
Fiber (g/1000 kcal)	8.9 (2.8)	8.8 (2.6)	8.5 (2.4)	8.5 (2.3)	<0.0001
Starch (g/1000 kcal)	106.1(23.4)	102.2(22.0)	98.5 (20.7)	92.1 (20.1)	<0.0001
Alcohol (drinks/month)	2.4 (10.9)	2.7 (11.4)	2.8 (10.6)	3.3 (11.9)	0.0002
Soft drinks (drinks/month)	1.5 (6.8)	2.0 (6.4)	3.1 (9.3)	4.3 (10.5)	<0.0001
Juice (drinks/month)	1.2 (4.2)	1.5 (5.7)	1.9 (5.5)	3.0 (6.4)	<0.0001
Coffee (drinks/month)	36.5 (14.8)	38.9 (33.8)	38.8 (33.9)	39.3 (34.7)	<0.0001
Black tea (drinks/month)	6.0 (14.8)	6.2 (15.6)	7.0 (15.5)	8.6 (16.9)	<0.0001
Green tea (drinks/month)	8.6 (22.9)	8.6 (21.8)	9.3 (23.5)	9.4 (23.1)	0.035

[1]All values mean (standard deviation) except [2]Moderate activity mean (standard error)
SCHS= The Singapore Chinese Health Study
Fast food= Hamburgers, French fries, fast food sandwiches, pizza, deep fried chicken, hot dogs

Table 6.5: Participant characteristics according to frequency of western fast food and soft drink consumption: SCHS

Characteristic	Frequency of Western fast food + soft drink consumption Never n=7,407	Monthly n=6,270	1x/week n=2,316	2-3x/week n=2,320	4x+/week n=1,764	*P*
Age	54.8 (7.3)	53.4 (6.8)	52.3 (6.5)	51.6 (6.3)	51.0 (5.7)	<0.0001
Female (%)	75.1	73.7	71.4	67.2	61.1	<0.0001
BMI (kg/m^2)	22.9 (3.2)	23.0 (3.2)	23.1 (3.2)	22.9 (3.2)	23.1 (3.2)	0.022
Weight (kg)	56.9 (9.2)	57.4 (9.2)	58.0 (9.2)	58.2 (9.5)	59.0 (9.8)	<0.0001
[2]Moderate Activity min/wk	59 (2.2)	58 (2.4)	50 (2.3)	50 (2.3)	44 (2.2)	<0.0001
Strenuous Activity (% ever)	7.6	9.5	11.6	12.9	12.1	<0.0001
Sleep (hr/day)	7.0 (1.0)	7.0 (1.1)	7.0 (1.1)	7.1 (1.1)	7.0 (1.1	0.0203
Education (% secondary)	31.5	36.1	42.2	47.4	49.5	<0.0001
Dietary Intakes						
Total energy (kcal/day)	1412 (451)	1501 (459)	1583 (462)	1720 (497)	1901 (563)	<0.0001
Carbohydrate (% energy)	60.3 (7.0)	58.6 (6.7)	57.6 (6.6)	56.6 (6.7)	56.8 (7.1)	<0.0001
Fat (% energy)	24.4 (5.3)	25.9 (5.1)	26.9 (5.0)	27.8 (5.2)	27.8 (5.4)	<0.0001
Saturated fat (% energy)	8.4 (2.4)	9.1 (2.4)	9.5 (2.3)	9.9 (2.4)	10.1 (2.4)	<0.0001
Monounsaturated fat (% energy)	8.1 (2.0)	8.7 (1.9)	9.1 (1.9)	9.4 (1.9)	9.5 (2.0)	<0.0001
Polyunsaturated (% energy)	5.2 (2.0)	5.4 (1.9)	5.5 (1.8)	5.6 (1.8)	5.4 (1.8)	<0.0001
Protein (% energy)	15.2 (2.5)	15.4 (2.3)	15.5 (2.3)	15.6 (2.2)	15.3 (2.3)	0.04
Soy protein (% total protein)	10.4 (6.9)	10.1 (5.9)	10.0 (5.7)	10.2 (5.8)	9.7 (5.6)	<0.0001
Fiber (g/1000 kcal)	9.0 (2.8)	8.8 (2.6)	8.6 (2.4)	8.5 (2.3)	7.8 (2.1)	<0.0001
Starch (g/1000 kcal)	106.8 (23.5)	102.0 (21.9)	98.8 (21.0)	94.2 (20.5)	89.9 (19.6)	<0.0001
Alcohol (drinks/month)	2.2 (10.5)	2.7 (11.1)	2.3 (9.6)	3.2 (11.6)	4.6 (14.2)	<0.0001
Soft drinks (drinks/month)	0	0.4 (0.8)	1.4 (1.6)	3.9 (3.9)	19.0 (20.0)	<0.0001
Juice (drinks/month)	1.1 (3.7)	1.5 (5.2)	1.9 (4.8)	2.5 (5.1)	3.8 (9.3)	<0.0001
Coffee (drinks/month)	35.7 (32.6)	38.6 (33.3)	38.8 (34.2)	39.7 (35.2)	40.7 (36.5)	<0.0001
Black tea (drinks/month)	5.6 (14.4)	5.9 (14.5)	7.8 (16.9)	7.9 (15.1)	10.8 (20.0)	<0.0001
Green tea (drinks/month)	8.6 (22.8)	8.8 (22.6)	8.8 (22.6)	9.1 (22.5)	8.6 (21.5)	0.80

[1]All values mean (standard deviation) except [2]Moderate activity mean (standard error)
SCHS= The Singapore Chinese Health Study
Fast food= Hamburgers, French fries, fast food sandwiches, pizza, deep fried chicken, hot dogs

Table 6.6: Mean weight change (kilograms) according to quintile of dietary pattern score and frequency of western fast food intake in non-smokers: The Singapore Chinese Health Study

Dietary patterns					
VFS pattern	Mean (SE)§	*P*	**DSM pattern**	Mean (SE)§	*P*
Q1	0.48 (0.07)	<0.0001	**Q1**	0.31 (0.07)	<0.0001
Q2	0.34 (0.07)	<0.0001	**Q2**	0.20 (0.07)	0.0052
Q3	0.40 (0.07)	<0.0001	**Q3**	0.37 (0.07)	<0.0001
Q4	0.40 (0.07)	<0.0001	**Q4**	0.40 (0.07)	<0.0001
Q5	0.23 (0.07)	0.0024	**Q5**	0.57 (0.08)	<0.0001
P trend for change		0.04	*P* trend for change		0.004

Western fast food intake[1]					
Western fast food*			**Western fast food + soft drinks**		
Frequency	Mean (SE)¥	*P*	**Frequency**	Mean (SE)¥	*P*
Never	0.32 (0.05)	<0.0001	**Never**	0.22 (0.05)	<0.0001
1x/month	0.38 (0.07)	<0.0001	**Monthly**	0.33 (0.06)	<0.0001
2-3x/month	0.40 (0.07)	<0.0001	**1x/week**	0.45 (0.09)	<0.0001
1x +/week	0.44 (0.08)	<0.0001	**2-3x/week**	0.59 (0.09)	<0.0001
			4x+/week	0.71 (0.11)	<0.0001
P trend for change		0.009	*P* trend for change		<0.0001

Data are means (standard error) for n=20,077
VFS= Vegetable, fruit and soy rich dietary pattern
DSM= Dim sum and meat rich dietary pattern

§ Adjusted for age, sex, dialect, year of interview, time between baseline and follow up, baseline BMI, education, moderate and strenuous physical activity, sleep, TV hours

¥ Adjusted for age, sex, dialect, year of interview, time between baseline and follow up, baseline BMI, education, moderate and strenuous physical activity, sleep, TV hours, fruit and fruit juice intake, vegetable intake, dairy intake, meat intake, dessert and candy, alcohol, coffee, black tea, green tea, and deep fried foods at home

[1]Western fast food= Hamburgers, French fries, fast food sandwiches, pizza, deep fried chicken, hot dogs

*Additionally adjusted for soft drink intake for Western fast food

Table 6.7: Mean weight change (kilograms) according to quintile of dietary pattern score and frequency of western fast food intake in non-smokers with BMI < 23.0 kg/m^2, age ≤ 54 and no reported physical activity (n=8,639): The Singapore Chinese Health Study

Dietary patterns					
VFS pattern	Mean (SE)§	*P*	**DSM pattern**	Mean (SE)§	*P*
Q1	0.89 (0.10)	<0.0001	**Q1**	0.55 (0.12)	<0.0001
Q2	0.55 (0.10)	<0.0001	**Q2**	0.39 (0.11)	0.0004
Q3	0.68 (0.10)	<0.0001	**Q3**	0.68 (0.10)	<0.0001
Q4	0.63 (0.11)	<0.0001	**Q4**	0.80 (0.10)	<0.0001
Q5	0.50 (0.11)	<0.0001	**Q5**	0.80 (0.11)	<0.0001
P trend for change		0.05	*P* trend for change		0.02

Western fast food intake					
Western fast food*			**Western fast food + soft drinks**		
Frequency	Mean (SE)¥	*P*	**Frequency**	Mean (SE)¥	*P*
Never	0.56 (0.08)	<0.0001	**Never**	0.47 (0.09)	<0.0001
1x/month	0.67 (0.11)	<0.0001	**Monthly**	0.58 (0.08)	<0.0001
2-3x/month	0.70 (0.10)	<0.0001	**1x/week**	0.68 (0.13)	<0.0001
1x +/week	0.79 (0.11)	<0.0001	**2-3x/week**	0.90 (0.13)	<0.0001
			4x+/week	1.08 (0.15)	<0.0001
P trend for change		0.07	*P* trend for change		0.001

Data are means (standard error) for n=8,639
VFS= Vegetable, fruit and soy rich dietary pattern
DSM= Dim sum and meat rich dietary pattern

§ Adjusted for age, sex, dialect, year of interview, time between baseline and follow up, baseline BMI, education, moderate and strenuous physical activity, sleep, TV hours

¥ Adjusted for age, sex, dialect, year of interview, time between baseline and follow up, baseline BMI, education, moderate and strenuous physical activity, sleep, TV hours, fruit and fruit juice intake, vegetable intake, dairy intake, meat intake, dessert and candy, alcohol, coffee, black tea, green tea, and deep fried foods at home

[1]Western fast food= Hamburgers, French fries, fast food sandwiches, pizza, deep fried chicken, hot dogs

*Additionally adjusted for soft drink intake for Western fast food

Table 6.8: Relative risks of incident obese status (BMI ≥ 27.5) according to quintile of vegetable, fruit, and soy rich dietary pattern score (a) and according to dim sum and meat rich dietary pattern score in those of overweight status (BMI=23.0-26.9) at baseline: Singapore Chinese Health Study

Vegetable, fruit and soy rich pattern (a)

	Q1	Q2	Q3	Q4	Q5	
N/PY	190/20,769	173/20,758	192/21,064	178/20,648	195/20,871	*P* for trend
	(lowest)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	
Model I[1]	1.0	0.93 (0.76, 1.15)	1.00 (0.82, 1.22)	1.01 (0.82, 1.24)	1.18 (0.96, 1.44)	0.08
Model II[2]	1.0	0.94 (0.76, 1.15)	1.00 (0.82, 1.23)	1.02 (0.83, 1.25)	1.20 (0.98, 1.47)	0.06
Model III[3]	1.0	0.91 (0.74, 1.12)	0.95 (0.77, 1.17)	0.94 (0.76, 1.17)	1.05 (0.84, 1.31)	0.64

Dim sum and meat rich pattern (b)

	Q1	Q2	Q3	Q4	Q5	
N/PY	127/8,014	160/8,981	148/8,587	199/8,555	225/8,947	*P* for trend
	(lowest)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	
Model I[1]	1.0	1.16 (0.92, 1.47)	1.11 (0.88, 1.41)	1.60 (1.28, 2.00)	1.62 (1.30, 2.02)	<0.0001
Model II[2]	1.0	1.16 (0.92, 1.47)	1.11 (0.87, 1.41)	1.59 (1.27, 1.99)	1.62 (1.29, 2.02)	<0.0001
Model III[3]	1.0	1.16 (0.91, 1.46)	1.10 (0.86, 1.40)	1.56 (1.24, 1.97)	1.56 (1.22, 1.99)	<0.0001

P value for trend was modeled as a continuous variable with the use of the median value of each quintile
All data presented as RR (95% CI) unless otherwise noted
N= number of participants whose BMI increased to ≥ 27.5 kg/m^2 at follow up from baseline, PY=person years
[1]Adjusted for age, sex, dialect, year of interview, baseline BMI, education
[2]Adjusted further for physical activity, hours of sleep and television
[3]Adjusted for aforementioned variables and energy intake

*N=18,436, 928 person with new obese status, person years (PY) follow up total 104,110 for VFS pattern

**P* interaction between baseline BMI and DSM pattern =0.08

*69 persons with BMI < 23.0 at baseline reported incident obese status at follow up

Chapter 7: Manuscript 2: Dietary patterns and risk of type 2 diabetes: The Singapore Chinese Health Study

Introduction

Rates of type 2 diabetes mellitus in Asia are reaching epidemic proportions. The prevalence has increased three to five fold in Southeast Asia during the past three decades and there is evidence this increase is occurring rapidly in areas of China and India and in younger age groups.[44] In Singapore the prevalence in Chinese nearly doubled from 1984 (4.7%) to 1998 (8.0%).[165] These increases in Southeast Asia are beyond the increase in rates observed in the United States and other parts of the world.[44, 166] Substantive shifts in socioeconomic, demographic and lifestyle patterns are thought to be responsible.[1, 167]

Central to these epidemiologic patterns, as well as prevention and etiology of type 2 diabetes, through its role in energy balance, and other pathways of physiological significance such as insulin resistance, sensitivity and glycemic control, is dietary intake. The majority of research on diet and type 2 diabetes has focused on individual foods and nutrients which are part of a larger dietary pattern of consumption of many foods containing many different nutrients. The data from this single food/nutrient approach is valuable, but best interpreted in the scheme of all the related research as the data can be confounded by the overall dietary pattern, and have effects too small to identify due to methodological issues. [118] Additionally, people eat food rather than nutrients in isolation, and consume mixed meals with potential interactions among food and nutrients.[119] Thus, consideration of the whole spectrum of a dietary pattern may be most germane to health.[168]

Analysis of food consumption patterns in populations in relation to health is becoming more common.[121] Most use data driven techniques such as principal components analysis (PCA), factor analysis, or cluster analysis to derive dietary patterns from surveys or food frequency questionnaires. Multiple epidemiological studies have examined associations between dietary patterns and type 2 diabetes risk.[122-124, 126, 127] Generally, these studies have suggested that higher intakes of vegetables and fruit, whole grains, fish and low fat dairy may be protective for diabetes risk and higher intakes of processed grains, sugars through different mediums, processed and red meats, and fried foods may be pernicious for diabetes risk. In light of the similar dietary intakes, patterns, and composition of the populations previously studied, research considering dietary patterns in a Chinese population may provide useful information for similar Asian populations and further insight to the diet-diabetes association.

The Singapore Chinese Health Study (SCHS) is a population-based prospective cohort investigation of over 63,000 Chinese men and women in Singapore. The aim of this paper was to derive dietary patterns and examine their association with risk of incident type 2 diabetes in this cohort.

Subjects and Methods

Study Population

The design of the Singapore Chinese Health Study has been previously described.[154] Briefly, the cohort was drawn from men and women, aged 45 to 74 years, who belonged to one of the major dialect groups (Hokkien or Cantonese) of Chinese in Singapore. Between April 1993 and December 1998, 63,257 individuals completed an in-person interview that included questions on demographics, height, weight, use of tobacco, usual physical activity, menstrual and reproductive history (women only), medical history, family history of cancer and a 165-item food frequency section assessing usual dietary intake of the previous year. A follow-up telephone interview took place between 1999 and 2004 for 52,325 cohort members (83% of recruited cohort), and questions were asked to update tobacco and alcohol use, medical history, and menopausal status of women. The institutional review boards at the National University of Singapore and the University of Minnesota approved this study.

Assessment of diet

A semi-quantitative food frequency questionnaire specifically developed for this population assessing 165 commonly consumed food items was administered during the baseline interview. During the interview the respondent referred to accompanying photographs to select from eight food frequency categories (ranging from ‘‘never or hardly ever’’ to ‘‘two or more times a day’’) and three portion sizes. Additionally, frequency of eating breakfast, lunch and dinner at Hawker centers/restaurants was also assessed. Hawker centers are ubiquitous in Singapore and other parts of Asia, serve a variety of foods all day long, and resemble fast-food courts in U.S. shopping malls. The food frequency questionnaire has subsequently been validated against a series of 24-hour dietary recall interviews in a random sample of 1000+ participants that occurred on one weekday and one weekend day approximately two months apart,[154] as well as selected biomarker studies.[155, 156] A range of 0.24 to 0.79 in correlation coefficients of energy/nutrients was obtained using two methods, and the majority of macro-nutrients and food groups display correlation coefficients in the high end of this reported range.[154]

In conjunction with this cohort, the Singapore Food Composition Table was developed, a food-nutrient database that lists the levels of 96 nutritive/nonnutritive components per 100 g of cooked food and beverages in the diet of the Singaporean Chinese. By combining information obtained from the food frequency questionnaire with nutrient values provided in this food-nutrient database accounting for raw and cooked foods, and utilizing food composition and nutrient data from the cancer research center of Hawaii as well as composition tables from China, Malaysia and Taiwan, we were able to compute the mean daily intakes of nutrients for each subject.[154]

Assessment of Diabetes

Self-reported diabetes as diagnosed by a physician was evaluated at baseline and participants with a history of diagnosed diabetes were excluded from analysis. Diabetes status was assessed again by the following question asked during the follow-up telephone interview: "Have you been told by a doctor that you have diabetes (high blood sugar)?" If yes: "Please also tell me the age at which you were first diagnosed?" Participants were classified as having incident diabetes if they reported developing diabetes anytime between the initial enrollment interview and the follow up telephone interview that occurred between July 1999 and October 2004.

A validation study of the incident diabetes mellitus cases used two different methods and is reported in detail in Odegaard et al.[152] First, cases were ascertained through linkage with hospital records in a nationwide hospital-based discharge summary database, an administrative database in the Singapore Ministry of Health.[169] If subjects in the study had been admitted to hospitals for diagnoses carrying diabetes-related ICD codes (250.00-250.92) after recruitment into the cohort, they were considered a valid case. Cases that did not have hospitalization records available with diabetes-related diagnoses were contacted to answer a supplementary questionnaire regarding symptoms, diagnostic tests and hypoglycemic therapy during a telephone interview. A valid case had the following 3 criteria: 1) confirmed diagnosis later than the baseline interview date, 2) diabetes still present at time of interview, and 3) use of oral medications or insulin injections to treat diabetes.

Statistical Analysis

Participants who died before the follow up interview (7,722), reported baseline diabetes (5,469), cancer, heart disease or stroke (5,975), reported extreme sex specific energy intakes (<600 or >3,000 kcal women) (<700 or >3,700 kcal men), and 17 (0.03%) subjects from the initial cohort that migrated out of Singapore suggesting that emigration or lost to follow up among the study participants is negligible. These, along with further exclusion of 20 participants whose diabetes status was not clear after the validation effort, left 43,176 participants in the present analysis.

Dietary patterns were derived using principal component analysis (PCA) SAS version 9.1 (SAS Institute Inc, Cary, NC). The aim of PCA in nutritional analyses is to account for the maximal variance of dietary intake by combining the many different dietary variables into a smaller number of factors based upon the intercorrelations of these variables. All 165 foods and beverages, including alcohol, were first standardized to the same frequency/month unit before the PCA method was applied and factors were extracted. The factors were rotated orthogonally to maintain an uncorrelated state and improve interpretability, and a two factor solution was retained based upon eigenvalues, scree plot and factor interpretability. The factor loadings presented are highly statistically significant ($p<0.0001$) in consideration of a formula accounting for sample size and the critical value in a table for correlation as suggested by Stevens.[161] For comparability and interpretability of our results we present factor loadings > 0.20 even though values <0.20 are statistically significant due to the large sample size of the study. This cutoff aligns with previous studies,[122-124, 126, 127] although these studies did not specify if the factor loadings presented were chosen on statistical significance. Factor scores for each participant were calculated by multiplying the intake of the standardized food item by their respective factor loadings on each pattern. The scores are linear variables and represent the weighted sum of all 165 food items. Participants were divided into quintiles by score to indicate the level their dietary intake corresponded with each pattern, i.e. a higher score corresponds with greater conformity to the derived pattern. Factors were initially extracted by sex, dialect and smoking status and were highly similar in loading structure and disease prediction to the reported whole cohort factors, so the factors derived from the overall cohort were used. The patterns were named vegetable, fruit and soy rich (VFS) and dim sum and meat rich (DSM) as these foods loaded strongest and most frequently on the respective patterns. The sensitivity and reproducibility of the patterns have previously been shown to be strong.[162]

Baseline and dietary characteristics were calculated for participants who remained free of and developed type 2 diabetes during follow up; as well as across quintiles of each dietary pattern score. Tests for trend across dietary patterns scores were performed by assigning the median value of the quintile to the respective categories and entering this as a continuous variable into the models. Person-years for each participant were calculated from the year of recruitment to the year of reported type 2 diabetes diagnosis, or year of follow up telephone interview for those who did not report diabetes diagnoses. Relative risks per quintile of dietary pattern score were estimated by Cox proportional hazards regression models using SAS statistical software. There was no evidence that proportional hazards assumptions were violated as indicated by the lack of significant interaction between the dietary pattern scores and a function of survival time in the models. Other known or suspected risk factors for diabetes assessed with the baseline questionnaire included: Age (years), smoking habits/status (age started/quit, amount, frequency, type), highest educational level reached, BMI (kg/m^2) calculated using self-reported height and weight, amount (hours) of moderate (e.g. brisk walking, bicycling on level ground) and strenuous (e.g. jogging, bicycling on hills, tennis) physical activity on a weekly basis.

