Genetic Predisposition and Changes in Dietary Patterns may contribute to increased Development of Type 2 Diabetes in the Chinese Population

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Acknowledgements

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II

Abstract

Lifestyle diseases, such as type 2 diabetes (T2D) and cardiovascular diseases (CVDs), are related to overweight in the western world. Although lower occurrence of overweight has been documented in China compared to western countries, an increase in such lifestyle diseases has been observed during the last decades. The aim of this thesis was to study the relationship between lifestyle and the development of T2D and CVDs in the Chinese population. The results may provide further knowledge concerning lifestyle diseases and may therefore contribute to reduce disease development in the future. The experimental data presented in this thesis was extracted from various research areas within molecular biology, genetics and epidemiology.

Asian populations show higher concentrations of the pro-inflammatory mediator PAI-1 and lower concentrations of the anti-inflammatory mediator adiponectin compared to other ethnic groups. These differences suggest that Asians may be genetically predisposed to developing metabolic inflammation, which may increase the risk of developing T2D and CVDs. In China, the inflammation is most likely amplified due to altered nutritional patterns. Urban populations in China have increased rapidly during the last decades. Highly influenced by westernization processes, dietary changes have been introduced to these urban areas. Western diets include high consumption of fat, resulting in high kilocalorie (kcal) intake that might trigger overnutrition. Furthermore, an altered dietary carbohydrate composition has been observed through increased consumption of high glycemic indexed (GI) carbohydrates. The traditionally northern Chinese diet contains more kcal than the southern diet and has a higher GI content. These dietary differences might provide an explanation for higher prevalence of T2D and CVDs observed in north China compared to south China.

Genetic changes *in utero* and during childhood due to the Chinese Famine in the mid1940s has proven to explain a small part of the increased development of T2D in China. Individuals who during early development were subjected to malnutrition and later consume a rich western diet are at increased risk of developing T2D. However, these genetic differences do not explain the disease development in Chinese children and adolescents. The one-child policy has been blamed for the increase as it reduces competition between siblings. None of the results in this thesis support the hypothesis that the one-child family policy is to be blamed for the disease development. Therefore, the main factors contributing to the lifestyle disease development in China appear to be genetic predisposition and dietary changes.

Norwegian abstract

Livsstilsjukdomar som type 2 diabetes (T2D) og hjarte- og karsjukdomar (CVDs frå engelsk: cardiovascular diseases) er relatert til overvekt i den vestlege verden. Sjølv om ein lågare del av befolkninga i Kina er overvektig samanlikna med vestlege land, har tilfella av dei nemnte livsstilssjukdommane auka dei siste tiåra. Målet med denne tesen var å studere forholdet mellom livsstil og utvikling av T2D og CVDs i den kinesiske populasjonen. Resultatet kan auke kunnskap om livsstilssjukdomar og difor vere med på å redusere sjukdomsutvikling i framtida. Eksperimentelle data presentert i denne tesen blei henta frå ulike forskingsområder innan molekylærbiologi, genetikk og epidemiologi.

Asiatiske populasjonar har vist høgare konsentrasjonar av den pro-inflammatoriske mediatoren plasminogenaktivator-inhibitor-1 og lågare konsentrasjonar av den anti-inflammatoriske mediatoren adiponektin. Desse forskjellane indikerer at asiatar er genetisk predisponert for å kunne utvikle metabolsk inflammasjon, som kan auke sjansane for å utvikle T2D og CVDs. Denne inflammasjonen er truleg forsterka grunna eit endra ernæringsmønster i Kina dei siste tiåra. Urbane populasjonar har auka kraftig og dei urbane område er sterkt påverka av vesterniseringsprosessen der ernæringsendringar har blitt introdusert. Dei vestlege diettane består av høgt feittinntak som resulterer i auka inntak av kilokaloriar som kan føre til overeting. Prosessen fører ofte med seg eit endra karbohydratinntak, der eit høgare inntak av karbohydrat med høg glykemisk indeks har blitt observert. Den tradisjonelle dietten i nord-Kina har høgare innhald av kilokaloriar og karbohydrat med høg glykemisk indeks enn den tradisjonelle sørlege dietten. Dette kan forklare dei observerte forskjellane i sjukdomsmønster mellom nordlege og sørlege Kina, der fleire tilfelle av T2D og CVDs er registrert i nordlege delar av landet.

Genetiske endringar under fosterutviklinga og i dei fyrste barndomsåra grunna den kinesiske hungersnauda på midten av 1940-tallet kan vere ein bidragsytar i den auka utviklinga av T2D og CVDs i Kina. Personar som blei underernært i tidleg utvikling og som seinare lev på ein energirik vestleg diett er meir utsatt for å utvikle livsstilsjukdomar. Dei genetiske endringane kan forklare noko av sjukdomsutviklinga i Kina, men dei kan ikkje forklare utviklinga blant unge. Eittbornspolitikken har fått noko av skulda då den reduserer konkurransen mellom sysken. Ingen av resultata presentert i denne tesen støtter hypotesen om at eittbornspolitikken har skulda for sjukdomsutviklinga i Kina. Konklusjonen er difor at genetisk predisposisjon og endra ernæringsmønster er to viktige årsakar til sjukdomsutviklinga i Kina.

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Abbreviations

AA	arachidonic acid
ATP III	Adult Treatment Program III
BMI	body mass index
CHD	coronary heart disease
CHNS	China Health and Nutrition Survey
CVD	cardiovascular disease
DBP	diastolic blood pressure
DR-NCD	diet-related, noncommunicable disease
E%	percentage of total energy intake
EFA	essential fatty acid
FA	fatty acid
FAO	Food and Agricultural Organization of the United Nations
FFA	free fatty acid
FNB	the Food and Nutrition Board
G	guanine
GI	glycemic index
HDL-C	high-density lipoprotein cholesterol
I/G	insulin:glucagon
IL	interleukin
InterASIA	the International Collaborative Study of Cardiovascular Disease in Asia
INTERMAP	the International Study of Macro- and Micro-nutrients and Blood Pressure
IOTF	International Obesity Task Force
IR	insulin resistance
kcal	kilocalorie
LA	linoleic acid
MetS	metabolic syndrome
MUFA	monounsaturated fatty acid
n-3	omega-3 (ω-3)
n-6	omega-6 (ω-6)
NFκB	nuclear factor kappa B
NHS	Nurses' Health Study
OR	odds ratio
PAI-1	plasminogen activator inhibitor-1
PAL	physical activity level
PG	prostaglandin
PLA$_2$	phospholipase A$_2$
PUFA	polyunsaturated fatty acid
RDA	recommended daily allowance
RR	relative risk
SBP	systolic blood pressure
SES	socio-economic status

SFA	saturated fatty acid
SSB	soft-sweetened beverage
t-PA	tissue-type plasminogen activator
T2D	type 2 diabetes
TFA	trans fatty acid
TNF	tumor necrosis factor
u-PA	urokinase-type plasminogen activator
USFA	unsaturated fatty acid
WC	waist circumference
WHO	World Health Organization
WHR	waist-hip ratio
WHtR	waist-height ratio
ya	years ago

X

1   Introduction

Type 2 diabetes (T2D) is a diet-related disease developing to become a worldwide epidemic (figure 1.1) with more than 366 million people affected in 2011. The number of people affected increases in every country and 80% of the cases are represented by low- and middle-income countries [1]. It appears that part of the explanation lies in the increasing globalization that results in dietary changes in which the human body is not able to adapt. A diet comprising too many kilocalories (kcal) combined with high carbohydrate intake may over time lead to overweight and obesity, another problem growing throughout the world. Overweight is characterized by constant metabolic inflammation and is responsible for 44% of the diabetes incidences [2, 3]. In 2011, diabetes cost 465 billion dollars in the US alone, representing approximately 11% of total health expenditure in adults [1]. T2D is a serious condition by itself, but counting for the additional diseases it may lead to, such as cardiovascular, endocrine, and inflammatory diseases, it becomes evident how this may result in high medical costs [4]. Furthermore, as T2D is a growing problem particularly in low-income countries, it is important to reduce the number of occurrences and halt T2D as a worldwide epidemic.
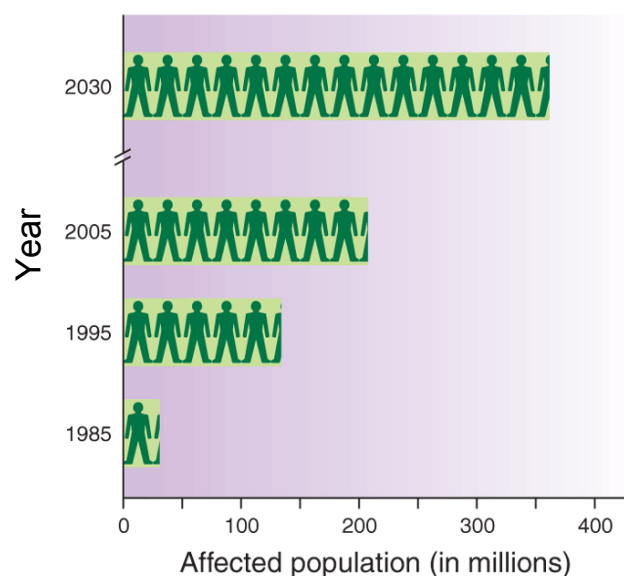

Figure 1.1 Number of people affected by T2D worldwide the over last decades. Altered, from [5].

1.1   Excess weight increases risk of developing metabolic syndrome

World Health Organization (WHO) states that "*overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health*" [2], and it occurs when there

is unbalance between food intake and energy expenditure. This is regulated by complex physiological systems where the hypothalamus in the brain functions as a central regulator [6]. Signals from the body are sent to the hypothalamus and inform the brain how to behave. For example, when a person consumes carbohydrates, the pancreas responds by secreting insulin into the blood allowing glucose to be transported into the cells [7]. Insulin then promotes leptin secretion, which informs the hypothalamus that fat reserves are adequate. The signaling is followed by a decrease in appetite [8, 9]. Raised leptin concentrations are often seen in overweight people with excess adipose tissue [10]. However, obesity is also linked to leptin resistance resulting in decreased uptake of leptin by the central nervous system. Thus, the hypothalamus does not reduce appetite [11].

Different methods are used to test for overweight and obesity, where body mass index (BMI) is the most common one.

1.1.1 Body Mass Index is a measure of overweight

BMI is a measurement of weight-for-height commonly used to classify overweight and obesity in adults. It is calculated by dividing a person's weight in kilograms by the square of his or her height in meters (kg/m^2). WHO defines overweight as BMI greater than or equal to 25, whilst BMI greater than or equal to 30 is classified as obesity [2]. Other measurements of overweight used in specific situations are addressed in section 1.3.2.

1.1.2 Lifestyle and nutrition affects body mass

Lifestyle is defined as "*the way in which a person or a group of people lives and works*" [12]. Thus, lifestyle includes organization of household, daily planning, spare time activities, and planning the future, among others. It also includes nutritional patterns, such as type of foods consumed and why.

In order to keep a balanced weight, consumption and expenditure of energy must be equal. As previously mentioned, consuming more kcal than the body requires may cause overweight. The increasing meal size contributes to the rising kcal intake in the US as meal size increases both inside and outside the home. In parallel with globalization, serving size appears to be increasing throughout the rest of the world as well [13, 14]. When given unlimited amounts of food, people tend to eat more than what is needed. This is connected to evolution in a sense that humans previously gathered food in great amounts as to stockpile for harder times. When

presented the opportunity, it was also important to eat excessive kcal for later [15]. In modern times it has been shown that reducing the size of a meal does not affect hunger post meal. However, larger meal size did induce people to eat approximately 423 additional kcal per day, and 4636 in an 11 day period [16, 17]. Restaurant foods and fast foods are often more energy-dense compared to home cooked food, and a shift towards eating out can be seen worldwide [13, 18]. Energy-dense food is food with a high number of kcal per gram [19]. Thus, energy-dense foods contain carbohydrates with high glycemic index (GI); explained in the next section, and have a high fat content, as fat comprises twice the amount of energy per gram compared to carbohydrate and protein [13, 20]. People seem to eat the same amount of food, regardless of energy density. Thus, a focus on energy density is important as increasing serving size and energy density may be a dangerous combination [13]. However, fat should always be part of the diet due to the importance it play in the body. An example is the fatty acids (FAs) that control the fluidity of the cell membrane. FAs that the body cannot synthesize itself are called essential fatty acids (EFAs). Consequently, these are acquired through the diet in the form of unsaturated fatty acids (USFAs). To illustrate, the EFA linoleic acid (LA) is needed to make phospholipids; the fundamental building blocks of the cell membranes [15, 21]. In addition, healthy FAs have anti-inflammatory benefits, explained in later chapters.

Obesity and consumption of soft-sweetened beverages (SSBs) have risen in parallel the last years. SSBs are defined as *"beverages that contain added, naturally derived caloric sweeteners such as sucrose (table sugar), high-fructose corn syrup, or fruit-juice concentrates, all of which have the same metabolic effect"* [22], and are considered to be sport drinks, fruit drinks, lemonade, iced tea, and soft-drinks such as sodas [23]. SSBs are often consumed as an addition to meals rather than a substitution, and in that way SSBs increase the overall energy consumption [24]. It has therefore been proposed that SSB intake is part of the obesity epidemic [13, 23, 24]. Energy intake from SSBs has increased by 135% in the US from 1977 to 2001 [25]. This increase may be explained by three components [25]:

1) Increase in all age groups
2) Increase in portion size
3) Increase in number of servings

A cross-sectional study done by Malik et al. [23] showed positive associations between high SSB intake and overweight in children, adolescents, and adults. This association might be due

to increased kcal consumption when drinking SSBs. A study using Nurses' Health Study (NHS) II researched women's altered soft drink consumption in the time periods 1991-1995 and 1995-1999. They found that women increasing their intake from less than one drink a week to more than one drink a day had an increased energy intake, and vice versa (figure 1.2) [26].
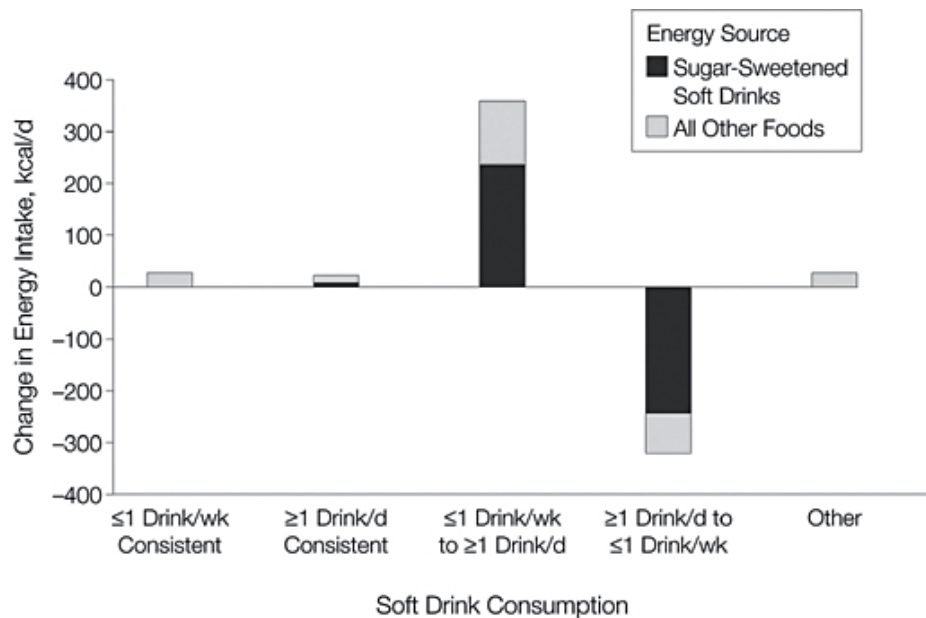

Figure 1.2 Participants in an NHSII-study changing their soft drink intake from less than one drink per day to more than one drink per week also increased their total energy intake. Participants reducing their intake reduced energy intake [26].

In the same study as mentioned in the previous paragraph, women that increased their soft drink consumption gained more weight than women with reduced or equal consumption. Figure 1.3 shows how the different groups changed their weight over a time period of eight years. Fruit juice intake gave same results [26]. Thus, the SSB intake might partly explain the obesity epidemic.
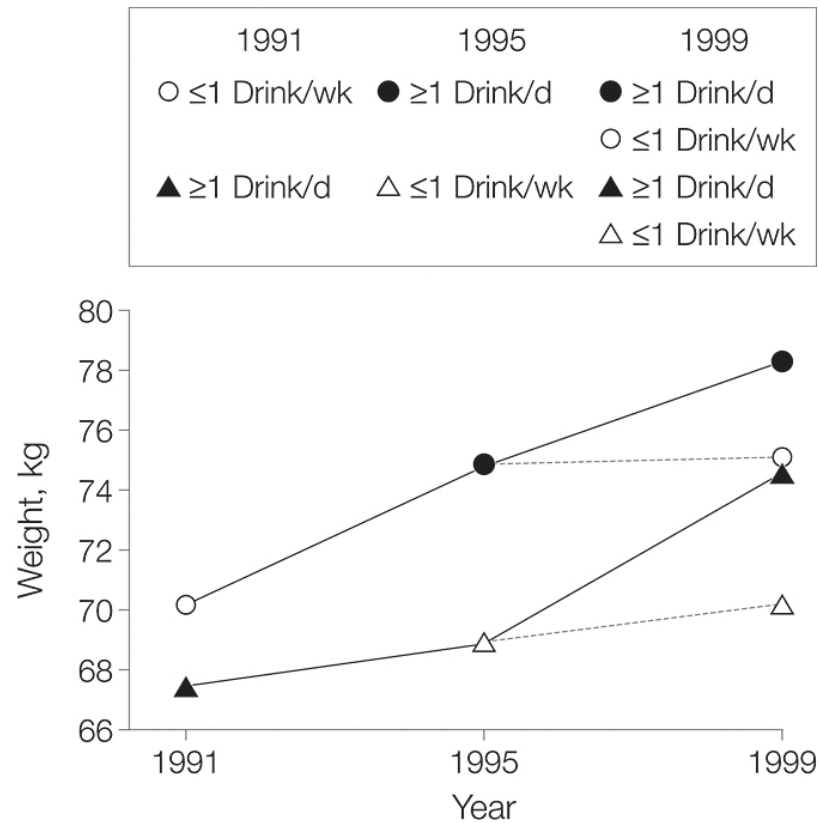
Figure 1.3 In a study using NHSII, women with increased soft drink consumption had the highest raise in bodyweight after an eight year period, when compared to women having the same or reduced consumption [26].

SSBs have a high GI due to the high sugar content. The role of dietary carbohydrate is explained in the next section.

1.1.2.1 Dietary carbohydrates affect metabolic inflammation

All foods consist of three macronutrients: carbohydrate, fat, and protein. There have long been discussions on how to compose a meal based on these three macronutrients, and so far, there are no definite way to build a *healthy meal* [27, 28]. In the 1960s and 70s, governments of many western countries recommended people to substitute some of their fat-intake with carbohydrates. Even though people followed these advices, it did not seem to affect the dangerous trend of obesity. Barry Sears, a lipid researcher, has explained why the increase in carbohydrates may have caused an obesity epidemic [29, 30]. His first concern is the way carbohydrates are stored post intake; carbohydrates are broken down to build glycogen, which is a polysaccharide made up by several glucose molecules. Glycogen is stored either in the muscles where it is unavailable to the brain, or in the liver where it can be broken down to glucose. Approximately 400 g glucose can be stored in the muscles and is used during

exercise. The storage capacity of the liver is limited (~90-110 g) and excess carbohydrates from the diet are converted to fat and stored in fatty, adipose tissue [31-33].

Sears' second point concerns the widespread lack of knowledge on GI; Jenkins et al. [34] coined this term in 1981 when they gave volunteers 62 different types of foods and subsequently tested their blood glucose levels over a 2-hour period post intake. Low GI-carbohydrates, such as brown rice and dark bread, need more time to be broken down and absorbed compared to high GI-carbohydrates, such as white rice and white bread. The index depends on the sugar's structure; a structure more difficult to break down to glucose takes longer to absorb, and vice versa [34-36]. Fiber content is also of vital importance as its content increases absorption time [35]. Low fiber – high GI foods trigger rapid glucose absorption, which in turn trigger increased insulin levels (figure 1.4) [37]. Over time, such diet will initiate insulin resistance (IR), defined as "*an inadequate response by insulin target tissues, such as skeletal muscle, liver, and adipose tissue, to the physiologic effects of circulating insulin*" [38], resulting in elevated blood glucose concentration (see section 1.2.1) [37]. Studies show that a high-fiber diet improves glycemic- and insulin responses [39]. As carbohydrate-containing foods, like fruits and vegetables, are important sources of secondary plant metabolites, contributing vitamins, minerals and antioxidants [40], and functions as energy source for the brain, it is essential to include them in the diet. However, for the reasons just mentioned, it is advantageous to choose medium to low-GI foods with high fiber content.
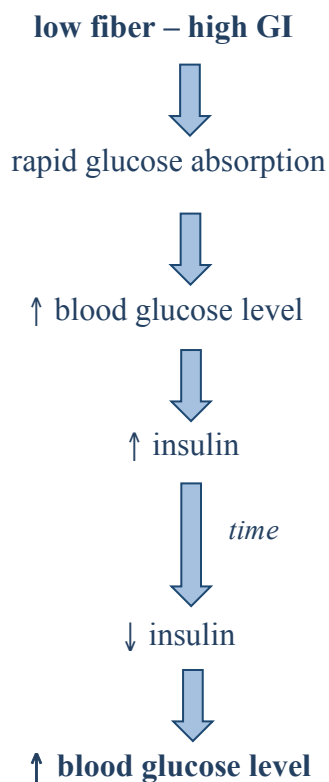
low fiber – high GI

↓

rapid glucose absorption

↓

↑ blood glucose level

↓

↑ insulin

↓ *time*

↓ insulin

↓

↑ blood glucose level

Figure 1.4 A *low fiber – high GI* diet may over time result in reduced insulin action, IR, and elevated glucose concentrations. Inspired by [37].

The third point to be made relates to the hormone release after carbohydrate intake. Intake of carbohydrates results in raised blood glucose level, which in turn triggers insulin secretion by β-cells in the pancreas. This insulin stimulates nearly all cells in the body to take up glucose from the blood and thereby reduces blood glucose concentration. The primary storage sites are the liver and the muscles. Adipose cells are the secondary storage site and are used if kcal intake is high and the primary storage sites are full [15, 41]. Thus, a diet high in carbohydrates may lead to excess adipose tissue. Glucagon, secreted by α-cells in the pancreas in response to certain amino acids, stimulates the liver in the opposite way of insulin and it triggers release of carbohydrates from glycogen stores and fat. Glucagon and insulin are related such that release of glucagon lowers the release of insulin and vice versa; related to blood glucose level. Insulin triggers glucose uptake by the cells when blood glucose level rises, while glucagon makes the liver release glucose when blood glucose level is reduced. To avoid storage of fat, it is important to keep the insulin:glucagon (I/G) ratio at low levels, promoting mobilization of nutrient stores [42]. Increased I/G ratio is seen in the blood when consuming a carbohydrate rich diet, because carbohydrates trigger insulin secretion. Reduction of I/G ratio, however, can be seen when consuming a protein rich diet. A study on dogs found that 17 out

of 20 amino acids, the building blocks in protein molecules, resulted in rise of glucagon secretion [43]. In another study, rats fed on high-protein diets had increased glucagon concentrations compared to rats on other diets [44]. Thus, dietary proteins might trigger glucagon release. If this is the case, the ratio of protein to carbohydrate in each meal will affect the I/G-ratio. Overnutrition, consuming excess kcal during one day or one meal, affects the I/G-ratio as it increases insulin requirements and may over time result in obesity. The pancreas fulfills these requirements by increasing insulin secretion. Overnutrition and obesity may also contribute in the development of metabolic inflammation [45], defined by Gregor and Hotamisligil [46] as *"low-grade, chronic inflammation by metabolic cells in response to excess nutrients and energy."*

1.1.2.2 Inflammation may strengthen development of metabolic syndrome

As mentioned above, overnutrition, independent of macronutrient composition, may result in excess body weight and contribute to the development of metabolic inflammation. This inflammation strengthens development of metabolic syndrome (MetS), which triggers development of T2D and cardiovascular diseases (CVDs) [47]. There are several definitions on MetS and the definition proposed by the Adult Treatment Program III (ATP III) is described in box 1.1. Definition on children set by the International Diabetes Federation is explained in box 1.2.

Box 1.1 Definition on MetS as described by ATP III. Information collected from [48].

MetS is identified when having three out of these conditions:

- abdominal obese: WC > 102 cm for men; WC > 88 cm for women
- triglyceride level ≥ 150 mg/dL
- high-density lipoprotein concentration (HDL-C) < 40 mg/dL in men; < 50 mg/dL in women
- systolic blood pressure (SBP) ≥ 130 mmHg and/or diastolic blood pressure (DBP) ≥ 85 mmHg

Box 1.2 Definition on MetS in children set by International Diabetes Federation. Information collected from [49, 50].

> **MetS in children is defined as**
>
> - being abdominal obese: ≥ 90th percentile using WC
>
> and having at least two out of these disorders:
>
> - triglycerides ≥ 1.7 mmol/L
> - HDL-C > 1.03 mmol/L
> - SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg
> - serum fasting glucose ≥ 5.6 mmol/L

In obese subjects, macrophages; immune system cells, are present in much higher numbers in adipose tissue than in lean subjects (figure 1.5) [47], and "*the percentage of macrophages in adipose tissue is positively correlated with adiposity and adipocyte size*" [51]. An adipocyte is an "*animal cell specialized for fat storage, containing large globules of fat (triacylgylcerols) in the cytoplasm*" [52]. Macrophages are the major source of inflammatory mediators and are responsible for nearly all adipose tissue expression of tumor necrosis factor (TNF)-α [47, 51]. TNF is a pro-inflammatory cytokine that binds to TNF receptors and activates a pathway producing nuclear factor kappa B (NFκB). NFκB translocates into the nucleus and turns on transcription of several genes that participates in inflammatory responses [51, 53]. Inflammation is necessary to fight off infections as it starts various cascades of cytokine production to kill off the infection. Problem is when cytokines are present without any infection, as this may result in metabolic inflammation.
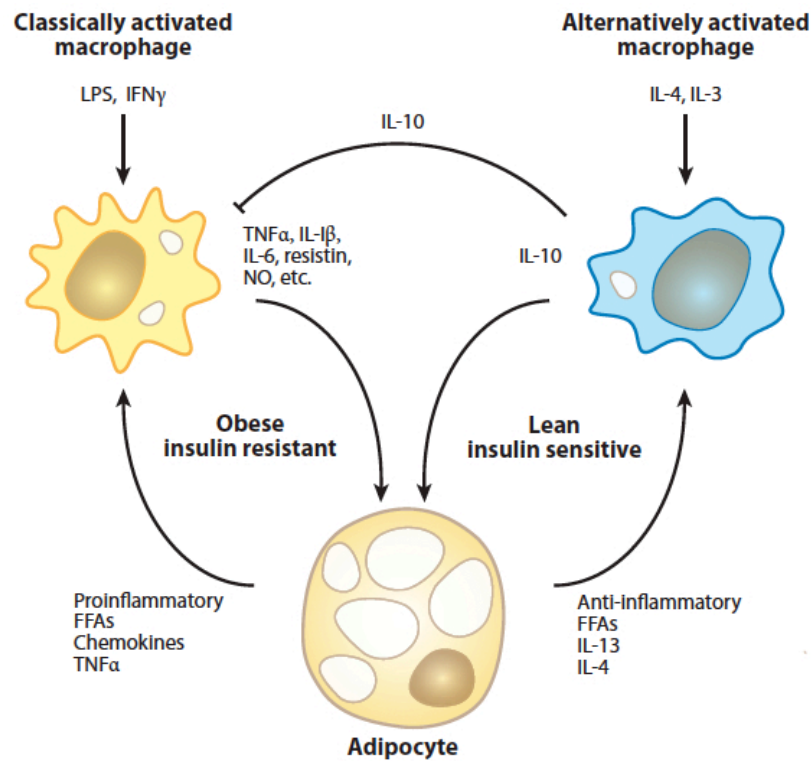
Figure 1.5 Adipocytes in lean subjects secrete anti-inflammatory factors such as interleukin (IL)-4 and -13. These promote alternative activation of macrophages, which secrete anti-inflammatory mediators, such as IL-10. Obesity triggers changes in adipocyte metabolism and gene expression, and adipocytes in obese subjects secrete pro-inflammatory free fatty acids (FFAs) and factors that recruit and activate macrophages. These macrophages produce large amounts of pro-inflammatory mediators, such as TNF-α and IL-1β that act on adipocytes and induce an IR-state. A positive feedback loop further strengthens inflammation and IR. Thus, lean individuals have less inflammatory responses due to adiposity than obese subjects [47].