Three main models were constructed to examine the association between dietary pattern score and risk of type 2 diabetes: Model 1 included baseline age (<50, 50-54, 55-59, 60-64, 65+), year of interview (1993-95 and 1996-98), dialect (Hokkiens vs. Cantonese), sex and total energy intake (kcal/day). Model 2 included variables in model 1 plus education (none, primary, secondary+), smoking (no, former, current), moderate activity (none, ½ hr-3 hrs/wk, 4+ hrs/wk) and strenuous activity (yes vs. no), and history of hypertension (yes vs. no). Model 3 included those variables in Model 2, plus baseline BMI {kg/m^2 as the original BMI and its quadratic term (BMI^2) as this may represent a mediator in this diet-diabetes relationship. Analyses testing for interactions of sex, age, smoking, physical activity and BMI with the dietary pattern scores as well as stratification, were completed. Additional analyses examined how the association of the

VFS or DSM pattern varied by the score on the other respective pattern. Lastly, sensitivity analyses excluding cases with less than two years of follow up were also carried out to account for potential reverse causation.

Results

Of 43,176 men and women with 246,898 person-years of follow up, 2,252 developed type 2 diabetes, or approximately 5.2%. Characteristics of participants who developed type 2 diabetes over follow up are compared to participants who remained disease free in **Table 7.1.** Incident cases of diabetes were older, had increased BMI, reported less physical activity, less education and smoked more. There were no highly significant differences in consideration of dietary macronutrients.

Two main dietary patterns were derived from principal components analysis. The first pattern was named vegetable, fruit and soy rich (VFS) and factor loadings for this pattern are shown in **Table 7.2.** The higher the loading (correlation) between a food and a factor the more that food uniquely contributes to the pattern score. Of 45 foods loading above the noted minimum threshold on this pattern, 23 were vegetables, 5 were fruits and 5 were soy based items. Additionally, different types of fresh and preserved seafood loaded highly on this pattern. The dim-sum and meat rich pattern (DSM) **(Table 7.3)** contained 54 items, predominantly dim-sum, a variety of fresh and processed meats and seafood, noodle and rice dishes consumed at levels beyond other dietary patterns, sweetened foods and deep fried foods. Only one food (ung choi, a type of spinach) loaded above 0.20 on both patterns. Most dim sum foods are savory pastries- steamed or deep fried dumplings, filled buns, noodles, or sweet pastries, meats and some vegetables.

Dim sum is usually served in small quantities so a wide variety of foods may be sampled, and is part of small to large meals.

Baseline characteristics and relative risks are presented by smoking status (ever vs. never) as there was evidence that the association between the dietary patterns and type 2 diabetes was modified by smoking (P=0.06 for interaction). Overall, 31,326 participants reported no history of smoking, and 1,570 developed type 2 diabetes (5.0%) and 11,850 reported a history of smoking, and 682 developed type 2 diabetes (5.8%). **Table 7.4** shows baseline characteristics of the study sample according to smoking status by quintile of the VFS dietary pattern score. On average, both ever and never smokers were more physically active and a higher percentage female with a higher VFS dietary pattern score. Ever smokers were older on average and had a lower BMI as well. Dietary-wise, ever and never smokers with higher scores on this pattern had increased fiber, dietary fat and dietary fatty acid ratios, protein and soy protein, and decreased carbohydrate and starch intakes. **Table 7.5** shows baseline characteristics by smoking status according to quintile of the DSM dietary pattern score. On average, both ever smokers and never smokers were younger, less physically active and more educated across increasing quintiles of DSM dietary pattern score. The percentage of men increased across increasing quintiles of the DSM pattern. In contrast to the VFS pattern, participants had lower fiber intake, soy protein intake and dietary fatty acid ratios across increasing quintiles of DSM dietary pattern score.

We also looked at the frequency of consumption of different dishes and foods by how they were grouped and assessed in the baseline interview FFQ while also considering their culinary/nutrient profile across quintiles of VFS rich pattern score

(**Table 7.6)** and the DSM rich pattern score (**Table 7.7**). Rice dishes display a similar range of intake across both patterns; however, the DSM pattern factor loadings suggest that rice is consumed more often in different preparations compared to the VFS pattern. Noodle based dishes, as well as pork and other meats, have a narrower range and lower level of consumption on the VFS pattern compared to the DSM pattern across increasing pattern scores. Further, consumption of whole grain and dairy based items decreased across the DSM pattern and increased across the VFS pattern score. Of note, consumption of dim sum and snack type foods displayed increasing trends across quintiles of both dietary patterns, however the range and amount of reported intake was significantly greater across the DSM pattern. Additionally, eating at hawker stands and restaurants decreased across the VFS pattern and significantly increased across the DSM pattern. One other area of note where intakes went in different directions across pattern scores were in western fast food consumption (hamburgers, French fries, sandwiches, pizza, etc) and soft drinks where intakes decreased across VFS pattern score and increased across DSM score. Lastly, beverages such as coffee displayed a wider range and higher level of consumption across the DSM pattern, green tea intake appeared higher and displayed a wider range in the VFS pattern and black tea intake appeared higher and displayed a wider range across the DSM pattern. Alcohol intake levels are low in the cohort and did not associate with the VFS pattern, but increased significantly across the DSM pattern.

In summary, and as aptly noted in Butler et al.[170] the traditional Singapore Chinese diet consists primarily of mixed dishes that are generally high in refined carbohydrates (e.g., noodles and white rice), soy foods, and green leafy vegetables, and contain relatively small quantities of meats, such as chicken and pork. However, indicative of a population that has transitioned from low to high socioeconomic status, there was a wide distribution of more traditional dietary components (e.g. vegetables, soy, and fish) and non-traditional (e.g., meats and dairy) as displayed in Tables 6 and 7. Furthermore, other traditional foods typically reserved for special occasions and thus typically consumed infrequently, (e.g. Dim Sum and meat centered dishes) are occupying a more prominent role in the usual diet.

Relative risks for incident type 2 diabetes mellitus by smoking status are presented in **Table 7.8.** The decision to present results stratified by smoking status was based on the potential interaction between the DSM pattern and ever-smoking (p=0.06) and visible differences in hazard ratio (HR) and trend across the quintiles of both dietary pattern scores. Overall, there was no association with the DSM or VFS dietary pattern score and type 2 diabetes in ever smokers. Attempts to account for potential confounding through stratification by sex, BMI, age, physical activity, and smoking habits (current vs. ex, duration and amount) did not change this null finding.

Conversely, in never smokers an inverse association was observed for type 2 diabetes mellitus risk in quintiles 2-5 of VFS dietary pattern score compared to the first quintile of the VFS pattern. The association persisted after adjustment for all potential confounders including BMI. Because of the apparent threshold of the association in quintiles 2-5 of the VFS score they were combined into one group and compared to quintile 1 of the VFS score. With this approach a 21% reduction in relative risk was observed (HR=0.79; 95% CI 0.70-0.90). Hypothesized tests for interaction between VFS pattern score in never-smokers and BMI, physical activity (ever) and age, as well as stratification efforts provided no evidence of any effect modification with this pattern. Excluding cases with less than two years follow up did not materially change the association.

Because each participant receives a score for each pattern we examined how eating on the VFS pattern may differ by eating on the DSM pattern by cross tabulating the pattern scores and comparing the relative risks across categories. For this analysis approach in never smokers, quintiles 2-5 of the VFS pattern were grouped and compared to VFS quintile 1 according to DSM dietary pattern score (quintile 1, quintiles 2-4 and quintile 5). **Figure 7.1** displays the results. The point estimates of relative risk in quintiles 2-5 of the VFS pattern do not appreciably differ from the main models according to DSM pattern quintiles 1 and 2-4; although the association is non-significant in DSM quintile 1. However, participants who reported a dietary pattern score in the highest quintile of the DSM pattern appeared to have potential benefit of the VFS pattern nullified, (HR=0.95; 95% CI 0.71-1.29).

In the main models for the DSM pattern in never smokers the hazard ratio increased similarly in the second through fourth quintiles of DSM dietary pattern score compared to the first quintile of DSM pattern score. A 55% increase in risk was observed in the full model (2) in the 5^{th} quintile of DSM score (HR=1.55; 95% CI 1.29-1.86, *P* for trend=<0.0001) compared to the first quintile. This was nominally attenuated upon adjustment for BMI (**Table 7.8**). A test for interaction between BMI (median) and DSM dietary pattern score was not statistically significant (p=0.12), however the association was more pronounced and displayed a robust trend in the higher end of BMI;

where only DSM dietary pattern scores in the 5th quintile were significant in the lower end of the BMI spectrum **(Figure 7.2)**.

Similarly, a test for interaction of baseline age (<60 vs. 60+) by DSM dietary pattern score suggested (p=0.76) that the association does not differ by age. Yet, an age stratified analysis (**Figure 7.3)** suggests a more marked association in never smokers aged 60+ (n=7,992) in the 5th vs. 1st quintile of DSM pattern score (HR=1.76; 95% CI 1.26-2.46, *P* for trend=0.003) where a lesser association in younger participants (age <60, n=23,334) in the 5th vs. 1st quintile was observed (HR=1.31; 95% CI 1.05-1.63, *P* for trend=0.05). **Figure 7.4** presents results from an analysis considering the DSM pattern and diabetes risk stratified by any physical activity (moderate or strenuous n=8,888) vs. no reported physical activity (n=22,418). A statistical test for interaction between physical activity and DSM dietary pattern score did not reveal strong evidence for risk differing by activity level (p=0.16). However, in participants reporting any physical activity there was a non-significant increase in risk that was considerably attenuated compared to the main model. In participants reporting no physical activity the association increased in a similar trend to the main model with nominally larger relative risks.

The results from an analysis examining risk of type 2 diabetes after collapsing the DSM pattern score into quintiles 1, 2-4 and 5 and stratifying by quintiles 1 and 2-5 of VFS pattern score is displayed in **Figure 7.5.** Compared to quintile 1 of the DSM pattern participants scoring in the 5th quintile of the DSM pattern while also scoring on quintiles 2-5 of the VFS pattern had a 42% increase in risk (HR=1.42; 95% CI 1.16-1.74). Non-significant increases in risk were observed among the other categories, potentially due to lack of power. Lastly, excluding diabetes cases with less than two years of follow-up time did not materially alter the results in any analysis considering the DSM dietary pattern score.

Discussion

In this large prospective study of Chinese Singaporeans, two main dietary patterns were identified. A pattern characterized by high consumption of vegetables, fruit, and soy products and some fish and seafood was termed vegetable, fruit and soy rich. The other dietary pattern was characterized by high consumption of dim sum, fresh and processed meats, higher levels of noodles and rice dishes, and some sweetened deep fried foods and was termed dim sum and meat rich. The results from the Cox regression analysis were modified by smoking status and neither pattern was associated with an increased risk of diabetes in ever-smokers even though ever-smokers had a higher rate of incident diabetes. In never-smokers the VFS dietary pattern was associated with a lower risk for type 2 diabetes. In contrast, the DSM dietary pattern was associated with a significant increased risk of type 2 diabetes. Both patterns in never-smokers were still highly significant after adjustment for all potential confounders in this cohort including BMI, physical activity and age. In addition, although not statistically significant, the association of the DSM pattern with type 2 diabetes was more pronounced in overweight participants, participants older than 60 years of age, and participants reporting no physical activity. Lastly, a diet corresponding to the highest level of the DSM pattern appears to suppress any benefit of the VFS dietary pattern.

Five previous studies have examined the association between dietary patterns and risk of incident type 2 diabetes.[122-124, 126, 127] There are some consistencies, similarities and differences between the studies. First, the age range of participants was similar in all of the studies except for a small portion of participants who were younger and slightly older in the Melbourne Collaborative Cohort Study.[126] All of the previous studies were primarily persons of Caucasian descent except for the study from MESA,[127] a multi-ethnic study in the United States. In the derivation of the dietary patterns all studies used PCA to derive the dietary patterns. However, Hodge et al.[126] was the only other study besides the present that derived patterns on individual foods rather than food groups. PCA utilizing epidemiological nutritional data involves multiple steps with an arbitrary decision component. Analyzing individual foods avoids a step involving assumptions, potentially simplifying the approach and the end public health message. The end point (type 2 diabetes) in each study appears to be valid and even conservative in some instances.[122-124, 126, 127]

The VFS pattern in the Singapore Chinese health study has similarities in loading structure and association with type 2 diabetes to dietary patterns termed “prudent” in the Nurses’ Health Study[123], The Health Professionals Follow up Study[122], and a Finnish study;[124] all of which found suggestively inverse or inverse associations between this pattern and type 2 diabetes. These patterns were all high in vegetables, fruits, whole grains, legumes, fish, and poultry and low fat dairy to an extent. The cooking methods of the fish and poultry were undefined. Of note, the study by Montonen et al.[124] did not account for physical activity in their analysis so the interpretation of this inverse association with the “prudent” dietary pattern should occur with caution. In the present study, the VFS pattern differs from previous populations examined in that a relatively high level of soy products are consumed in this population and essentially all the grains are refined or processed. Furthermore, dairy and non-soy legumes are not prominent usual dietary components in this Chinese population. Regardless of the differences, this pattern was associated with higher fiber intake and potentially beneficial fatty acid intake and ratios beneficial for diabetes risk.[78, 171] Soy has also been shown to be beneficial in diabetes risk.[172, 173] The other aforementioned studies derived similarly beneficial dietary patterns that were rich in vegetables, whole grains and fish,[126] and whole grains, fruit, nuts and fish.[127] They also reported patterns loaded with vegetables and fish[127] and vegetables and legumes[126] with null results. While seemingly similar to the other patterns in the same study and the aforementioned prudent dietary patterns, a potential explanation for the null results is these two studies were comparatively heterogeneous in ethnic makeup, and the dietary assessment tools in these studies were not ethnic-specific, even though valid, potentially adding further noise than usual to a risk estimate as the complete diet may not have been assessed or reported. Potential residual confounding by ethnicity should also be considered as well as these patterns could be considered factorially complex, since some food items and groups load significantly across patterns. In short, the VFS pattern displays similarities with other dietary patterns as well as individual food components healthful for delaying or preventing type 2 diabetes. Moreover, the racial, cultural and geographical difference with previous studies on this topic highlight important dietary similarities and differences, points to the complicated and heterogeneous nature of the diet-diabetes association, and provides other similar Asian populations a dietary pattern to identify with.

The dim-sum and meat rich dietary pattern (DSM) was the other main pattern in the Singapore Chinese Health Study. Similar to the previous studies on this topic that presented a dietary pattern with higher consumption of meats, fried foods, sweetened foods and beverages, SCHS participants eating a diet highly conforming to the DSM pattern observed a significantly increased risk of type 2 diabetes. These previous studies also noted higher levels of refined grains on their "western" and "conservative" patterns.[122-124] The DSM pattern differs on this respect as refined grains such as white rice and noodles made up essentially all the grain component of the usual diet in this population. However, on average, there were higher levels of noodles and rice on this pattern, as well as decreased whole grains compared to the VFS pattern in this population or the lowest quintile of DSM dietary pattern score. In addition to the DSM dietary pattern having foods more commonly consumed that have been associated with type 2 diabetes such as sugar sweetened beverages,[174, 175] meats,[123] and fried foods[176] the nutrient composition and decreasing fiber and dietary fatty acid ratios are less favorable for glucose and insulin metabolism.[171, 177]

The interactions of the DSM pattern with age, physical activity and BMI did not present as statistically significant, but similar trends were observed in relation to previous studies. Risk was more pronounced on those with higher relative weights, age and no physical activity. In the Health Professionals Study the western dietary pattern- type 2 diabetes association was significantly more pronounced in obese persons, persons with low levels of physical activity and higher ages.[122] The Nurses' Health Study suggested a more pronounced and similar risk pattern in obese women as well.[123] In the Finnish based study the prudent dietary pattern appeared to be more beneficial in the older portion of the cohort.[124] Lastly, the data from the SCHS show that the associations observed were limited to never-smokers. Only the Finnish study appeared to check for any difference in association by smoking. They found that the association between the meat and fried food rich conservative pattern was stronger in current smokers vs. ex or never smokers and the potential benefit of the prudent dietary pattern was limited to ex or never smokers.[124]

The attempts to look at any potential difference in the associations of the VFS pattern or DSM pattern score by dietary pattern score on the other respective pattern in a cross tabulation analysis showed that eating higher on the VFS pattern had an inverse association with diabetes risk unless one ate on the highest quintile of the DSM pattern score. Further, it appears if SCHS participants eat a diet to the highest conformity of the DSM pattern there is still an increased risk of type 2 diabetes when eating high on the VFS dietary pattern, suggesting a diet mainly of the constituents correlating highly with the DSM pattern nullify the benefits of increased vegetables and fruit and other components of the VFS pattern on average in this population. The only other study to look at diabetes risk by cross-tabulating dietary pattern scores was the Finnish study,[124] which found that the association with a pernicious diet was higher among persons with a lower prudent diet score. The higher prudent score did not improve among persons with low conservative scores, a nutritionally poor diet.

Unlike previous studies on this topic the association in the SCHS only occurred in never-smokers. Smoking has been shown to be a significant, independent causal risk factor for type 2 diabetes in a recent meta-analysis.[178] Indeed, ever-smokers in the SCHS had a higher incident rate of type 2 diabetes. Multiple pathways of pathophysiological significance appear to be involved in the smoking-type 2 diabetes association that could confound the association between dietary intake and type 2 diabetes including smoking contributing to insulin resistance,[179, 180] oxidative stress and beta cell dysfunction,[181-183] accumulation of greater abdominal fat compared to non-smokers, [180, 184] and weight gain in those who quit, cycle, or are heavy smokers.[180] Potential non-causal contributors to the association include the clustering of non-healthy behaviors such as low levels of physical activity and poor diets, especially in lower socioeconomic statuses.[178] However, the dietary intake and activity patterns in the SCHS were highly similar between ever and never smokers. It has also been shown that smoking has significant effects on oral and intravenous glucose tolerance tests thus influencing detection of diabetes.[185, 186] These potential causal and non-causal mechanisms may help explain why no inverse association was found in the VFS pattern in ever-smokers. Limited evidence along these lines examining oxidative stress and type 2 diabetes provides support for this hypothesis as dietary factors did not explain the long term effects of smoking on glucose homeostasis.[187] Additionally, a prospective study investigating serum carotenoid levels as a marker of a high plant food diet suggested that smoking annuls the potentially protective effect of high antioxidant consumption on diabetes risk, and antioxidant metabolism may behave different in smokers vs. nonsmokers.[188]

On the other hand and in consideration of the DSM dietary pattern and the evidence on this topic, hypothesizing a further increased risk in the DSM pattern in ever smokers would not seem to be out of line with current dietary and smoking evidence in relation to diabetes. Montonen et al.[124] has been the only other study to investigate this association and observed a greater increased risk in current smokers eating a poor diet compared to ex or never smokers. With limited evidence to draw on, one hypothesis to explain this null association could be that competing risks and thus other outcomes occurring before diabetes limit the ability to detect any association in those eating a diet conforming highest to the DSM pattern and smoking. The incident rate in ever smokers increases across the DSM dietary pattern in the first three quintiles and then drops off. Otherwise, our data may be evidence that smoking alters glucose/insulin metabolism. Indeed, we were not able to specifically assess any parameters to provide evidence for or against this and do not make any conclusions related to this topic beyond needing further research.

Only a handful of other studies have prospectively investigated the association between dietary patterns and type 2 diabetes risk. The SCHS is unique in the dietary and lifestyle habits, and ethnic composition of its population. The use of a food frequency questionnaire that was specifically developed and validated in the population and has been shown to be internally consistent and reproducible for dietary patterns is another strength. The prospective nature, high participant response rate, detailed collection of data through face to face interview, very low level of participants lost to follow up, and validated diabetes case status are other strengths to consider in interpreting the results.

Limitations to consider in the interpretation of our data include the subjective nature of principal components analysis- determining the number, labeling and interpreting the patterns specifically; however, we attempted to maintain objectivity in each of these steps. Inevitably diet was measured with some error, although this would most likely result in non-differential misclassification and likely under-estimation of risk. The self report of other lifestyle related data such as smoking, physical activity and BMI may also result in some misclassification and residual confounding in our models. Related, no data on family history of type 2 diabetes was collected. Additionally, even though type 2 diabetes case status was validated, blood samples in the whole cohort were not measured for blood glucose levels so cases of type 2 diabetes are likely underestimated.

In conclusion, after empirically deriving dietary patterns we found a pattern characterized by high vegetables, fruits and soy foods was inversely associated with risk of incident type 2 diabetes and a pattern characterized by high dim sum, meat and processed meat, sweetened foods and beverages and fried foods was associated with a significantly increased risk of type 2 diabetes in a large cohort of Chinese men and women in Singapore. These associations were limited to never smokers although smokers had higher incident rates of type 2 diabetes. Dietary patterns are unique to the populations they are derived from, yet consistencies across populations suggest that increased plant food intake such as vegetables, fruits, soy, whole grains and legumes are beneficial for diabetes risk, where as higher level of meat, processed meat, sweetened foods and beverages and fried foods increase diabetes risk. Further large studies on dietary patterns and the risk for type 2 diabetes homogeneous in different racial and ethnic groups and in different geographical areas are warranted and may provide further insight into, as well as confirming, diet-diabetes associations. Lastly, efforts to curb smoking in South and Southeast Asia, where diabetes rates have greatly increased,[44] may have wide ranging public health benefits especially when combined with an improved quality of diet.

Table 7.1: Baseline characteristics by type 2 diabetes status during follow-up: SCHS

Characteristic	Free of T2DM	Incident T2DM	
N	40,924	2,252	*P*
Sex (% female)	57.6	57.2	0.73
Age	55.2 (7.6)	56.1 (7.5)	<0.0001
BMI	22.9 (3.3)	24.8 (3.1)	<0.0001
[2]Moderate Activity min/wk	51 (0.9)	47 (4.0)	0.25
Strenuous Activity (% ever)	7.9	5.7	0.0002
Education (% secondary)	31.0	24.5	<0.0001
Smoking, Ever (%)	27.3	30.3	0.018
Hypertension (%)	18.6	35.9	<0.0001
Dietary Intakes			
Total energy (kcal/day)	1567 (520)	1558 (537)	0.43
Alcohol (drinks week)	1.0 (3.9)	0.9 (4.2)	0.24
Carbohydrate (% energy)	59.1 (7.2)	59.0 (7.4)	0.66
Fat (% energy)	25.2 (5.3)	25.1 (5.7)	0.70
Saturated fat (% energy)	8.9 (2.5)	8.9 (2.6)	0.79
Monounsaturated fat (% energy)	8.5 (2.0)	8.5 (2.1)	0.72
Polyunsaturated (% energy)	5.1 (1.9)	5.1 (1.9)	0.18
Omega-3 fatty acids (g/day)	0.9 (0.4)	0.9 (0.4)	0.48
Omega-6 fatty acids (g/day)	8.0 (4.2)	7.9 (4.3)	0.14
Protein (% energy)	15.2 (2.4)	15.3 (2.5)	0.004
Soy protein (% total protein)	9.8 (6.2)	9.8 (6.1)	0.53
Fiber (g/1000 kcal)	8.2 (2.6)	8.1 (2.5)	0.003
Starch (g/1000 kcal)	104.1 (23.4)	104.9 (23.4)	0.12
Starch/Fiber ratio (g)	14.4 (7.0)	14.7 (7.0)	0.03
Poly/Saturated fat ratio (g)	0.63 (0.32)	0.62 (0.32)	0.25
Mono/Saturated fat ratio (g)	0.99 (0.20)	0.98 (0.19)	0.24

[1]All values mean (standard deviation) except [2]Moderate activity mean (SE)
SCHS= The Singapore Chinese Health Study
T2DM= type 2 diabetes mellitus
P for difference by *t* test (continuous variables) or χ^2 (categorical variables).

Table 7.2: Factor loadings for foods with vegetable, fruit and soy rich dietary pattern in Singapore Chinese Health Study

Food Item	*Food type*	*Loading*		
Cauliflower	V	0.53		
Green beans/peas	V	0.52		
Yin choi, po choi	V	0.49		
Other tau kwa	S	0.47		
Carrots	V	0.47		
Other plain tofu	S	0.45		
Head cabbage, wong nga pak	V	0.44		
Tung goo	O, Pr	0.43		
Broccoli	V	0.43		
Tou gay, tai tau nga	V	0.42		
White potatoes	V, St	0.42		
Gum jum, dried fungus	O, Pr	0.41		
Choi sum	V	0.41		
Corn	V	0.39		
Fu kua, mo qua	V	0.39		
Tomatoes	V	0.39		
Kai lan	V	0.39		
Pak choy, siew pak choy	V	0.37		
Foojook vegetarian meats	S	0.36		
Other dark green leaves	V	0.35		
Head lettuce, Chinese lettuce	V	0.35		
Watercress	V	0.34		
Fish ball/cake	Fi	0.33		
Kai choi	V	0.33		
Other tau pok	S	0.31		
Celery	V	0.33		
Yong tau foo	S	0.31		
Cucumber	V	0.31		
Canned baked beans	L	0.30		
Ikan bilis	Pr, Fi	0.30		
Ung choi	V	0.29		
Onions	V	0.29		
Boiled/steamed fish	Fi	0.27		
Apples	F	0.26		
Pan/stir fried fish	Fi	0.26		
Pan/stir fried chicken	P	0.26		
Gee choi	V	0.26		
Other dried seafood	Fi, Pr	0.24		
Bananas	F	0.23		
Salted leafy vegetables	V, Pr	0.23		
Pears	F	0.23		
Chinese chives	V, O	0.22		
Fermented bean paste	O, Pr	0.21		
Papaya	F	0.20	Dietary variance explained	6.7%
Watermelon	F	0.20		

*Factor loads correspond to Pearson correlation coefficients between the food and the respective dietary pattern.
-Definitions of abbreviations: B-beverage; C-condiment; Da-dairy; DS- dim sum/snack dish;
F-fruit; Fi-fish/shellfish/seafood; L-legumes; M-meat; O-other; P-poultry; Pr- preserved; S-soy food; St-high starch item (e.g. noodle dish, rice dish); Sw-sweet; WG-whole grain

Table 7.3: Factor loadings for foods with dim-sum and meat rich dietary pattern in Singapore Chinese Health Study

Food Item	***Food type***	***Loading***	***Food Item***	***Food type***	***Loading***
Gravy noodle	**St, M**	**0.42**	**Salted roots**	**Pr, V**	**0.21**
Chicken rice	**St, P**	**0.41**	**Red/green bean soups**	**DS**	**0.21**
Siew mai	**DS, M**	**0.41**	**Ung choi**	**V**	**0.21**
Chicken, mutton curry	**M**	**0.39**	**Balachan**	**C**	**0.20**
Other steamed snack	**DS, M**	**0.38**	**Chee cheong fun**	**DS,M**	**0.20**
Roasted duck or goose	**P**	**0.37**	**Deep fried fish**	**Fi**	**0.20**
Other pig organs (intestine)	**M**	**0.37**	**Western Cakes**	**DS,Sw**	**0.20**
Otar otar	**DS**	**0.37**	**Deep fried shallots**	**C**	**0.20**
Preserved eggs	**O, Pr**	**0.36**	**Fresh Chilis**	**C**	**0.20**
Belly pork	**M**	**0.36**			
Steamed meat bao	**DS, M**	**0.36**			
Pork satay	**M**	**0.35**			
Roti prata	**St**	**0.35**			
Glutinous rice dumpling	**St, M**	**0.35**			
Other flavored rice	**St, M**	**0.35**			
Dry noodle dish	**St, M**	**0.35**			
Coconut rice	**St**	**0.35**			
Deep fried chicken	**P**	**0.34**			
Ngor hiang	**DS, M**	**0.33**			
Curry rice	**St**	**0.33**			
Other fried noodle	**St, M, Fi**	**0.32**			
Puffs, curry or bean	**DS, V**	**0.32**			
Chinese rojak	**DS, V**	**0.32**			
Deep-fried snacks	**DS**	**0.32**			
Popiah	**DS, M**	**0.32**			
Luncheon meat	**M**	**0.31**			
Chicken satay	**P**	**0.31**			
Lup chong	**M**	**0.30**			
Squid	**Fi**	**0.30**			
Coconut desserts	**DS, Sw**	**0.29**			
Soft drinks	**B, Sw**	**0.29**			
Fried rice	**St**	**0.28**			
Pork liver	**M**	**0.28**			
Canned sardine	**Fi**	**0.28**			
Salted fish	**Fi, Pr**	**0.28**			
Shrimp	**Fi**	**0.27**			
Eggs	**O**	**0.27**			
Salted leafy vegetables	**V, Pr**	**0.27**			
Sweet kuey	**DS, Sw**	**0.26**			
Coffee	**B**	**0.25**			
Sugar (added to coffee)	**Sw, C**	**0.24**			
Steamed sweet bao	**DS, Sw**	**0.23**			
French fries	**St, O**	**0.23**			
Other pork	**M**	**0.23**	**Dietary variance explained**	**6.5%**	
Other dried seafood	**Fi, Pr**	**0.22**			

*Factor loads correspond to Pearson correlation coefficients between the food and the respective dietary pattern.
-Definitions of abbreviations: B-beverage; C-condiment; Da-dairy; DS- dim sum/snack dish; F-fruit; Fi-fish/shellfish/seafood; L-legumes; M-meat; O-other; P-poultry; Pr-preserved; S-soy

Table 7.4: Participant characteristics by smoking status across quintiles of vegetable, fruit and soy rich dietary pattern score

	Ever Smoke n=11,850			Never Smoke n=31,326		
Characteristic	**Q1**	**Q3**	**Q5**	**Q1**	**Q3**	**Q5**
Age	56.2 (7.8)	57.1 (7.6)	57.3 (7.8)	54.3 (7.5)	54.6 (7.4)	54.6 (7.4)
BMI	22.6 (3.2)	22.8 (3.5)	22.7 (3.1)	23.1 (3.2)	23.2 (3.1)	23.1 (3.3)
[2]Moderate Activity min/wk	36 (2.7)	53 (3.1)	63 (3.4)	38 (2.1)	52 (2.0)	64 (1.9)
Strenuous Activity (% ever)	6.8	7.4	9.5	7.7	7.3	9.3
Education (% secondary)	29.5	26.8	29.1	35.0	31.3	31.9
Female (%)	12.4	16.3	16.2	67.3	75.2	75.6
Hypertension (%)	15.6	18.7	17.3	20.4	20.3	20.9
Dietary Intakes						
Total energy (kcal/day)	1530 (529)	1678 (513)	2084 (575)	1307 (460)	1456 (432)	1822 (503)
Carbohydrate (% energy)	61.2 (8.0)	59.5 (6.9)	55.1 (6.9)	61.8 (7.4)	59.7 (6.6)	55.6 (6.7)
Fat (% energy)	22.2 (5.9)	24.1 (5.1)	28.1 (5.1)	23.2 (5.7)	24.9 (5.0)	28.6 (4.8)
Saturated fat (% energy)	8.4 (2.7)	8.4 (2.7)	9.8 (2.6)	8.5 (2.6)	8.7 (2.4)	9.7 (2.5)
Monounsaturated fat (% energy)	7.6 (2.2)	8.2 (2.0)	9.5 (2.0)	7.9 (2.1)	8.4 (1.9)	9.5 (1.9)
Polyunsaturated (% energy)	4.0 (1.4)	4.7 (1.5)	5.7 (2.0)	4.4 (1.5)	5.2 (1.7)	6.2 (2.2)
Omega-3 fatty acids (g/day)	0.7 (0.3)	0.9 (0.3)	1.3 (0.5)	0.7 (0.3)	0.8 (0.3)	1.2 (0.5)
Omega-6 fatty acids (g/day)	6.0 (3.0)	7.7 (3.4)	11.8 (5.3)	5.7 (2.9)	7.4 (3.2)	11.2 (5.2)
Protein (% energy)	13.9 (2.5)	14.8 (2.2)	15.8 (2.4)	14.4 (2.4)	15.3 (2.2)	16.1 (2.4)
Soy protein (% total protein)	6.8 (4.9)	9.1 (5.3)	12.6 (7.4)	7.6 (5.4)	9.6 (5.4)	13.2 (7.4)
Fiber (g/1000 kcal)	6.2 (2.1)	7.3 (2.1)	8.5 (2.3)	7.4 (2.5)	8.5 (2.5)	9.8 (2.6)
Starch (g/1000 kcal)	112.9 (26.5)	108.4 (22.3)	94.1 (20.2)	112.1 (25.6)	105.3 (21.6)	91.2 (19.7)
Starch/Fiber ratio (g)	20.6 (9.7)	16.4 (6.8)	12.0 (4.8)	17.3 (8.4)	13.6 (5.6)	10.0 (4.0)
Poly/Saturated fat ratio (g)	0.51 (0.22)	0.59 (0.28)	0.65 (0.35)	0.56 (0.24)	0.64 (0.32)	0.70 (0.39)
Mono/Saturated fat ratio (g)	0.94 (0.19)	0.98 (0.20)	1.00 (0.20)	0.95 (0.19)	0.99 (0.20)	1.01 (0.21)

[1]All values mean (standard deviation) except [2]Moderate activity mean (standard error)

SCHS= The Singapore Chinese Health Study

Incidence rate (€ cases per 10,000 person years follow-up)

Table 7.5: Participant characteristics by smoking status across quintiles of dim sum and meat rich dietary pattern score

	Ever Smoke n=11,850			Never Smoke n=31,326		
Characteristic	**Q1**	**Q3**	**Q5**	**Q1**	**Q3**	**Q5**
Age	60.6 (7.3)	57.5 (7.6)	54.6 (7.3)	56.6 (7.8)	54.2 (7.3)	52.5 (6.7)
BMI	22.8 (3.2)	22.8 (3.1)	22.6 (3.1)	23.0 (3.2)	23.2 (3.3)	23.2 (3.3)
[2]Moderate Activity min/wk	68 (4.3)	47 (3.1)	47 (2.5)	62 (1.8)	50 (2.0)	45 (2.1)
Strenuous Activity (% ever)	6.9	6.4	8.8	6.7	7.2	11.1
Education (% secondary)	21.5	16.0	33.7	27.4	30.1	39.9
Female (%)	28.2	16.3	8.8	82.0	74.2	60.3
Hypertension (%)	21.4	17.6	14.3	22.4	19.5	18.2
Dietary Intakes						
Total energy (kcal/day)	1371 (427)	1507 (421)	2148 (564)	1283 (385)	1455 (402)	2019 (522)
Carbohydrate (% energy)	64.3 (6.8)	60.8 (6.9)	54.9 (6.8)	62.7 (6.7)	58.9 (6.4)	54.2 (6.2)
Fat (% energy)	21.5 (5.4)	23.0 (5.3)	27.4 (5.3)	23.1 (5.2)	25.5 (4.9)	29.3 (4.8)
Saturated fat (% energy)	7.3 (2.4)	8.2 (2.3)	10.2 (2.4)	7.8 (2.4)	8.9 (2.2)	10.7 (2.2)
Monounsaturated fat (% energy)	7.1 (2.0)	7.8 (1.9)	9.4 (1.9)	7.6 (2.1)	8.6 (1.9)	10.0 (1.8)
Polyunsaturated (% energy)	4.8 (2.0)	4.5 (1.7)	4.9 (1.5)	5.2 (2.1)	5.2 (1.8)	5.5 (1.6)
Omega-3 fatty acids (g/day)	0.8 (0.3)	0.8 (0.3)	1.1 (0.4)	0.8 (0.4)	0.9 (0.4)	1.2 (0.5)
Omega-6 fatty acids (g/day)	6.6 (4.0)	6.7 (3.5)	10.4 (4.5)	6.8 (2.9)	7.5 (3.7)	11.1 (5.2)
Protein (% energy)	13.9 (2.5)	14.6 (2.5)	15.3 (2.2)	14.6 (2.4)	15.4 (2.3)	16.1 (2.2)
Soy protein (% total protein)	10.1 (8.0)	8.9 (6.3)	8.8 (5.0)	10.4 (7.6)	9.9 (5.8)	10.0 (5.3)
Fiber (g/1000 kcal)	9.1 (2.9)	7.2 (2.2)	6.6 (1.8)	10.0 (3.0)	8.3 (2.5)	7.7 (1.9)
Starch (g/1000 kcal)	117.9 (24.8)	112.5 (23.1)	95.4 (20.5)	110.3 (24.7)	103.3 (21.5)	90.8 (18.6)
Starch/Fiber ratio (g)	15.1 (8.1)	17.9 (8.6)	15.8 (6.8)	12.6 (6.6)	14.0 (6.5)	12.9 (4.0)
Poly/Saturated fat ratio (g)	0.74 (0.43)	0.59 (0.27)	0.50 (0.19)	0.75 (0.42)	0.62 (0.29)	0.54 (0.21)
Mono/Saturated fat ratio (g)	1.01 (0.25)	0.97 (0.19)	0.94 (0.15)	1.02 (0.25)	0.99 (0.19)	0.95 (0.15)

[1]All values mean (standard deviation) except [2]Moderate activity mean (standard error)

SCHS= The Singapore Chinese Health Study

Table 7.6: Mean (SD) monthly frequency of dishes, foods and beverages by quintile of VFS dietary pattern stratified by smoking status

	Ever Smoke n=11,850			Never Smoke n=31,326		
Food/Dish	Q1	Q3	Q5	Q1	Q3	Q5
Rice dishes	63.8 (18.7)	66.7 (16.9)	68.9 (18.1)	57.5 (17.9)	61.5 (16.6)	63.6 (17.1)
Noodle dishes	11.8 (9.5)	12.3 (9.5)	15.1 (11.8)	11.1 (9.4)	10.9 (8.8)	12.9 (10.3)
Pork	12.3 (10.0)	16.4 (11.8)	22.1 (17.6)	9.9 (8.4)	14.4 (10.8)	19.8 (16.7)
Other meats (□)	5.5 (5.6)	7.4 (6.3)	10.2 (8.5)	5.8 (5.3)	7.4 (5.8)	10.6 (8.8)
Fresh fish/shellfish	16.6 (10.3)	24.7 (11.8)	34.7(18.5)	16.1 (9.6)	24.1 (11.0)	34.0 (17.4)
Eggs	5.5 (6.6)	6.1 (6.5)	7.9 (7.8)	4.5 (5.4)	5.3 (5.4)	6.9 (6.5)
Tofu/tofu dishes	6.9 (5.5)	12.7 (7.5)	25.1 (16.0)	6.7 (5.1)	12.3 (7.1)	24.4 (14.9)
Fresh vegetables	39.3 (17.4)	70.6 (18.4)	127.2 (41.6)	41.9 (16.0)	70.2 (17.2)	127.1 (40.1)
Preserved meats	1.6 (3.3)	1.7 (2.9)	2.9 (4.3)	1.6 (3.8)	1.6 (3.0)	2.5 (3.9)
Preserved/canned fish or seafood	4.4 (3.9)	6.8 (5.6)	11.8 (10.2)	3.9 (3.5)	6.0 (5.2)	10.6 (9.5)
Beans	0.3 (0.8)	0.7 (1.4)	1.4 (2.4)	0.3 (0.8)	0.6 (1.1)	1.4 (2.4)
Other preserved foods €	4.8 (5.2)	8.3 (7.0)	15.9 (12.1)	4.9 (5.3)	7.9 (6.3)	15.7 (11.3)
Condiments	43.0 (25.8)	58.6 (27.3)	71.6 (37.3)	40.1 (23.3)	54.4 (24.4)	66.5 (34.3)
Fresh fruits	27.1 (23.3)	34.3 (26.3)	49.9 (33.2)	25.3 (22.0)	38.0 (25.8)	55.7 (32.8)
Whole grain based items	3.3 (8.7)	3.8 (8.4)	6.3 (11.7)	4.8 (10.3)	6.8 (11.9)	9.2 (13.8)
Processed grain based items	13.6 (13.7)	17.3 (14.3)	21.9 (16.4)	14.2 (13.4)	17.9 (14.2)	22.2 (15.5)
Dairy	10.8 (16.2)	13.4 (17.8)	15.4 (19.4)	13.5 (17.6)	16.3 (19.2)	20.5 (21.1)
Spreads	10.9 (16.8)	15.2 (19.2)	21.3 (24.1)	13.2 (17.5)	19.4 (21.2)	24.1 (23.9)
Snacks and Dim Sum	12.4 (14.0)	12.5 (11.8)	18.0 (14.8)	12.2 (12.5)	12.0 (11.0)	16.9 (13.6)
Nuts	1.1 (3.1)	1.4 (3.6)	2.5 (5.5)	0.8 (2.5)	1.0 (2.9)	1.8 (4.0)
Western fast foods	0.7 (2.9)	0.4 (1.7)	0.5 (1.9)	1.0 (3.4)	0.5 (1.6)	0.5 (1.8)
Juices	1.3 (4.4)	1.3 (3.8)	2.3 (6.8)	1.5 (4.8)	1.3 (4.0)	2.2 (6.5)
Soft drinks	5.7 (15.6)	2.6 (8.8)	2.8 (9.9)	3.9 (11.6)	2.0 (6.8)	1.8 (6.2)
Coffee	54.8 (42.8)	54.1 (41.2)	54.3 (42.0)	39.8 (35.3)	37.8 (33.2)	37.8 (33.7)
Black tea	9.7 (21.7)	7.8 (18.1)	9.6 (19.9)	7.2 (17.1)	5.9 (14.2)	6.6 (15.3)
Green tea	8.3 (23.8)	11.3 (27.5)	14.9 (31.4)	6.5 (19.8)	7.9 (21.6)	11.0 (25.2)
Alcohol	11.7 (25.6)	9.2 (22.9)	10.3 (24.5)	2.9 (12.5)	2.3 (10.7)	3.0 (12.5)
Hawker/restaurant breakfast	16.7 (12.8)	13.3 (12.6)	12.7 (12.8)	12.2 (12.4)	8.9 (11.1)	8.1 (10.8)
Hawker/restaurant lunch	18.8 (11.2)	14.8 (11.9)	14.6 (12.5)	15.0 (11.7)	10.8 (11.5)	9.7 (11.5)
Hawker/restaurant dinner	7.7 (10.0)	3.4 (7.0)	2.9 (6.8)	6.2 (8.8)	2.6 (5.5)	2.3 (5.6)
Hawker/restaurant total	43.3 (24.9)	31.6 (22.8)	30.3 (23.6)	33.4 (24.3)	22.3 (20.5)	20.1 (20.1)