Obesity is characterized by low grade inflammation; in addition to being storage of excess kcal, adipose tissue actively secrets free fatty acids (FFAs) and polypeptides such as hormones and cytokines [38]. Figure 1.5 shows how adipocytes in obese subjects function by producing pro-inflammatory FFAs and other factors that activates macrophages. This will in turn produce large amounts of pro-inflammatory mediators such as TNF-α, interleukin (IL)-1β, IL-6, plasminogen activator inhibitor-1 (PAI-1), and resistin [47, 54]. These pro-inflammatory mediators increase leptin synthesis, which, as previously mentioned, makes the hypothalamus reduce appetite when energy is being consumed. The hypothalamus' response reduces further food intake, increases energy expenditure and decreases metabolic efficiency [8]. Studies show that leptin levels increase during inflammation and also acts in macrophages by inducing synthesis of eicosanoids [8]. Eicosanoids are lipid mediators involved in the regulation of inflammation and are mainly produced from arachidonic acid (AA) bound to phospholipid molecules in the cell membrane [51, 55]. AA is released by the activity of

phospholipase A_2 (PLA$_2$). PLA$_2$ hydrolyzes membrane phospholipids, resulting in a released USFA; often being AA, from the sn-2 position of membrane phospholipid (figure 1.6) [56]. Eicosanoids may be both pro-inflammatory and anti-inflammatory, but in the case of AA, they are mainly pro-inflammatory [51]. AA is an omega-6 (n-6) polyunsaturated fatty acid (PUFA) produced from dietary LA found in vegetable oils and animal fat [57, 58]. Eicosanoids in the prostaglandin (PG) 2-series such as PGE$_2$, produced from AA, increase production of TNF-α, IL-1, and IL-6 [57]. Thus, even though LA is an EFA (section 1.1.2), it is important to keep intake at a controlled level. Saturated fatty acids (SFAs) also induce pro-inflammatory responses proven through deletion of immune receptor toll-like receptor 4 in obese individuals resulting in impaired inflammation. FFAs stimulate these receptors and initiate immune response [47, 51].
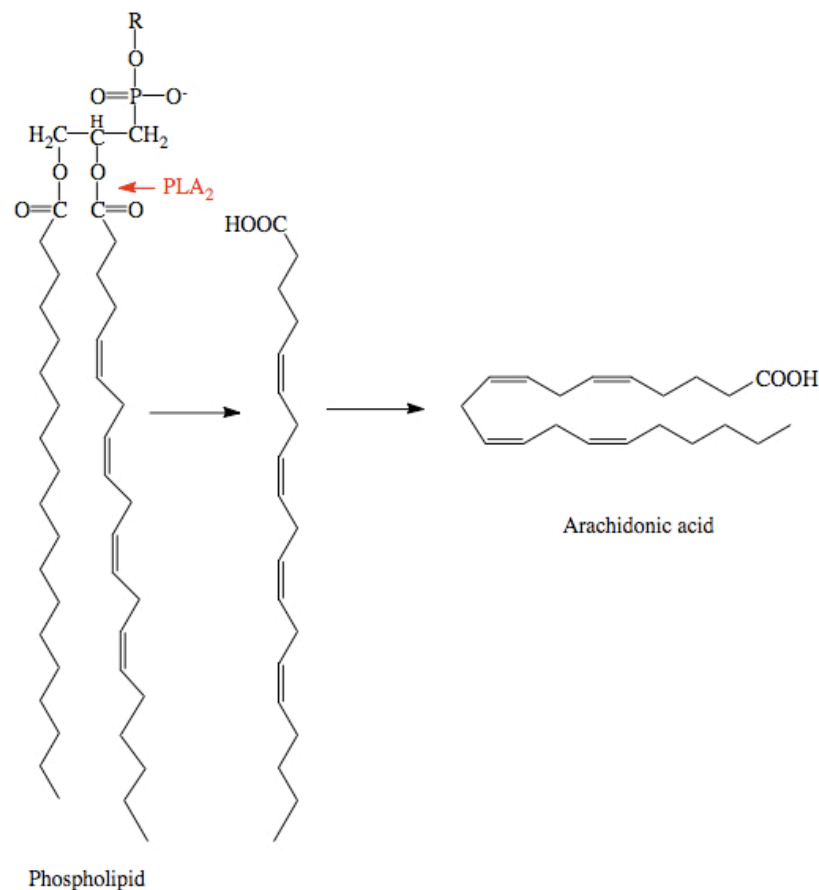

Figure 1.6 AA is synthesized from phospholipid in the cell membrane when activated PLA$_2$ hydrolyzes the phospholipid in the sn2-position.

Omega-3 (n-3) PUFAs are anti-inflammatory as opposed to SFAs and n-6 PUFAs. For example, eicosapentaenoic acid-derived eicosanoids have anti-inflammatory effects as well as inhibiting effects on the synthesis of pro-inflammatory eicosanoids, such as PGE$_2$ and thus

counteracts the effects of n-6 PUFAs [57, 59]. Consequently, it is important to keep a low n-6:n-3 ratio and SFA intake in every meal, to maintain a balance of pro- and anti-inflammatory eicosanoids. It is also important to restrict trans fatty acid (TFA) intake. TFA is made during hydrogenation of vegetable oils, stabilizing polyunsaturated oils. Fast foods, bakery products, and fried foods typically contain high TFA content [60, 61]. Various results have been presented regarding TFA and inflammatory responses. Nevertheless, one study using the NHSI and -II showed relations between TFA intake and TNF concentrations. It was found that women with higher BMI also displayed positive associations between TFA intake and IL-6 concentrations [60]. Another study also using the NHS found the same associations between TNF and IL-6 concentrations and resistin levels [62].

Pro-inflammatory cytokines seem to suppress anti-inflammatory mechanisms. Both TNF-α and IL-6 have proved to suppress adiponectin expression. Adiponectin is an adipokine secreted by adipocytes and has anti-inflammatory properties [62]. It circulates in the bloodstream in three different forms: trimer, hexamer, and high-molecular weight. In contrast to other adipokines, such as leptin, adiponectin is under-expressed in T2D patients. Moreover, the high-molecular weight form is the form that is most related to insulin sensitivity. Some *in vitro* (test tube) studies show that adiponectins reduce TNF-α induced inflammatory responses [63]. All of the adiponectins function mainly through their receptors AdipoR1 and AdipoR2, and signaling through AdipoR1 promotes insulin sensitivity [63, 64]. This may explain lower expression of AdipoR1 revealed in T2D patients [65].

Inflammation is related to fibrinolysis, mainly through the cytokines TNF and PAI-1. TNF and PAI-1 concentrations seem to affect each other and when TNF were infused in mice, PAI-1 concentration increased [66]. PAI-1 inhibits plasminogen activators, mainly tissue-type plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA). These play an important role in the fibrinolysis cascade where they are accountable for the final degradation of fibrin and extracellular matrix proteins. PAI-1 is the most important inhibitor and is produced in macrophages and adipocytes, among others. It is mainly stored in platelets from where they can be released into the bloodstream. It has been found in *in vivo* (in a living organism) studies that an increased expression of PAI-1 suppresses fibrinolysis, resulting in pathological fibrin deposition and tissue damage. Inflammatory cytokines, growth factors, and hormones affect PAI-1 activity (figure 1.7). As excess adipose tissue up-regulate the expression of pro-inflammatory cytokines, obesity is related to impaired fibrinolysis by increasing the production of PAI-1 [67].
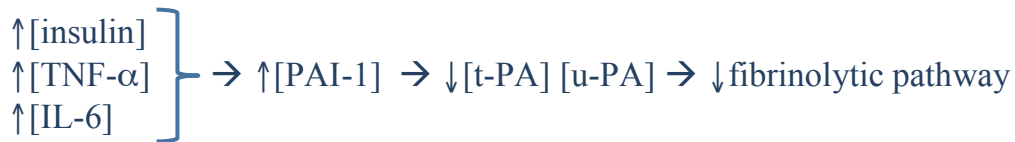
$$\left.\begin{array}{l} \uparrow[\text{insulin}] \\ \uparrow[\text{TNF-}\alpha] \\ \uparrow[\text{IL-6}] \end{array}\right\} \rightarrow \uparrow[\text{PAI-1}] \rightarrow \downarrow[\text{t-PA}]\,[\text{u-PA}] \rightarrow \downarrow \text{fibrinolytic pathway}$$

Figure 1.7 Increased amounts of cytokines such as TNF-α and IL-6, in addition to hormones such as insulin triggers increased PAI-1 concentrations. This increase leads to reduced t-PA and u-PA concentrations. Thus, inflammation inhibits fibrinolysis.

Mertens et al. [54] have showed that people with MetS risk factors have higher concentrations of PAI-1 compared to people without MetS risk factors (figure 1.8). Differences in PAI-1 concentrations are also seen in obese and non-obese individuals; Erikson et al. [68] used biopsy to test PAI-1 expression and found that obese participants had a mean of 36 U/mL versus 5.6 U/mL in non-obese participants. Thus, obesity is an indicator of increased PAI-1 expression.
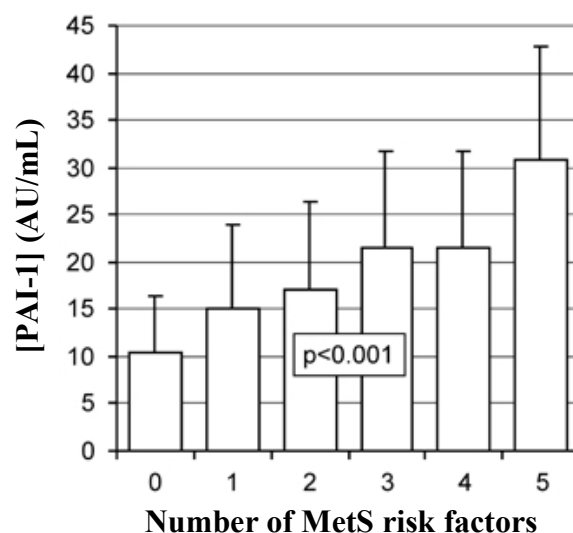

Figure 1.8 People with increased number of risk factors have increased PAI-1 concentrations (AU: arbitrary units). Risk factors being those described in box 1.1. Altered, from [54].

The chronic activation of pro-inflammatory pathways often seen in obese individuals induces IR, often resulting in T2D. Thus, metabolic inflammation may escalate progression of metabolic diseases such as CVDs or T2D (figure 1.9) [47].
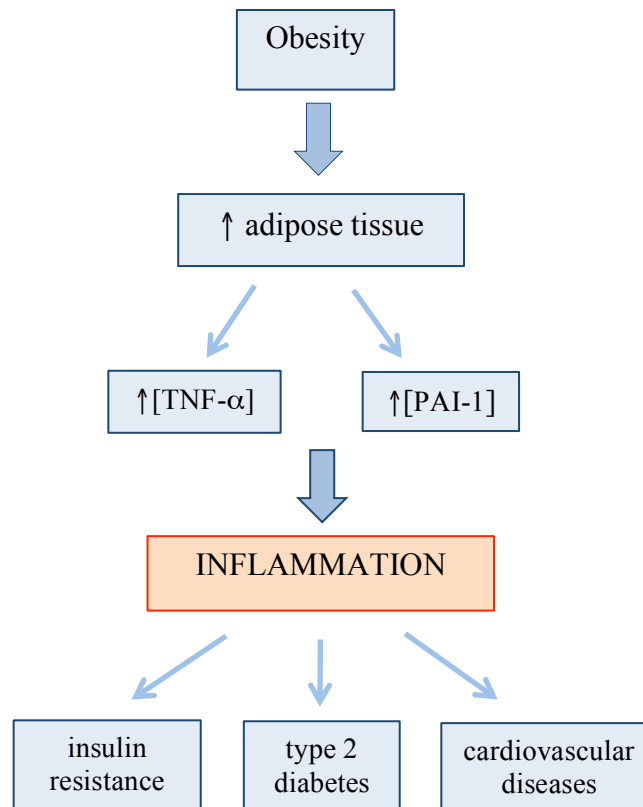
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                    ┌──────────────┐
                    │   Obesity    │
                    └──────────────┘
                           │
                           ▼
                  ┌──────────────────┐
                  │ ↑ adipose tissue │
                  └──────────────────┘
                      ↙         ↘
           ┌───────────┐      ┌───────────┐
           │ ↑[TNF-α]  │      │ ↑[PAI-1]  │
           └───────────┘      └───────────┘
                       │
                       ▼
              ┌────────────────────┐
              │   INFLAMMATION     │
              └────────────────────┘
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       ┌──────────┐ ┌──────────┐ ┌──────────────┐
       │ insulin  │ │ type 2   │ │cardiovascular│
       │resistance│ │ diabetes │ │  diseases    │
       └──────────┘ └──────────┘ └──────────────┘
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Figure 1.9 Expansion of adipose organ during obesity is responsible for increased inflammation. Over time, this inflammation strengthens development of diseases such as CVDs, IR, and T2D. Inspired by [69].

1.2 The industrialization process results in increased occurrence of lifestyle diseases

Metabolic diseases are *diseases of affluence* or *lifestyle diseases*. Lifestyle diseases include obesity, T2D, and raised blood pressure and cholesterol levels, all of which are risk factors of CVDs and often seen in people with high income. These risk factors often appear during the industrialization process when life expectancy is prolonged, parallel to the *Western disease paradigm*; a shift from infectious diseases to lifestyle diseases. Changing nutritional patterns in developing countries following this paradigm may have great effect on development of diseases such as T2D and CVDs [70].

1.2.1 Inflammation strengthens development of type 2 diabetes

Increased pro-inflammatory responses are seen with increased adipose tissue. The cytokines produced in adipose tissue make cells more resistant to insulin, resulting in higher insulin

production. The higher insulin production will in turn increase the cytokine production and may result in metabolic inflammation and strengthened development of IR and T2D [38, 47].

Diabetes is a chronic disease that develops over a long period of time and is therefore more common in older people. An unhealthy diet, physical inactivity and exposure to smoke from cigarettes among others, contributes to the development of diabetes. A rapid unplanned urbanization and globalization of unhealthy lifestyles also force the development. Thus, younger age groups may also be affected [71, 72].

Diabetes mellitus is a disease where either the pancreas is unable to produce adequate amounts of insulin or the body cannot effectively use insulin. In an individual without diabetes, insulin is produced as the blood glucose level rises after food intake. As explained in section 1.1.2.1, this insulin stimulates nearly every cell in the body to absorb glucose and thereby reducing blood glucose level to a normal value around 90 mg / 100 mL. If this response is inadequate, the result is raised blood sugar, also known as hyperglycemia. T2D is characterized by target cells that are unable to respond to insulin and therefore do not absorb glucose from the blood [15, 72].

The tissue's responsiveness to insulin, called insulin sensitivity, changes during life, where sensitivity is especially low during puberty, pregnancy, obesity, and at old age. As a reaction, the β-cells produce more insulin, stimulating target cells to absorb appropriate amounts of glucose from the blood [7]. Increased insulin production also occurs in early development of T2D, however, only for a short period of time, as the pancreas does not have the capacity to sustain the hyperproduction. After some time, β-cells' production fails, resulting in a small production of insulin. Since the target cells have low sensitivity, these small amounts are not sufficient to remove glucose from the blood. The result is raised blood glucose level, which may eventually result in IR and T2D [35, 38].

As stated in section 1.1.2.2, there is a relationship between inflammation and T2D. The relationship often appears in obese subjects, and TNF-α was the first link found between obesity and IR. In a study on obese mice, those lacking TNF-α and TNF receptors had improved insulin sensitivity. This has also been observed in humans where obese subjects show higher expression of TNF-α in adipose tissue compared to leaner subjects [11]. IL concentrations are also related to T2D and elevated levels of IL-6 have been confirmed in

individuals with IR and T2D [38]. Moreover, mice lacking IL-1α show lower fasting glucose and insulin levels and improved insulin sensitivity [11].

Some people may be predisposed of developing T2D, especially first-degree relatives of T2D patients as they might develop impaired β-cell function more easily than people without T2D relatives. However, lifestyle and environmental factors appear to be the chief contributors to the obesity and T2D epidemic. Increased kcal intake seems to reduce insulin secretion over time. In addition to regulating glucose absorption, insulin is found to act on the hypothalamus where it controls body weight. Impaired β-cell function may therefore be associated with weight gain and worsening of IR [7].

WHO recommends keeping a healthy body weight by daily exercising for a minimum of 30 minutes of moderate-intensity activity to avoid T2D. Furthermore, having a healthy diet is also recommended; consumption of three or four fruits and vegetables per day, as well as reducing the intake of sugar and SFAs [72].

T2D may result in damage of the heart, blood vessels, eyes, kidneys, and nerves, and it may result in death; about 50% of T2D patients die from CVDs, primarily heart disease and stroke [72].

1.2.2 Lifestyle changes and inflammation strengthen development of cardiovascular diseases

CVDs are disorders of the heart and blood vessels. Heart attacks and strokes are commonly caused by a blockage in blood flow that hinders the flow to the heart or brain [73]. Heart attacks often are result of coronary heart disease (CHD). CHD is a build-up of plaque inside the coronary arteries, where oxygen-rich blood flows to the heart. The build-up is called atherosclerosis and develops over many years. If the plaque rupture it results in a blood clot that may block the blood flow, causing a heart attack [74].

CVDs are the number one cause of deaths on a world basis. As previously mentioned, low- and middle-income countries are most affected where 80% of CVD deaths occur in these countries. WHO states that "*most cardiovascular diseases can be prevented by addressing risk factors such as tobacco use, unhealthy diet and obesity, physical inactivity, raised blood pressure, diabetes and raised lipids*" [73]. Intermediate risk factors such as hyperglycemia and excess weight can easily be measured in care facilities. These facilities might also counsel

patients with increased risk of developing CVDs. WHO recommends "*cessation of tobacco use, reduction of salt in the diet, consuming fruits and vegetables, regular physical activity and avoiding harmful use of alcohol*" to reduce the risks [73].

Low- and middle-income countries may have poorer access to health care services than high-income countries. They are also more exposed to risk factors and they rarely have the same prevention programs as high-income countries [73]. These countries are commonly non-western countries, many found in the east. In China, a hospital admission due to a chronic disease may cost up to half of the annual income of an urban resident, and up to three times as much as a rural residents' income. The high cost may prevent people from seeking health care. However, the Chinese government's reform *Healthy China 2020*'s goal is universal health are in China by the year 2020 [75, 76].

1.2.3   Relative risk and odds ratio are used to estimate risk of diseases in a groups of people

When researching probability of developing different types of diseases, such as T2D and CVDs, different statistical analyses are used. When comparing two absolute risks the ratio between them will give the relative risk (RR). "*Absolute risk is the chance or probability that a woman* (or man) *will develop a specific disease during a specified period of time*" [35]. The top part of the ratio is the participants having a particular characteristic or risk factor. The bottom part is the participants without the risk factor, the reference group. Hence, the size of RR implies the extent to which a particular characteristic increases or decreases risk of the disease in study (box 1.3) [35].

Box 1.3 Conclusions drawn from RR [35].

- **RR=1**: the same percentage of disease is seen in both groups
- **RR>1**: people with the characteristic in study have higher risk of developing disease than the reference group
- **RR<1**: people with the characteristic in study have lower risk of developing disease than the reference group

Odds ratio (OR) is also used when looking at diseases, to "*measure association between an exposure and an outcome. The OR represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that*

exposure" [77]. OR is used to compare the occurrence of a disease when exposed to a specific characteristic. It may also be used to determine if a particular exposure is a risk factor of the disease in study (box 1.4) [77].

Box 1.4 Conclusions drawn from OR. Collected from [77]

> - **OR=1**: exposure does not affect odds of outcome
> - **OR>1**: exposure is associated with higher odds of outcome
> - **OR<1**: exposure is associated with lower odds of outcome

1.3   The eastern world is affected by the western lifestyle

The world is commonly divided into east and west. The western world, called the Occident, is considered to mainly be Europe and North America. The contrast is the eastern world, the Orient, being Asian countries, mainly eastern Asian countries such as China and Japan [12].

For many years, T2D has been considered a western problem and a *disease of affluence*, although this is no longer the case. As stated above, 80% diabetes cases are found in low- or middle-income countries and "*Asia accounts 60% of all the world's diabetes population*" [1, 78].

1.3.1   Asian countries are undergoing the nutrition transition

Several Asian countries are going though the nutrition transition, defined as the "*shift from basic unrefined foods such as pulses, grain, fruit and vegetables, fish or lean meat, to highly processed foods*" [18]. During this transition, daily energy intake is changing; more kcal are consumed and refined carbohydrates and fatty food intake also increase [18]. The nutritional shift may occur in just one decade, making it difficult for the human body to handle as evolutionary adaptations normally takes several generations [18].

In 1994, Popkin proposed five stages in the nutrition transition [79].

1) Collection of Food: This pattern is seen before industrial processes begin, called the pre-agricultural period. It is characterized by a relatively high carbohydrate intake and low fiber and fat intake (especially SFAs, see section 1.3.3). As mentioned in section 1.3.3, protein intake is also relatively high mostly due to a high meat intake. As a consequence of infectious diseases, life expectancy is low.

2) Famine: In this pattern, diet is less varied due to food shortage. Famine often triggers development of agriculture.

3) Receding famine: More animal proteins, fruit and vegetables are consumed while starch intake decreases.

4) Degenerative disease: The diet is high in total fat, cholesterol, sugar and other refined carbohydrates, while low in PUFAs and fiber.

5) Behavioral Change: This is the last stage and here, nutritional patterns move back to a pre-agricultural diet (stage 1). The goal is to increase intake of complex carbohydrates, fruit and vegetables and to reduce intake of refined foods, meats, and dairy products.

The transition from pattern 3 to 4 often appears due to urbanization and results in increased intake of fats, processed foods, and sugars (figure 1.10). This sugar is not necessarily sweet tasting and may be naturally occurring sugars such as starch or added sugar often camouflaged in the nutritional labeling hiding behind names as maltose, syrup or cane sugar [80]. Starch is a polysaccharide made up by glucose molecules. It is the main storage carbohydrate in plants and the largest source of carbohydrate in human food; potatoes, pasta, rice, and bread among others [52, 81]. The increased intake of fats, processed foods, and sugars triggers obesity and increased diet-related, noncommunicable diseases (DR-NCDs). It is preferable to move quickly into pattern 5 where incidences of DR-NCDs are reduced, rather than staying in pattern 4.
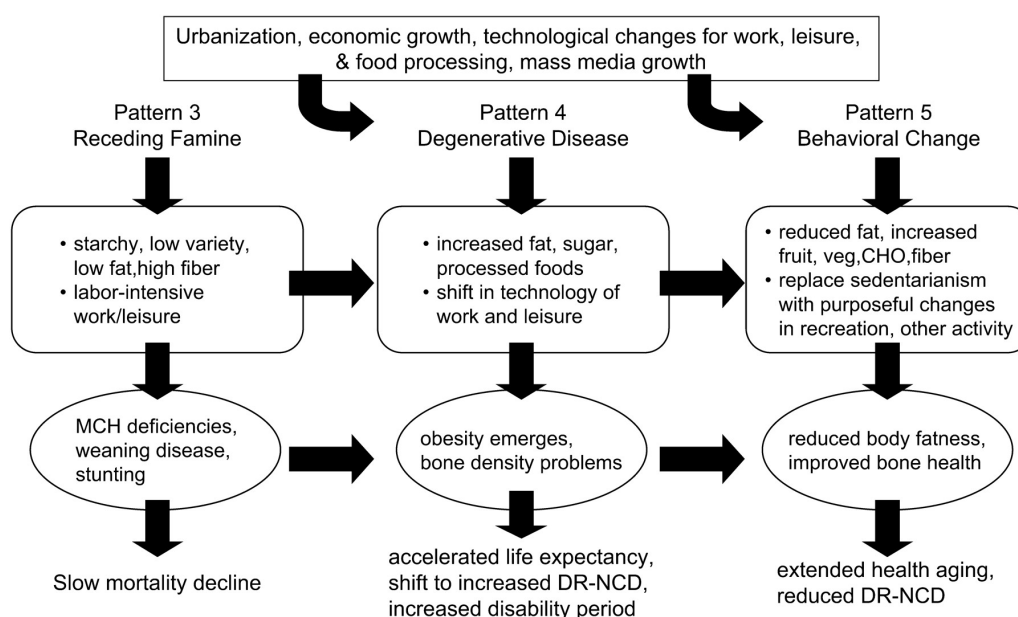

Figure 1.10 Pattern 3 to 5 in the nutrition transition are induced by urbanization and food processing, among others [82].

According to a review article by Holmboe-Ottensen and Wandel [83], South Asians migrating to Europe tend to change their diet towards a more western type; increased intake of fatty and energy-dense foods, substitution of whole grain with refined sources such as carbohydrates, increased intake of meat and dairy products and decreased fruit and vegetable consumption. The altered diet results in higher energy intake, less fiber and lower micronutrient and antioxidant intake. The South Asians changing their diet had higher risk of developing obesity, T2D and CVDs than South Asians that did not change their diet. This indicates that westernization of the east may contribute to increase in lifestyle diseases.

1.3.2 Prevalence of overweight is increasing in the east

BMI values determining overweight and obesity (section 1.1.1) are set based on morbidity and mortality and it reflects the risk of developing T2D and CVDs. Data used to define these cut-off values are predominantly collected from western populations, and it is currently unknown if they are relevant for Asian populations. Some studies have shown that they might not be, and the burden of diabetes related to excess weight might be underestimated in Asia [4]. WHO has proposed separate cut-off values for Asian populations based on studies from eastern countries; 23 kg/m^2 for overweight and 25 kg/m^2 for obesity [84]. Researchers have argued that 23 kg/m^2 is too low as it results in 50% of the Chinese population being overweight. Such high numbers would be a heavy burden to the Chinese society [85]. Zhoud [85] found that 24 kg/m^2 might be a better cut-off point for overweight after comparing risk factors of different diseases and BMI values in the Chinese population. In addition, he recommended 28 kg/m^2 as cut-off point for obesity.