€ Preserved foods-eggs, fruit, vegetables, roots, fungus etc (□) Other meats (poultry, mutton, beef)

Table 7.7: Mean (SD) monthly frequency of dishes, foods and beverages by quintile of DSM dietary pattern stratified by smoking status

	Ever Smoke n=11,850			Never Smoke n=31,326		
Food/Dish	Q1	Q3	Q5	Q1	Q3	Q5
Rice dishes	61.2 (14.3)	63.7 (16.3)	72.1 (19.7)	58.0 (15.1)	60.2 (16.7)	67.3 (19.0)
Noodle dishes	6.4 (6.6)	10.8 (8.5)	18.0 (10.9)	6.3 (6.3)	11.6 (8.2)	18.5 (11.2)
Pork	9.7 (9.7)	13.8 (10.5)	22.3 (14.9)	10.4 (10.2)	14.9 (11.1)	22.3 (16.1)
Other meats (□)	3.5 (3.8)	5.6 (4.8)	11.2 (8.2)	4.6 (4.7)	7.5 (5.5)	13.3 (8.8)
Fresh fish/shellfish	21.6 (12.9)	22.7 (13.0)	28.0 (16.0)	21.9 (12.9)	24.8 (13.2)	30.0 (16.6)
Eggs	3.8 (4.9)	5.5 (6.1)	8.6 (8.2)	3.8 (4.4)	5.6 (5.4)	8.2 (7.3)
Tofu/tofu dishes	13.1 (12.5)	12.1 (10.2)	15.5 (11.7)	13.3 (12.2)	13.3 (9.7)	17.0 (12.0)
Fresh vegetables	77.6 (44.5)	67.9 (36.7)	78.7 (39.3)	80.2 (41.8)	74.2 (33.9)	86.0 (40.0)
Preserved meats	0.4 (1.1)	1.2 (2.1)	3.6 (4.9)	0.5 (1.4)	1.5 (2.6)	4.3 (5.5)
Preserved/canned fish or seafood	4.4 (4.8)	6.2 (5.9)	9.5 (8.2)	4.7 (5.1)	6.6 (6.2)	9.9 (8.4)
Beans	0.4 (1.3)	0.6 (1.3)	1.0 (1.8)	0.5 (1.3)	0.7 (1.4)	1.1 (1.9)
Other preserved foods €	7.3 (9.4)	7.3 (6.9)	11.6 (9.9)	7.8 (8.3)	8.5 (7.1)	13.3 (10.9)
Condiments	47.2 (26.0)	52.8 (27.1)	65.9 (35.4)	48.1 (25.2)	54.4 (27.2)	65.2 (33.3)
Fresh fruits	40.0 (31.9)	30.3 (25.6)	36.9 (28.5)	43.6 (31.6)	37.5 (27.1)	44.4 (29.6)
Whole grain based items	9.8 (15.2)	3.9 (9.0)	3.2 (7.8)	11.4 (16.0)	5.5 (10.2)	4.8 (9.3)
Processed grain based items	19.5 (16.3)	15.8 (14.3)	17.6 (14.9)	18.9 (15.2)	17.7 (14.5)	18.9 (14.7)
Dairy	16.8 (20.5)	11.1 (16.9)	12.5 (17.2)	19.9 (21.4)	15.2 (18.9)	17.3 (18.9)
Spreads	22.6 (25.3)	14.2 (19.4)	13.9 (18.7)	23.6 (23.5)	17.8 (20.5)	17.3 (20.4)
Snacks and Dim Sum	5.2 (6.0)	9.3 (8.0)	22.8 (16.5)	5.9 (6.0)	12.2 (8.5)	27.2 (16.1)
Nuts	0.8 (2.8)	1.0 (2.8)	2.4 (5.0)	0.7 (2.5)	1.1 (3.0)	2.1 (4.3)
Western fast foods	0.1 (0.5)	0.2 (1.2)	1.0 (3.2)	0.2 (1.0)	0.5 (1.6)	1.6 (3.9)
Juices	1.3 (4.8)	1.3 (4.4)	2.1 (5.8)	1.1 (4.7)	1.5 (5.1)	2.7 (6.1)
Soft drinks	0.4 (2.3)	1.8 (6.4)	7.5 (17.2)	0.4 (2.1)	1.8 (6.0)	6.6 (14.3)
Coffee	33.6 (31.4)	52.2 (38.1)	65.4 (44.7)	26.0 (26.1)	40.6 (33.4)	48.9 (39.1)
Black tea	5.8 (15.1)	7.5 (18.6)	12.2 (23.5)	3.9 (11.6)	6.1 (14.4)	9.8 (19.1)
Green tea	10.3 (25.8)	11.4 (26.8)	11.6 (27.6)	7.4 (21.0)	8.5 (22.4)	9.7 (23.3)
Alcohol	2.8 (11.8)	7.4 (18.6)	15.9 (29.9)	0.9 (6.0)	2.5 (11.0)	5.4 (16.5)
Hawker/restaurant breakfast	7.4 (11.3)	13.3 (12.7)	18.1 (12.3)	5.1 (9.2)	10.0 (11.4)	14.2 (12.2)
Hawker/restaurant lunch	10.1 (11.8)	15.3 (12.1)	19.7 (10.7)	7.0 (10.3)	11.8 (11.6)	16.2 (11.5)
Hawker/restaurant dinner	1.8 (5.4)	4.0 (7.7)	6.3 (9.3)	1.8 (5.0)	3.2 (6.3)	5.4 (8.2)
Hawker/restaurant total	19.4 (20.9)	32.7 (23.6)	44.1 (22.8)	14.0 (17.8)	25.1 (20.9)	35.7 (22.6)

€ Preserved foods-eggs, fruit, vegetables, roots, fungus etc (□) Other meats (poultry, mutton, beef)

Table 7.8: Relative risks of type 2 diabetes according to quintile of dietary pattern score by smoking status: Singapore Chinese Health Study

Vegetable, fruit and soy rich pattern: Ever smoke

	Q1	Q2	Q3	Q4	Q5	
Incident cases/PY	169/17,918	151/14,578	134/13,104	109/11,917	119/11,474	
Incidence rate €	94	104	102	92	104	
	(lowest)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	*P* for trend
Model I[1]	1.0	1.10 (0.89, 1.37)	1.09 (0.87, 1.37)	0.98 (0.77, 1.26)	1.13 (0.88, 1.45)	0.56
Model II[2]	1.0	1.11 (0.89, 1.39)	1.08 (0.86, 1.35)	0.97 (0.76, 1.25)	1.15 (0.89, 1.48)	0.51
Model III[3]	1.0	1.08 (0.87, 1.36)	1.05 (0.84, 1.33)	0.95 (0.74, 1.22)	1.14 (0.89, 1.47)	0.55

Vegetable, fruit and soy rich pattern: Never smoke

	Q1	Q2	Q3	Q4	Q5	
Incident cases/PY	321/31,177	301/35,847	321/36,510	299/37,244	328/37,129	
Incidence rate €	102	84	88	80	88	
	(lowest)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	*P* for trend
Model I[1]	1.0	0.80 (0.68, 0.94)	0.83 (0.71, 0.97)	0.75 (0.64, 0.89)	0.81 (0.69, 0.96)	0.03
Model II[2]	1.0	0.80 (0.69, 0.94)	0.83 (0.71, 0.98)	0.75 (0.64, 0.88)	0.81 (0.68, 0.95)	0.02
Model III[3]	1.0	0.79 (0.68, 0.93)	0.83 (0.71, 0.97)	0.75 (0.63, 0.88)	0.80 (0.68, 0.95)	0.02

Dim sum and meat rich pattern: Ever smoke

	Q1	Q2	Q3	Q4	Q5	
Incident cases/PY	72/7,230	110/10,759	154/13,846	162/16,581	184/20,575	
Incidence rate €	100	102	111	98	89	
	(lowest)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	*P* for trend
Model I[1]	1.0	1.02 (0.76, 1.37)	1.09 (0.82, 1.45)	0.94 (0.71, 1.25)	0.83 (0.61, 1.12)	0.12
Model II[2]	1.0	1.02 (0.76, 1.38)	1.10 (0.83, 1.46)	0.96 (0.72, 1.28)	0.87 (0.64, 1.18)	0.22
Model III[3]	1.0	1.06 (0.79, 1.42)	1.12 (0.84, 1.48)	0.99 (0.74, 1.32)	0.95 (0.70, 1.29)	0.50

Dim sum and meat rich pattern: Never smoke

	Q1	Q2	Q3	Q4	Q5	
Incident cases/PY	331/42,313	362/39,074	304/35,555	285/32,520	288/28,445	
Incidence rate €	78	93	86	88	101	
	(lowest)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	*P* for trend
Model I[1]	1.0	1.23 (1.06, 1.42)	1.17 (1.00, 1.37)	1.26 (1.06, 1.48)	1.55 (1.29, 1.86)	<0.0001
Model II[2]	1.0	1.21 (1.04, 1.40)	1.17 (1.00, 1.38)	1.27 (1.07, 1.49)	1.55 (1.29, 1.86)	<0.0001
Model III[3]	1.0	1.18 (1.02, 1.37)	1.14 (0.97, 1.33)	1.21 (1.02, 1.43)	1.46 (1.21, 1.75)	0.0002

Incidence rate € = Incident cases per 10,000 person years follow-up
All data presented as RR (95% CI) unless otherwise noted
[1]Adjusted for age, sex, dialect, year of interview, energy intake
[2]Adjusted further for hypertension, education, and physical activity
[3]Adjusted for aforementioned variables and BMI (continuous quadratic)

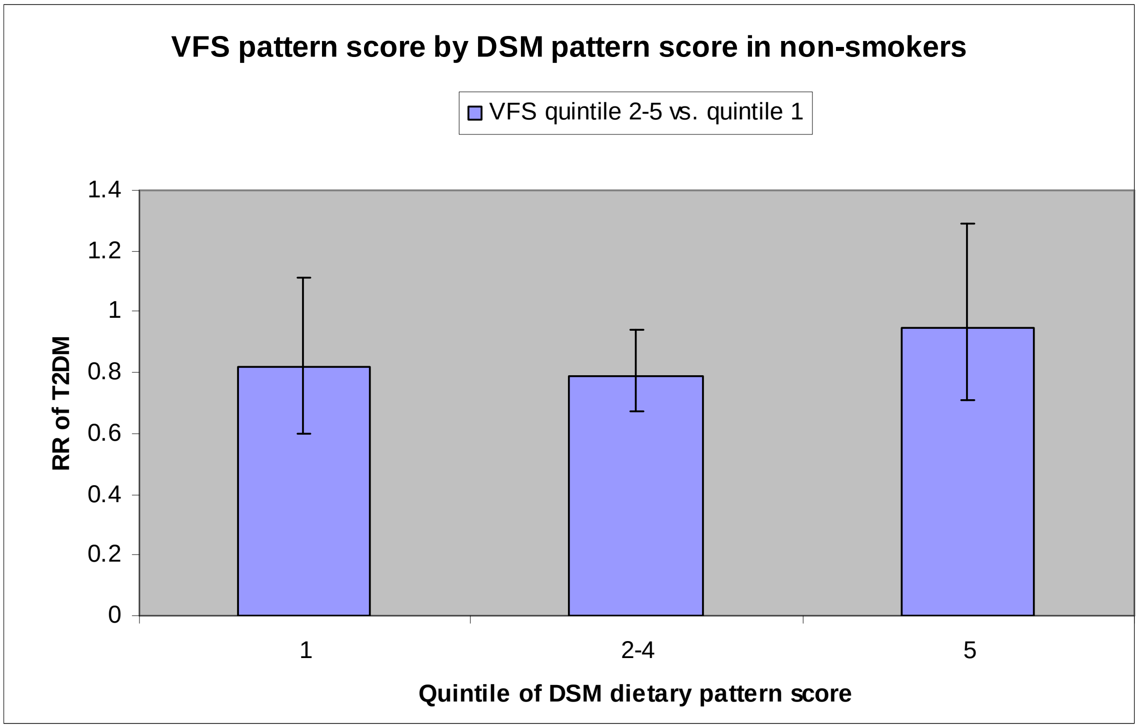

Figure 7.1: Relative risk (adjusted for age, sex, dialect, year of baseline interview, energy intake, hypertension, education, physical activity and body mass index) of type 2 diabetes in quintiles 2-5 of vegetable, fruit and soy rich dietary pattern score compared to the first quintile in non-smokers according to quintiles 1 (n=7,388), 2-4 (n=18,852) and 5 (n=5,086) of Dim Sum and meat rich pattern in the Singapore Chinese Health Study.

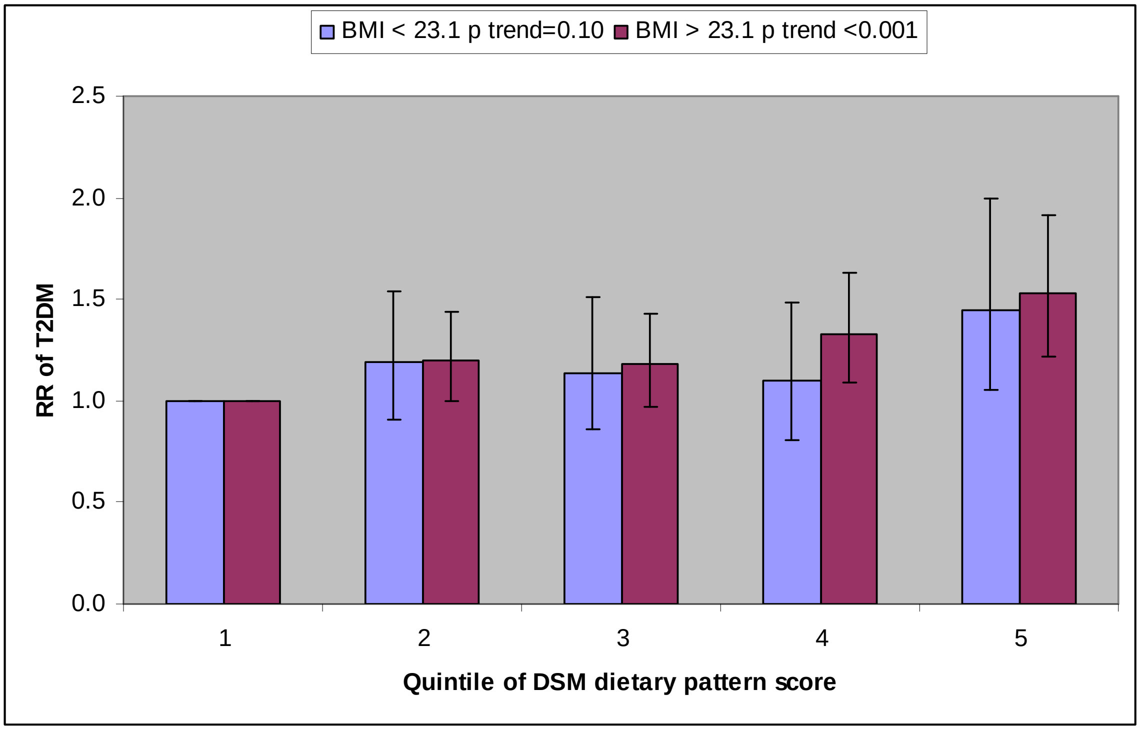

Figure 7.2: Relative risks (adjusted for age, sex, dialect, year of baseline interview, energy intake, hypertension, education, and physical activity) of type 2 diabetes according to quintile of Dim Sum and meat rich dietary pattern score stratified by the median BMI (=23.1kg/m^2) in never-smokers in the Singapore Chinese Health Study. P value for interaction between dietary pattern score and BMI=0.12.

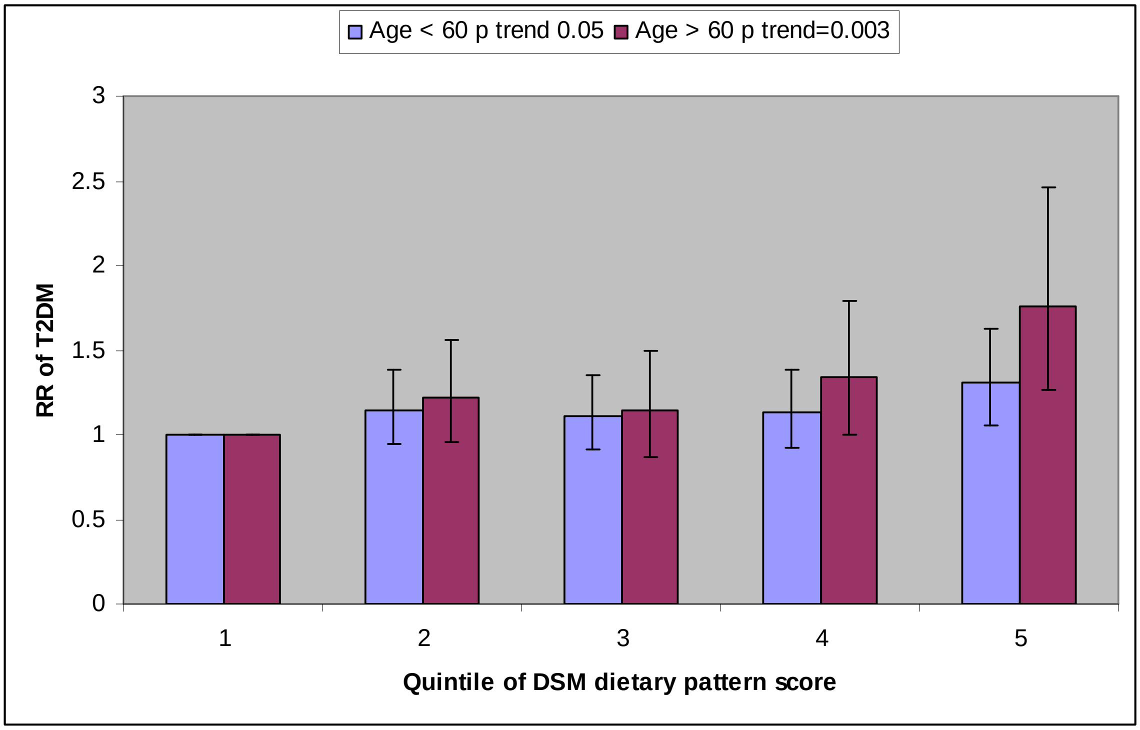

Figure 7.3: Relative risks (adjusted for sex, dialect, year of baseline interview, energy intake, hypertension, education, physical activity and body mass index) of type 2 diabetes in non-smokers according to quintile of Dim Sum and meat rich dietary pattern score stratified by baseline age (<60 n=23,334; ≥60 n=7,992) in the Singapore Chinese Health Study. P value for interaction between DSM dietary pattern score and age=0.76.