The global BMI has increased for both men and women during the last decades and this trend has also been seen in China [86]. Figure 1.11 shows that urban populations in China have the highest prevalence of overweight [87, 88]. This is alarming as China is urbanizing at a rapid pace [89]. The increase in BMI is also seen in low-, middle-, and high-income groups, where highest occurrence is seen among high-income groups. Figure 1.11 only displays numbers till 1997. Since then the increase has continued: in 2009 21.8% of the Chinese population was overweight or obese according to WHO standards (BMI ≥ 25 kg/m^2). According to Chinese standards (BMI ≥ 24 kg/m^2) 29.9% was overweight or obese [90, 91]. Despite the increase in BMI, China were among the 30% countries with the lowest BMI in 2008 [86].
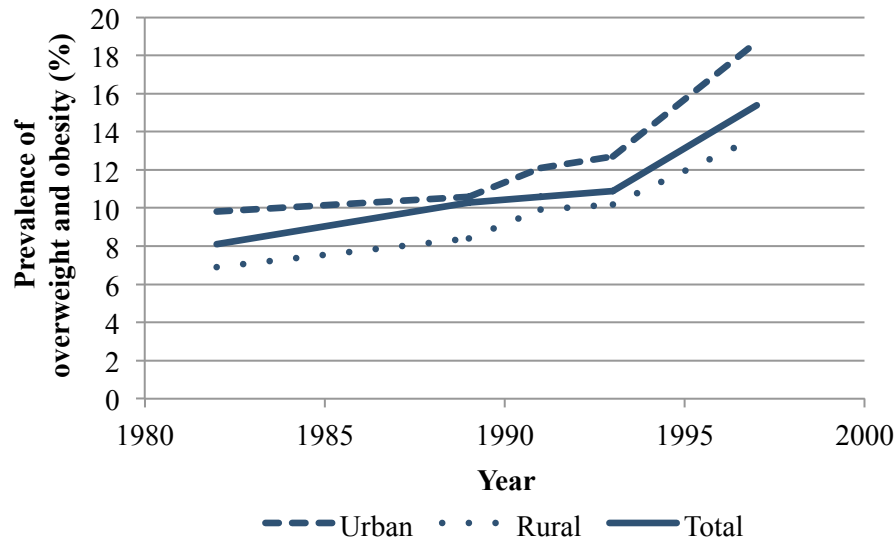
Figure 1.11 Percentage of overweight and obese (BMI $\geq$ 25 kg/m^2) adult Chinese aged 20 - 45 years old, from 1982 to 1997. Numbers collected from [87, 88].

The increase in Chinese BMI has proven to increase the CVD risk factors, such as hypertension and high fasting serum glucose (figure 1.12). The study proving this relationship used participants from different parts of China, in a nine-year follow-up study. The same study also showed that incidences of stroke and CHD increase in parallel to BMI levels.
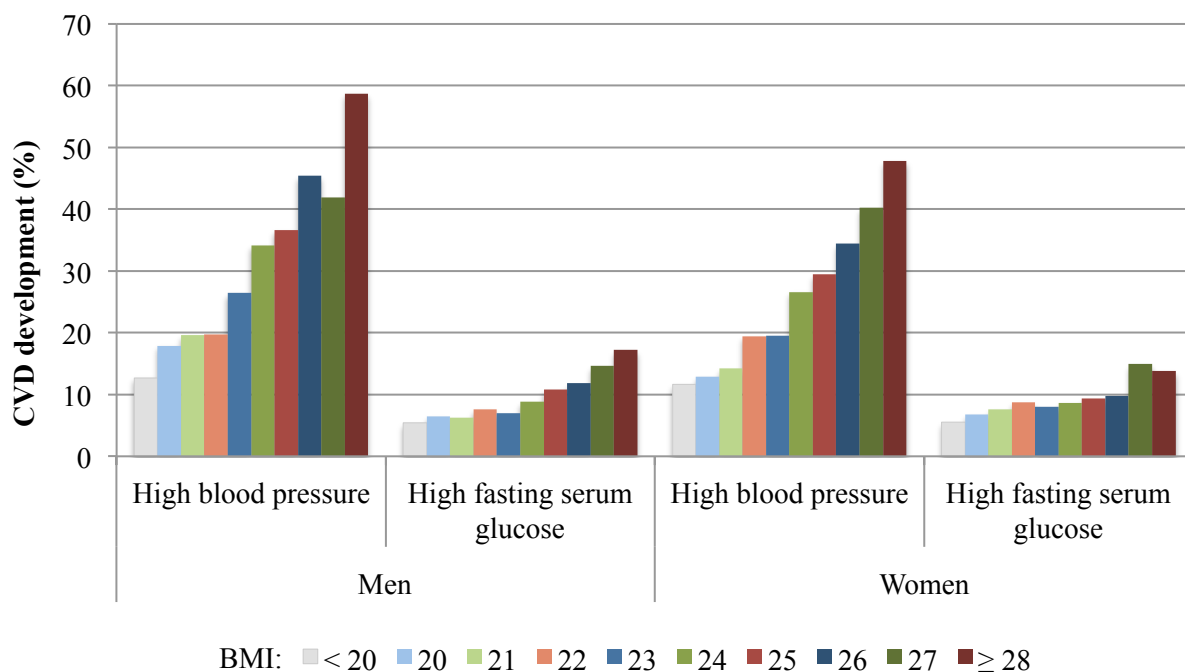
Figure 1.12 Increase in CVD risk factors; hypertension (high blood pressure defined as; SBP $\geq$ 140 mmHg and/or DBP $\geq$ 90 mmHg or taking antihypertensive drugs within the past 2 weeks) and high fasting serum glucose (defined glucose $\geq$ 110 mg/dL) are seen parallel to an increase in BMI. Numbers collected from Zhou et al. [92].

BMI may be a sufficient measurement of overweight and obesity as it measures excess weight in a population. Nonetheless, it does not always reflect reality. The relation between BMI and percentage body fat is affected by age, sex, and ethnicity. Some Asian populations have higher percentage of body fat than Europeans, although BMI is the same [93, 94]. Both individuals in figure 1.13 have a BMI of 22.3 kg/m^2. Yet, dual X-ray absorptiometry imagery reveals differing percentage of body fat: the left person has 9.1% while the right person has 21.2% (figure 1.13). This might be explained by their different lifestyle as the left person runs marathons and the right person keeps his activity level at a minimum. Genetics may also be involved; the right person underwent intrauterine undernutrition, which resulted in low birthweight [95]. The key differences point to the fact that BMI does not separate fat from bones and muscles. Therefore, an athlete who has a higher percentage of muscle mass will consequently have a BMI higher than 25 kg/m^2. In addition, BMI does not specify where the excess fat is concentrated, something that varies. Although excess body fat is considered unhealthy, its location plays a crucial role to a person's health. Researchers claim abdominal fat to be the worst type [96-98].
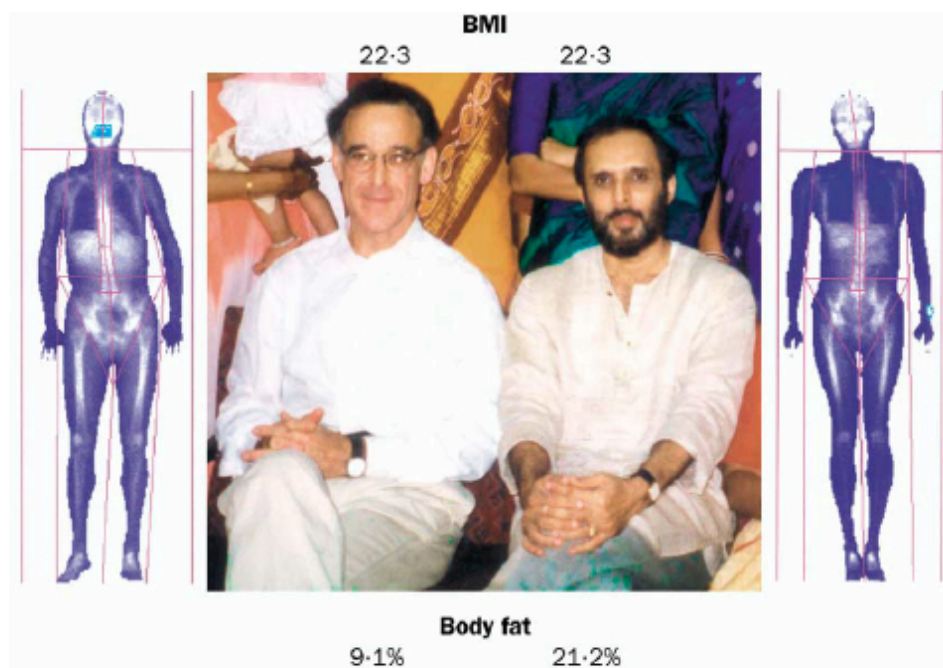

Figure 1.13 Two individuals with same BMI may have different amounts of body fat, as shown in the picture [95].

It has been suggested that measurements indicating abdominal obesity should replace BMI, as it may better indicate risks of CVDs and T2D. Abdominal obesity is characterized by excessive visceral fat and measurements are waist circumference (WC), waist-hip ratio

(WHR), and waist-height ratio (WHtR) [4, 99]. Cut-off points for abdominal obesity based on WC and WHR are presented in table 1.1. These values are calculated using data from Dutch populations and it is not clear if they are true for other ethnic groups [4].

Table 1.1 WC and WHR cut-off points for abdominal obesity set by the WHO, reflecting BMI values 25-29.9 kg/m^2 [4].

	Men	Women
WC	94-101.9	80.0-87.9
WHR	> 0.8	> 0.9

No study found can provide clear answers as to why abdominal fat is the worst type. One research group proposes that resistin levels might partly explain it as it triggers IR in mice [100], but there is no conclusive evidence from humans [62]. Nonetheless, abdominal adipose tissue from humans have higher expression of resistin than adipose tissue from thighs and breast (figure 1.14), and if resistin levels have the same effect on IR in humans as in mice, it would, at least partly, explain the danger of excess abdominal tissue [100].
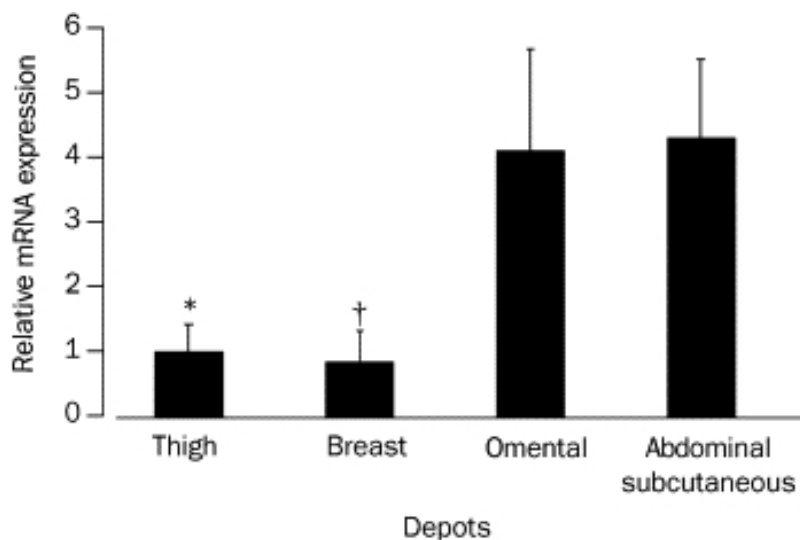

Figure 1.14 Expression of mRNA of resistin varies with localization of adipose tissue [100].

As mentioned above, the relationship between inflammation, obesity, and resistin in humans is still controversial. Another candidate behind the danger of abdominal tissue relates to PAI-1 expression as increased expression is found in individuals with high BMI. Sam and colleagues [101] showed that PAI-1 expression is positively associated with visceral adipose

tissue, even after adjusting for BMI. Thus, the amount of visceral adipose tissue provides more information about fibrinolytic status than BMI. This might be explained by the cytokine secretion in adipose tissue, which increases the PAI-1 expression [67]. Landin and colleagues [102] showed the same relationship; women with WHR higher than 0.8 had increased PAI-1 concentrations compared to women with WHR less than 0.8 (figure 1.15).
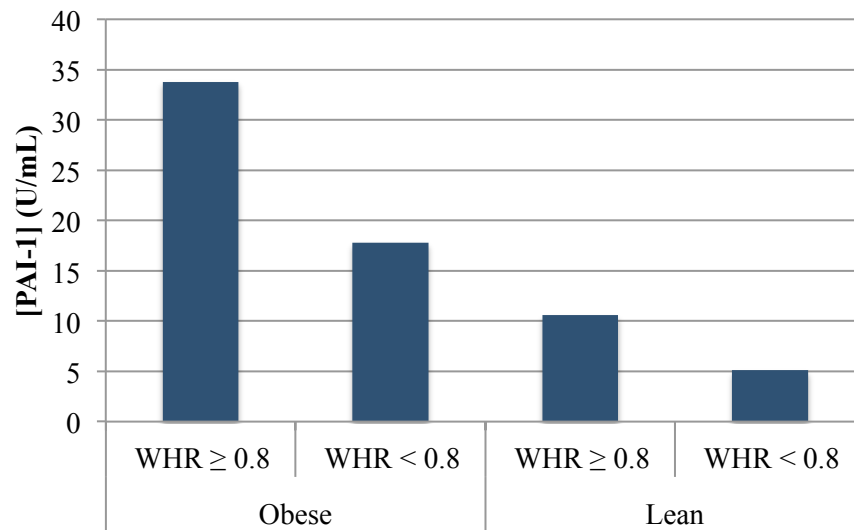

Figure 1.15 Women with WHR ≥ 0.8 have higher PAI-1 concentrations compared to women with WHR < 0.8. Numbers collected from Landin et al. [102].

Abdominal overweight is a growing problem, especially among Asian populations. Asians have kept normal BMI values and have therefore been considered healthy. However, during the last years, an increase in BMI has been observed in China (figure 1.11) as well as an increase in WC [4]. The evolution of humans in the eastern and western parts of the world might partly explain the low BMI values in Asia.

1.3.3 Evolution is a slower process than the nutrition transition

The genus *Homo* has existed for approximately 2 million years, most of the time spent in Africa. Foley [103] displays human evolution through figure 1.16, using paleobiology; "*the study of the biology of extinct plants, animals and microorganisms*" [52].
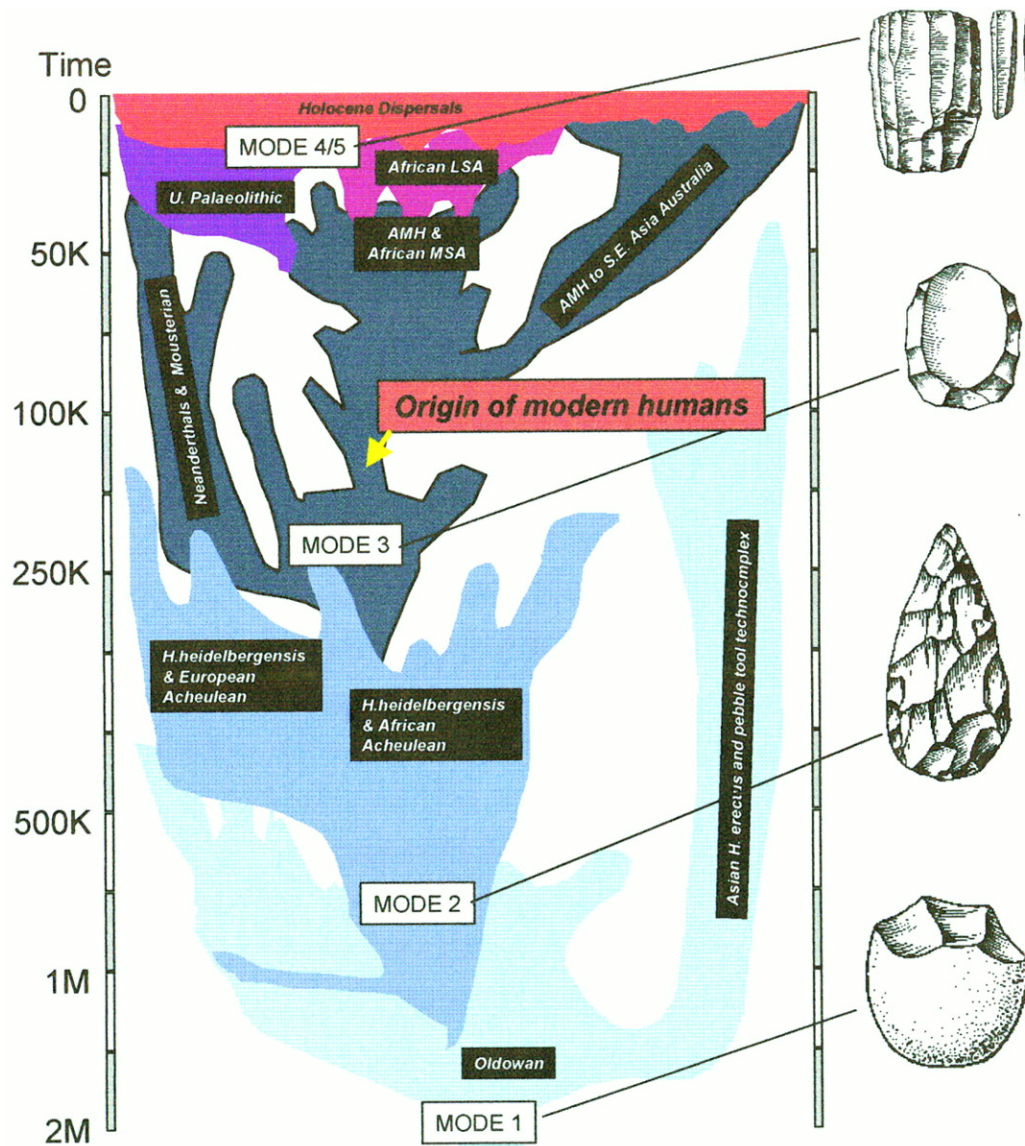
Figure 1.16 Evolution of the genus *Homo* started ~2 million years ago (ya) in Africa. Origin of the modern human dates back to ~175,000 ya. The spread to Asia and Australia happened ~80,000 ya, shown on the top right of the figure, and to Europe for ~60,000 ya; top left [103].

It is wildly accepted that human beings developed in Africa and spread to the rest of the world from there, called the out-of-Africa hypothesis (figure 1.17). This has been verified genetically; more variation is found in African populations compared to the rest of the world, due to the bottleneck, also called founder effect. Furthermore, non-African genetic variation is often a subset of African variation. Exactly how humans spread is not clear, but a coastal-hypothesis has arisen, claiming a spread along the coast to Eurasia, over to Australia and Asia [103]. The earliest modern humans in East Asia are dated back to ~30,000 years ago (ya), and some archeological evidence suggest that modern humans were present in South Asia as early as 60,000 ya [103, 104].
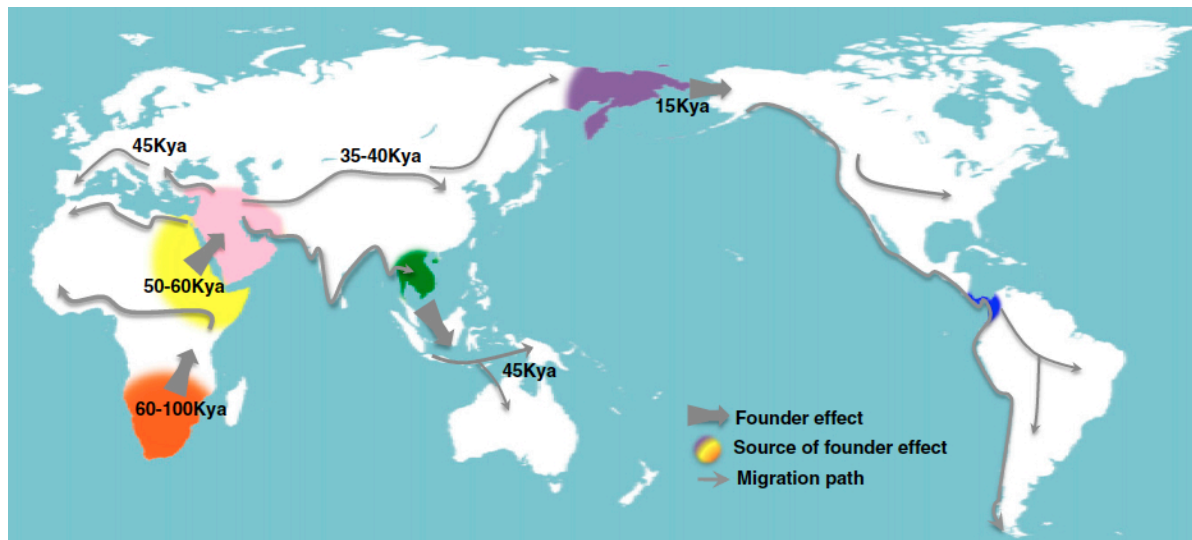
Figure 1.17 The out-of-Africa hypothesis supposes that *Homo* developed in Africa and spread throughout the world from there. This figure shows a time estimate for the spread [105].

Exactly when humans wandered out of Africa is not clear. Nonetheless, time estimates are given. According to figure 1.17, emigration started ~50-60,000 ya. Settlement in Asia is estimated to have been ~35-40,000 ya. American settlement originated in Asia and consequently appeared later; ~15,000 ya [105]. Thus, Asians might be better adapted to their environment than Americans.

Present-day living has developed in a short amount of time, triggering evolutionary concerns considering the human genome. The period were *Homo* evolved is called *paleolithic* and began more than 2 million ya expanding to ~10,000 ya, when humans started agriculture [27]. The combination of "*ancient, genetically determined biology and the nutritional, cultural, and activity patterns in contemporary Western populations*" has resulted in many of today's *diseases of civilization* [106]. In a hunter-gatherer society, diet varies with climate, temperature, season, and geographic location. This variation is not as apparent after introduction of agriculture, and later the Industrial Revolution and the *fast food revolution* [27, 106]. Several types of food eaten today were never a part of the pre-agricultural diet, also called *paleo-* or *hunter-gatherer diet*. Examples are cereal, refined sugar, vegetable oils, dairy products, and salt, all of which largely contribute to the *western diet* today [106].

Some foods from the Paleolithic times are part of today's diet. However, foods such as meat have altered content. Quantity of body fat in a wild animal varies with body mass, age, sex, and season. Normally, the dominant FAs in adipocytes are SFAs, while PUFAs and monounsaturated fatty acids (MUFAs) are dominant in muscles and other organs. As body fat

percentage is low most of the year, PUFAs and MUFAs predominate in wild animals. Today, the agricultural technology has changed most meat consumed; a domestic steer can be slaughtered 14 months old weighing 545 kilograms, containing higher amounts of body fat compared to a wild animal at the same age. Thus, meat in the western diet have high SFA content and may trigger inflammation (section 1.1.2.2) [106]. The increase in SFA intake was shown by Simopoulos [107] using cross-sectional analysis (figure 1.18). An increase in n-6 intake was also seen, parallel to a reduction in n-3 intake. Hunter-gatherers consumed n-6 and n-3 in a ratio close to 1-2:1. Today, this ratio is somewhere between 10-20:1 [106, 107]. As explained in section 1.1.2.2, it is important to keep a nutritional balance of n-6 and n-3 due to their inflammatory responses.
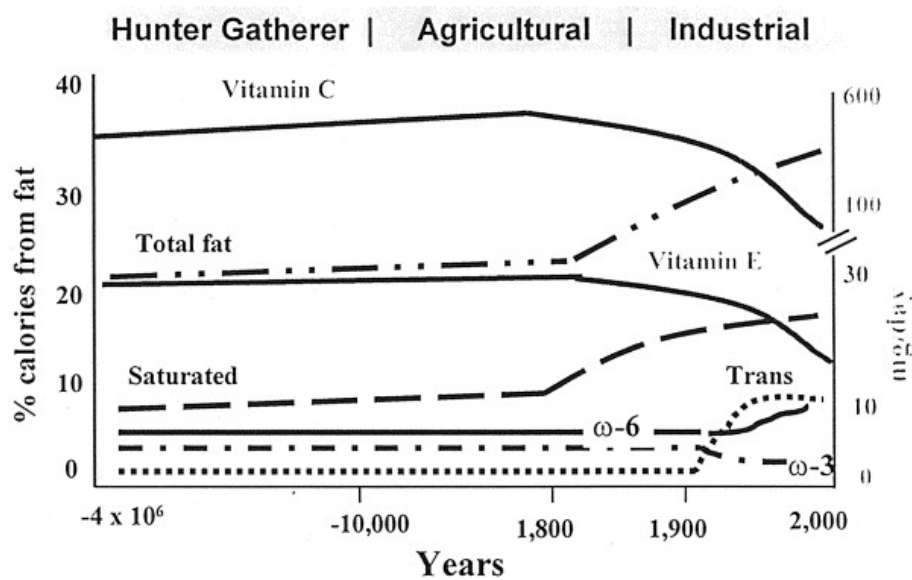

Figure 1.18 The total fat intake has increased since hunter-gatherer times. SFA and n-6 (ω-6) intake has also increased, while n-3 (ω-3) intake has decreased. All shown in percentage of kcal from fat [107].

Fat content of meat is not the only change seen since paleolithic times. Carbohydrate intake among hunter-gatherers is estimated to be lower than today's recommendations (table 1.2). The lower carbohydrate intake might partly explain the better insulin sensitivity and lower BMI and WHtR values observed in hunter-gatherers. Lower incidences of chronic diseases such as T2D and CVDs are also reported [108]. With this in mind, Frassetto and colleagues [27] studied sedentary, slightly overweight men and women on a paleolithic diet; free of cereal grains, dairy, and legumes. Without any weight loss or increased activity level, participants had reduced fasting plasma insulin concentration and improved insulin sensitivity [27].

Table 1.2 Recommended macronutrient intake from The Food and Nutrition Board (FNB) and estimated paleolithic macronutrient intake. Numbers collected from [109, 110].

	FNB	Paleolithic diet
Fat	20-35	28-58
Carbohydrates	45-65	22-40
Proteins	10-35	19-35

Today's women have more body fat and less muscle mass compared to Stone Age women. Eaton and colleagues [111] suggest that insulin receptors and the percentage body fat might explain the increased risk of developing T2D seen in women today. Insulin attached to one insulin receptor is unavailable to other receptors. Since muscles and adipose tissue have the same type of receptors they compete for insulin circulating in the blood. An activated receptor in muscles induces 7-10 times more glucose clearance than an activated receptor in adipose tissue. Thus, lean, muscular individuals have improved insulin sensitivity compared to obese individuals. Increased amounts of adipose tissue results in raised insulin production per carbohydrate load; illustrated in figure 1.19. Location of adipose tissue also determines which receptors *win the competition* and bind more insulin. Adipose tissue around the liver is neatly localized, close to the pancreas. Thus, more fat around the liver means that less is sent to other parts of the body, as opposed to abdominal lean individuals where less insulin is taken up immediately after secretion. This might help explain the importance of abdominal measurements, put forward in section 1.3.2.
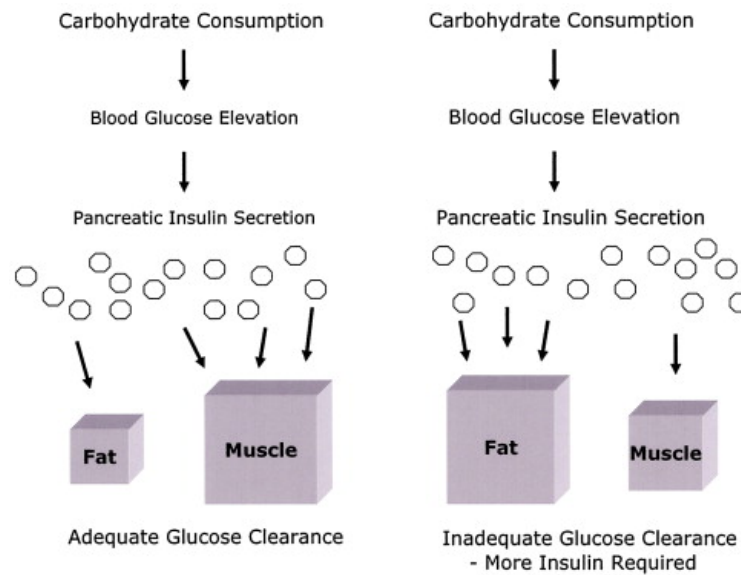
Figure 1.19: Difference in glucose absorption by an individual with low fat mass/high muscle mass vs. high fat mass/low muscle mass [111].