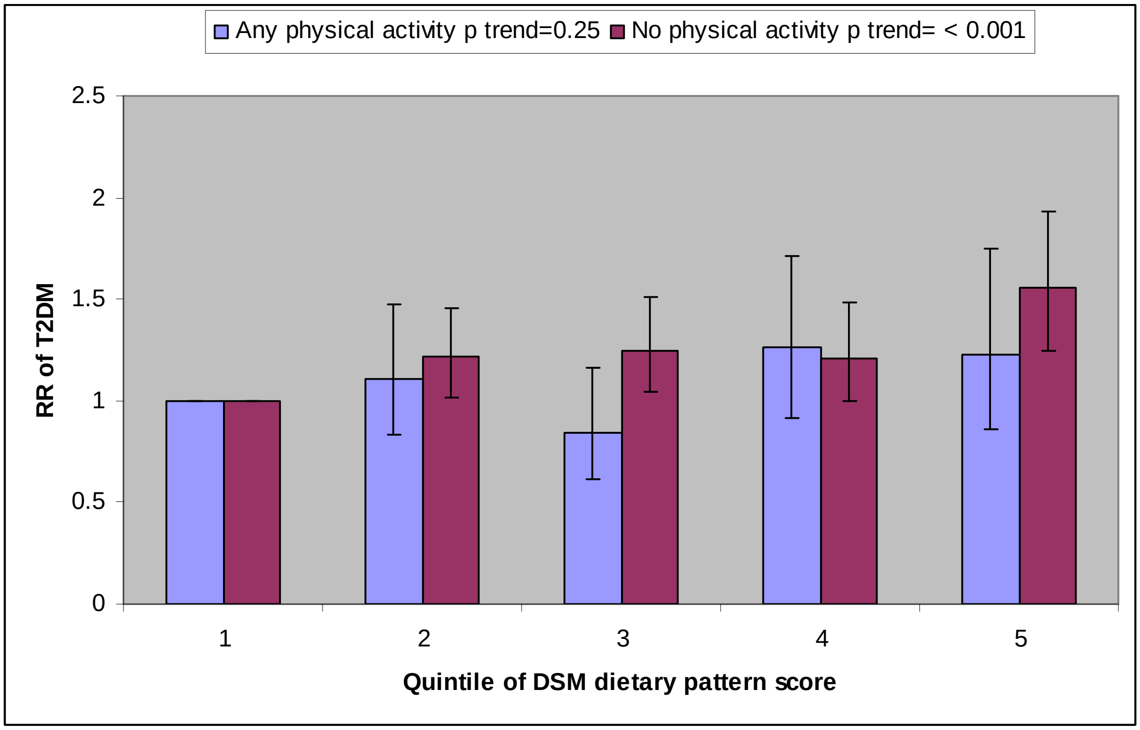

Figure 7.4: Relative risks (adjusted for age, sex, dialect, year of baseline interview, energy intake, hypertension, education, and body mass index) of type 2 diabetes in non-smokers according to quintile of Dim Sum and meat rich dietary pattern score stratified by physical activity (Any n= 8,888 and None n=22,418) in the Singapore Chinese Health Study. P value for interaction between DSM dietary pattern score and any physical activity=0.12.

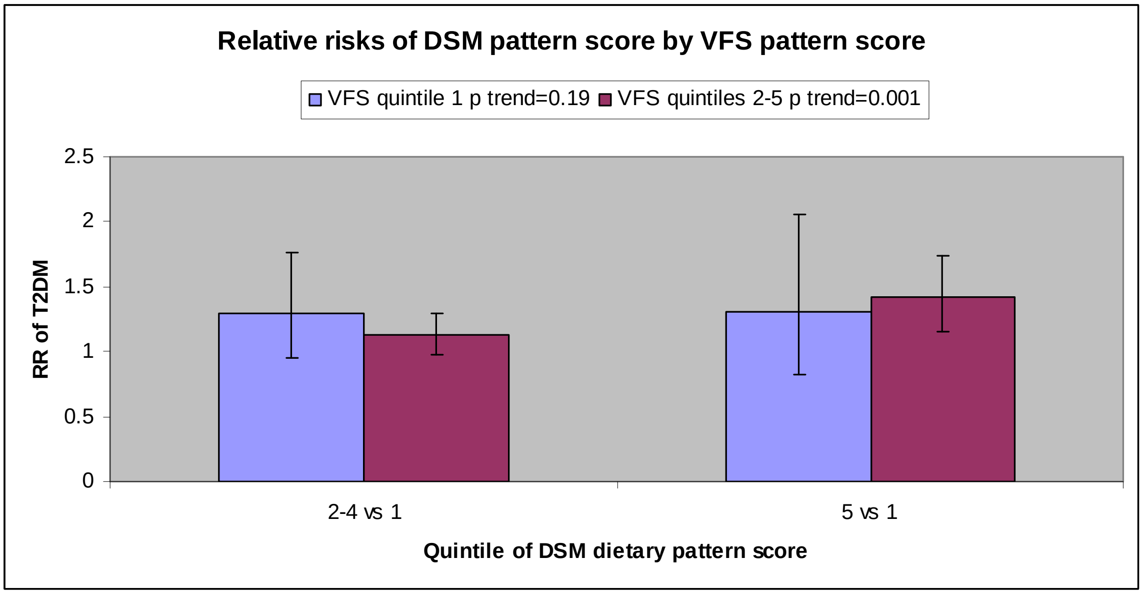

Figure 7.5: Relative risks (adjusted for age, sex, dialect, year of baseline interview, energy intake, hypertension, education, physical activity and body mass index) of type 2 diabetes in quintiles 1 (n=7,388), 2-4 (n=18,852), and 5 (n=5,086) of the Dim Sum and meat rich dietary pattern score in non-smokers stratified by quintile 1 (n=5,561) and 2-5 (n=25,765) of Vegetable, fruit and soy rich dietary pattern score in the Singapore Chinese Health Study.

Chapter 8: BMI and all-cause mortality: The Singapore Chinese Health Study

Introduction

The prevalence of obesity continues to increase in developed and developing Asian nations and the levels of chronic disease have mirrored this trend.[44] Concomitant with the global obesity trends is the heightened attention paid to the relation between body weight and mortality. Many studies on this topic, mostly on western populations, have produced somewhat divergent results. Some studies suggest that BMI acts in a near dose-response fashion with mortality, some indicate a U-shaped or J-shaped curve, and finally some suggest BMI may have little or no impact on longevity.[131] Although, a recent collaborative analysis of over 900,000 adults in prospective cohorts, most from western Europe and North America, found the optimum BMI range to be approximately 22.5-25.0 kg/m^2, with progressive excess all-cause mortality in BMI ranges above and below the optimum range.[189] Similar associations have been observed in the few prospective Asian studies on the topic.[145-150]

Indeed, there are multiple methodological issues and considerations in the study of body weight and mortality. The great majority of studies have used body mass index (BMI, kg/m^2), which is a reasonable and easily applicable surrogate measure of adiposity in a large population.[95, 190] However, use of BMI as a marker of adiposity still receives criticism.[191] The main methodological issues focus on accounting for cigarette smoking,[132, 192] reverse causation due to prevalent and antecedent disease,[132, 193, 194] control of intermediate variables in the causal pathway in statistical modeling,[95, 132] and how age may modify the association in addition to the use of elderly participants where

BMI is a less reliable marker of adiposity due to differential loss of muscle and lean body mass.[132]

The investigation of BMI and mortality in Asians presents an intriguing study as they have a larger proportion of the population with low BMI's, and research on Asian populations is comparatively sparse. Furthermore, most Asians appear to be anthropometrically different than other ethnic groups. Asians have generally low BMI's, but high body fat percentages comparable to World Health Organization (WHO) BMI strata for overweight or obesity in Europid based populations.[56, 57] Certainly, the discussion of an optimal weight range in Asian populations is separate from the debate in Western populations.

The Singapore Chinese Health Study (SCHS) is a population-based prospective cohort investigation of over 63,000 Chinese men and women in Singapore. The SCHS provides a unique Asian population relative to other studies on this specific topic. Participants are all afforded a high level of health care, live in a densely populated, affluent country with western influences, have very low levels of physical activity and many have adapted a diet with western influences. Therefore, the aim of this paper was to examine the association between BMI and all-cause mortality in a large prospective cohort study of Chinese men and women living in Singapore.

Subjects and Methods

Study Population

The design of the Singapore Chinese Health Study has been previously described.[154] Briefly, the cohort was drawn from men and women, aged 45 to 74, who belonged to one of the major dialect groups (Hokkien or Cantonese) of Chinese in

Singapore. Between April 1993 and December 1998, 63,257 individuals completed an in-person interview that included questions on demographics, educational attainment, height, weight, use of tobacco and alcohol, usual physical activity, menstrual and reproductive history (women only), medical history, family history of cancer and a 165-item food frequency section assessing usual dietary intake of the previous year. The institutional review boards at the National University of Singapore and the University of Minnesota approved this study.

Exposure Assessment

Self reported height and weight were collected at the baseline interview. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m). Age was defined as age in years at the time of the baseline examination. Education was categorized into no formal education, primary school, and secondary school or above. Cigarette smoking was classified into never smoker, former smoker, and current smoker based on the participant's choice of 3 possible responses to the question, "Have you ever smoked at least 1 cigarette a day for 1 year or longer?" Subjects who answered "no" were classified as nonsmokers; those who answered "yes, but I quit smoking were classified as ex-smokers; and those who answered "yes, and I currently smoke" were classified as current smokers. Current and former smokers were grouped together for this analysis. Participants reporting a history of physician diagnosed cardiovascular disease, diabetes, or respiratory disease before the baseline interview were considered to have a history of prevalent disease. Physical activity was assessed by the average time in a week using eight continuous categories ranging from never to 31 hours or more they spent doing strenuous sports (e.g. jogging, bicycling on hills, tennis, squash, swimming laps or aerobics); vigorous work (e.g. moving heavy furniture, loading or unloading trucks, shoveling or equivalent manual labor); and moderate activities (e.g. brisk walking, bowling, bicycling on level ground, tai chi and chi kung). The physical activity questionnaire was modeled after and had similar questions as the questionnaire used in the EPIC Study of lifestyle and cancer, which has been shown to have good validity and high repeatability, with a weighted kappa statistic of 0.6 ($p < 0.0001$) and r = 0.73.[159, 160]

A semi-quantitative food frequency questionnaire specifically developed for this population assessing 165 commonly consumed food items was administered during the baseline interview. During the interview the respondent referred to accompanying photographs to select from eight food frequency categories (ranging from ‘‘never or hardly ever’’ to ‘‘two or more times a day’’) and three portion sizes. The food frequency questionnaire has subsequently been validated against a series of 24-hour dietary recall interviews in a random sample of 1000+ participants that occurred on one weekday and one weekend day approximately two months apart,[154] as well as selected biomarker studies.[155, 156] A range of 0.24 to 0.79 in correlation coefficients of energy/nutrients was obtained using two methods, and the majority of macro-nutrients and food groups display correlation coefficients in the high end of this reported range.[154] Dietary patterns were derived for this study population including consumption of alcoholic beverages using principal component analysis, (PCA) SAS version 9.1 (SAS Institute Inc, Cary, NC) and methods were reported in detail in the prior chapters. Frequency of alcohol intake as the summation of beer, rice wine, other wine and hard liquor was considered as an individual variable and grouped as nondrinker/monthly drinker, weekly drinker, daily drinker.

Assessment of Mortality

Information on date and cause of death is obtained through linkage with the Singapore government's Vital Statistics Office. This is done through sharing of the participants NRIC number (national registration identity card number) with the study. The exact date of death as well as primary cause, secondary cause and underlying causes are noted for each death. ICD-9 codes specifying cause(s) are decided by the coder at the Ministry of Home Affairs and come from the person's death certificate. Up to six causes may be given. For the current analysis mortality has been updated through December 31, 2007. Only 17 (0.03%) subjects from the initial cohort had migrated out of Singapore suggesting that emigration among the study participants is negligible and that vital statistics follow up was virtually complete.

Statistical Analysis

Of the original 63,257 participants we excluded 1,936 subjects with a history of invasive cancer (except non-melanoma skin cancer) or superficial, papillary bladder cancer at baseline, and 10,070 participants missing either or both height and weight measures. The present analyses included 51,251 participants.

Study participants were grouped according to 8 categories of BMI, as reported at the baseline interview (< 18.5, 18.5-19.9, 20.0-21.4, 21.5-22.9, 23.0-24.4, 24.5-25.9, 26.0-27.4, ≥ 27.5). These categories were created to allow a detailed examination of the association between BMI and all-cause mortality across the spectrum of BMI, as well as accounting for WHO cut point criteria for under, normal, over and obese weight statuses using BMI in this population without assumptions of the nature of the association. Additionally, the low end of BMI (< 18.5) was further divided in sensitivity analyses (<

17.0, 17.0-18.4). Alternatively, deciles of BMI were used in an attempt to perform a data-driven analysis relying on the distribution of BMI in the cohort. For each study subject, person-years were counted from the date of baseline interview to the date of death, date of last contact (for the few subjects who migrated out of Singapore) or 31 December 2007, whichever occurred first. Baseline characteristics were calculated for participants across each category of BMI. Tests for trend across categories were performed by assigning the median value of BMI to the respective categories and entering this as a continuous variable into the models. Age-standardized mortality rates were calculated using the age distribution of the cohort and the specific mortality rates of the following age categories (<50, 50-54, 55-59, 60-64, 65+) of the cohort.

Proportional hazards (Cox) regression methods were used to examine the associations between BMI and death. All regression analyses were conducted using SAS statistical software version 9.1 (SAS institute, Cary, NC). We estimated the hazard ratio (HR) for levels of the BMI and the corresponding 95% confidence interval (CI). There was no evidence that proportional hazards assumptions were violated as indicated by the lack of significant interaction between BMI and a function of survival time in the models. The referent BMI category was 18.5-19.9 because this group had the lowest age standardized mortality rate. Our primary Cox regression model included the following covariates: Age and its quadratic term (age^2), sex, year of interview (1993-95 and 1996-98), dialect (Hokkien vs. Cantonese), education (none, primary, secondary+), moderate activity (none, ½ hr-3 hrs/wk, 4+ hrs/wk) and strenuous activity (yes vs. no), and quintile of vegetable, fruit and soy rich dietary pattern score. The presence of a linear or quadratic (U-shaped) association was tested using the median BMI in each category as a continuous variable in the regression models. Analyses testing for multiplicative interactions of smoking, prevalent disease, age and sex with BMI were completed. Main and stratified models that excluded deaths occurring within 5 years of the baseline interview date were created as an attempt to account for reverse causation and the potential bias that may occur due to preexisting disease or illness-related weight loss. Including alcohol intake as a covariate was a non-significant contributor to the model and this did not change when including it with and without the dietary pattern score, so only the dietary pattern score was included since this encompassed usual alcohol intake.

We further examined the relationship between BMI and all-cause mortality by looking at the shape of the association with a non-parametric (local polynomial) regression analysis using the statistical package ‘R’ version 2.4.1. The purpose of such analysis is to produce a trend graph taking advantage of the large sample size and as an exploratory procedure to confirm the initial analysis using Cox regression methods. The log odds of mortality are modeled with a generalized additive model (GAM) specifying BMI as a loess fit and adjusting for the same possible confounders as in the above Cox regression model including adjustment for person-years time. In contrast to the Cox models, there is no reference group, as the parameters are estimated using local fitting while controlling for the degree of smoothing and polynomial fit. The degree of smoothing was set at a modest parameter (0.5 of 1.0, where 1.0 is the highest level of smoothing) and the polynomial degree was set to a curvilinear fit for each model.

Results

Baseline characteristics of the study participants according to eight categories of BMI by smoking status are presented in **Table 8.1.** There was evidence (P interaction between ever smoking and BMI=0.0012) that the relation between BMI and mortality in smokers and non-smokers differed so results are presented according to this finding. Males smoked at significantly higher levels than females in the study population. In non-smokers the level of education decreased with increasing BMI's greater than 23.0. Self-reported physician diagnosed hypertension and prevalent disease status increased across the spectrum of BMI. Mean physical activity levels displayed an inverted U-shape across increasing BMI with lower levels on the ends of the spectrum and higher levels in the middle. Age displayed a U-shaped association with BMI and was lowest in the BMI range of 18.5-23 and was greatest in BMI's greater than 23 and at BMI < 18.5.

Conversely, ever-smokers displayed a strong inverse relationship between age and BMI as baseline age declined with increasing BMI. Education and physical activity both displayed inverted U or J-shaped trends across the spectrum of BMI. Higher alcohol consumption was more prevalent in ever-smokers with low BMI as well, and hypertension and prevalent disease displayed a similar association to non-smokers with step wise increases across increasing BMI. Participants excluded due to missing BMI (N=10,070) were not materially different across the noted demographic and lifestyle characteristics according to smoking status compared to participants with full data and included in the analysis (51,251).

In 35,766 non-smokers (4,590 with prevalent disease), during a mean follow up of 11.8 years there were 3,740 deaths. Upon exclusion of the 4,590 participants with a history of disease the average follow up time slightly increased to 11.9 years. In 15,485 ever-smokers, during a mean follow up of 11.0 years there were 3,839 deaths. There was a statistically significant "backwards" J-shape between BMI and all-cause mortality in ever smokers with the lowest age standardized mortality among those with BMI's 23-24.4 as presented in **Table 8.2**. Compared to this referent group, ever-smokers with a BMI ≥ 27.5 had an increased hazard ratio (HR) for death (HR=1.19; 95% CI=1.03-1.36). On the other end of the BMI spectrum participants with a BMI < 20 had an increasing hazard ratio for death with each lower BMI group and participants with a BMI of 20.0-21.4 had a suggestive increased hazard ratio for death (HR=1.11; 95% CI 0.99-1.25).

In non-smokers there was a significant U-shaped quadratic association between BMI and all-cause mortality with inclusion and exclusion of prevalent disease and with exclusion of deaths occurring within 5 years of the baseline interview (P<0.001) (Table 2). In addition to the physiological rationale for the exclusion of persons with prevalent disease there was suggestive statistical evidence that the association between BMI and mortality differs in those with a history of disease (P interaction between BMI and prevalent disease =0.09). Compared to the referent BMI group (18.5-19.9), disease free, non-smokers with a BMI < 18.5 had an increased hazard ratio for death (HR=1.32; 95% CI=1.09-1.59). Risk also began to increase in the BMI group 26.0-27.4 (HR=1.21; 95% CI=1.01-1.46) and further increased at BMI's ≥ 27.5. After excluding deaths that occurred within 5 years of the baseline interview risk increased in both the low end of the BMI spectrum (BMI < 18.5, HR=1.41; 95% CI=1.12-1.76) and the high end (BMI ≥ 27.5, HR=1.49; 95% CI=1.22-1.83). Excluding extreme BMI's (< 15.5 and > 35.0) did not alter the results.

In an alternative analysis of the non-smoking disease free participants, BMI was grouped as deciles and a similar trend of association was observed between BMI and all-cause mortality (**Figure 8.1)** and upon exclusion of deaths occurring within 5 years of baseline **(Figure 8.2)**. However, the hazard ratio of death in the lowest decile of BMI (< 19.1) was a suggestive but non-significant association. In a sensitivity analysis using the BMI groups from the main analysis and creating lower BMI groups (BMI < 17 and 17-18.4) there was evidence that a BMI < 17.0 was strongly associated with an increased hazard ratio for death compared to the referent group (18.5-20) as presented in **Figure 8.3.** The association for participants in the BMI range of 17.0-18.4 displayed a suggestive increased hazard ratio for death (HR=1.19; 95% CI=0.96-1.48). Upon exclusion of deaths occurring within 5 years of the baseline interview both point estimates were strengthened (**Figure 8.4).** In a further sensitivity analysis that divided the upper BMI group into 27.5-28.9 and 29+ we observed no material difference between the groups with hazard ratios comparative to the initial HR estimate (HR=1.30; 95% CI=1.10-1.54) in the main model. In an analysis testing for an interaction between BMI and sex in non-smokers there was no evidence of any difference (P interaction = 0.39). The association was similar upon stratification as well (Data not presented).