1.3.4   Phenotypic plasticity may increase development of type 2 diabetes

Another part of the evolutionary changes is phenotypic plasticity; "*the range of variability shown by the phenotype in response to environmental fluctuations*" [52]. It is thought that epigenetic changes in the fetus during pregnancy may affect later life events. Epigenetic change is "*viewed as an adaptive mechanism by which the developing organism adjust its metabolic and homeostatic systems to suit the anticipated extrauterine environment*" [112]. Thus, the fetus develops according to the mother's environment, preparing for life after birth. Metabolic adaptation becomes harmful when the environment later in life differs from the mother's environment during pregnancy. If individuals exposed to malnutrition *in utero* and during childhood eat abundant later in life they might be predisposed and can therefore more easily developing T2D. The thrifty phenotype hypothesis was coined over 20 ya when a research group found a relationship between low birthweight and development of impaired glucose tolerance in men from Hertfordshire. The hypothesis proposes that T2D mainly develops due to environmental factors [112, 113].

Hales and Barker [113] suggest that malnutrition *in utero* results in poor development of β-cells' mass and function. If a malnourished fetus grows up to be thin and still malnourished, high insulin-sensitivity will increase survival. However, if the fetus grows up with abundant food supply, it will trigger overnutrition and the person will easier end up with glucose intolerance due to β-cell dysfunction. Some changes in the fetus may also trigger IR and

eventually T2D (figure 1.20) [113]. Most research have been done on under- or malnourished women, however, overnutrition also seem to affect the fetus [112].
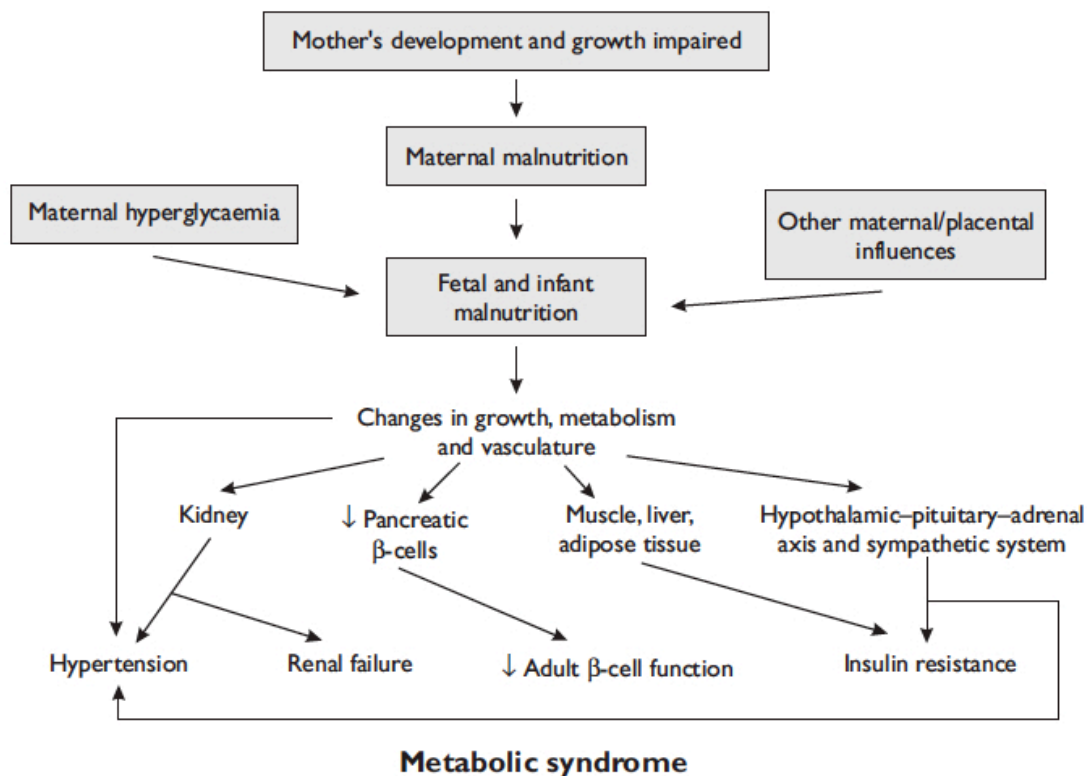

Figure 1.20 This figure, made by Hales and Barker [113], shows how the relation between malnutrition *in utero* might affect fetus as adult, by changing growth and metabolism.

Phenotypic plasticity is part of the natural selection; a concept put forward by Charles Darwin, the founder of evolution. Present-day species are different from previous species due to changes in the genetic composition via allele frequencies. Traits more advantageous to an individual's survival are favored and that individual is more likely to reproduce than others [15, 114]. Conversely, a trait not favorable will make the bearer not reproduce and that trait will disappear. It is therefore reasonable to think that a gene triggering diabetes or obesity would vanish over time. However, there are studies showing genes related to both diabetes and obesity. Of course, if individuals bearing these genes reproduce, they pass on the gene(s) to the next generation, spreading the diabetes-causing gene(s).

1.3.5 Asians may be genetically predisposed to developing obesity and type 2 diabetes

Ethnic differences in development of T2D indicate that some populations may be genetically predisposed. In a national health study, McNeely and Boyko [115] found that Asian Americans are 60% more at risk of developing T2D than whites, after adjusting for age, sex,

and BMI. However, as Chinese Americans have higher diabetes rates than Chinese living in rural China there have to be other factors than genetics [116]. The most popular view today is that lifestyle, such as nutrition, plays the greatest role in the diabetes epidemic.

Obesity tends to run in families and is more common in twins. Thus, genetic factors may also be involved in development of obesity. These genetic factors are thought to be polygenic; "*phenotype characters (such as height in humans) that are determined by the collective effects of a number of different genes*" [52], and therefore have changing expression parallel to environmental factors [13]. Several factors affect obesity, all of which have balance of food intake and energy expenditure at base. As mentioned in section 1.1, the hypothalamus functions as a control system receiving information about energy balance from other cells. The hormones insulin and leptin both seem to be involved in signaling. Leptin is involved in long-term regulation of adiposity, and increasing adiposity may trigger increased levels of leptin [6]. The mouse obesity gene is linked to the leptin production in mice, and the human homolog might have the same effect. Mutations in this gene may therefore trigger obesity [117]. Mutations in genes encoding leptin receptors may explain obesity in the same way [6]. Familial trends might be due to parenting and the family's lifestyle [18].

1.3.6   Culture affects lifestyle

In some cultures, body fat is a sign of good health and good social position. In parts of Africa, young girls are fed on high-fat diets till obese, making them ready for marriage. In Asia, fat is a "*sign of accomplishments, affluence, and social status*" [18].

Culture has developed over a long period of time, and affected dietary habits. China is originally an agricultural country, divided into two groups: north, where they grew millet along grains, and south, where they harvested mostly rice and some other grains. In both groups they collected fruits and vegetables, in addition to hunting and fishing. For approximately 6,000 ya they raised animals such as sheep and pigs, and later chickens and goats, but they rarely ate them. The food culture has changed over time, but they have always enjoyed vegetables, which are used in many meals besides grains and sometimes a few pieces of meat [118].

China was of the first countries to start agriculture with rice as main product, at least in the eastern parts; by the Yangtze River (figure 1.21) [119]. Evidence of rice production is dated back to ~11,000 ya [120]. Yet, establishment of rice agriculture was not seen before ~7,500-

9,000 before present. Analyses from the Jiahu site indicate domestication there; human influenced plants' evolutionary process, intentional or unintentional. Fish bones and some animal bones are also found, indicating that the Jiahu people lived on fishing and gathering, and that domestication products only supplemented their diet. Transition to rice agriculture, intentional influence on plant evolution, was a slow evolutionary process where fishing and gathering activity declined and agriculture increased to be the main food source. To date, the area by the lower Yangtze River is found to be the establishment of rice agriculture. The population increased sharply ~5,000 ya and the need for rice therefore increased. The hypothesis is that agriculture spread to South China from lower and middle parts of the Yangtze River [119].
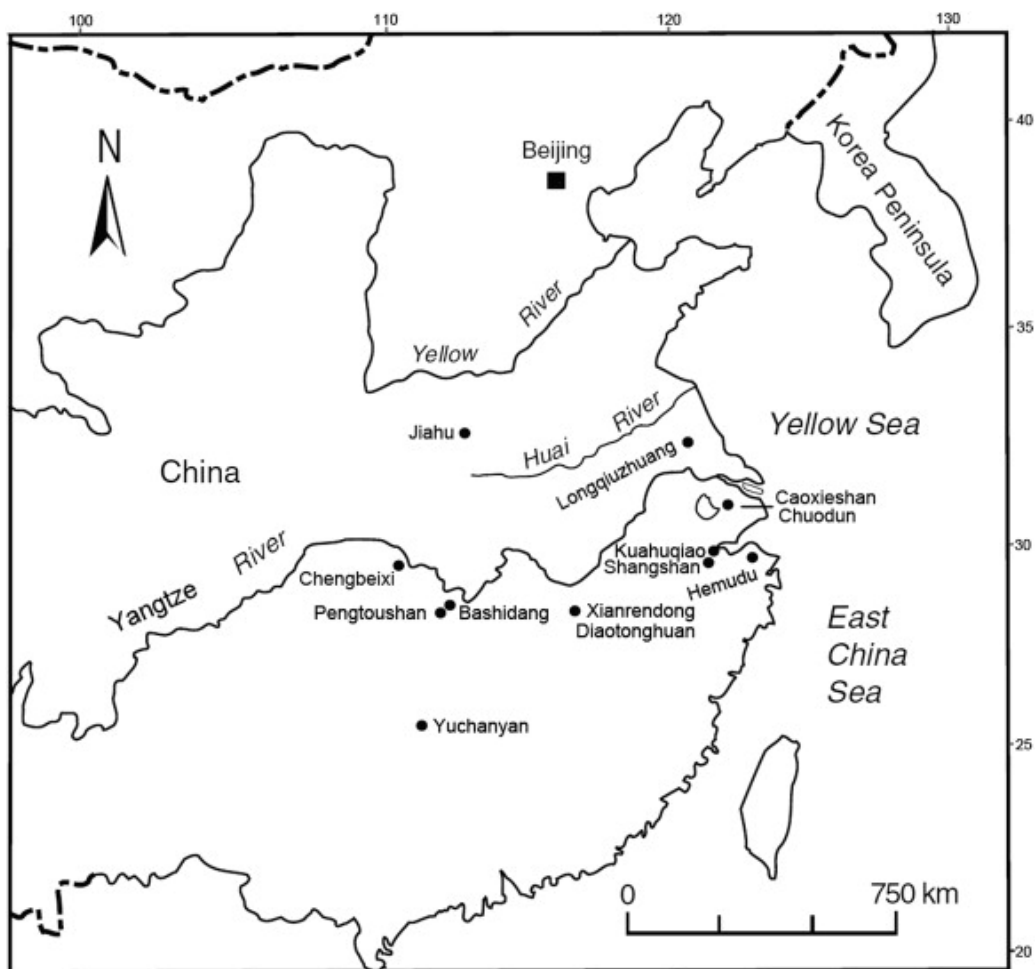

Figure 1.21 Map of China, where important pre-agricultural sites and places of agricultural origin are named [121].

Traditionally, China is a country of rural settlement. Due to their agricultural traditions, eating out has been a rare activity. In addition, the restaurants were limited and too expensive. Most

dining out experiences came with special occasions such as birthdays, weddings, and funerals [118].

In recent years, increased intake of snack food and sweets has been observed. This is food more available in the larger markets, where frozen and prepared foods also are easily accessed. Chinese do not consider snacking to be a meal, since a meal should contain "*grains or staple foods with dishes to flavor them*" [118]. Snacking is not new in China, and they often snack in the morning, when travelling to and from work, and at night. These snacks are often purchased in tiny eateries or street vendors. Food courts have also arisen in China, and often contain different ethnic Chinese food as well as foods popular in Asia and Western countries. Western-style fast food is also increasing in popularity, as is sodas, consumed by children and adults. McDonald's and Kentucky Fried Chicken are popular, the latter one having more costumers every day than in any other worldwide franchises. Some eateries are remaking Chinese food into fast food and fill the needs of many young Chinese people, which often snack instead of having a *real meal* [118].

1.4 Aim of thesis

During the last decades a rapid increase of T2D has been observed in China. Still, China is among the countries having the lowest BMI values in the world. In the western world, lifestyle is mostly to blame for the T2D epidemic. Is the same relationship seen in Asia? This thesis would like to explain the T2D development in Asia by finding conditions triggering the disease development.

The focus of this thesis is the changing lifestyle patterns in the eastern world. Lifestyle is a comprehensive concept and due to nutrition's importance in people's every day life, it will be the main focus when discussing overweight and T2D problems. The definition of the eastern world is too broad for this thesis, and China has therefore been chosen as a representative country. China is currently going through the nutrition transition explained by Popkin, mostly being in pattern 4 (section 1.3.1). In some parts of the discussion Asia in general will be discussed, and where it is applicable, other Asian countries will be used as examples. Mapping China's development may help other eastern countries being in nutrition patterns 1-3, as they can learn from China's pitfalls as well as correct actions. The aim of this thesis is to answer the questions in box 1.5.

Box 1.5 The aim of this thesis is to answer the given questions.

Why do Asians develop T2D?

- How have lifestyle and nutritional patterns changed in Asia, China, over the last 50-70 years? May this explain development of overweight and T2D?

- Are Asians genetically predisposed to T2D? Are there any differences between the eastern and western world?

- What actions are seen from the governments to slow development of overweight and T2D? Are there more that can be done?

2 Methods

Articles from various research areas within molecular biology, genetics, and epidemiology have been used to study the relationship between lifestyle and development of T2D and CVDs in the Chinese population. The search engines Google Scholar, Medline, and ProQuest were used and data were mainly extracted from articles published by the public health society at Harvard of the authors Frank B. Hu, Walter Willett, and Vasanti Malik, in addition to Barry M. Popkin from The University of North Carolina. Furthermore, articles from these authors were used to find other related articles.

In regards to the aims outlined above, this thesis wanted to evaluate China the last 50 years. However, for some topics it has been difficult to find data dated that far back. Many of the articles used cite the *China Health and Nutrition Survey* (CHNS), a collaborative study between the Carolina Population Center at the University of North Carolina at Chapel Hill and the National Institute of Nutrition and Food Safety at the Chinese Center for Disease Control and Prevention. The project was launched to gain information on how economic growth and implementation of various policies affect the health and nutritional status of the Chinese population. Initiated in 1989, the CHNS is an ongoing project where the participants include 26,000 individuals from 4400 households spread over nine provinces. The provinces (figure 3.12) differ in geography, development, public resources, and health indicators [122]. It was desirable to use results from the CHNS, however, due to difficulties around downloading datasets and limited time for analysis, articles using data from the project were used instead. This also applies to similar projects such as The International Study of Macro- and Micro-nutrients and Blood Pressure (INTERMAP) and The International Collaborative Study of Cardiovascular Disease in Asia (InterASIA). The latter project examined CVD risk factors in Asia and included urban and rural regions in the north and south of China [123]. Some nutritional data were collected from FAOSTAT's web page. Food and Agricultural Organization of the United Nations (FAO) has a goal of achieving food security for all, and keeps statistics of nutritional patterns as far back as 1961 [124]. Numbers collected from this source are just indicators as the data are referring to available rather than actual food consumption [125].

The goal has been to use original references. However, in some cases this has proven difficult, mostly due to the time limitation. In addition, there have been difficulties regarding accessibility and language, as some articles are published in Chinese.

3 Results and discussion

The twin epidemic of obesity and T2D in the west is demonstrated in figure 3.1, showing the rise in USA from 1994 to 2010. The escalating problem of T2D is related to the increase in obesity, indicating the relationship, which was explained in chapter 1.
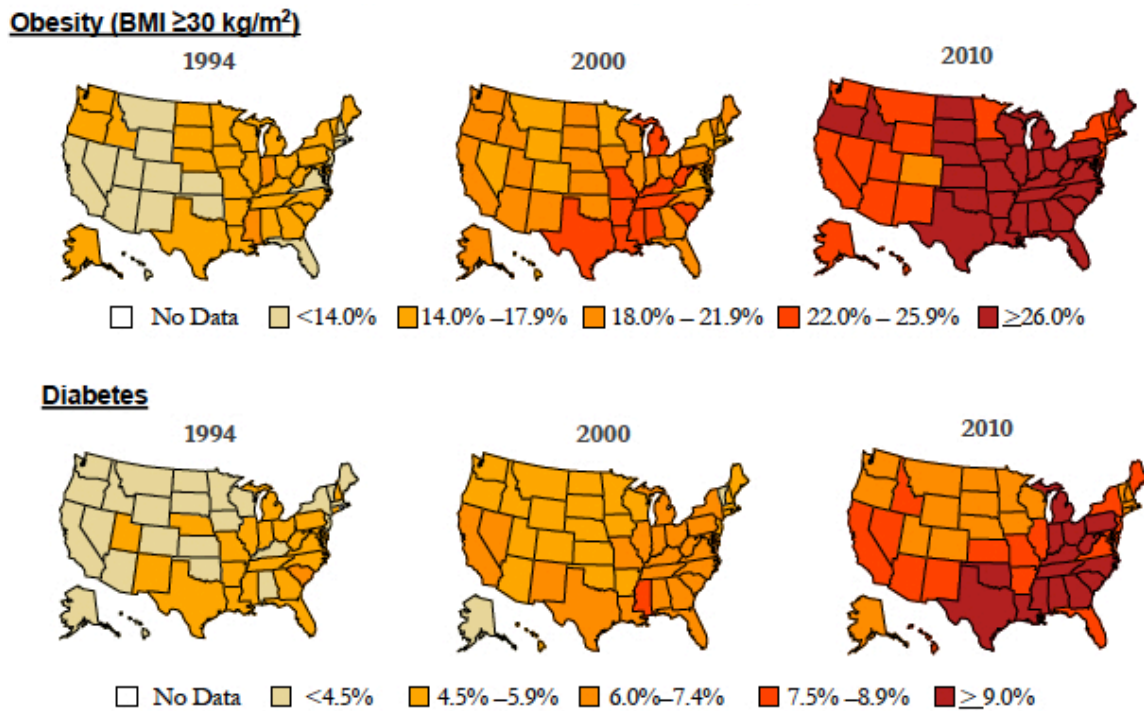
Obesity (BMI ≥30 kg/m²)

No Data | <14.0% | 14.0% – 17.9% | 18.0% – 21.9% | 22.0% – 25.9% | ≥26.0%

Diabetes

No Data | <4.5% | 4.5% – 5.9% | 6.0% – 7.4% | 7.5% – 8.9% | ≥9.0%

Figure 3.1 Obesity prevalence has increased in the US the last couple of decades. In parallel to the rise of obesity occurrence there has been an increase in T2D cases [126].

Along with the nutrition transition in China, a shift from infectious to metabolic diseases is seen, and more Chinese people are diagnosed with T2D (figure 3.2). In the following sections, this thesis will try to partly explain why T2D incidences have increased in China the last decades.
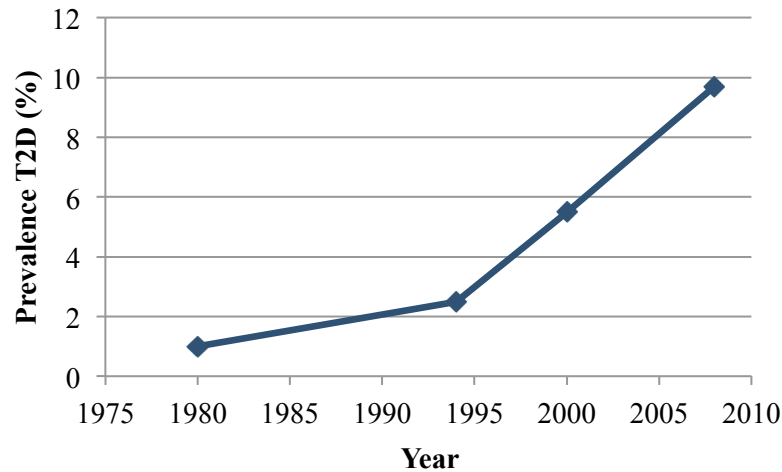
Figure 3.2 An increase in T2D prevalence has been seen in China the last decades. Numbers collected from [78, 127, 128].

3.1 The Chinese body composition has changed

3.1.1 Prevalence of overweight and abdominal obesity is increasing in China

Prevalence of overweight and obesity is increasing in China (figure 1.11); however, occurrence is still low compared to the US (figure 3.3). Comparing T2D incidences, the two populations are almost equal (figure 3.3). Thus, the prevalence of T2D is at the same level in China and USA, even though close to four times as many Americans are overweight or obese.
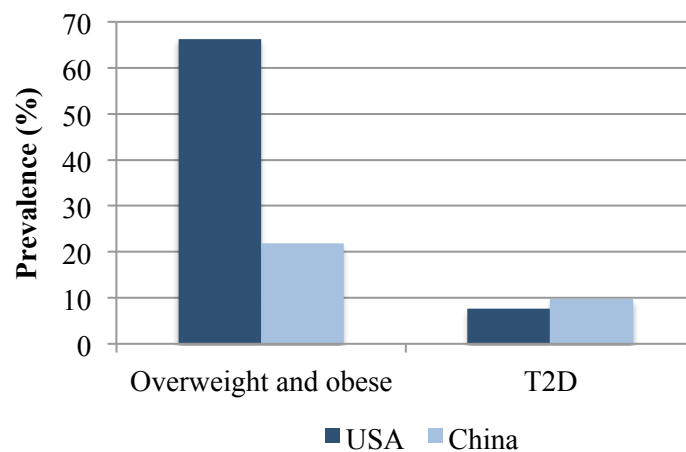
Figure 3.3 Prevalence of overweight and obesity is higher in USA than China, while T2D rates are almost equal. Numbers on USA are from 2006, collected from [129]. Numbers on overweight from China are from CHNS 2002 and collected from [91]. Numbers on T2D in China are from 2008 and collected from [128].

As shown in section 1.3.2 and figure 1.12, prevalence of overweight and obesity is increasing in China. The higher prevalence increases CVD risk factors as it is characterized by constant metabolic inflammation. It also increases T2D risk among the Chinese population (figure 3.4). However, since there are large differences in prevalence of overweight and T2D in China and USA, there have to be other explanations. Figure 3.4 shows that urban life increases the risk (discussed in section 3.2) as well as abdominal obesity.
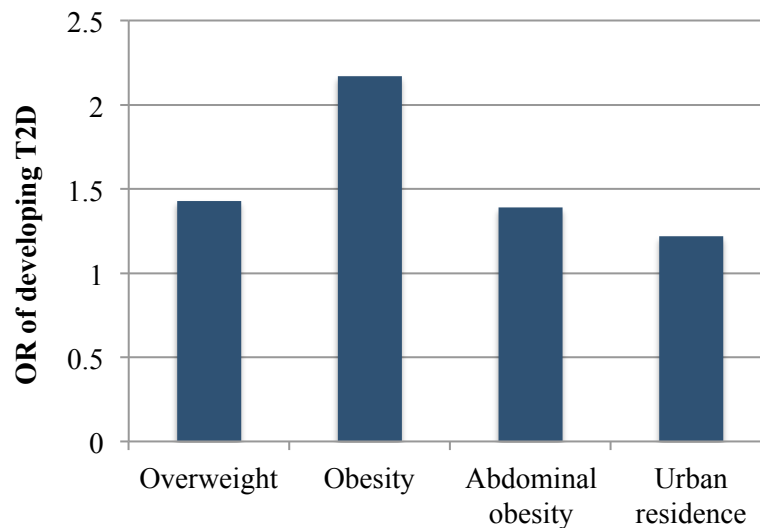
Figure 3.4 The OR of developing T2D is higher among Chinese adults (> 20 years) when overweight (25.0 ≤ BMI > 30), obese (BMI ≥ 30), abdominal obese (WC ≥ 90 cm in men; ≥ 80 cm in women) or when living in an urban area. Numbers collected from [128].

Prevalence of abdominal obesity has increased in China the last decades (figure 3.5). In a study using CHNS 1993-2009, Du et al. [130] found that prevalence of abdominal obesity (WC ≥ 90 cm in men; ≥80 cm in women) was almost doubled from 11.9% to 21.2% in normal BMI individuals.

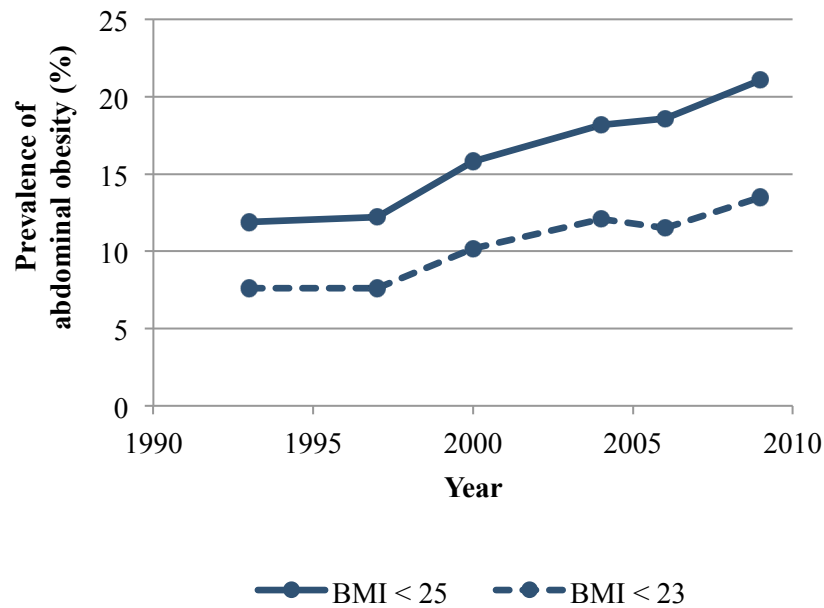**Figure 3.5** Prevalence of abdominal obesity (WC ≥ 90 cm in men; ≥80 cm in women) has increased in normal weight individuals in China from 1993-2009. Numbers collected from [130].

The Chinese population has higher risk of developing MetS at lower BMI levels compared to western populations. They also tend to have more body fat at the same BMI, especially in the abdominal region [93]. Figure 3.6 shows differences in white Americans and Chinese adults; even though total body fat percentage was higher in whites, the Chinese participants had higher percentage of trunk fat; fat in the torso region. Abdominal measurements may therefore be a better predictor of overweight in Chinese and maybe Asian populations in general. After adjusting for age, height, and BMI, Chinese had more body fat and more trunk fat; 3.9% and 12.1% more in men, and 2.3% and 11.8% more in women, respectively, even though the Americans had higher mean BMI value than the Chinese participants [131].
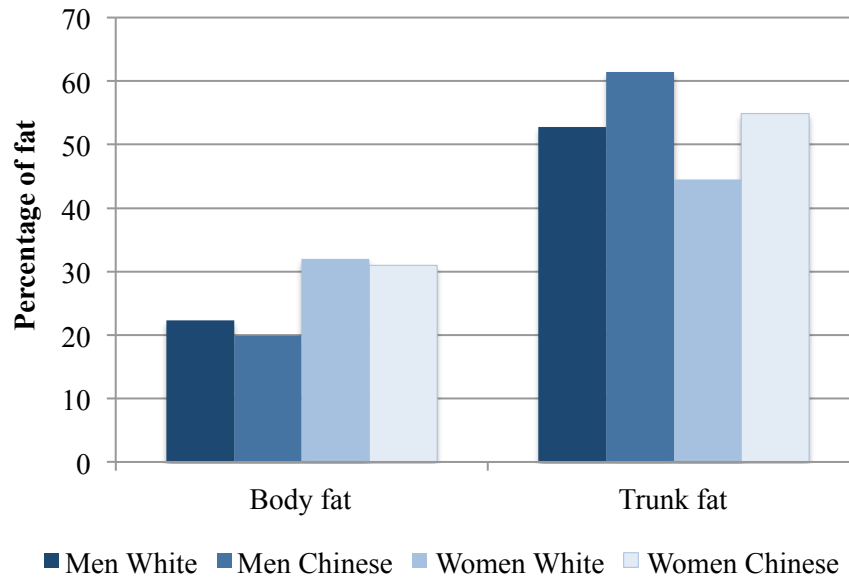
Figure 3.6 Chinese have higher percentage of trunk fat compared to white Americans, even though the Americans have higher percentage of body fat. However, after adjusting for age, height and BMI, Chinese had higher %BF as well. Numbers collected from [131].