Figure 8.5 presents age stratified mortality rates by BMI category. The overall mortality rate increased with each increasing age group while maintaining a similar shape across age groups. A test for interaction between age and BMI provided statistical evidence (P=0.006) that the association between BMI and all-cause mortality may differ by age at which BMI was reported. **Figure 8.6** presents hazard ratios stratified by age 65. Although there was a significant age-BMI interaction the shape of the association held across the age stratified groups. However, the HR in the BMI groups < 18.5 was more pronounced in those aged 65 and above. Upon exclusion of deaths occurring within 5 years the HR for those < 65 years at baseline was attenuated in the low BMI groups (BMI < 17.0, HR=1.34; 95% CI=0.90-1.99, BMI=17.0-18.4 HR= 1.05; 95% CI=0.78-1.40), whereas the HR for these low BMI groups in those 65+ maintained the magnitude and statistical significance of association (**Figure 8.7)**.

A further examination of the shape of the association between BMI and all-cause mortality is shown in the non-parametric graphs (**Figures 8.8-11)**. These results provide visual evidence for the nature and shape of the association using different modeling assumptions. In smokers (Figure 8.8) the graph suggests that the nadir of the BMI-mortality curve is shifted to the right in the BMI spectrum and the association flattens out as BMI increases; and the association between BMI and mortality increases throughout the lower end of the spectrum of BMI. Figures 8.9-11 are of the same stepwise analysis of non-smoking participants found in Table 8.2. These figures all suggest a similar nadir of the BMI-mortality curve occurring around 18.5-20 with the association being generally flat through the middle ranges of BMI and the curve starting to climb slowly as BMI approaches the higher end of overweight status, BMI ~ 26.0 and also climbing at BMI's ~ < 18.5.

Discussion

In this large study of relative weight and all-cause mortality in Chinese Singaporeans we observed a backwards J-shape association between BMI and mortality in participants with a history of smoking. In never-smokers we observed a U shaped association between BMI and mortality with inclusion and exclusion of prevalent disease and further exclusion of deaths earlier in follow up. The strength of the association was strengthened in those who were underweight as well as overweight and obese when excluding the early deaths. Evidence from sensitivity analyses investigating the extreme low end of BMI suggests that participants with BMI < 17.0 drive the increased risk in participants with a BMI in the WHO underweight category (< 18.5). Stratified analysis by age 65 found a similar U-shaped association in the older age group, but with a stronger association in those considered underweight compared to younger ages, even with significantly higher overall mortality rates. Furthermore, excluding early deaths in the age stratified analysis suggested that the increased risk observed in those considered underweight is largely driven by participants who were aged 65 and above at baseline in the study. Our results showing an increased HR at BMI > 26 in ages 65+ suggests that being considerably overweight in this age range is still detrimental. Analyses utilizing non-parametric trend graphs and approaching the question with different statistical assumptions were confirmatory of the shape of the association in smokers and non-smokers. There was only a small degree of variation in the graphs of non-smokers when different exclusions were applied.

Overall, when considering healthy, non-smoking Chinese Singaporean men and women, and excluding early deaths to account for possible reverse causation, BMI's from the normal range through the middle range of overweight status are not associated with risk of premature all-cause mortality.

The question of BMI and mortality has received significant attention in Western and European populations[189], but comparatively less research has addressed the topic in Asian populations. Recently the Shanghai Women Health study evaluated the relationship between BMI and mortality and potential methodological biases.[150] This study began with 74,896 women with BMI, waist and hips measured at baseline (1996-2000) from age 40-70 and followed up through April 2007. Participants were also asked to recall weights from age 20 and age 50 if over age 50 at baseline. From the original study population, 62,779 participants were never smokers without a history of previous disease, did not die during the first 3 years of follow up, and reported not having lost 10% of their body weight since age 50, thus making this the relevant population for study. The mean age of the cohort was 52 years and mean baseline BMI was 24.0 with mean follow up of 7.4 years. In an age adjusted cubic spline Cox regression analysis of the 62,779 participants using the median BMI as a referent point, a dose-response type of association of increased risk above BMI of ~ 25.0 was observed. Fully adjusted models were not presented. The rest of the presented analysis focused on small sub-groups of quartiles of BMI using the lowest quartile as the referent group and showing increased risk at each increasing quartile beginning at a BMI > 24.4. Appropriate adjustments were made in these models but the overall interpretation of this study and its role in the literature is not clear because of decisions to not present the full set of data, as well as not present any data on waist circumference which may add to understanding the data. Furthermore, results from the SCHS are not directly comparable due to participants from the Shanghai study being grouped into fewer but wider BMI groups.

Gu et al. [145] examined the question of body mass index and all cause mortality in a nationally representative sample of 154,736 Chinese men and women aged 40 years or older in 1991. At a single baseline visit, height and weight were measured using a standardized protocol. Other demographic and lifestyle variables were also assessed.

Work-related physical activity was assessed because leisure time physical activity was rare. Follow up was conducted in 1999-2000. BMI was divided into the following categories (<18.5, 18.5-19.9, 20-20.9, 21-21.9, 22-22.9, 23-23.9, 24-24.9, 25-26.9, 27-29.9, ≥ 30). Cox proportional hazards regression models were used for analysis. Adjustments for baseline age, sex, cigarette smoking, alcohol, work related physical activity, education, geography, urbanization were done. The referent group was BMI=24.0-24.9 because this group had the lowest mortality. In mean 8.3 years of follow up 17,687 deaths were documented. A statistically significant U-shaped association was observed in all analyses and sub-group and sensitivity analyses between BMI and all-cause mortality. This included checks by age, sex and disease status. A sensitivity analysis that excluded deaths within the first 3 years of follow up observed a similar pattern of relative risks. A similar pattern was observed in a cause specific analysis in both cardiovascular disease and cancer and was also consistent among men and women.

The data show the range of BMI where it is not associated with increased risk of mortality was 24-26.9 overall. Essentially, being underweight, normal weight, and obese by BMI measures is associated with an increased risk of death in this study since the only non-increased risk is in the overweight range in the study. The authors concluded that their data do not support different or lower BMI cut points for obesity in this population. They note the increased risk of BMI's > 27 and BMI's < 18.5 but do not address the significant increase in risk of early all cause mortality in the BMI range of 18.5-24 in the overall cohort as well as "healthy" participants, which are not clearly defined. The results between the SCHS and this study are similar in findings of overall general shape; however our data suggest a wider BMI range of non-increased risk that includes what is considered a healthy or normal BMI. A question remains whether the associations observed in the low end and in normal weight individuals are an artifact of the high level of smoking in the leaner individuals of this population, or likewise, residual confounding by not stratifying or excluding these participants.

Jee et al. [146] examined the question of body mass index and mortality in 1,213,829 Korean men and women between 30 and 95 years of age who had undergone a biennial medical exam between 1992 and 1995 for the national health insurance corporation. All persons were free of atherosclerotic disease, cancer, liver disease, diabetes or respiratory illness before the initial study visit, and participants missing any relevant information or a BMI < 16.0 kg/m^2 were also excluded. An attempt to minimize the effect of underlying conditions was also done by excluding those with an event within the first two years of follow up. Height and weight were directly measured and data was collected on other lifestyle and demographic factors. Participants were followed up for death through December 31, 2004. BMI was categorized as < 18.5, 18.5-19.9, 20.0-21.4, 21.5-22.9, 23.0-24.9, 25.0-26.4, 26.5-27.9, 28.0-29.9, 30.0-31.9 and >32.0. Model covariates included age at enrollment (continuous), alcohol intake (g/day), participation in regular physical activity (y/n), and smoking status. The mean BMI of the study population was 23.2 for both sexes and mean age was 45 for men and 49 for women. A total of 82,372 deaths were recorded. The referent category was 23.0-24.9 as this had the lowest risk of death from any cause. A J-shaped association was observed for all cause mortality regardless of smoking status. Specifically, men with a BMI <18.5 who did not smoke had an elevated risk of death (HR=1.29, 95% CI 1.15-1.44) and those with a BMI >30 had an elevated risk of death also (HR=1.71, 95% CI 1.44-2.03). Similar, but not as strong associations were observed in smokers and in women. No association was found in BMI levels between 18.5 and 30 for all cause mortality. For participants greater than 64 years of age at baseline there was no association between BMI and mortality. Related to this, it is important to keep in mind when interpreting the data that this study included persons aged 30-95, a wider age range than any other study with BMI having divergent meanings and reflecting different aspects throughout this age range. Otherwise, this study was executed with appropriate methods and the cause-specific results further add to the literature, but are beyond the scope of this discussion and study.

Song et al. [147] also investigated the relationship between BMI and all cause mortality in women in the same Korean cohort utilizing a national insurance corporation similar to Jee et al.[146] The study comprised 338,320 women aged 40-64 who had all relevant measures and were free of cancer at baseline and did not die during the baseline examination period (1993-94). In the appropriate adjustment model for all-cause mortality that also excluded early deaths, a U-shaped association was observed with increased risk of mortality in BMI < 21 and BMI ≥ 27.0 compared to the referent group of BMI=21-22. They also stated the association did not differ when excluding smokers. We observed similar results in the non-smoking, disease free participants with a slight shift downward in the nadir of the curve and points of increased risk.

Tsugane et al. [148] examined the association of relative body weight and mortality in a Japanese population of 40,815 men and women aged 40-59 years who self reported height and weight and were free of cancer, cerebrovascular disease, history of myocardial infarction, or chronic liver disease at baseline as well as having a BMI between 14.0 and 40.0. Cox proportional hazards was used to analyze the data and sex stratified models adjusting for age (continuous), smoking status, alcohol consumption, education, sports and physical exercise, geographic area of Japan and weight change since 20 years old. BMI was divided into the following categories: 14.0-18.9, 19.0-20.9, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-29.9, ≥ 30.0. The BMI range of 23.0-24.9 (middle BMI category) was chosen as the referent category; however the rationale for the decision was not reported. A U-shaped association was observed for all-cause mortality in men with increased risk in BMI's < 23 and > 27. Estimates excluding early deaths showed an increased risk only in BMI < 23 and of never-smokers in BMI < 19. However, interpretation of these findings should be cautious because of the potential instability of the estimates due to small numbers. Women with a BMI < 19.0 and >30.0 also were at increased risk of all cause mortality and the association was maintained in never-smokers. Similar to the SCHS, a disproportionate amount of men smoked vs. women. This study may have increased their power of examining the never-smokers if they would have stratified on smoking status, rather than sex, and then looked at sex differences.

Yuan et al. [149] analyzed the association in the Shanghai cohort study of 18,244 Chinese men aged 45-64 years in Shanghai, China. BMI was determined by self-reported height and weight and numerous other lifestyle and demographic factors were gathered at baseline. Cox proportional hazards regression methods were used to analyze the data with adjustments for age (< 54, 55-59, 60-64, 65+), education level, alcohol consumption, smoking status and specific number of cigarettes a day if a current smoker as well as age started. The referent BMI category chosen was 21-23.5 as this was determined to be the most healthful range by metropolitan insurance tables according to the authors. Of lifetime never-smokers those with BMI's < 18.5 and > 26.0 had an increased risk of mortality. Of ever-smokers and current smokers there was no association. A limit in interpretation of the results is that there did not appear to be any adjustment for physical activity levels related to work, leisure time or general lifestyle. Overall, our results are very similar when looking at the range of BMI of no increased risk of death.

In summary, the studies to date looking at BMI and all-cause mortality in Asian populations have not been uniform in methodological approach. Comparing data from the Women's Shanghai cohort study is difficult because of the approach taken to analyzing the data. Gu et al found a U-shaped association with the only range of non-increased risk of mortality was in BMI's 24-26.9. However, in the main analyses smoking was only adjusted for and it wasn't clear in sensitivity analyses if smokers were actually excluded, thus this may have affected the results. In a study of Korean national health insurance participants utilizing a sound methodological approach, with the referent (23-24.9) being the lowest risk, a J-shaped association was observed with risk increasing in BMI's < 18.5 and > 30, however this study had a wide age range of study (30-95). Utilizing a national sample of Korean woman a U-shaped association between BMI and all-cause mortality was also observed when applying appropriate methods with increased risk in BMI's < 21 and ≥ 27.0. In the Japanese study of disease free men and women, including smokers, men with a BMI of 23-27 were not at increased risk for premature mortality and women, who smoked much less, had no increase in risk between BMI's of 19-30 after adjustment and exclusion of smokers. Because of the approach taken, the results beyond the noted are not interpretable or potentially applicable. In a population similar to the SCHS, of

Shanghai men, a U-shaped association was observed with risk increasing at BMI < 18.5 and > 26.0.

There are multiple methodological considerations in the analysis of BMI and all-cause mortality. It is important to approach this type of study with understanding of sound methodological and statistical approaches to looking at the data. Yet, it is equally important to consider how the question being asked changes when exclusions and stratification of participants occurs; and how the underlying pathophysiology and morbidity of overweight, obesity and underweight and ultimately mortality is affected by including and excluding participants who are elderly, smoke or smoked, have prevalent disease or died in a short period of time after starting to be followed. As aptly noted by Manson et al.,[132] a different question is being asked when there is inclusion of smokers and prevalent disease in the model vs. only studying apparently healthy people. In the former, the question is essentially asking what the probability of death is at a certain BMI, where in the latter the question is more informative for contributions and recommendations for policy since it is essentially asking what a BMI level seemingly healthy individuals is should maintain to minimize premature mortality.

One methodological aspect that could help in comparability and interpretation of future studies is uniformity in approach of choosing a referent category as well as using the true distribution of the BMI data. If this was based upon the lowest age standardized mortality in a BMI group and according to smoking status, this may make future research in Asians more comparable since the methodological approaches and choices in this area generally left the studies less comparable than they could be. Additionally, excluding smokers or stratifying by smoking status regardless of statistical findings and presenting that data would help in interpreting the literature.

Furthermore, it is important to consider the recent history of the people of different regions of Asia in interpretation of the results and consider the potential impact of life course BMI on mortality. Moreover, approaching the question of BMI and all-cause mortality with a life course point of view may be the optimum approach, as decisions made on the impact of relative weight need to be considered with what BMI means throughout life in a respective population, when it was measured, how it relates to health statuses and behaviors, and the multiple aforementioned methodological issues that may arise in studying this question. Using the SCHS as evidence and an example, persons reporting a BMI in the normal to somewhat overweight status according to the WHO do not appear to be at increased risk of premature mortality where severe underweight status and high overweight and obese statuses are at increased risk. While other portions of China and Asia are undergoing a nutrition transition and low body weight may be a reflection of socioeconomic position or under-nutrition, Singapore is an established, wealthy and highly developed, urban nation. This development occurred rapidly in Singapore's history though, and the lifespan of most of the adults in Singapore spans this quick transition; and low body weights in adulthood leading to an increased hazard ratio of mortality may be a reflection of potential under nutrition or other physiologic or health conditions during childhood, adolescence and young-adulthood for the participants.

Strengths of our study include thorough assessment of potential lifestyle confounders of the BMI-mortality association, a large sample size and ample amount of events combined with a long follow up time. The participants are also representative of the population they came from and mortality assessment is thought to be complete. Study of this population may also allow for making inferences in other highly developed Asian regions or countries.

Limits include non-assessment of mental health conditions, not having complete info on chronic health conditions such as COPD, cirrhosis and some neurodegenerative diseases at baseline. However, since BMI was assessed during mid-life in the majority of these participants, all afforded a high level of medical care in a wealthy society; the prevalence of undiagnosed disease is of low probability. Further considerations include the use of self-reported height, weight and other demographic and lifestyle data. Additionally, further data on other measures of body habitus may complement BMI in this population and contribute to further understanding. Misclassification and measurement error need to be considered as possible explanations, although if non-differential in nature, this would most likely account for a lack of or attenuate the associations we observed. Multiple assessments may help interpret and contribute to understanding the data further as well.

In conclusion, we observed a U-shaped association between BMI and all-cause mortality in disease free non-smokers, where risk of premature mortality increased in persons with a BMI > 26.0 and < 18.5, though this association on the low end appears to be driven by BMI < 17.0. Our results suggest that maintaining a healthy weight is important in this population regardless of age as the association in overweight status was still apparent in persons 65+. These older participants appeared to be driving the strong positive association in the underweight category as well. Further study of cause-specific mortality is warranted to understand if deaths from different causes influence the shape and nature of the association in the SCHS. Our findings, while concurrently giving consideration to the association and impact of relative weight on chronic disease, have the potential to contribute to public health recommendations on what a optimum weight range may be in an Asian population where a higher proportion of BMI’s fall in a lower range compared to European and North American populations.

Table 8.1: Baseline characteristics by smoking status according to body mass index (BMI) in SCHS

Characteristics	Body Mass Index (kg/m^2) <18.5	18.5-19.9	20.0-21.4	21.5-22.9	23.0-24.4	24.5-25.9	26.0-27.4	≥27.5	P
				Non-smokers, N=35,766					
N	2,260	3,612	5,643	6,422	6,210	4,779	2,937	3,903	
Age	55.5 (8.1)	54.8 (7.7)	54.8 (7.8)	54.9 (7.7)	55.1 (7.6)	55.4 (7.7)	55.3 (7.7)	55.6 (7.8)	<0.0001
Sex (% women)	75.7	76.0	72.1	71.5	68.9	70.2	67.3	74.6	<0.0001
Weight (Kg)	44.0 (5.0)	48.5 (4.7)	52.4 (5.1)	55.9 (5.4)	59.7 (5.7)	63.1 (6.1)	66.9 (6.7)	73.3 (9.8)	<0.0001
Body mass index	17.3 (1.0)	19.3 (0.4)	20.8 (0.4)	22.2 (0.4)	23.7 (0.4)	25.2 (0.5)	26.7 (0.4)	30.0 (2.8)	<0.0001
Education (% secondary)	34.8	37.3	36.6	34.2	33.4	29.1	29.7	24.9	<0.0001
Strenuous Activity ¥	6.8	8.4	8.8	9.0	9.2	8.0	7.6	6.0	0.007
[2]Moderate Activity €	49 (2.5)	51 (2.4)	56 (2.8)	60 (2.9)	56 (2.6)	62 (3.0)	61 (2.8)	50 (2.7)	0.47
Alcoholic drinks/wk	0.4 (1.9)	0.4 (2.2)	0.5 (2.5)	0.4 (2.2)	0.4 (2.1)	0.4 (2.1)	0.5 (2.6)	0.5 (3.0)	0.14
Hypertension (%)	10.2	12.9	16.4	21.4	26.6	31.3	35.5	42.2	<0.0001
§Prevalent disease (%)	10.4	9.4	10.9	11.5	13.7	13.9	15.0	18.1	<0.0001
				Ever-smokers, N=15,485					
N	1,590	1,860	2,590	2,585	2,513	1,834	1,100	1,413	
Age	59.5 (7.9)	58.2 (8.1)	58.0 (7.9)	57.9 (8.1)	57.3 (7.8)	57.2 (7.9)	57.2 (7.8)	56.4 (7.8)	<0.0001
Sex (% women)	17.9	14.8	13.0	15.6	12.4	12.5	13.1	18.1	0.41
Weight (Kg)	46.7 (5.2)	52.0 (4.8)	55.9 (4.9)	59.9 (5.4)	64.1 (5.7)	68.0 (5.9)	71.7 (6.2)	78.6 (9.8)	<0.0001
Body mass index	17.2 (1.1)	19.3 (0.4)	20.8 (0.4)	22.3 (0.4)	23.7 (0.5)	25.3 (0.4)	26.7 (0.4)	29.8 (3.0)	<0.0001
Education (% secondary)	22.5	27.6	28.3	29.7	33.3	31.6	29.9	26.4	<0.0001
Strenuous Activity ¥	4.5	7.0	7.3	7.0	9.6	8.2	7.8	7.7	<0.0001
[2]Moderate Activity €	44 (2.5)	47 (2.5)	53 (2.6)	58 (2.6)	57 (2.7)	64 (3.0)	69 (3.1)	50 (2.5)	0.0015
Alcoholic drinks/wk	2.8 (7.7)	2.6 (7.5)	2.5 (7.2)	2.1 (5.9)	2.1 (6.1)	1.9 (6.1)	2.1 (6.8)	1.9 (6.0)	<0.0001
Hypertension (%)	9.4	11.6	15.3	19.7	25.6	31.7	35.3	38.7	<0.0001
§Prevalent disease (%)	13.4	13.7	15.9	16.9	19.1	20.5	22.5	22.5	<0.0001

All values mean (standard deviation) except [2]Moderate activity mean (standard error)

§Prevalent disease= Self reported physician diagnosed baseline cardiovascular disease, diabetes mellitus or respiratory disease

Strenuous Activity ¥ (% ever)

[2]Moderate Activity € (Minutes/week)

Table 8.2: Age standardized all-cause mortality and Hazard ratios according to Body Mass Index: SCHS