Comparing BMI, WC, and MetS have proved that a WC of 80 cm is a good cut-off point in Chinese men and women. With these cut-off points, 46.6% of men and 37.8% of women are abdominal obese in China according to an InterASIA-study [132]. Others have proposed 85 cm as cut-off point for men, reducing prevalence to 30.4%. The studies presented in figure 3.4 and 3.5 used 90 cm as cut-off point for men. Using the cut-off points presented here would give higher prevalence of abdominal obese and therefore probably higher OR of developing T2D.

There are uncertainties to why abdominal fat triggers development of MetS, nevertheless, there are research showing that this is likely to be the case; figure 3.7 clearly shows that WC and WHtR are positively associated to MetS risk factors [93]. It is therefore important to use abdominal measurements when testing for MetS risk. The same study also showed positive association between BMI and MetS. Thus, several measurements might best evaluate the MetS risk.
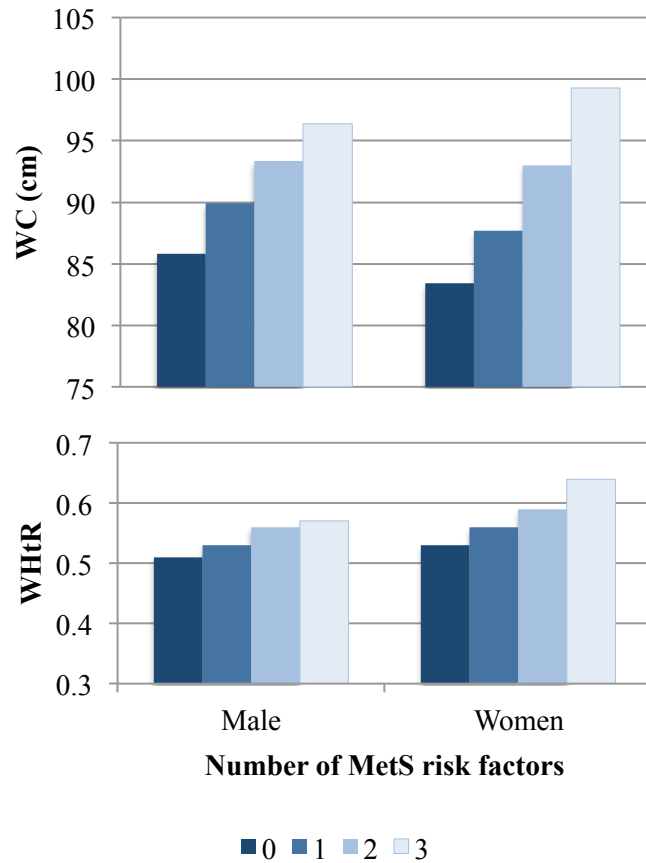
Figure 3.7 Number of MetS risk factors is positively associated with WC and WHtR in Chinese adults in 2008. Risk factors being: (1) high blood pressure; SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg, (2) dyslipidemia; triglyceride ≥ 1.695 mmol/L and/or HDL-C < 40 mg/dL, (3) fasting plasma glucose ≥ 5.6 mmol/L. Numbers collected from [93].

Increased prevalence of overweight, obesity, and abdominal obesity indicates an average increase in body weight in the population. Is the increased body weight seen regardless of weight just among those with normal and high BMI levels? Being underweight increases the risk of infectious diseases and it is therefore important to decrease the prevalence of underweight [133]. Is occurrence of underweight decreasing along with increased prevalence of overweight in China?

3.1.2 Prevalence of underweight has decreased in China

Prevalence of underweight is decreasing in China along with the nutrition transition. Figure 3.8 shows prevalence of underweight, using numbers from CHNS 1989-1997.
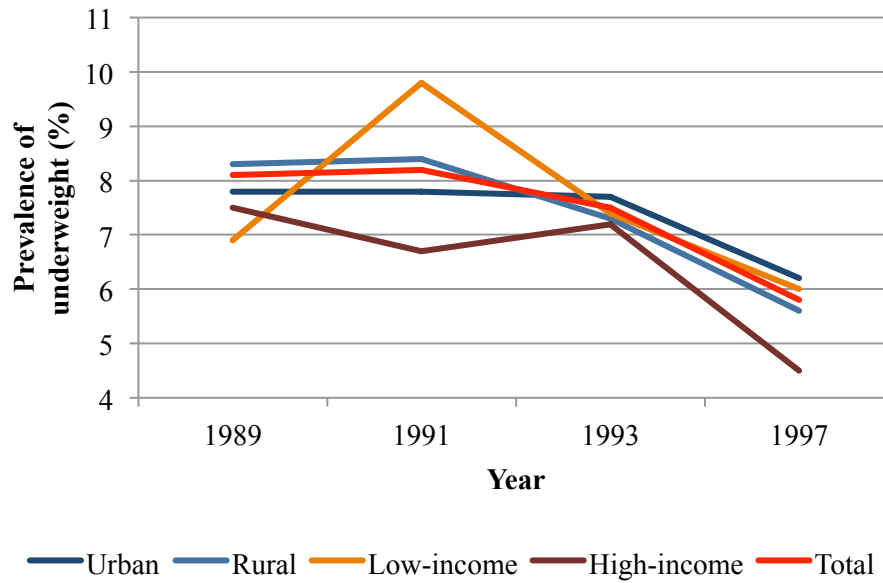
Figure 3.8 Prevalence of underweight (BMI < 18 kg/m^2) has decreased in China since early 1990s. Numbers collected from [87].

In the ten-year period 1992-2002, reduction in underweight is seen among children and adolescents in whole of East Asia (China, Hong Kong, Japan, South Korea and Taiwan). A higher prevalence of underweight was registered in South and West Asian children, most likely caused by undernutrition. The underweight seen in East Asia might partly be result of the *thin-desire* often seen among girls in well-developed places [134]. Fung and Yuen [135] did a study on female students from six different districts in Hong Kong; their desired weight was lower than their actual weight, even though just 4.8% were overweight. Desired BMI was also lower than actual BMI and 85.2% of the girls wanted to reduce their weight. However, no papers from reputable journals indicating that girls have higher prevalence of overweight than boys were found. Figure 3.9 shows some difference in under- and overweight among Chinese girls and boys. These differences are small, except in 2006 when boys were more overweight than girls. However, the difference in overweight does not necessarily mean that there are more underweight girls than boys. Thus, it is not possible to draw any conclusion using these numbers. Dong et al. [136] show that average BMI did not differ much in boys and girls in 2010; 18.6 kg/m^2 and 18.0 kg/m^2, respectively. Thus, explanations saying girls are more engaged in their looks and therefore are underweight do not hold. Low prevalence of underweight in China may be related to their one-child policy; discussed in section 3.6.
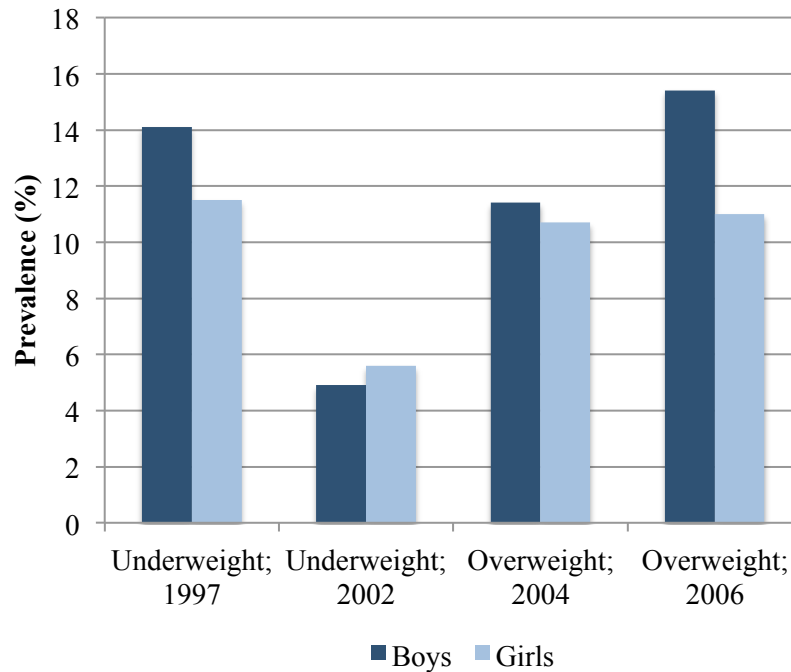
Figure 3.9 Prevalence of under- and overweight among boys and girls in China do not differ greatly. Numbers on underweight in 1997 are collected from Wang et al. [137] using children and adolescents (6-18 years) participating in CHNS. Definition on underweight were <5th percentile by Must et al. [138]. Numbers on underweight in 2002 are collected from Shi et al. [139] using adolescents aged 12-14 from the Jiangsu Province. Definition of underweight were WHO's <5th percentile (explained in section 4.6). Numbers on overweight were collected from [140] using children aged 7-17 participating in CHNS. Definition of overweight was International Obesity Task Force's (IOTF) cut-off points (explained in section 4.6).

A reduction in infectious diseases is seen in parallel to the decreased prevalence of underweight in China (figure 3.10). Underweight status and micronutrient deficiencies may trigger decreased immune and non-immune host defense; resulting in higher risk of catching an infectious disease [133]. Even though prevalence is decreasing, it is important to still have a health system able to treat these kinds of diseases. New challenges regarding overweight and metabolic diseases will occur along with the infectious diseases and evaluation and up-regulation of the systems are therefore required [141].
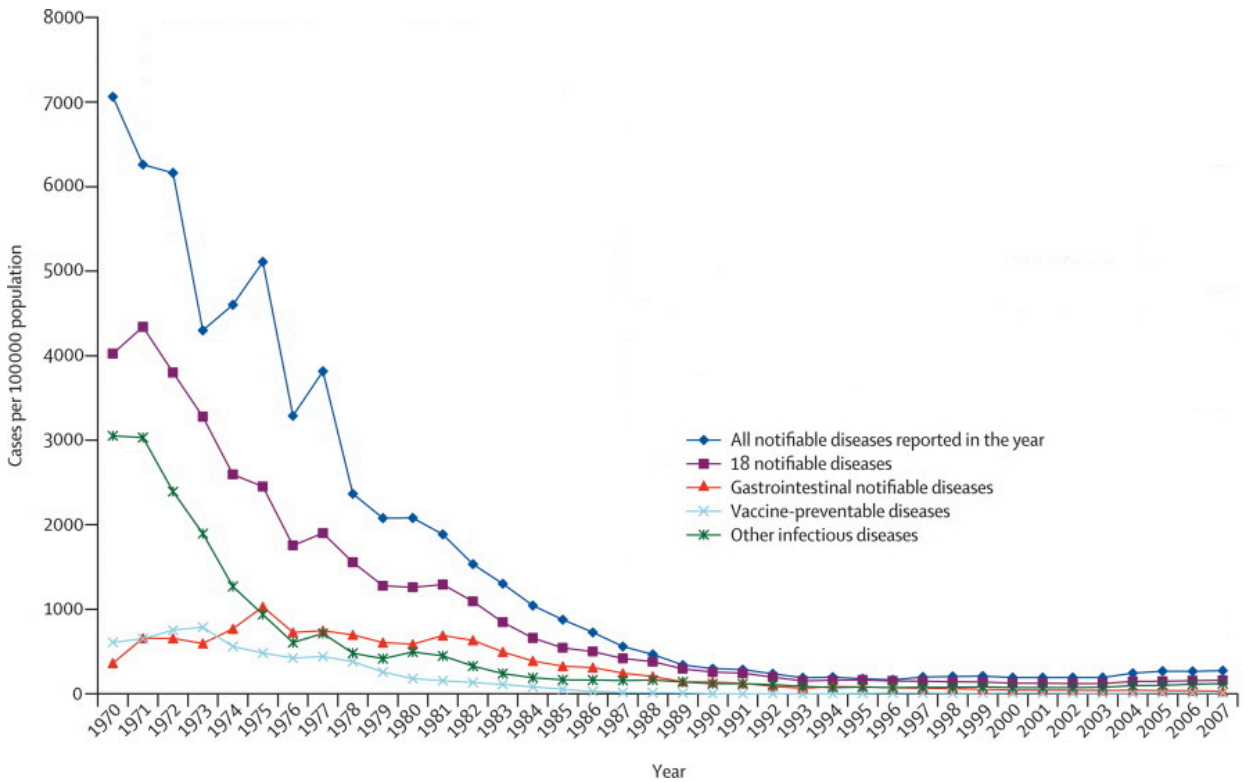
Figure 3.10 Incidences (cases per 100,000) of infectious diseases have decreased in China from 1970 to 2007 [141].

Although underweight is a decreasing problem, there might be some households where one member is underweight and another is overweight, causing difficulties when implementing governmental reforms and educational campaigns. Is under- and overweight in the same household a problem in China?

3.1.3 The dual burden households are a governmental challenge

In 1993 8.1% of Chinese households were so-called under/over households. These are households with at least one underweight and one overweight member, with or without normal weight persons. A shift from undernutrition to dual burden households is often seen in countries going through the nutrition transition, initially in the larger cities among high-income families. This is also seen in China; comparing under/over households with underweight households shows that the under/over are more likely to be urban and have high income [142]. It has been challenging to find more recent figures on dual burden prevalence, indicating less focus maybe due to an improvement of the situation.

Previously, underweight and malnutrition problems dominated in China. The underweight problem is now shifting towards an overweight problem, and governmental strategies have to

change. It is also important to keep in mind that both under- and overnutrition are malnutrition problems. The dual burden households challenge the government, as it has to deal with under- and overweight at the same time; strategies aiming to reverse undernutrition in one family member by increasing food-density may trigger overweight in another member. The same issue applies to the reverse situation [143].

Over the last decades, prevalence of overweight and obesity has increased while the prevalence of underweight has decreased in China. A lesser focus on the dual burden indicates that these rates also have decreased in China, and according to FAO *"both stunting and overweight are public health problems in children. Among adults, underweight is "insignificant" while prevalence of overweight is high or increasing. Infectious disease is declining, but diabetes and coronary heart disease are on the rise"* [144]. This means that the main challenge in China is to reduce the number of overweight people. Might the overweight increase be due to the westernization of the larger cities?

3.2 Urbanization and westernization of China triggers the nutrition transition

An urbanization process is seen in China the last decades; prevalence of people living in urban areas is close to 50%, over 30% increase from 1980 (figure 3.11). This increase in urban population obviously appears when people move into the cities. However, urbanization of smaller places also results in higher urban population. Furthermore, areas around a growing city will also be transformed from rural to urban [145], shown through the urbanization of all nine Chinese CHNS provinces (figure 3.12).
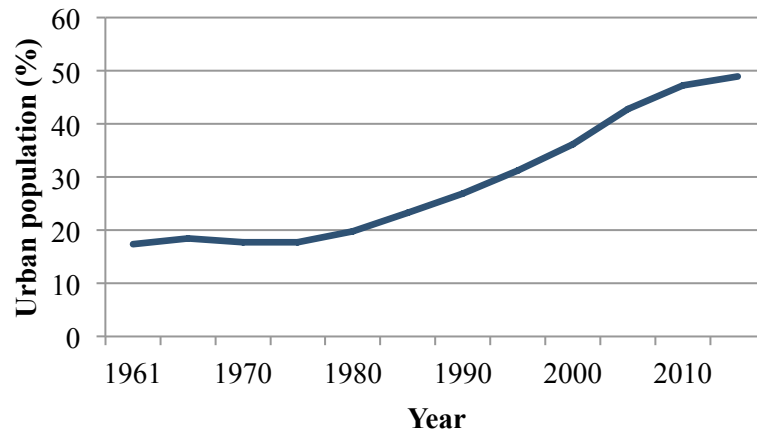
Figure 3.11 Percentage of urban Chinese population has increased since 1980. Numbers collected from [146].
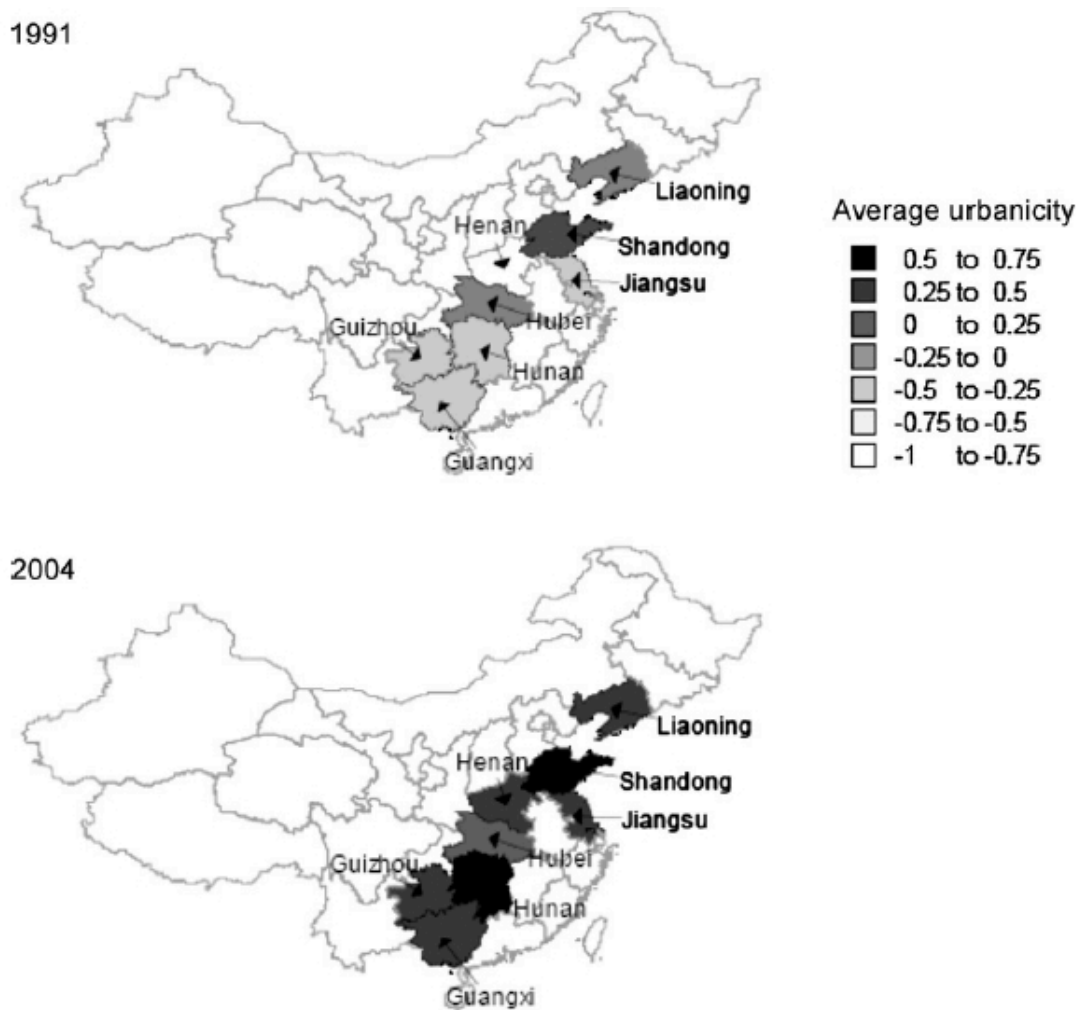

Figure 3.12 The urbanicity level has increased in all of the nine CHNS provinces [89].

Ebrahim et al. [147] showed that the Indian urban populations have higher BMI, WHR, percentage body fat, and fasting insulin level than the rural population. The same trend is seen in China; higher BMI and WHR values are registered in urban citizens than rural citizens (table 3.1) [148].

Table 3.1 There are differences in BMI and WHR among Chinese urban and rural citizens. Numbers collected from [148].

	Urban men	Rural men	Urban women	Rural women
BMI (kg/m^2)	24.4	22.8	24.2	23.3
WHR	0.88	0.86	0.83	0.83

WHR measurements in table 3.1 indicate that the urban populations have higher occurrence of abdominal obesity. This is confirmed in table 3.2, showing 10.2% vs. 7.2% occurrence of abdominal obesity in urban vs. rural areas, respectively. More urban than rural people have BMI $\geq$ 25 kg/m^2 and they have higher fasting glucose level.

Table 3.2 There is higher prevalence of abdominal obesity, high fasting glucose, and BMI $\geq$ 25 kg/m^2 in the Chinese urban populations compared to the rural populations. Numbers collected from [148].

	Abdominal obesity	High fasting glucose or medical use	BMI $\geq$ 25 kg/m^2
Urban (%)	10.1	15.1	39.1
Rural (%)	7.2	12.1	26.6

As explained in chapter 1, obesity is characterized by constant metabolic inflammation and therefore amplifies development of chronic inflammatory diseases, such as T2D and CVDs. Disease patterns are therefore different in urban and rural areas. From figure 3.13 it is obvious that the problem of T2D and other types of chronic diseases is an increasing problem parallel to increased urbanicity level in China. Also shown in the figure is the steep increase of incidences the last decade.
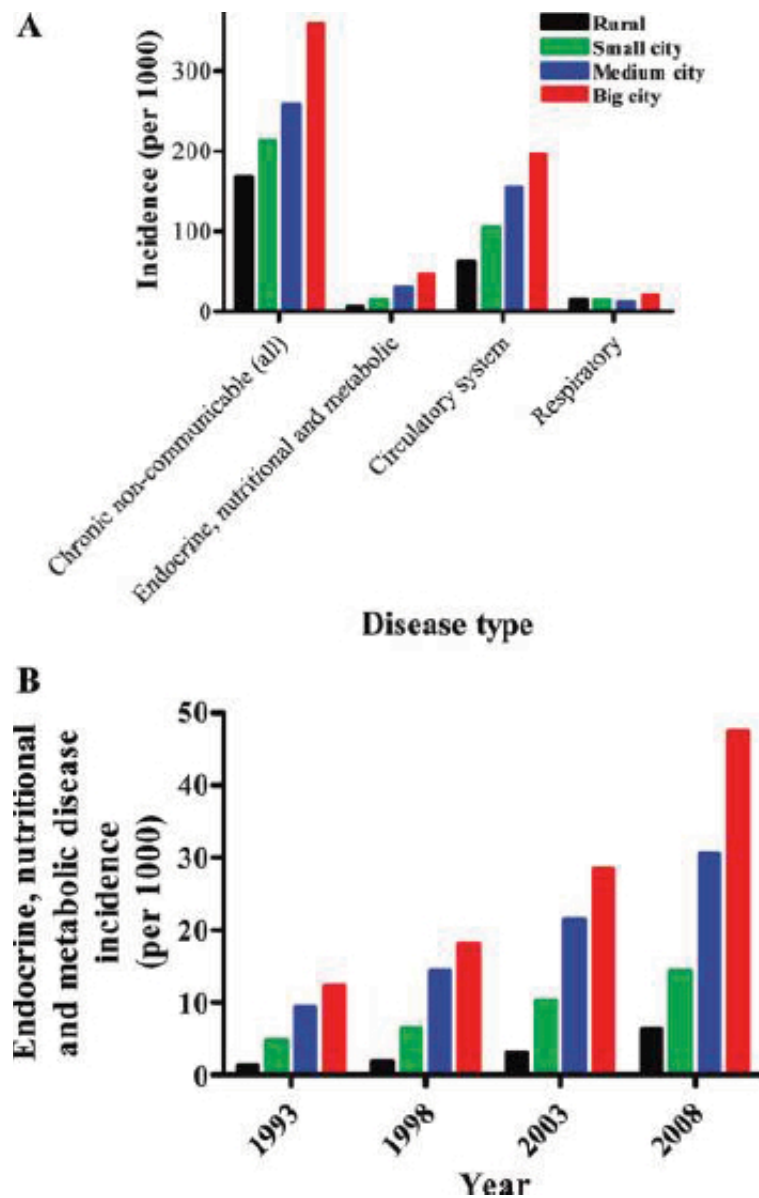
Figure 3.13 A) Chronic diseases appear more in Chinese urban areas than rural areas. Numbers are from 2008. B) Rates of endocrine, nutritional, and metabolic diseases from 1993 to 2008 show a steep increase, especially in the big cities [145].

Prevalence of T2D is also higher in urban Chinese areas compared to rural areas (figure 3.14). 12.8% of urban men are diagnosed with T2D versus 8.9% in rural areas. For women, the prevalence is 10.1% and 7.7% in urban and rural areas, respectively. The high number of T2D patients indicates the importance of preventable strategies, especially in urban areas where the prevalence is greatest. The strategies will become even more important as the Chinese urban populations grow.
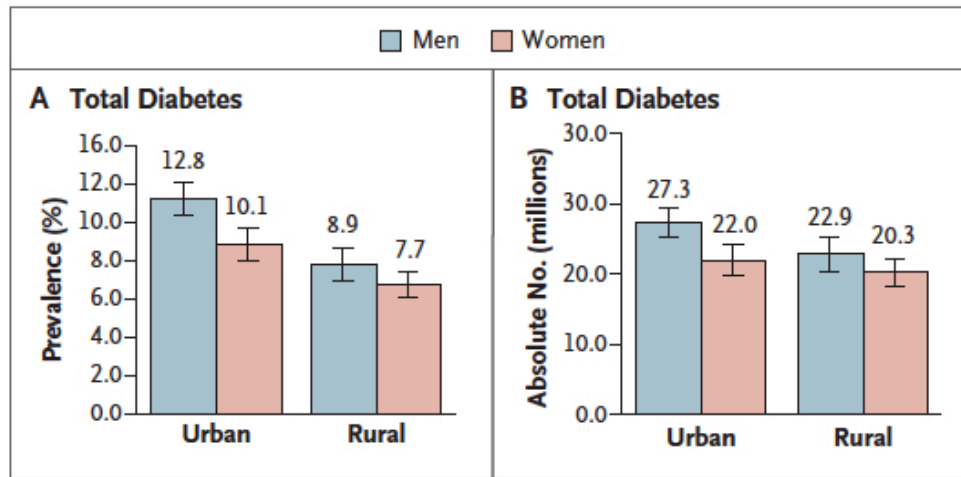
Figure 3.14 Prevalence of T2D in China is greater in urban areas than rural areas [128].

Urbanization is part of the westernization process; "*to bring ideas or ways of life that are typical of western Europe and N America to other countries*" [52]. Parallel to the urbanization process, an altered nutrition pattern often occurs; number of western fast-food chain restaurants has exploded in China over the last decades. Yum! Brands Inc., the world's largest fast food restaurant company, has 5700 restaurants in China today. The first KFC restaurant opened in 1987 and today there are 4200 restaurants [149, 150]. The next section will look into the risks behind an increased fast food intake.

Until now, this thesis has confirmed an increase in overweight and abdominal obesity in China, characterized by inflammation, strengthening development of diseases such as T2D and CVDs. The hypothesis is that a genetic predisposition and the nutrition pattern together might be the main explanation to the T2D epidemic in China. The next section will look into the nutrition patterns; *how have the nutritional patterns changed in Asia, China, over the last 50-70 years?*

3.3 Nutritional patterns are changing in China

The nutritional patterns in China have changed drastically the last decades, and as mentioned above, there has been an explosion of western fast food chains. The western fast foods are usually high in salt, refined carbohydrates, and unhealthy fats such as SFAs, which all may contribute to development of abdominal obesity and IR [149].