	Body Mass Index (kg/m^2)								
	<18.5	**18.5-19.9**	**20.0-21.4**	**21.5-22.9**	**23.0-24.4**	**24.5-25.9**	**26.0-27.4**	**≥27.5**	
				Ever-smokers N=15,485, No. deaths=3,839					
No. deaths/N	506/1,590	525/1,860	647/2,590	609/2,585	543/2,513	442/1,834	242/1,100	325/1,413	P trend
Age Standardized rate*	301	261	234	213	194	217	199	208	
[1]HR	1.36	1.26	1.11	1.03	1.0	1.09	1.05	1.19	< 0.0001
(95% CI)	(1.21-1.54)	(1.12-1.43)	(0.99-1.25)	(0.92-1.16)		(0.96-1.23)	(0.90-1.22)	(1.03-1.36)	
				Non-smokers including prevalent disease N=35,766, No. deaths 3,740					
No. deaths/N	227/2,260	330/3,612	520/5,643	654/6,422	608/6,210	496/4,779	340/2,937	515/3,903	
Age Standardized rate*	105	78	78	86	83	88	99	115	
[1]HR	1.23	1.0	0.94	0.99	0.93	0.97	1.09	1.20	< 0.0001
(95% CI)	(1.05-1.44)		(0.82-1.08)	(0.87-1.13)	(0.81-1.06)	(0.85-1.12)	(0.93-1.27)	(1.04-1.38)	
				[2]Non-smokers and Disease free N=31,176, No. deaths=2,524					
No. deaths/N	204/2,024	227/3,271	374/5,030	448/5,681	395/5,359	331/4,117	228/2,496	317/3,198	
Age Standardized rate*	85	58	62	66	62	67	71	84	
HR	1.32	1.0	1.02	1.08	1.01	1.05	1.21	1.30	< 0.0001
(95% CI)	(1.09-1.59)		(0.86-1.20)	(0.92-1.27)	(0.86-1.19)	(0.88-1.24)	(1.01-1.46)	(1.10-1.54)	
				Excluding deaths with < 5 years follow up time N=30,538, No. deaths 1,886					
No. deaths/N	149/1,969	156/3,200	283/4,939	343/5,576	292/5,256	245/4,031	168/2,436	250/3,131	
Age Standardized rate*	63	42	47	51	46	50	60	66	
HR	1.41	1.0	1.12	1.20	1.08	1.12	1.31	1.49	0.0003
(95% CI)	(1.12-1.76)		(0.92-1.36)	(0.99-1.45)	(0.89-1.32)	(0.92-1.39)	(1.05-1.63)	(1.22-1.83)	

SCHS= the Singapore Chinese Health Study
Age standardized rate*= mortality rate per 10,000 person years using age distribution of Singapore Chinese Health Study
HR (95% CI) = Hazard Ratio; 95 % confidence interval: Model adjusted for age, sex, year of enrollment, dialect, education, dietary pattern score and physical activity
[1]HR (95% CI) also adjusted for prevalent disease status
P trend= *P* value for quadratic term (U or J shaped) using median of BMI in each category as continuous variable
[2]Exclusion of 4,590 participants with prevalent cardiovascular disease, diabetes mellitus, and respiratory disease
P value interaction between baseline BMI and ever-smoking status = 0.0012
P value interaction between baseline BMI and prevalent disease=0.09, (cardiovascular disease, diabetes mellitus and respiratory disease)

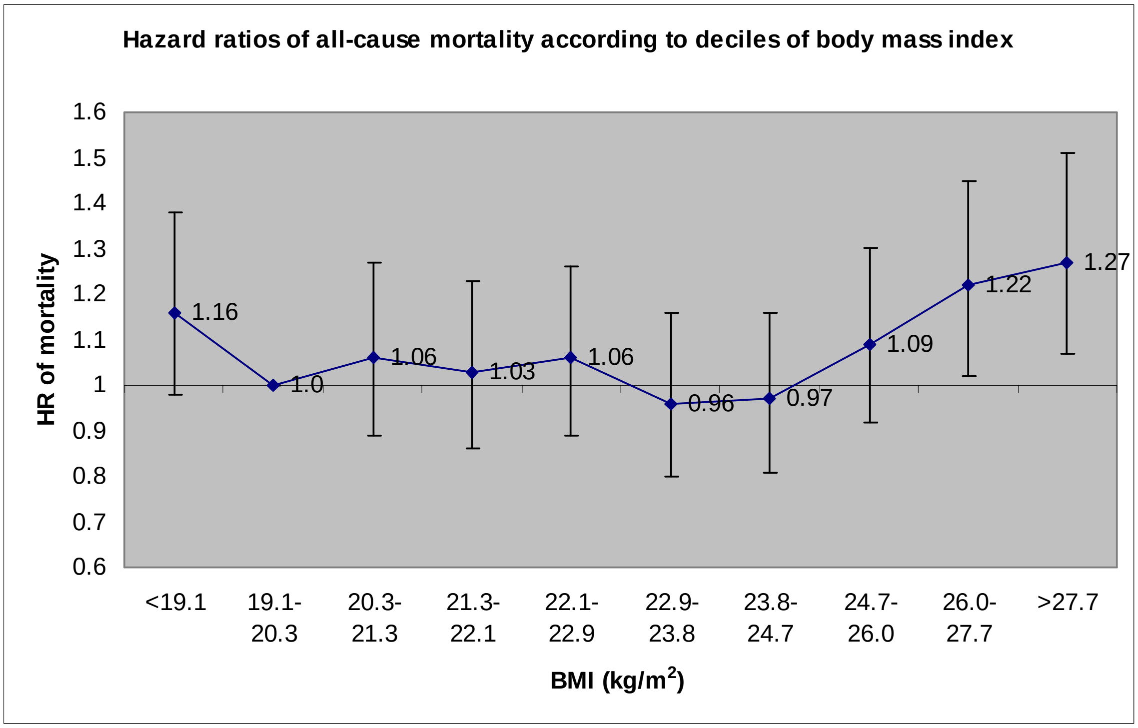

Figure 8.1: Hazard ratio of mortality according to deciles of BMI (kg/m^2) in 31,176 (No. deaths=2,524) disease free non-smokers adjusted for age, sex, year of enrollment, dialect, education, dietary pattern score and physical activity. Points represent HR point estimate and error bars represent 95% confidence intervals. *P* value for quadratic term of median BMI by deciles=0.0014

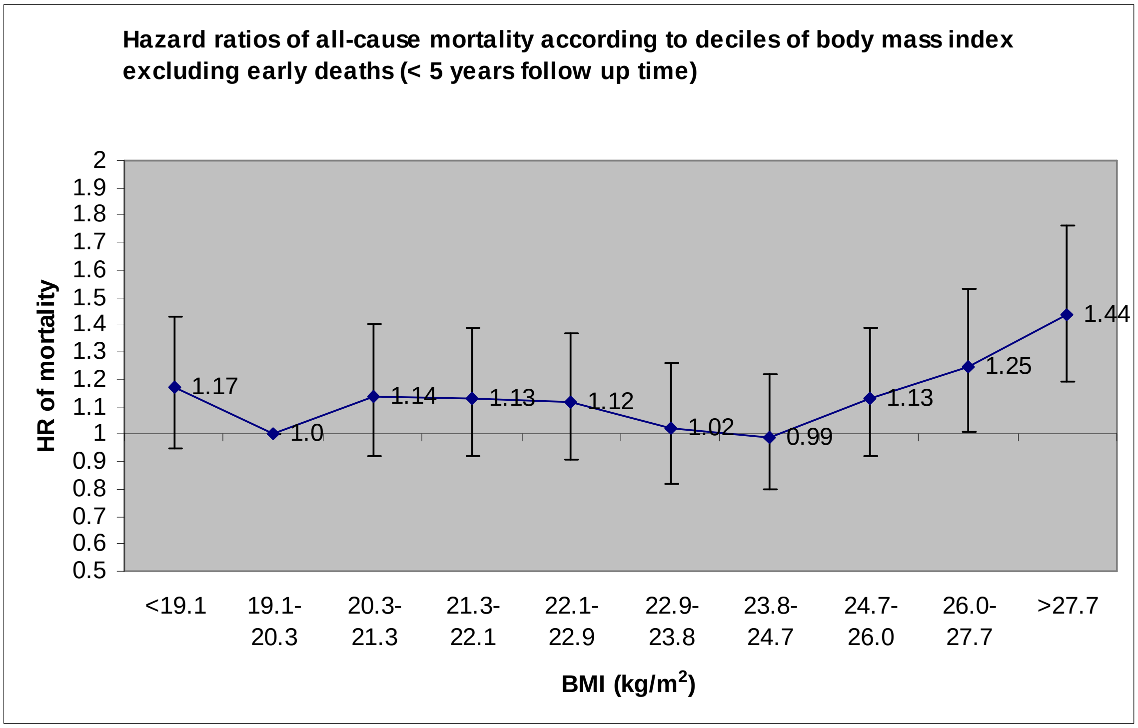

Figure 8.2: Hazard ratio of mortality according to deciles of BMI (kg/m^2) in 30,538 (No. deaths=1,886) disease free non-smokers excluding deaths occurring within 5 years of baseline interview date to account for potential reverse causality in model. Model adjusted for age, sex, year of enrollment, dialect, education, dietary pattern score and physical activity. Points represent HR point estimate and error bars represent 95% confidence intervals. *P* value for quadratic term of median BMI by deciles=0.002

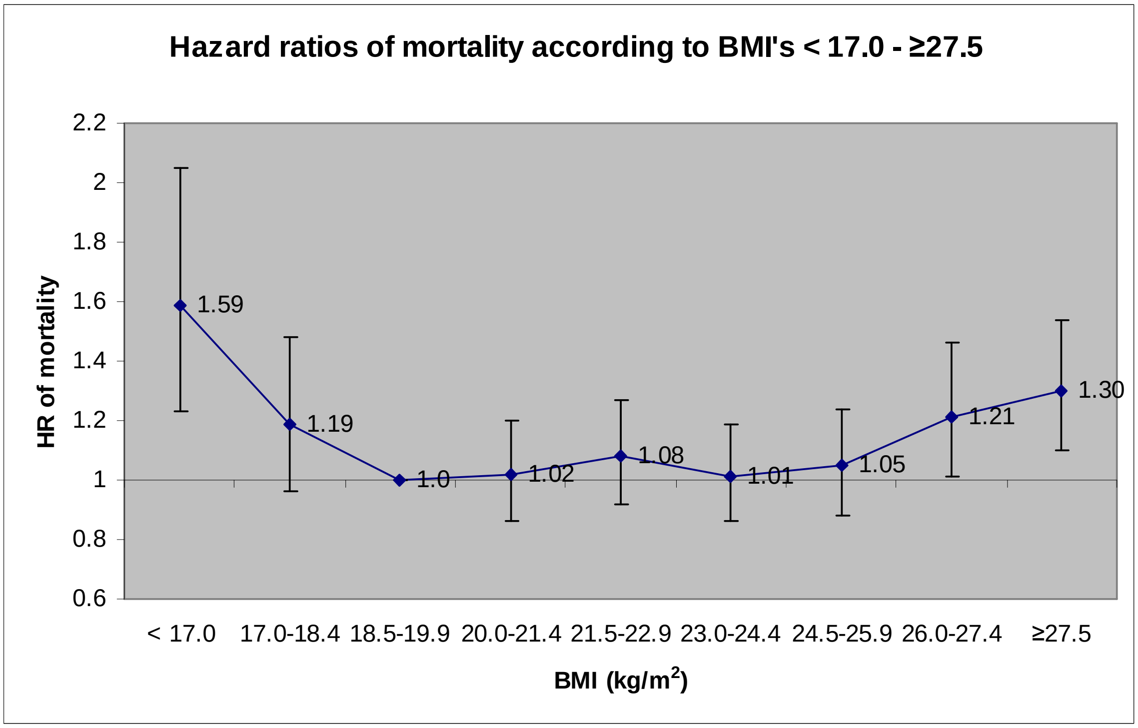

Figure 8.3: Hazard ratio of mortality incorporating lower cut-points of BMI (kg/m^2) in 31,176 (No. deaths=2,524) disease free non-smokers adjusted for age, sex, year of enrollment, dialect, education, dietary pattern score and physical activity. Points represent HR point estimate and error bars represent 95% confidence intervals. *P* value for quadratic term of median BMI by group=<0.0001

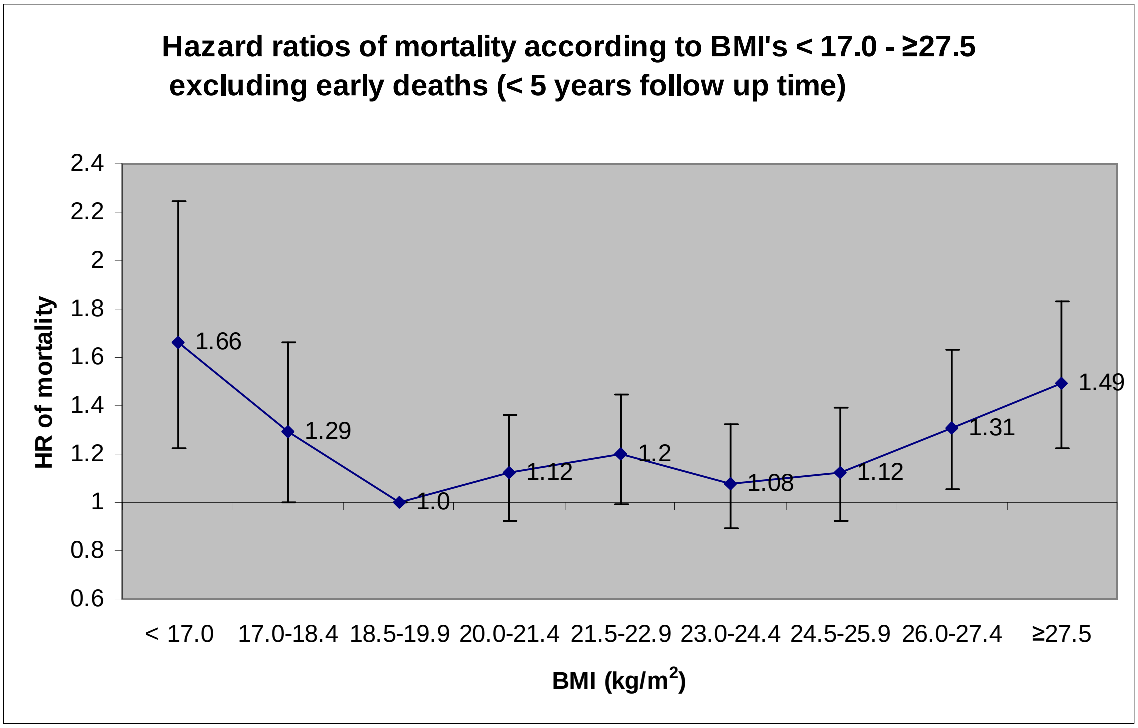

Figure 8.4: Hazard ratio of mortality incorporating lower cut-points of BMI (kg/m^2) in 30,538 (No. deaths=1,886) disease free non-smokers adjusted for age, sex, year of enrollment, dialect, education, dietary pattern score and physical activity. Points represent HR point estimate and error bars represent 95% confidence intervals. *P* value for quadratic term of median BMI by group=<0.0001

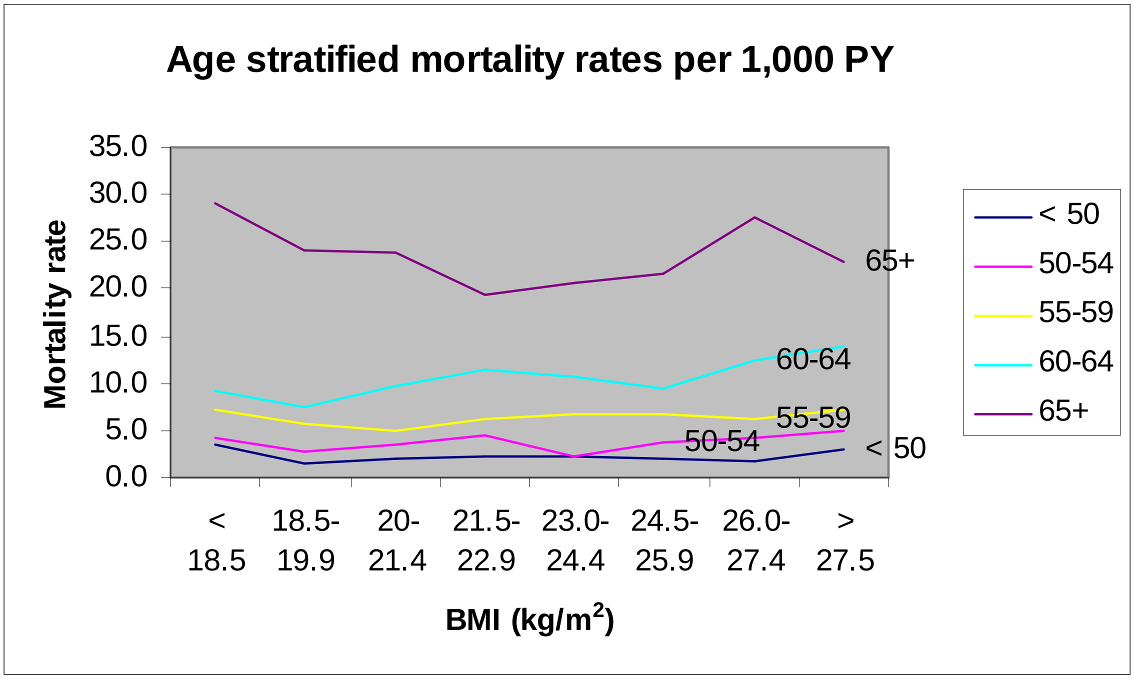

Figure 8.5: Age stratified mortality rates in 31,176 (No. deaths=2,524) disease free non-smokers. Numbers in legend correspond with age groups and PY= person years.

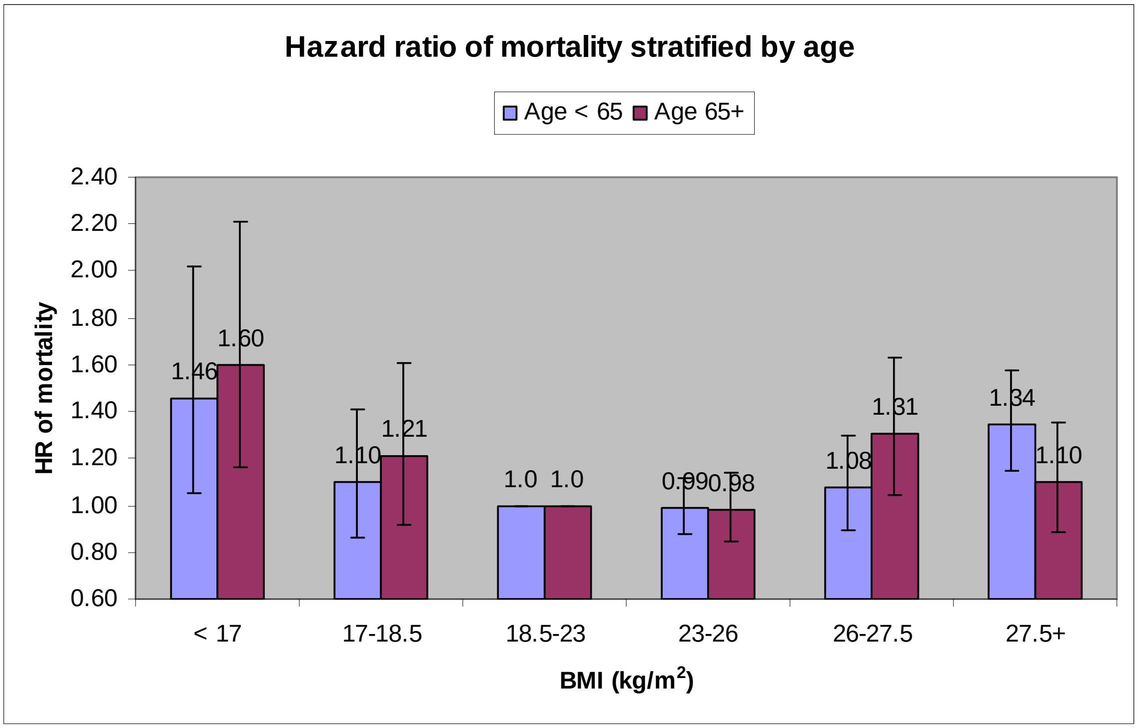

Figure 8.6: Age stratified hazard ratio of mortality in 31,176 (No. deaths=2,524) disease free non-smokers adjusted for age (continuous), sex, year of enrollment, dialect, education, dietary pattern score and physical activity using BMI's 18.5-23.0 as the referent group. Points represent HR point estimate and error bars represent 95% confidence intervals.

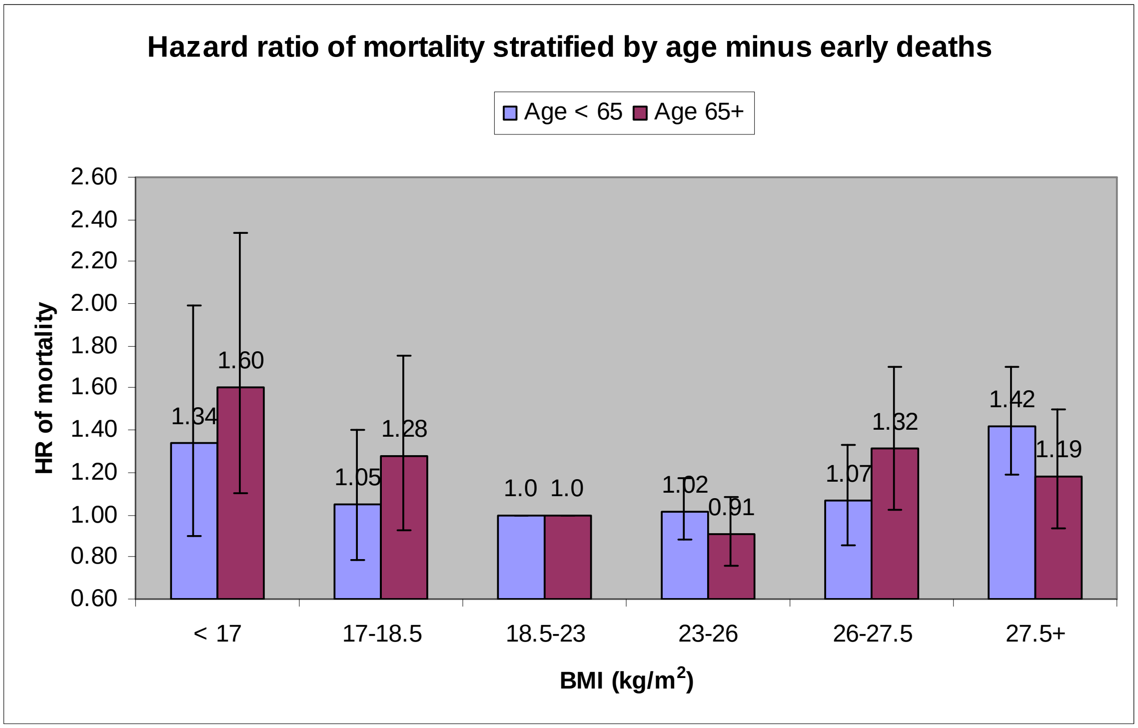

Figure 8.7: Age stratified hazard ratio of mortality in 30,538 (No. deaths=1,886) disease free non-smokers adjusted for age (continuous), sex, year of enrollment, dialect, education, dietary pattern score and physical activity using BMI's 18.5-23.0 as the referent group. Points represent HR point estimate and error bars represent 95% confidence intervals.

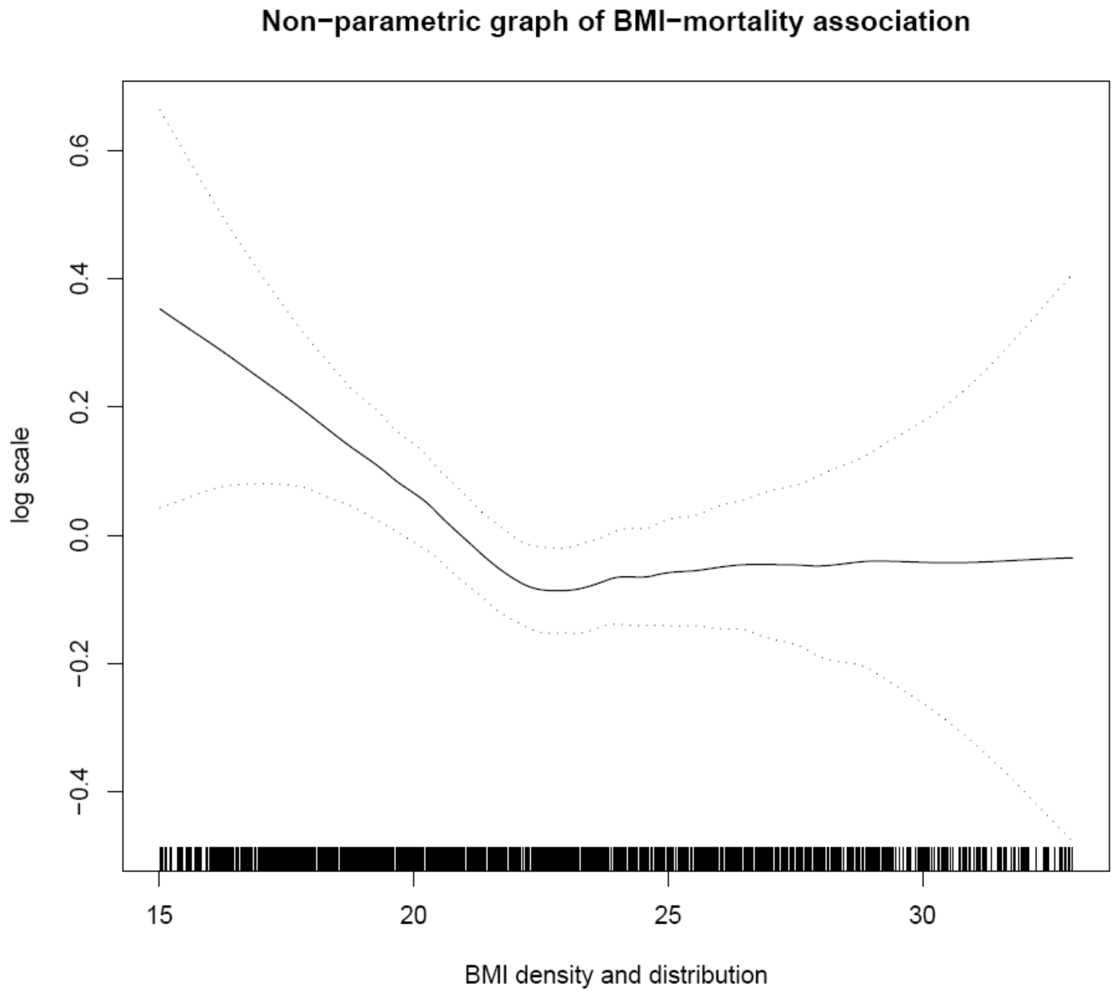

Figure 8.8: The fully adjusted non-parametric graph of the association between BMI (kg/m^2) and all-cause mortality in **ever-smokers** (N=15,485, No. deaths=3,839) on the log scale with the model set to modest smoothing and linear fit parameters. The solid line represents the point estimate of the curve, and the dotted lines represent the upper and lower 95% confidence bands. The shaded area at the bottom of the plot is the distribution of BMI data.

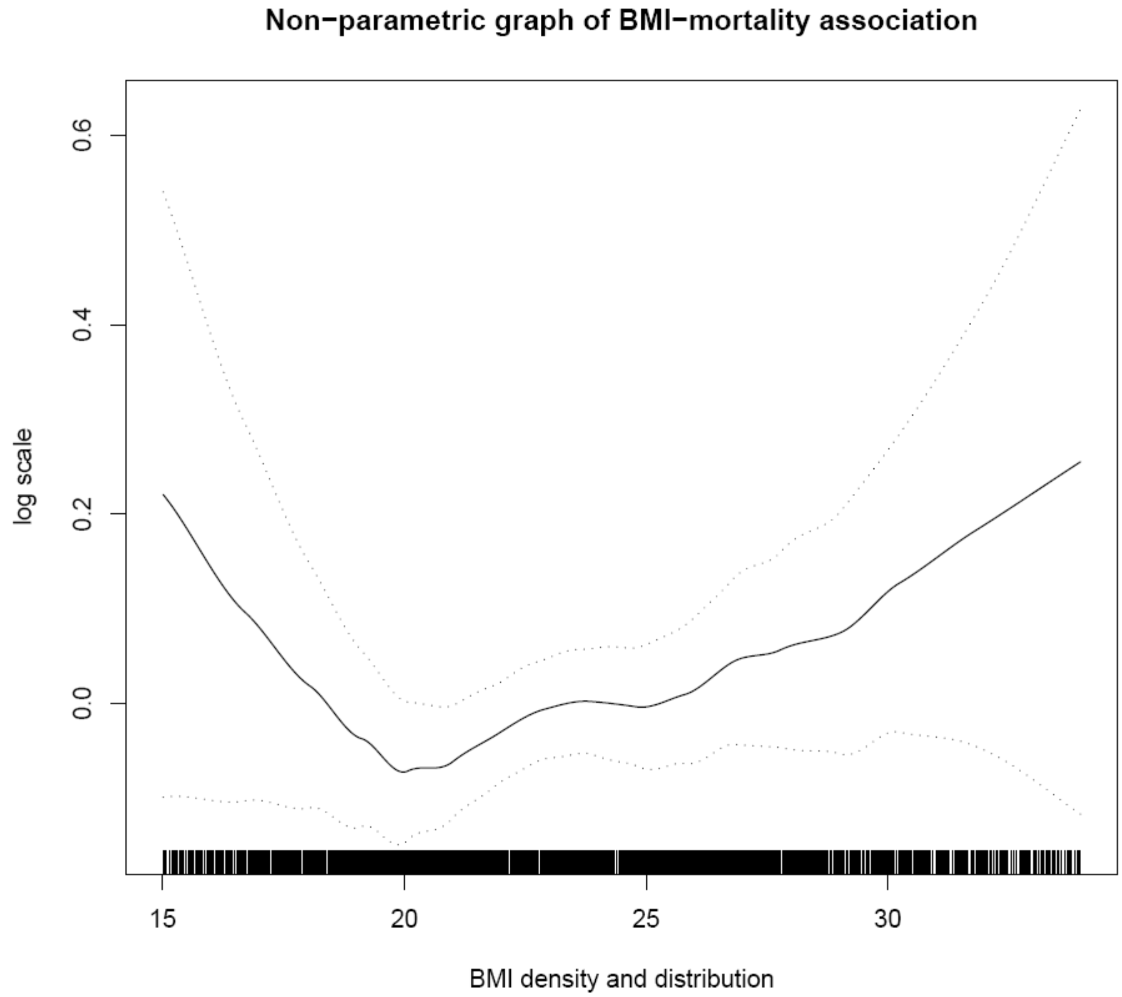

Figure 8.9: The fully adjusted non-parametric graph of the association between BMI (kg/m^2) and all-cause mortality in **Non-smokers including prevalent disease (**N=35,766, No. deaths 3,740) on the log scale with the model set to modest smoothing and linear fit parameters. The solid line represents the point estimate of the curve, and the dotted lines represent the upper and lower 95% confidence bands. The shaded area at the bottom of the plot is the distribution of BMI data.

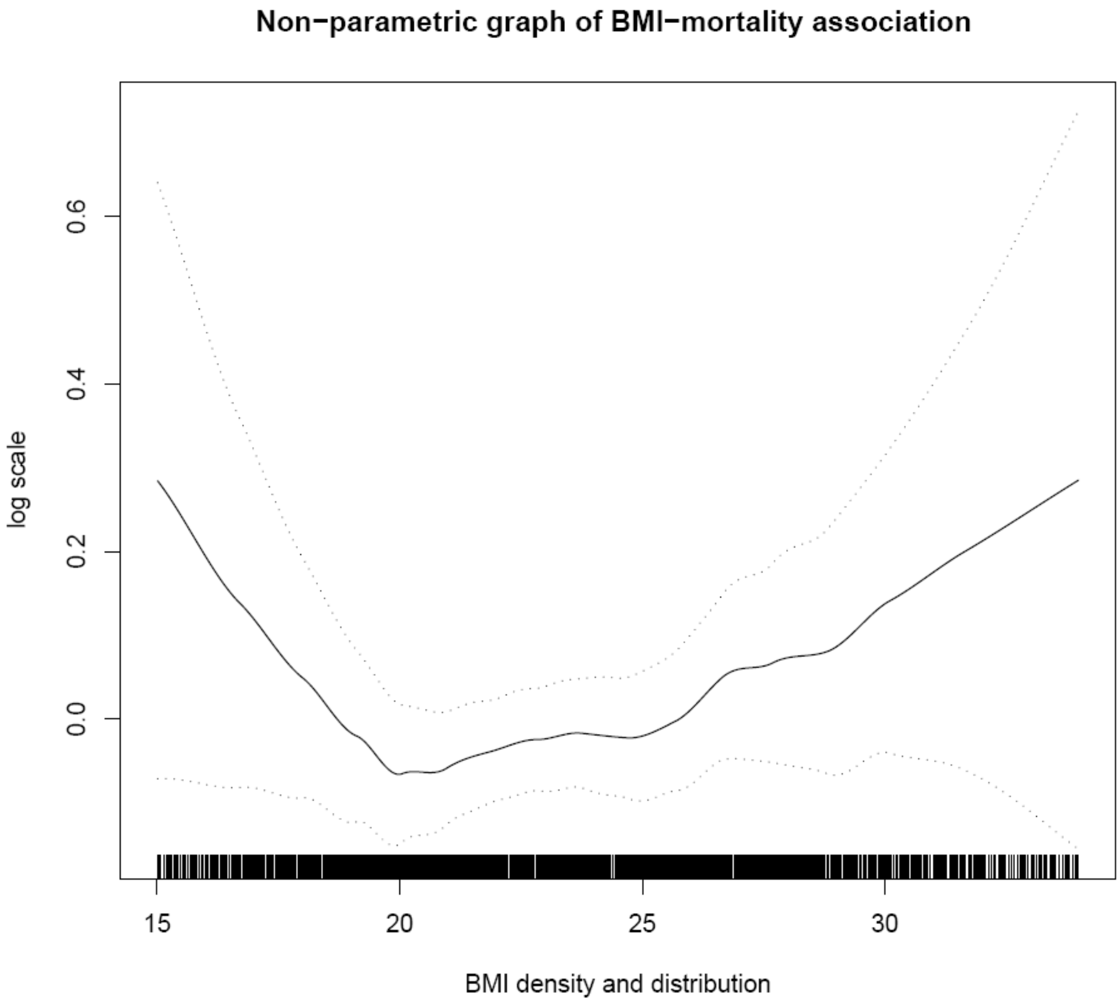

Figure 8.10: The fully adjusted non-parametric graph of the association between BMI (kg/m^2) and all-cause mortality in **Disease free**, **non-smokers**(N=31,176, No. deaths=2,524) on the log scale with the model set to modest smoothing and linear fit parameters. The solid line represents the point estimate of the curve, and the dotted lines represent the upper and lower 95% confidence bands. The shaded area at the bottom of the plot is the distribution of BMI data.

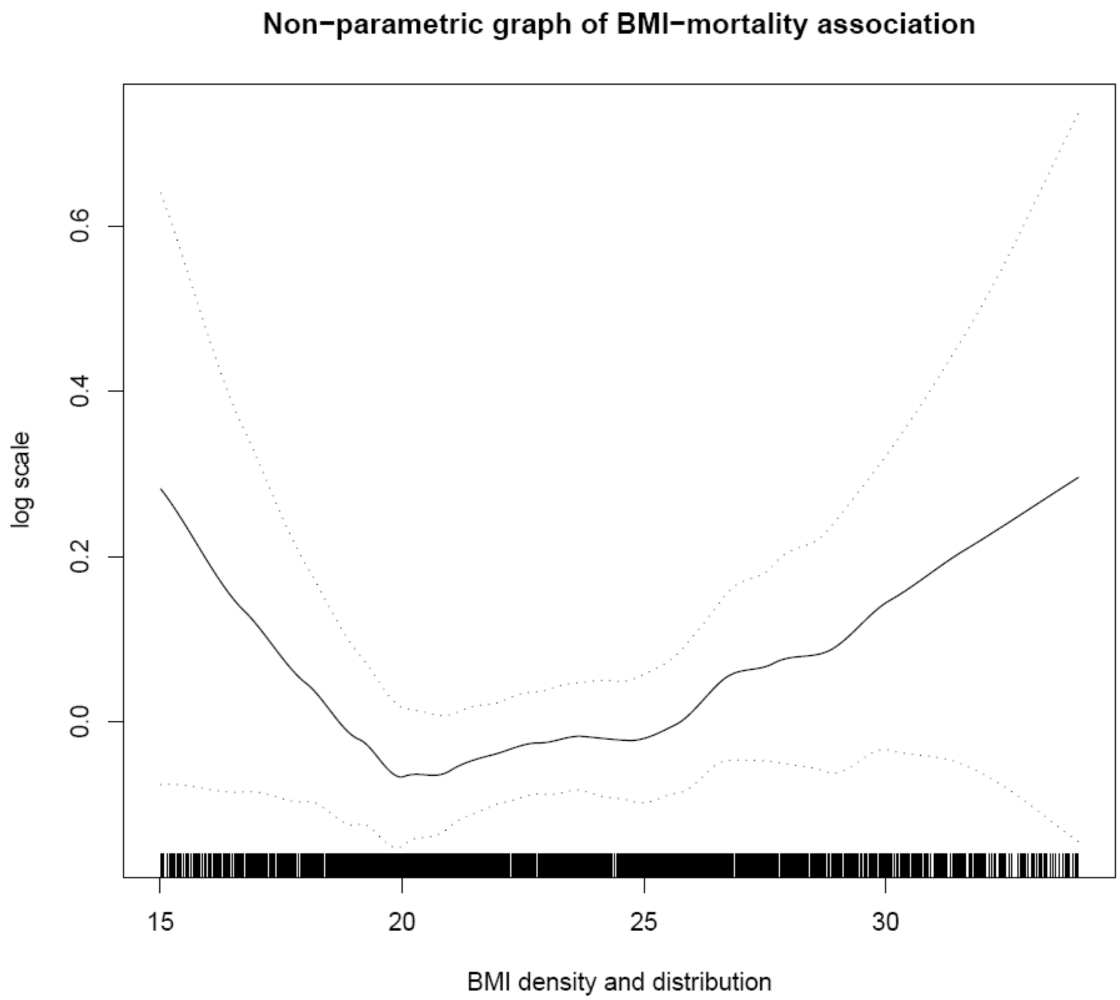

Figure 8.11: The fully adjusted non-parametric graph of the association between BMI (kg/m^2) and all-cause mortality in **Disease free non-smokers excluding early deaths** (N=30,538, No. deaths 1,886) on the log scale with the model set to modest smoothing and linear fit parameters. The solid line represents the point estimate of the curve, and the dotted lines represent the upper and lower 95% confidence bands. The shaded area at the bottom of the plot is the distribution of BMI data.

Summary

Diet and lifestyle are the primary channels in prevention of weight gain and type 2 diabetes, as well as being implicitly involved with body mass index (BMI). The literature on dietary factors related to obesity and type 2 diabetes has continued to expand, but little research has focused on Asian populations. Research on Asians is topical and relevant due to the high rates of diabetes and obesity observed in the region as it continues to develop rapidly, and lifestyle and diet evolve to adapt new influences. Furthermore, debate over the optimal BMI range in Asians is an important public health question in need of more thorough investigation. All-cause mortality is a highly applicable public health endpoint that is an important consideration with relation to adult BMI levels. By investigating the association of dietary patterns with weight gain, risk of obesity and risk of type 2 diabetes, as well as considering how western fast food relates to weight gain, and BMI with all-cause mortality we have aimed to characterize these areas in a Southeast Asian population. Research on these topics may contribute to public health initiatives and further understanding of the etiology of these health states and diseases.

We derived and observed two main dietary patterns in this population. A pattern characterized by high consumption of vegetables, fruit, and soy products with some fish and seafood was inversely associated with weight gain and no future risk of obesity in non-smokers. A pattern characterized by high consumption of dim sum, fresh and processed meats, higher levels of noodles and rice dishes, and some sweetened and deep fried foods was associated with increasing weight gain with higher consumption of the pattern as well as increased risk of future obesity and type 2 diabetes. Furthermore, each

small increase in western fast food and soft drinks was associated with an increase in weight gain. Consideration of the association of BMI with all-cause mortality found a U-shaped association, with BMI from the normal range through the middle range of overweight status (18.5-26) not associated with risk of premature all-cause mortality. Increased risk in BMI < 18.5 appeared to be driven by persons aged 65 and above. Future studies on diet, weight and obesity and type 2 diabetes are warranted in younger portions of similar Asian populations as this age group has adapted different lifestyle and dietary influences. Continued and further future research on body composition in relation to chronic disease and mortality is also justified. Studies accounting for years of functional and high quality life, assessing the distribution and location of adiposity and looking at influences of this adiposity may have great impact on understanding of the etiology as well as greatly contribute to public health initiatives.

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