As explained in section 1.1.2, high fat content in food make it more energy-dense. Regular consumption therefore tends to result in excess kcal intake. Over time, excess kcal intake

triggers general obesity and therefore increased insulin production, which, in turn, triggers development of IR and T2D. Figure 3.15 shows how kcal intake of an average Chinese individual has doubled from 1426 to 3036 over a 50-year period. Even though "*the diversity in body size, body composition and habitual physical activity among adult populations with different geographic, cultural and economic backgrounds does not allow a universal application of energy requirements*" [151], an average intake of over 3000 kcal a day is higher than recommended, especially in a population where physical activity level (PAL); estimated energy expenditure during one day, is decreasing [75]. In 2004, a joint FAO/WHO/United Nations University expert consultation estimated values for daily kcal intake requirements for all age groups, body sizes, and lifestyles. A 40-year-old man weighing 80 kg must have a PAL of 1.75; active or moderately active lifestyle, to require the daily energy intake of an average Chinese individual. The energy requirement is lower for older and less active people, as well as people with a lower bodyweight. To require 3000 kcal per day, a woman aged 30-59.9 weighing 70 kg needs a PAL of 2.20; vigorously active lifestyle, to keep a stable weight [151]. In the Daily Guidelines for Americans, 2400-3000 kcal per day is recommended for men and 1800-2400 kcal for women [152]. Again, total kcal intake depends on age and PAL. Overnutrition is one of the factors triggering metabolic inflammation as it often results in increased adiposity and therefore more pro-inflammatory action (section 1.1.2.2). Thus, the kcal intake seen in China today may explain parts of the T2D epidemic.
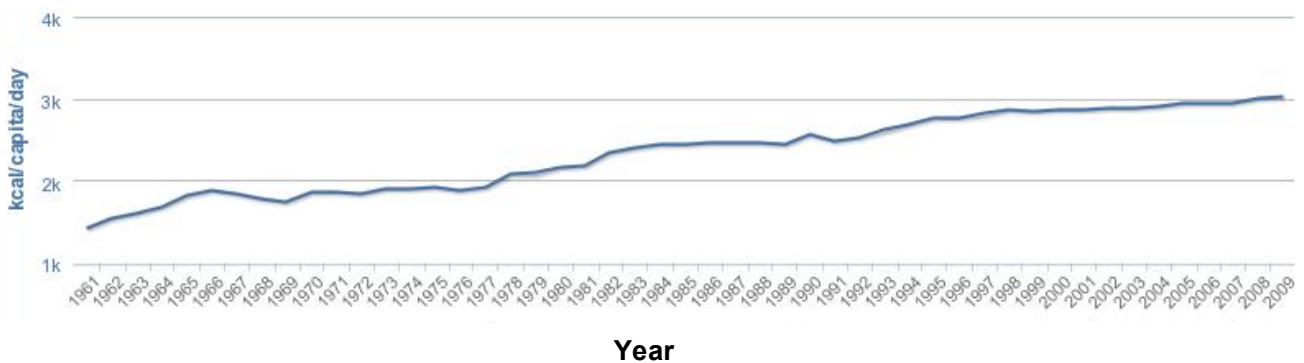

Figure 3.15 Food supply in kcal of an average Chinese person per day has increased from 1961 to 2009. Altered from [146].

The nutritional shift arising due to developmental processes in a country often triggers increased consumption of animal fat and energy-dense foods; is this trend seen in China?

3.3.1 Increased fat consumption in China might partly explain development of type 2 diabetes

Partly due to the increased fast food intake in China there has consequently been an increased fat consumption, as shown in figure 3.16.
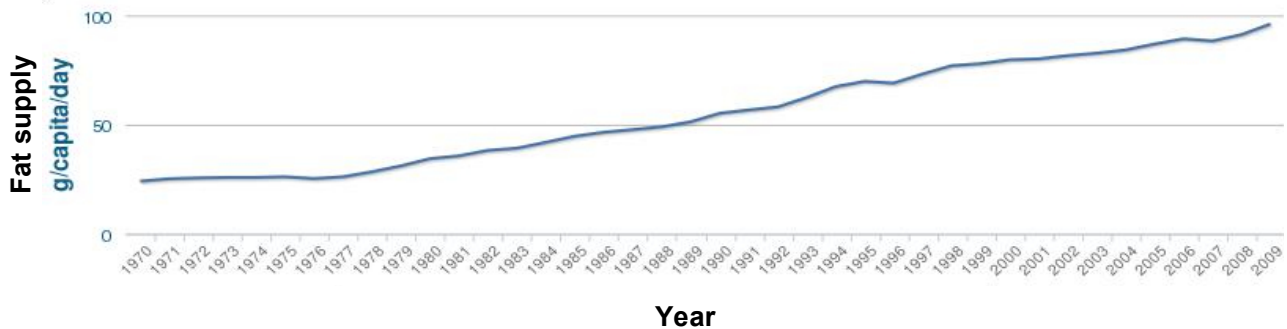

Figure 3.16 Average fat supply in grams has increased in China since the late 1970s. Altered from [146].

Increased fat intake is seen in every group of people in China: low- and high-income groups, rural and urban (figure 3.17). The increased trend is also seen in both males and females [153]. As expected, consumption is highest in urban areas as there are easier access to fast food and other types of western foods. Urban and high-income groups had an intake of 32.8% of total energy intake (E%) in 1997, which means that they are at the upper part of the recommended daily allowance (RDA) of 20-35 E% [110]. As the numbers in the figure is from 1997 and figure 3.16 shows a further increase, the urban and high-income groups are today probably consuming more fat than recommended.
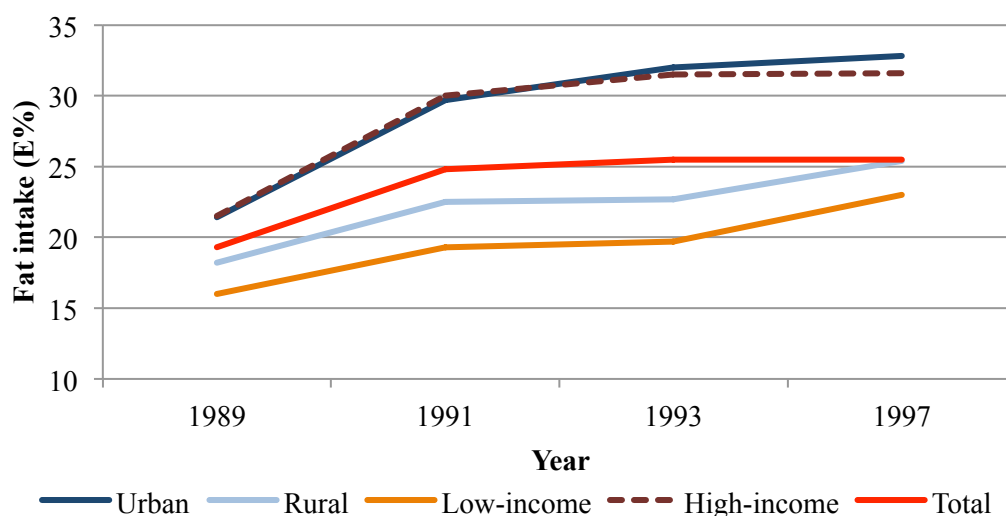

Figure 3.17 Fat intake has increased in every group of people in China, aged 20-45 years old. Numbers collected from [153].

As indicated in the previous paragraph, daily fat intake increases according to urbanicity level; figure 3.18 clearly shows this trend in China. The prevalence of obesity also increases in parallel to increased urbanicity level, indicating a relationship between increased fat intake and development of obesity.
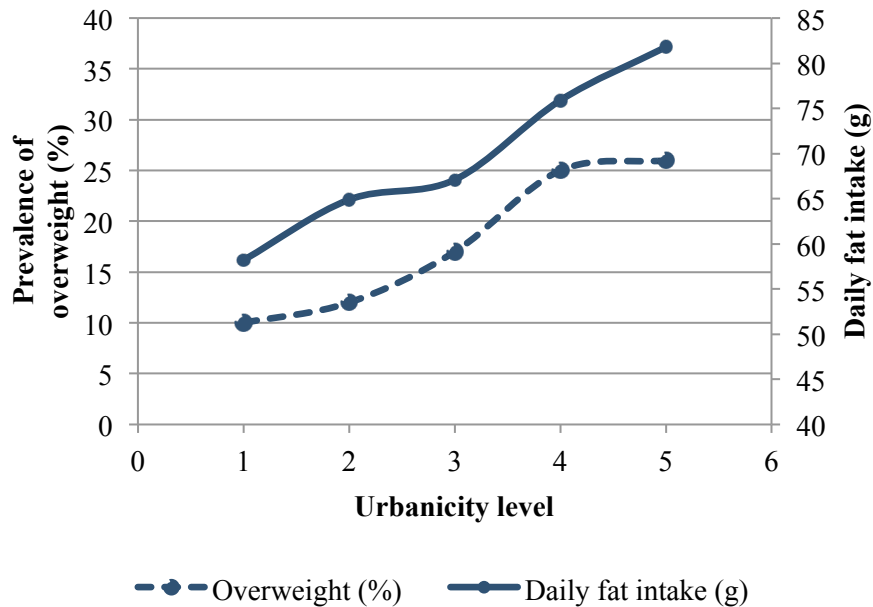

Figure 3.18 Daily fat intake and prevalence of overweight increase parallel to urbanicity level in China (1 = least urban, 2 = second least urban, 3 = middle, 4 = second most urban, 5 = most urban). Numbers collected from [89].

The argument is that the increased fat intake is due to urbanization and westernization of China. The increased fat intake leads to an increased kcal intake, which again trigger overweight and obesity. As overweight is characterized by metabolic inflammation it strengthens the development of T2D.

In addition to fat quantity, fat quality may also contribute to the T2D epidemic. Intake of animal fat has increased in China the last decades; indicating increased SFA intake (section 1.1.2.2 and 1.3.3) [82]. It has been difficult to find studies showing direct SFA intake, except from one on peasant Chinese, which found an intake of 7.45 E% [154]. Figure 3.19 shows how rape and mustard oil, palm oil, and animal fat have contributed to the Chinese diet from 1961 to 2009. The figure clearly shows an increased intake of animal fat; eight time increase from 0.5 g/capita/day in 1961 to 4.3 in 2009. Intake of palm oil, containing 45% SFA, has increased even more; from 0.3 to 7.1 g/capita/day, and is now a larger contributor to fat supply than animal fat [155]. Thus, there has most likely been an increased intake of SFAs in

China. Since SFAs are pro-inflammatory (section 1.1.2.2) a raised intake may partly explain the increased T2D incidences.
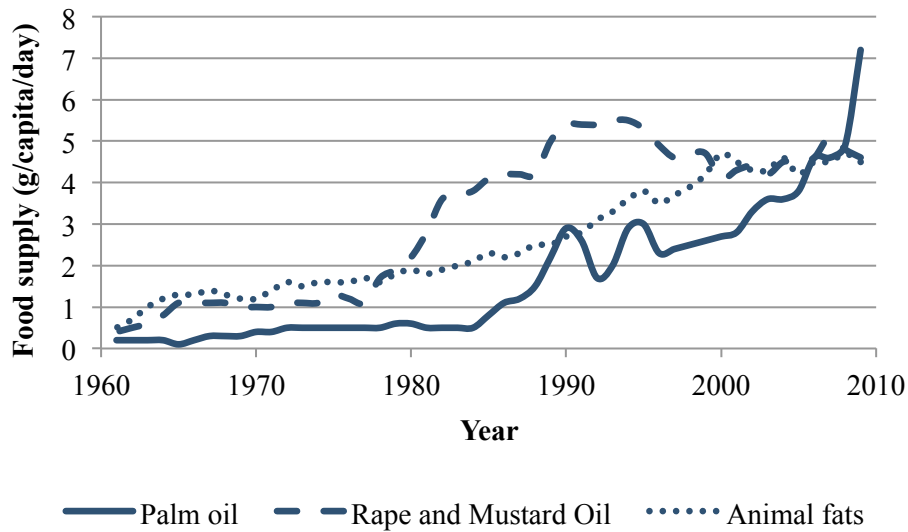

Figure 3.19 Fat supply from palm oil and animal fat has increased in China from 1961 to 2009, while intake from rape and mustard oil has stabilized after a decrease in the early 1990s. Numbers collected from [146].

In addition to a high SFA content, palm oil has a relatively high TFA content. In a report from the Food and Nutrition Board (FNB), TFA intake is recommended to be as limited as possible [110]. Vegetable oils, especially partly hydrogenated, have a high TFA content and trigger pro-inflammatory mechanisms due to LA transformed to AA after intake (section 1.1.2.2). In figure 3.20 it becomes evident that vegetable oil intake has risen in China the last decades, and a steep increase is seen from the late 1970s, a common trend during the developmental processes [78].
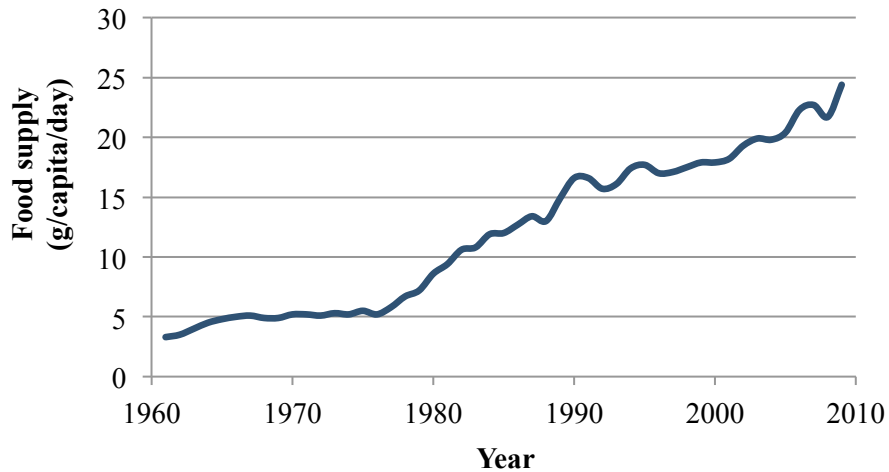
Figure 3.20 The vegetable oil intake in China has had a steep increase since 1980. Numbers from [146].

Palm oil is also high in n-6 PUFAs. It has been challenging to find other indicators on n-6 intake and also to find numbers on direct n-6 intake. However, when considering palm oil, n-6 PUFA intake has increased in China the last years. May the increased palm oil and n-6 PUFA intake partly explain the development of T2D?

n-3 PUFA intake is often reflected through intake of marine products [156]. According to Zhai et al. [157], fish intake in China has varied the last decades (figure 3.21), but an overall increase is seen from 24 g/day in 1989 to 30 g/day in 2004. The increased fish intake indicates an increase in n-3 intake among the Chinese population.
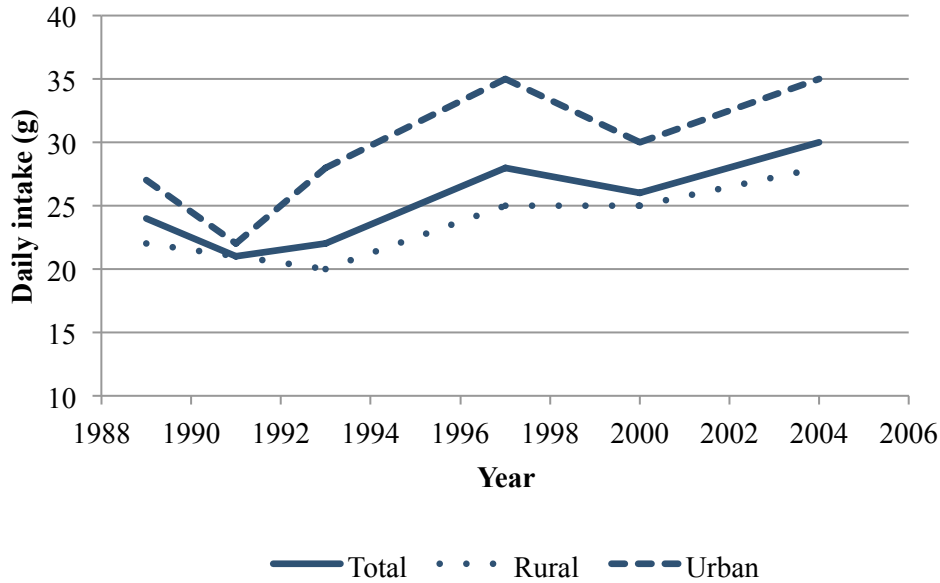
Figure 3.21 Fish intake (g/day) in China has increased in China from 1989 to 2004. Numbers from [157].

Numbers collected from FAOSTAT's web page [146] also display an increase in seafood intake (figure 3.22); indicating that the Chinese population most likely has increased n-3 PUFA intake since the 1980s. Still, China had the lowest n-3 intake in an INTERMAP-study when compared with Japan, USA, and UK [158]. On the one hand, n-3 intake has increased through a rise in fish intake. On the other hand, n-3 intake through rape and mustard oil has decreased the last years (figure 3.19). This decrease may partly explain a lower intake among the Chinese population.

Figure 3.22 Seafood supply (g/capita/day) has increased in China since 1980. Numbers collected from [146].

The ratio of n-6 and n-3 PUFAs in the western diet today is close to 20:1. As it is important to keep a nutritional balance due to inflammato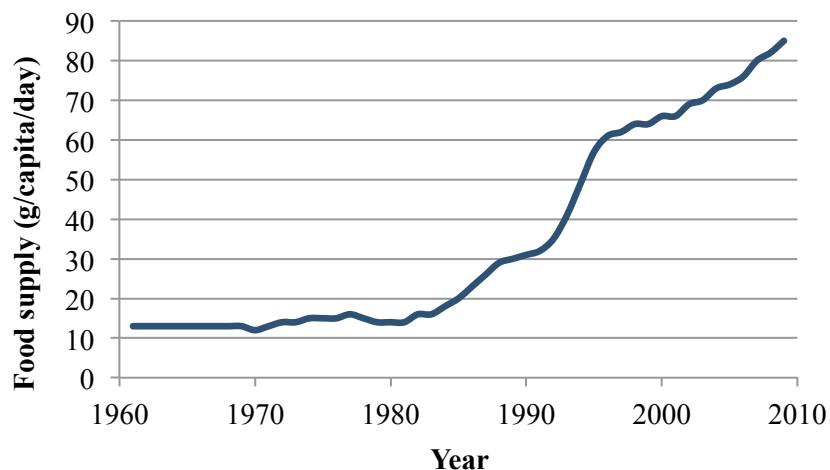ry effects, the ratio should be lower; in a paleolithic diet it the ratio was 1-2:1 (section 1.3.3). An increased intake of seafood may have contributed to an increase in n-3 intake in the Chinese population. However, when considering palm oil intake, n-6 intake has also increased. Transition from eating healthy plant oils to eating palm oil and animal fats with high SFA content may result in unbalance of eicosanoids and therefore trigger metabolic inflammation.

Due to limited information on fat quality in China, it appears difficult to conclude on whether or not it contributes to the disease pattern. The indications given regarding SFA and TFA intake, however, show that there might be some imbalance worthy of further research. Another aspect when considering fat intake is the quantity. In 1997 urban and high-income groups consumed amounts of fat at the upper limit of RDA. As the intake of fat has increased since then, it is reasonable to believe that these groups, and maybe others, are consuming too much fat. The increased fat intake contributes to an increased kcal intake, which plays a part in the development of overweight and diabetes. If quantity also contributes to inflammation, it is a dangerous combination.

Fat is probably not the only food group increasing inflammation in the Chinese population; has carbohydrate intake changed the last years? Can carbohydrate intake contribute to the explanation of disease patterns?

3.3.2 Increased intake of high glycemic indexed carbohydrates might partly explain development of type 2 diabetes in China

As opposed to fat intake, carbohydrate intake in China has decreased; in the overall population an 8.9% reduction was observed during a time window of eight years (figure 3.23). Today's intake meets RDA of 45-65 E% [110], however, carbohydrate intake is higher than estimated paleolithic intake of 22-40 E% (table 1.2, section 1.3.3). Even though carbohydrate intake was higher in 1989 than it is today, it is still too high.
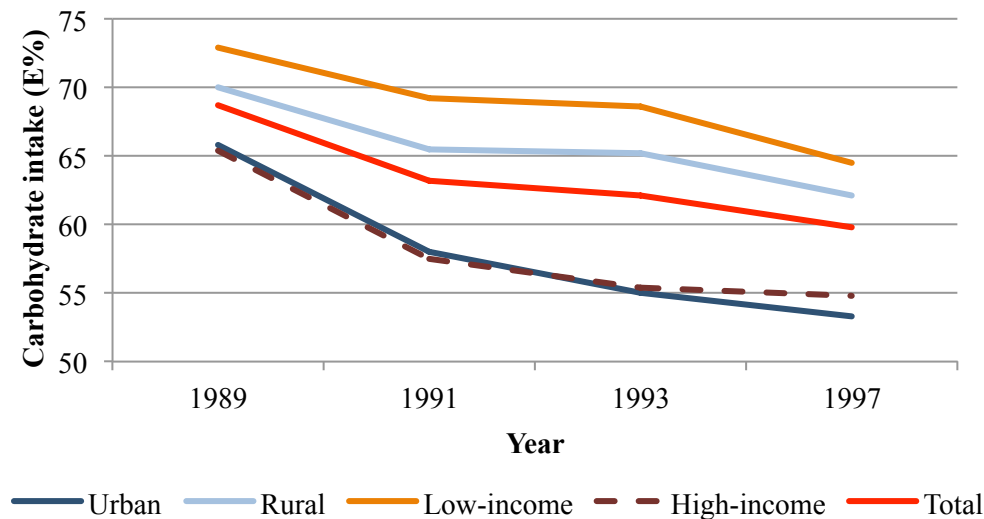
Figure 3.23 Carbohydrate intake among 20-45 year old Chinese adults has decreased since 1989. Numbers collected from [153].

A further decrease in carbohydrate intake is seen after 1997, at least in children and adolescents participating in the CHNS. A reduction from 311.0 g/day in 1997 to 254.1 g/day in 2009 was seen in a study by Cui and Dibley [159]. Carbohydrate intake is still high considering that FNB's recommendation is 130 g/day. Still, carbohydrate intake has been reduced parallel to the increase in T2D incidences (figure 3.2 and 3.23). It is therefore difficult to imagine that carbohydrate quantity has affected the T2D epidemic in China. The altered quality, on the other hand, may have influenced the epidemic.

The white rice intake in China contributes to an increasing GI, especially due to white rice being consumed before brown. Brown rice has greater nutritional value than white rice as a result of the production process; only the outermost layer is removed from the kernel when brown rice is produced and most of the nutritional value is therefore intact. White rice, on the other hand, is highly polished and therefore contains smaller amounts of nutrients [160]. In an international table on GI values, jasmine rice (white long grain, cooked in rice cooker, Bangkok, Thailand) has a GI of 109. Boiled brown rice from South India, on the other hand, has a GI of 50 [161]. Figure 3.24 displays Chinese intake for various foods, and it is clear that rice intake is high. Zhang et al. [160] did a study on rice intake among Shanghai habitants and found that as many as 94% consumed white rice every day, and only 25% of the participants had tried brown rice before the study. This is why GI value of white rice and not brown is presented in figure 3.24, as it is plausible that almost all rice consumption is white rice. In a NHS study [162]; participants consuming white rice more than five times a week had higher

risk of developing T2D compared to participants consuming white rice less than once a month. The opposite trend was seen when comparing brown rice intake; participants consuming brown rice more than once a month had decreased risk of developing T2D when compared to participants consuming brown rice less than once a month. When replacing 50 g of the white rice with brown rice, reduction in T2D risk was observed. As expected, due to the fact that brown rice has lower GI than white rice, the study indicates that a shift from white to brown rice might reduce T2D development.
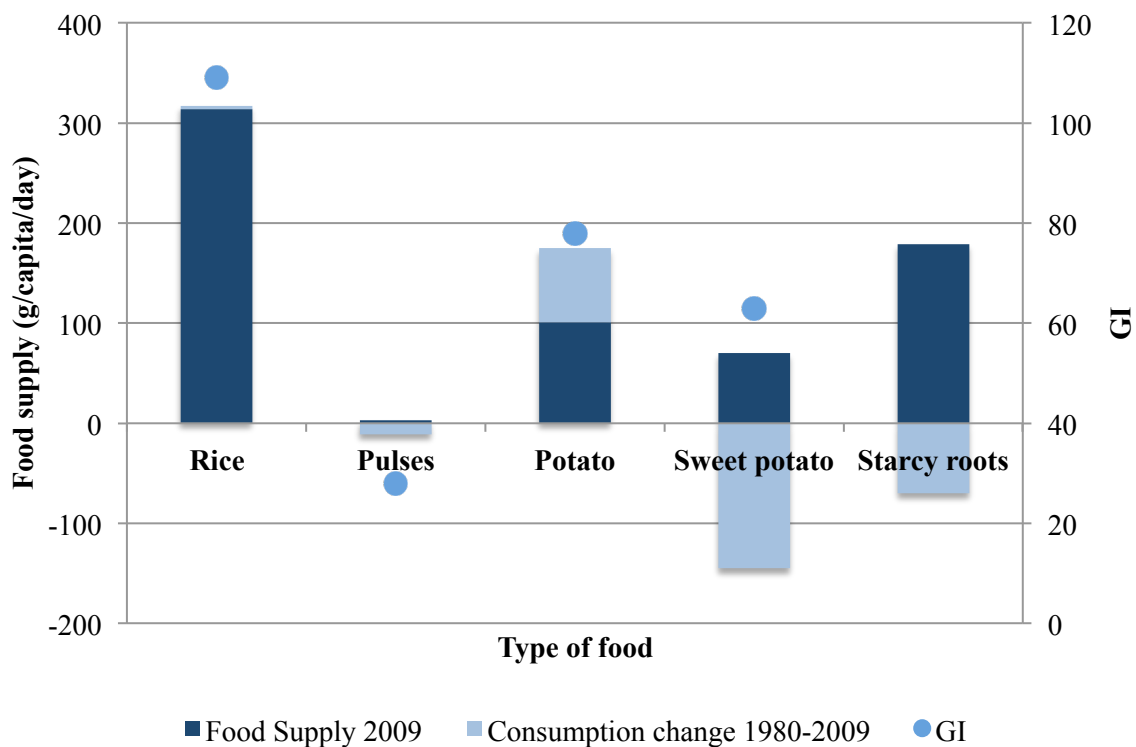

Figure 3.24 Rice intake in China is high compared to other food groups, and has almost not changed during the last 20 years. Intake of pulses, which has low GI, is reduced. Potato intake has increased parallell to decreased a food groups with lower GI, namely sweet potato. Starchy roots intake is fairly high, although intake has been reduced during the last couple of decades. Numbers on inake are collected from [146]. Jasmine rice from Bangkok were chosen as representative for GI on rice and collected from [161]. GI value on legumes is mean GI from [163]. GI on potato and sweet potato are collected form the same source as legumes, and are values on boiled versions of the vegetables. No GI value is given for starchy root vegetables as there are various types and therefore difficult to find an average value.

Hu et al. [164] they compared rice intake in the Chinese population (Shanghai Women Health Study) and the US population (NHS) and found that the consumption was higher among Chinese people. This difference might be a possible explanation to why Chinese people have the same prevalence of T2D as Americans, even though there are far more overweight people

in the US. Figure 3.25 presents results from a Shanghai Women's Health Study [165], showing how a raised consumption of rice increase RR of developing T2D. The figure also shows that the RR is higher in women with WHR over 0.85 than women with WHR below 0.85, indicating that abdominal measurements are important (section 1.3.2).
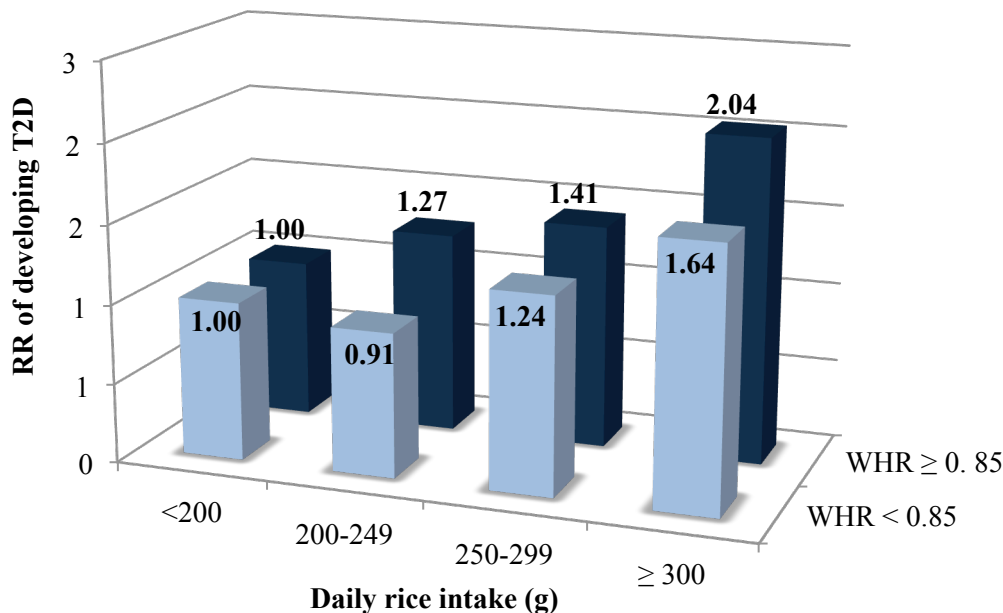
Figure 3.25 Increased daily rice intake contributes to higher RR of developing T2D. RR is higher in women with WHR over 0.85 than women with WHR < 0.85. Numbers collected from [165].

Back to figure 3.24, it also shows intake of potato and sweet potato in China. In parallel to a reduction in sweet potato consumption, there has been an increased consumption of potato, resulting in consumption of potato being higher than sweet potato intake. The relationship between potato and sweet potato intake has increased GI intake as potato has higher GI than sweet potato, with 78 against 63, respectively. The intake of starchy root vegetables as a whole has also been reduced. This indicates that fiber intake is reduced [125], contributing to increased GI.

Another indicator on reduced fiber intake is the reduction in consumption of pulses, from 14 g/capita/day in 1980 to 3 g/capita/day in 2009. Legumes have low GI values [161, 163], partly du to their fiber content [125], and a reduced intake of these foods with a relatively high fiber content suggests that the decrease in total carbohydrate consumption might be due to a reduction in low- and middle GI foods.

Finding values on direct fiber intake in the Chinese population has proven difficult. Nevertheless, reduced fiber intake is the common trend during the nutrition transition China is undergoing [125, 166]. An English abstract from a Chinese article concluded with a decreased fiber intake from 15.1 g/day in 1989 to 11.6 g/day in 2006 [167]. Thus, the Chinese population is consuming less fiber than adequate intake recommended by FNB; 38 g/day for men and 25 g/day for women [110]. Since reduced fiber content increase GI, it is conceivable that a reduced fiber intake in the Chinese diet might have contributed to the increased T2D rates (figure 1.4).

Over to more sweet tasting carbohydrates, sugar intake has increased in China. According to a review by Kearney [125], sugar contributed with 54 kcal/capita/day in 1983. This increased to 73 kcal in 2003. Part of this increase might be due to an increased SSB intake. SSBs are thought to have an impact on the worldwide obesity epidemic, partly due to their kcal content, but also due to the high-GI level as a result of the high sugar content. It has been difficult to find direct data supporting an increased SSB intake in China; however, several articles state the fact that it has increased [149, 168-170]. An indirect way to find out how SSB intake has changed is through sales numbers. A study using *Euromonitor International's Passport Global Market Information Database* compared sales data from 2000 to 2010 for all soft drink brands under the Coca-Cola Company and PepsiCo. Volume sold in China tripled from 9.1 mL/day in 2000 to 29.6 mL/day in 2010 (figure 3.26). Part of the sale is from drinks other than SSBs, but it is mostly from carbonated drinks [171].
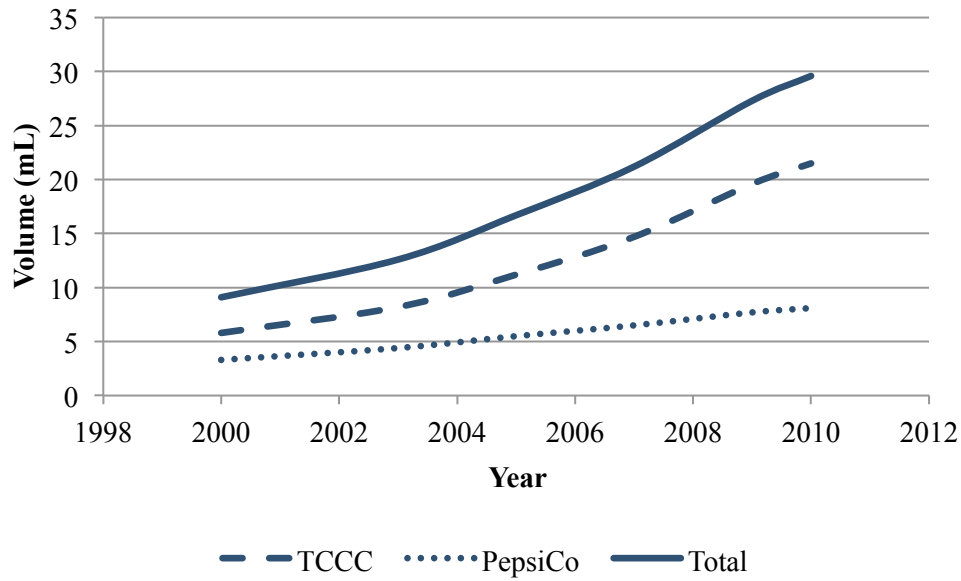
Figure 3.26 Sale of drinks from the Coca-Cola Company (TCCC) and PepsiCo has increased in China from 2000 to 2010. Numbers from [171].

The sales numbers in figure 3.26 implies that the SSB intake most likely has increased in China the last decade. If the trend in China is similar to the trend in the western world, it may trigger development of overweight and obesity, which escalates the progression of T2D (figure 1.9). An NHSII-study presented positive associations between increased SSB intake and development of T2D (figure 3.27). Women consuming more than one SSB per day had higher risk of developing T2D compared to the control group consuming less than one SSB per month [26]. There are two reasons why SSBs trigger overweight. The first reason is the increased kcal intake, and the second reason is the increased GI due to the sugar contents of these drinks. The increased SSB intake therefore strengthens the hypothesis that the T2D epidemic in China occurs due to both overnutrition and the quality of carbohydrate.
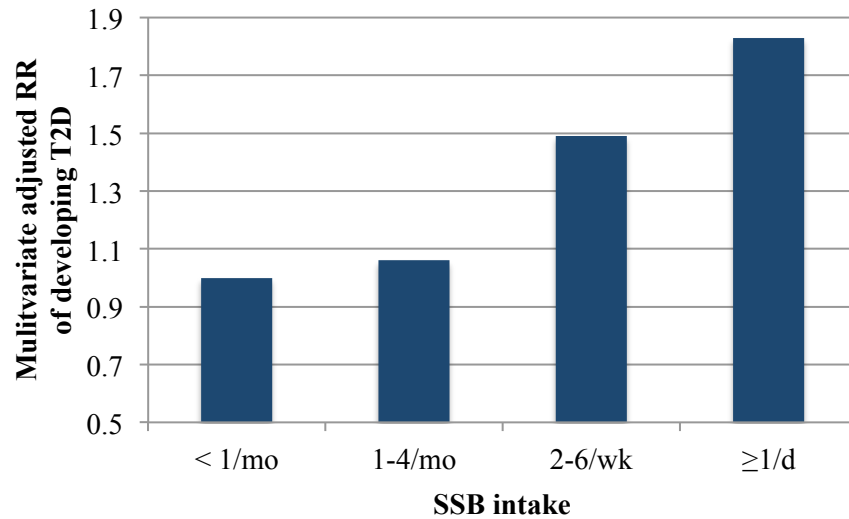
Figure 3.27 Increased SSB intake results in higher RR of developing T2D. A high cereal fiber intake reduces risk, while a low cereal fiber intake increases the risk. These results are from a study using the NHSII, numbers collected from [26].

Even though there are few numbers on the change in SSB consumption in China, there are studies showing the present SSB intake. One study on urban Chinese children found that 46.1% regularly consumed SSBs. These children had higher BMI and WC than children consuming milk on a regular basis (milk drinkers) (figure 3.28) after adjusting for numerous factors. The study also showed that the total energy intake was higher in SSB drinkers than milk drinkers [168].
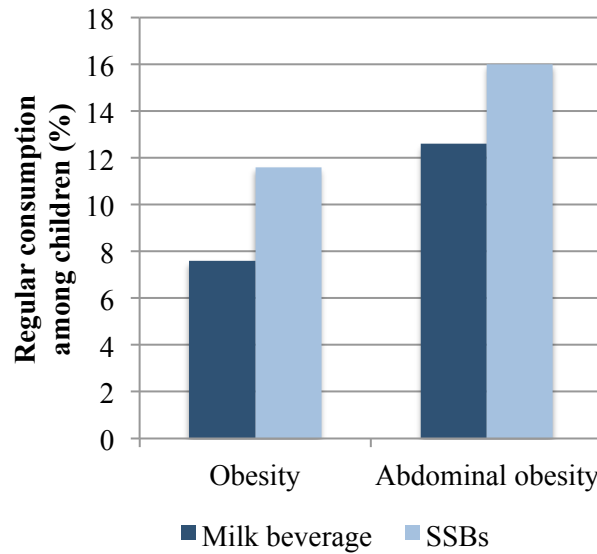
Figure 3.28 Higher prevalence of children consuming SSBs on a regular basis are obese (WHO's definition: BMI ≥ 95th percentile, explained in section 3.6) and abdominal obese (WC ≥ 90th percentile. See [172]) when compared to children regularly consuming milk. Numbers from [168].

A study done on adolescents from Xi'an city found that approximately half of the participants consumed soft drinks every day. They also found a positive association between soft drink intake and overweight (figure 3.29) [173].
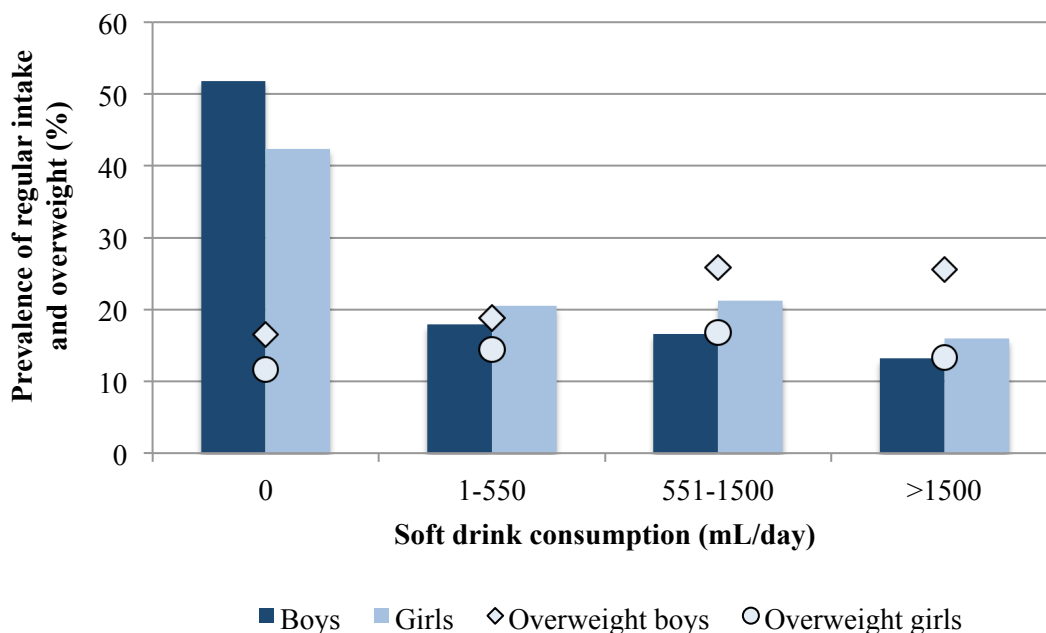
Figure 3.29 Prevalence of overweight and obesity among Chinese adolescents from Xi'an city increase parallel to soft drink consumption; trend most clear in boys**.** Numbers collected from [173].

In a study carried out in Hong Kong, 20.6% of the adult men consumed more than one unit SSB every day, against 9.6% of the women. Participants consuming two or more units every day where more likely to be obese (BMI ≥ 27.5 kg/m^2) and abdominal obese (WC ≥ 90 cm in men; ≥ 80 cm in women) when compared to participants consuming less than two units (figure 3.30) [174].
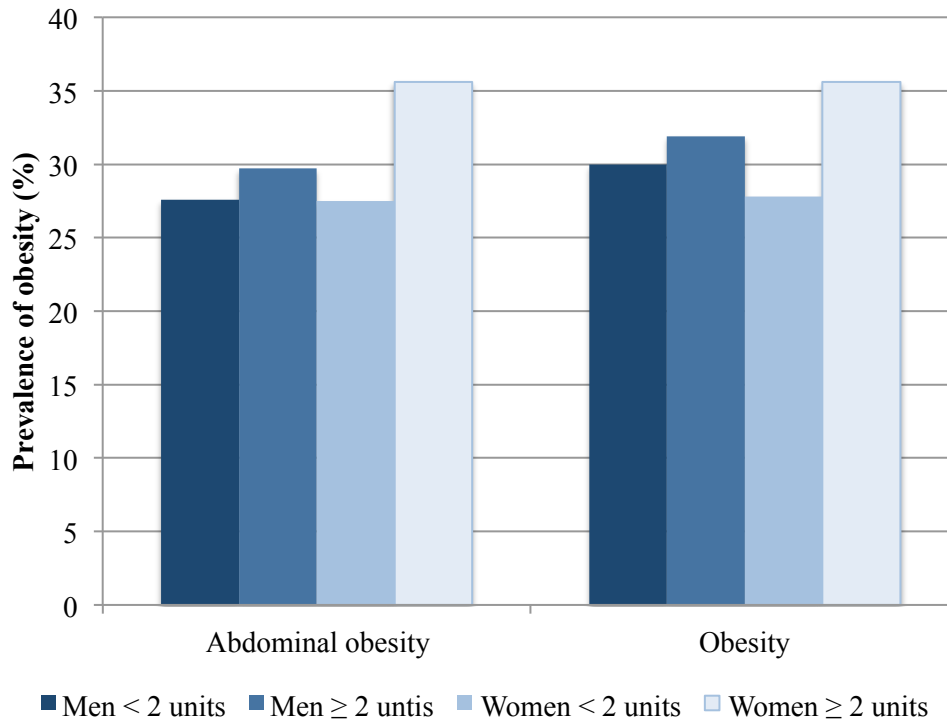
Figure 3.30 Prevalence of general and abdominal obesity is higher in adults consuming two or more units of SSBs compared to adults consuming less than two units. Numbers collected from [174].

As discussed in section 3.2, urbanization of China results in changed nutritional patterns. These changes are occurring at the same time as the population is becoming more sedentary. The result is an increased BMI level among all groups of people; however, prevalence of overweight and obesity is highest in the urban populations and in people with the highest income (figure 1.11). A study done on Chinese adolescents showed that those with higher socio-economic status (SES) consumed more fast food and SSBs than adolescents with lower status. 21.5% of boys from high SES families drank SSBs every day versus 4.2% of boys from low SES families. Without economic limitations, 65.9% of urban boys would have consumed more SSBs. The same prevalence among rural boys was 52.6% [175]. This economical issue may help explain why the low-income group has lowest prevalence of overweight and obesity (section 1.3.2).

Fruit intake has also increased in China [78, 146, 176]. This is a food group with medium GI values [163] and might therefore contribute to a reduced GI intake in China. Although this might be the case, there are several indications on a raised GI intake in China the last couple of decades. Especially the increased SSB consumption along with the high rice intake contributes to a diet with high GI carbohydrates. The reduction of pulses and starchy root vegetables intake also indicate increased GI, together with the switch from sweet potato to potato.

Carbohydrate intake has decreased in China the last decades and every groups of people are now consuming carbohydrate amounts within RDA. Thus, the quality might play a more important role than quantity in the development of T2D. The common diet has a high GI, especially due to the white rice and SSB intake, in addition to reduced intake of fiber rich foods as pulses and starchy root vegetables. The high GI intake triggers inflammatory responses and therefore strengthens development of T2D.

3.3.3 Altered dietary patterns in China might explain parts of the increased development of type 2 diabetes

Urbanization along with westernization of China have resulted in altered nutritional patterns. Increased consumption of fat has been observed, resulting in high kcal intake that may eventually trigger overnutrition. Furthermore, an increased intake of high GI carbohydrates has also been observed. This diet amplifies inflammation, which increase the risk of developing T2D and CVDs. This western diet also triggers overweight that is characterized by constant metabolic inflammation. Figure 3.31 displays the relationship between the changed nutrition pattern and development of disease.
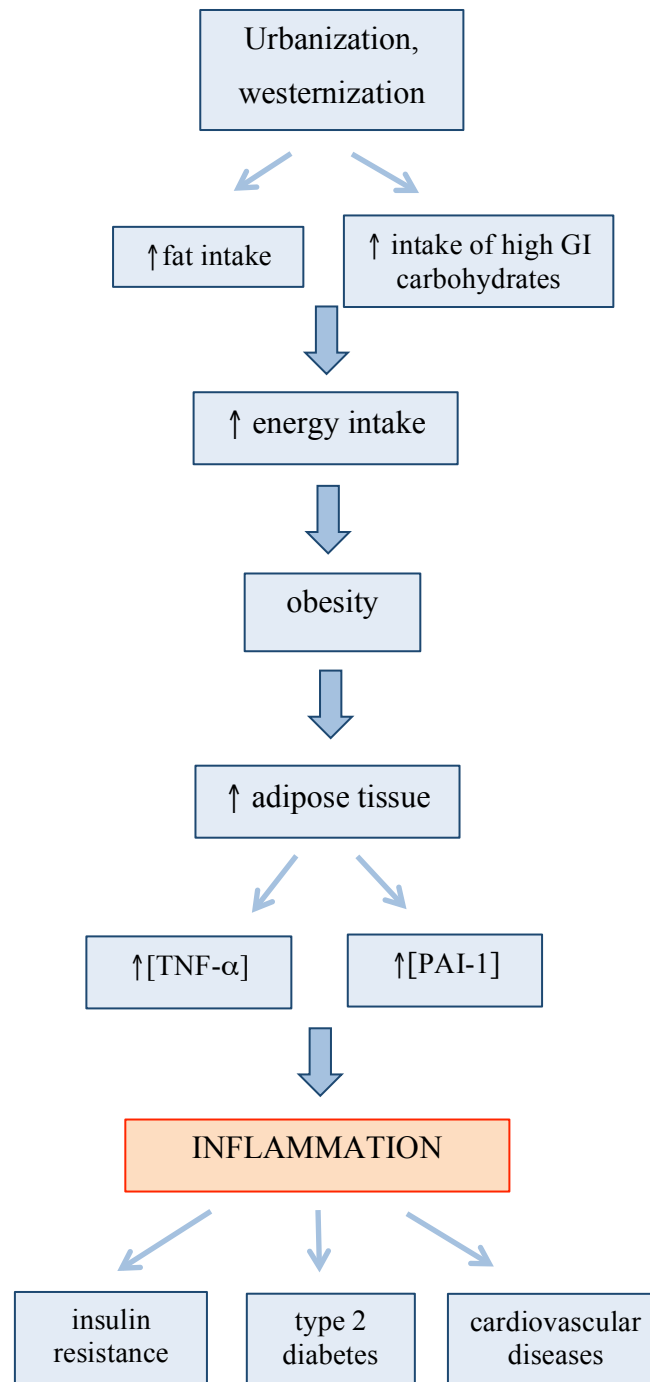
Figure 3.31 Urbanization and westernization seem to have resulted in increased intake of fat and high GI carbohydrates. This nutritional pattern triggers development of obesity, characterized by inflammation, strengthening development of IR, T2D, and CVDs.

The altered nutritional pattern in China might explain some of the increased T2D rates. However, since the Chinese population does not seem to develop as much overweight as western countries, there must be additional factors that trigger inflammation and strengthen the development of T2D. *Are Asians genetically predisposed to T2D? Are there any differences between the eastern and western world?* In the next section, genetic predisposition

will be discussed to see if the Chinese population has any genetic properties differing from western population that might trigger inflammation.

3.4 Asians might be genetically predisposed to developing inflammation and type 2 diabetes

As mentioned in section 3.1.1, some Asian populations tend to develop MetS at lower BMI levels than western populations and it is therefore conceivable that genetics may be a part of the explanation.

Ethnic differences in expression of inflammatory mediators might account for some of the increased T2D rates, as inflammation escalates progression of T2D. Several studies show positive associations between IL-6 expression and T2D development [177, 178]. However, larger studies do not report difference among ethnic groups [179, 180].

A study on middle-aged and elderly Chinese rural and urban citizens from Shanghai and Beijing found relationships between adiponectin concentrations and BMI, abdominal obesity, and MetS [181]; less adiponectin was positively associated with higher risk of developing one or more MetS risk factors (figure 3.32). The relationship between adiponectin and MetS has been found in other ethnic groups as well, and what is noteworthy is how adiponectin concentration differs among ethnic groups.
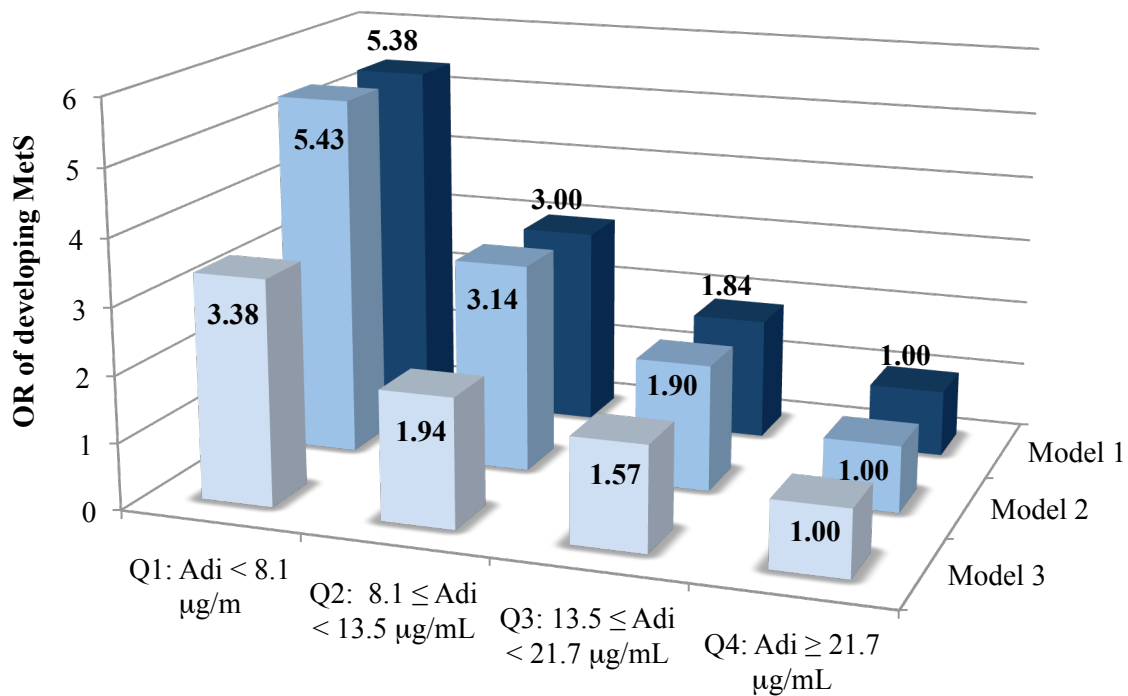
Figure 3.32 Reduced adiponectin concentrations triggers development of MetS in middle-aged and elderly Chinese. MetS is defined as ATP III (box 1.1). Q4 is used as reference. Model 1 is adjusted for age, geographic location and residence in male and female subgroups; adjusted for age, gender and residence in Beijing and Shanghai subgroups; and adjusted for age, gender, and geographic location in urban and rural subgroups. Model 2 was further adjusted for smoking, drinking, physical activity, anti-hypertensive medication, education level, and family history of chronic diseases. Model 3 was further adjusted for BMI. Collected from [181].

Mente and associates [182] found different levels of adiponectin concentrations in various ethnic groups living in Canada. Adiponectin concentration was lowest in Chinese participants and also low in South Asians (figure 3.33). The low adiponectin concentration indicates that these groups are more disposed to development of inflammation than Europeans and Aboriginals from Australia.
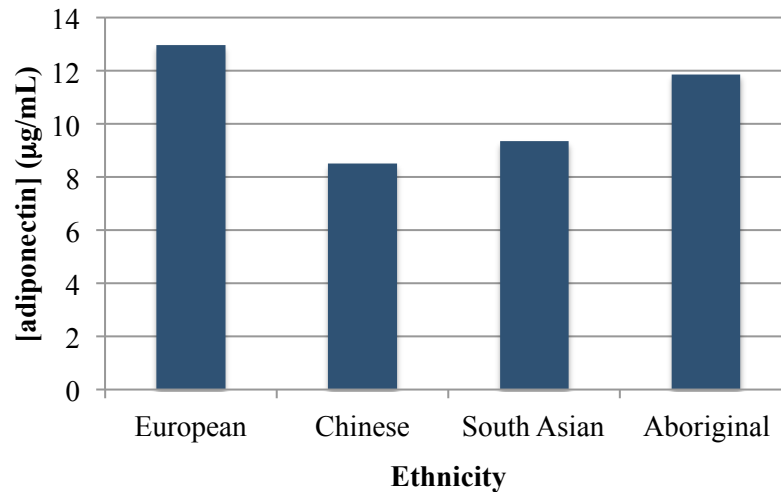
Figure 3.33 Chinese and South Asians have the lowest adiponectin concentration when compared to Aboriginals and Europeans. Numbers collected from [182].

In the same study [182], leptin concentration was also lowest in the Chinese participants, however, it was highest in South Asians. Thus, according to this study, South Asians are more prone to develop inflammation than Europeans, Aboriginals, and Chinese. This is because they have the highest concentration of pro-inflammatory leptin and lowest concentration of anti-inflammatory adiponectin. Since there are several other adipokines affecting inflammation, these results presented cannot be used to draw any definite conclusions. Even though leptin has proven to be part of the inflammatory response in some studies, its effect is still controversial [8]. Leptin studies are often performed on animal models and this makes it hard to draw inferences to how it relates in humans [183].

As shown in figure 3.34, Chinese adults have higher PAI-1 concentrations than Caucasians, Blacks and Hispanics [184], and as mentioned in section 1.3.2, there are positive associations between PAI-1 concentration and obesity. Since the Chinese population probably has the lowest BMI level among the groups in figure 3.34, it is plausible that they are genetically predisposed in some way. One explanation relates to the DNA composition. The suggestion is that a single base insertion resulting in five guanine (G) upstream the transcription start in the PAI-1 gene may interfere with the transcription process [67, 185]. Consequently, 4G homozygote individuals would have higher PAI-1 concentrations than 5G homozygotes. This is the exact relationship that was seen in a study by Panahloo et al. in 1995 [185]. 4G/4G genotype participants had an average PAI-1 concentration of 18.3 AU/mL, while 5G/5G genotype participants had a lower mean of 12.2 AU/mL. The heterozygotes had an in-between average of 13.7 AU/mL. Several other authors have also found differences in PAI-1

expression in different genotypes [186, 187]. In the study by Panahloo, genotypes in Caucasians, Afro-Caribbean, and Asians, and no significant difference between the populations were found. Thus, there must be another explanation to the high PAI-1 concentrations in the Chinese population.
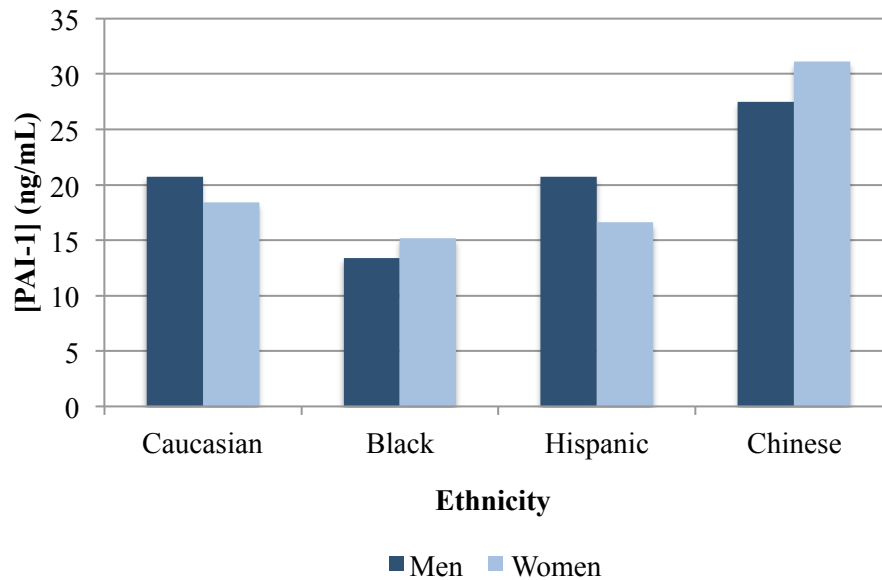
Figure 3.34 PAI-1 concentrations are highest in Chinese people when compared to Caucasians, Blacks, Hispanics. Values are adjusted for age, education, individual income, site, smoking, current alcohol use, BMI, leisure physical activity, sedentariness score, diabetes status, hypertension status, statin use and current hormone replacement therapy use among women. Numbers collected from [184].

Research implies that Chinese people have lower concentrations of the anti-inflammatory adipokine adiponectin and higher concentrations of the pro-inflammatory adipokine PAI-1, when compared to other ethnic groups. Even though other adipokines than PAI-1 and adipokine along with cytokines affect inflammation, the results presented in this section indicate that the Chinese population may be genetically predisposed to inflammation, which strengthens the development of T2D (figure 3.35). If this is the case, it would explain how the nutritional change might enhance inflammation and may cause stronger responses in Asian populations compared to western populations.
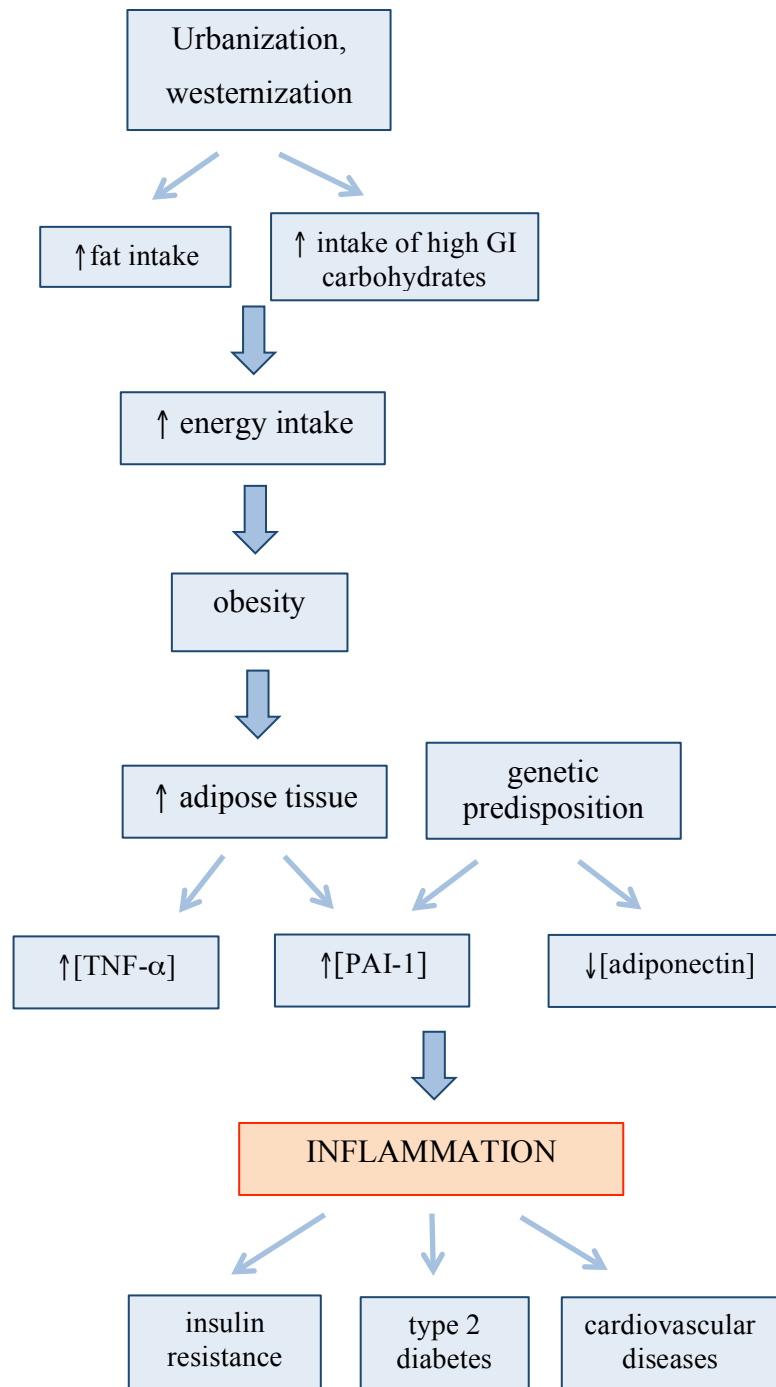
Figure 3.35 In addition to the affects previously explained, Asians seem to be genetically predisposed to develop inflammation and thus IR, T2D, and CVDs.

Part of the Chinese population might also be genetically predisposed to develop T2D and CVDs through phenotypic changes *in utero* or during childhood due to the Chinese Famine, as will be discussed in the next section.

3.5 Phenotypic plasticity explains small parts of the increased development of type 2 diabetes in China

Reduced food sources during The Dutch Famine from 1944 to 1945 might have affected development of T2D a couple of decades later. The Dutch Famine is the most researched phenotypic plasticity case, and was initiated by a railway strike from the Dutch government to stop transport of German reinforcements and troops during World War II. As a counterattack, Germans banned all food transport. When the strike ended in November 1944, food transport over water could recommence, however, an early winter made it impossible and the famine had started [188, 189].

When researching the Dutch population, different studies have shown a positive association between famine affection and development of diseases. Individuals affected *in utero* have shown to have higher prevalence of obesity and CHD, and have higher 120 minutes plasma glucose and insulin concentrations than non-exposed groups [188, 190]. These relationships are interesting as the Chinese population was exposed to a famine lasting from the late 1950s to early 1960s.

Li et al. [191] used CHNS 2002 to search for relationships between the Chinese Famine and development of hyperglycemia and T2D. Participants were divided into five groups: *in utero*, early-, mid-, late-childhood, and non-exposed, and the prevalence of hyperglycemia was 5.7%, 3.9%, 3.4%, 5.9%, and 2.4%, respectively. Thus, those affected by famine *in utero* and late-childhood were most disposed to developing hyperglycemia.

In the same study [191], all groups affected by the famine had higher blood glucose levels than the non-exposed group, and therefore lower insulin secretion or poorer insulin sensitivity. Associations were also seen for development of T2D; figure 3.36. The fetal-exposure did not have great effect, however, famine during early- and late-childhood seem to have affected the participants.
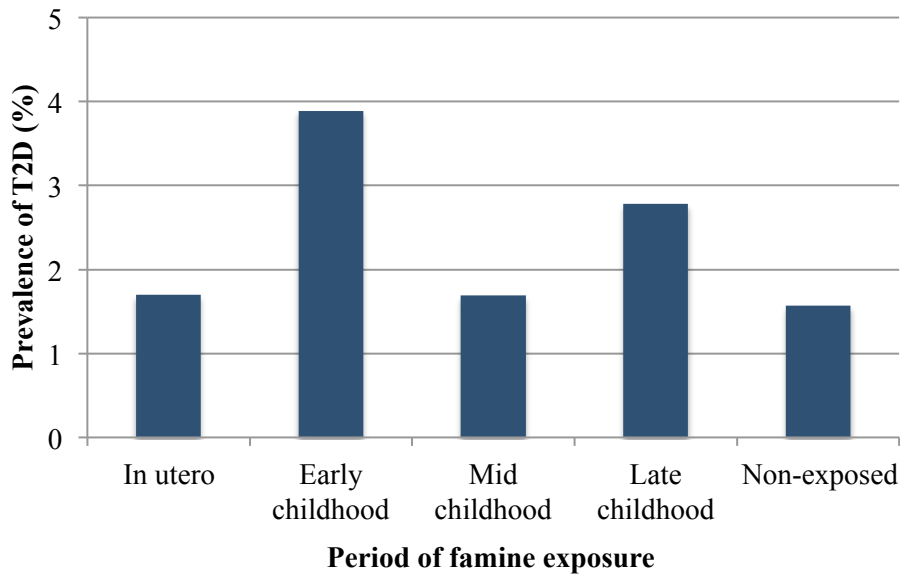
Figure 3.36 Prevalence of T2D in individuals prone to famine as fetus or childhood is greater than in non-exposed individuals. Individuals prone during early and late childhood are most affected. Numbers collected from [191].

Prevalence of T2D and hyperglycemia was greater in areas severely affected by the famine; excess death rate of > 50%, compared to less severely affected areas (figure 3.37). The trend was more obvious when studying hyperglycemia. Nevertheless, it was present in both groups.
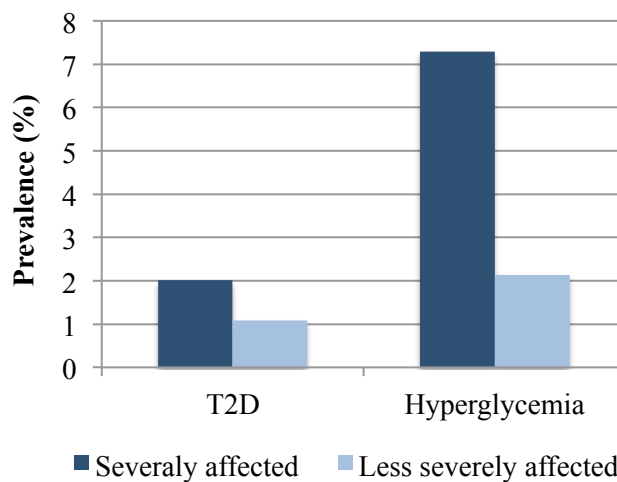
Figure 3.37 Prevalence of T2D and hyperglycemia were larger in severely affected areas; excess death rate of < 50% when compared to less severely affected areas. Numbers from fetal-exposed participants, collected from [191].

When comparing diets of individuals that were affected by the famine, higher prevalence of hyperglycemia was registered among participants living on an affluent, western diet compared

to participants following a traditional Chinese diet. The western diet "*...is characterized by a high intake of meat, eggs, dairy, sugary beverages, edible oils, and a low vegetable use*" [191]. This means that affected individuals consuming a rich western diet have a diet that does not fulfill expectations given when malnourished *in utero*. Affected individuals from higher SES show higher prevalence of hyperglycemia, most likely related to a rich diet. People from lower SES often eat more traditional plant food and little meat, and thus, have a diet closer to what they were prepared for as fetus [191].

Phenotypic plasticity is one possible explanation for the T2D increase in China. It seems as people affected by the famine as fetus or during childhood have higher risk of developing MetS risk factors than those not affected. This trend is probably stronger today due to westernization of the nutritional patterns, as explained above. Overnutrition among individuals prepared for a poor environment may be more prone to development of T2D than those not affected by famine.

Even though the Chinese Famine might strengthen the development of T2D in the Chinese population as the nutritional pattern change with westernization and urbanization, it does not explain the prevalence of T2D observed in younger age groups. There are increasing numbers of children and adolescents developing T2D in China, and some studies indicate that the one-child family policy might be to blame [137, 140].

3.6 The one-child family policy in China does not explain the increased development of type 2 diabetes

Phenotypic plasticity alone cannot explain the increase in overweight and T2D in China. If this were the case, it would be shown as a reduction of T2D in later generations. However, a reduction is not the case. Even still, increasing prevalence of overweight has been observed in children and adolescents in China.

There are several ways to measure overweight in children. Two are explained here, namely the International Obesity Task Force (IOTF) and WHO standards. WHO standards were developed based on data from US children. In children less than five years of age, overweight and obesity are defined as BMI-for-age Z scores ≥ 1 and ≥ 2, respectively. Growth reference curves are developed for children and adolescents 5-19 years; $> +1SD$ is characterized as overweight and $> +2SD$ as obesity [192]. For more information see [193].

WHO standards may not be applicable to Chinese children and adolescents as they were set using US children. The IOTF cut-off points, on the other hand, were developed using children from Brazil, Great Britain, Hong Kong, the Netherlands, Singapore, and the United States. Adult BMI cut-off points of 25 and 30 kg/m^2 were converted to cut-off points for children, shown in figure 3.38. Even though Hong Kong is a fairly good representation on China, more values from Asia were desired when establishing the standards [194].
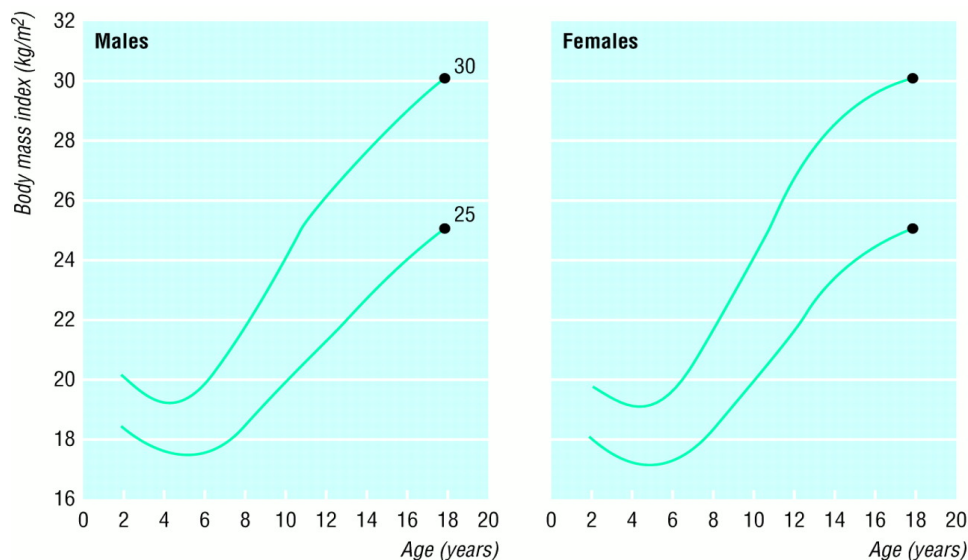
Figure 3.38 IOTF cut-off values for overweight and obesity in children and adolescents were developed by converting adult BMI cut-off points [194].

It has been suggested that abdominal measurements might be better predictors of T2D and CVD development than measurements for general obesity in Chinese children, just as in adults (section 3.1.1) [195, 196]. It seems as the definition on abdominal obesity given in box 1.2 (WC ≥ 90th percentile) is used in Chinese children [197].

There are other standards that can be used to estimate overweight and obesity in children and adolescents in addition to the two explained above. In a study specifically on Chinese children, Chinese standards were used. These standards are explained in a Chinese article, see [198]. Using these standards, prevalence of overweight and obesity doubled in Chinese children over a 15-year period, from 4.5% to 8.3% and 3.0% to 6.6%, respectively. An increase was also seen when using IOTF standards (figure 3.39) [140].
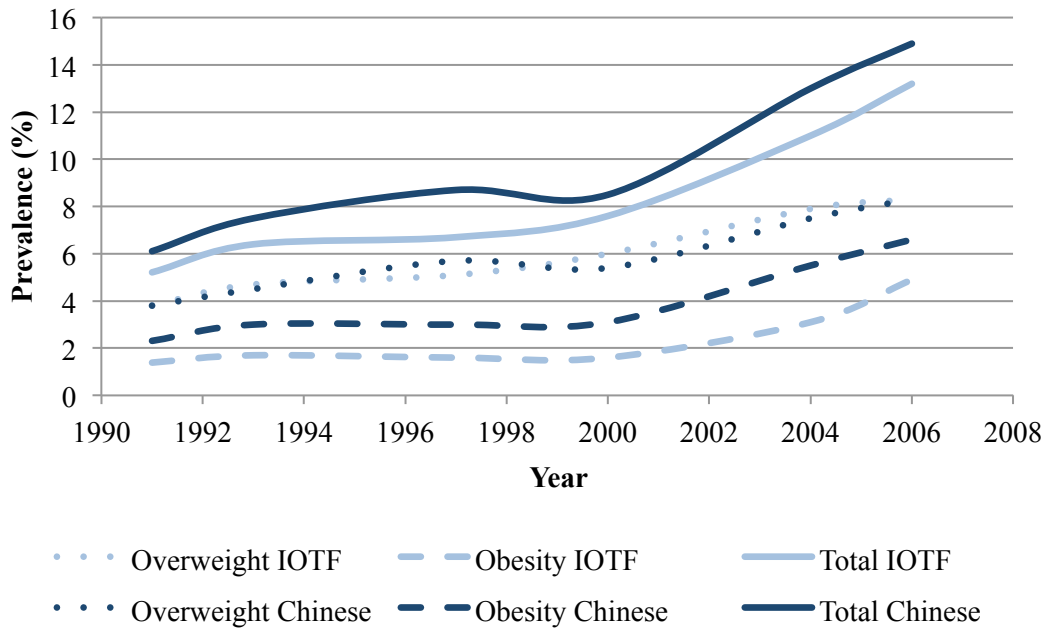
Figure 3.39 Prevalence of overweight and obesity in Chinese children aged 7-17 has doubled from 1991 to 2006. Numbers collected from [140].

Chen et al. [197] found a positive association between MetS and overweight in Beijing children. Overweight and obese children, classified by using IOTF standards, were more likely to develop MetS than normal weight children (figure 3.40). Occurrence of MetS risk factors doubled or tripled in overweight Beijing children. Obese and overweight children were 12.84 and 3.83 times more likely to be hypertensive, respectively. These children were also more likely to have impaired fasting glucose concentration [197]. The association has been shown in studies using children from other parts of China as well [50, 199], and thus, young children in China are more likely to develop MetS it they are overweight.
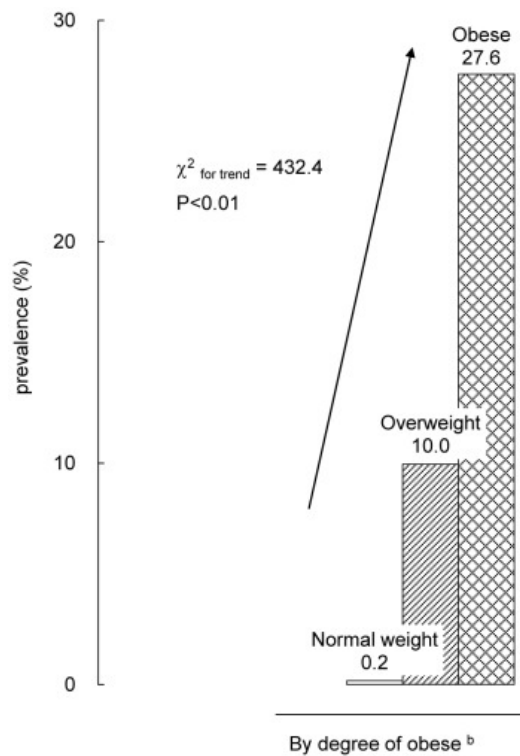
Figure 3.40 Prevalence of MetS in Beijing children increase with weight [197].

An US study displays associations between childhood MetS and adulthood MetS and T2D. As shown in figure 3.41, prevalence of adulthood MetS and T2D were higher among participants that had childhood MetS when compared to participants who did not have childhood MetS. A relationship between childhood and adulthood overweight was also presented; 63% of the participants in risk of childhood overweight were obese as adults [200]. This relationship explains why the emergent overweight problem among Chinese children and adolescents is a serious problem, and why T2D is likely to be a growing epidemic.
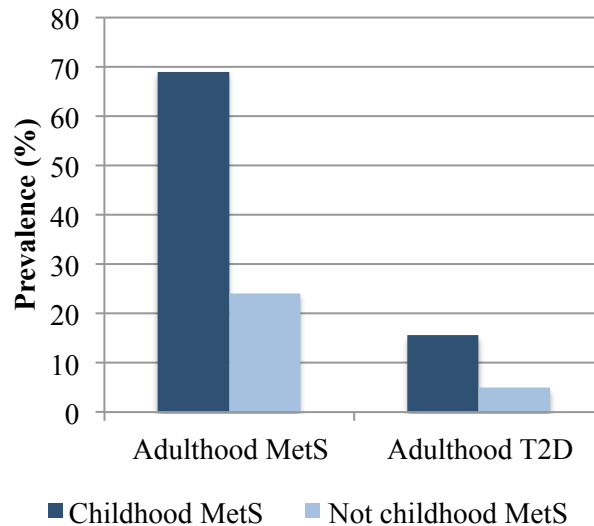
Figure 3.41 Prevalence of adulthood MetS and T2D is higher in individuals having childhood MetS. Numbers collected from [200].

The one-child policy in China is been accused for some of the growing overweight burden among children and adolescents [137, 140]. China experienced an extreme population growth before the late 1970s when the Chinese government learnt the value of demography. To develop better economy, population growth had to stop. The one-child policy was therefore introduced in 1978 when women giving birth to three or more children would suffer economically. Couples signing an agreement saying they would get no more than one child received a *single-child certificate* in addition to an economical reward. This reward was often more noticeable in urban areas than rural areas. Reduced salaries and other penalties punished couples having more than two children [201]. However, if the firstborn child in a rural family was a girl, they were often allowed one more child after five years [202]. Couples giving birth to only one child tended to be well educated, be employed in paid jobs and have a relatively high standard of living. Couples having more than two children tended to be poor, minimally educated and dependent of their children's income [201]. Overweight studies show that children from high SES are more likely to be overweight or obese than children from low- or middle SES families [140]. As couples signing the one-child agreement have shown to have a higher standard of living they might afford to spoil their child more than those having several children. Grandparents often live with the family and tend to spoil the child even more, especially boys [203]. As mentioned in section 1.3.6, overweight people indicate wellness in the Chinese culture. They are thought to be happy, lucky, rich, and have a high quality of life; over-feeding children will give this expression [204].

There are different policies in different parts of China and not all communities are equally strict when it comes to the one-child policy. In some parts, couples are allowed to have one more child if the firstborn is a girl and in other parts two children or more are permitted. Children living in a strict one-child policy community are more likely to be overweight compared to moderate and weak communities (figure 3.42). Children from moderately political communities, where two children are approved if the firstborn is a girl, have lower prevalence of overweight. Least prevalence is seen in the weak political communities where couples are allowed to have two children or more [203]. This indicates that the one-child policy might affect prevalence of overweight in Chinese children.
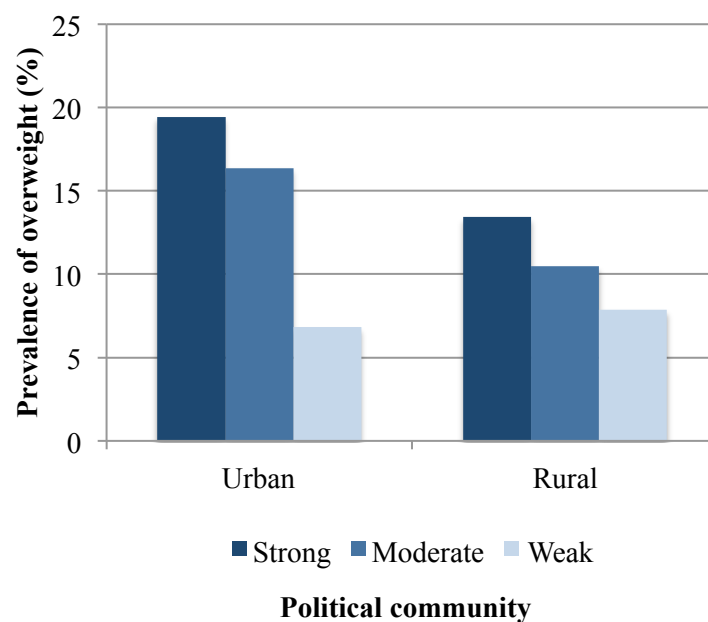
Figure 3.42 Prevalence of overweight children in China is higher in strong political communites than in moderate and weak communitites. Strong: one-child policy, moderate: girl-exception policy, weak: two-child policy. Numbers collected from [203].

According to a study by Yang [203], single children living in rural areas seem to have higher prevalence of overweight than non-single children. This relationship is not observed in urban children (figure 3.43). However, the relationship in rural areas disappears after adjustments. The difference of policy communities shown in figure 3.42 also becomes non-significant after adjustments. The author suggests that campaigns focusing on the negative consequences of overweight during the 1990s might have led to higher awareness on healthy nutrition [203]. Figure 3.39 does not show any sign of these campaigns having any affect, as the overweight prevalence has continued to grow after the year 2000.
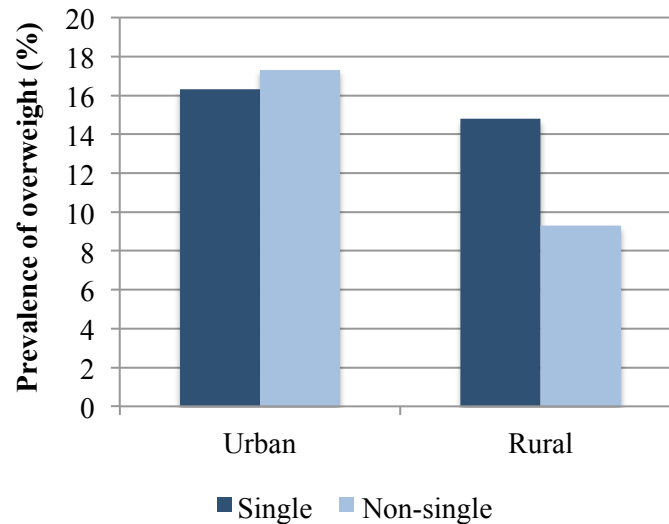
Figure 3.43 Prevalence of overweight among Chinese children is higher in single rural children when compared to non-single rural children. In urban areas, on the other hand, there are little differences. Numbers collected from [203].

Another study on family size and overweight presents similar results as the study in the previous paragraph. Before any adjustments, single children were more overweight than children with siblings. However, after adjusting for area, parental education, and sex, the differences were not significant. In this study the author proposes that the five-year rule might explain these results; a five year separation between sibling reduce competition for parents' attention [205].

In conclusion, the one-child policy may not have the large impact on children's overweight in China as some studies suggest. Still, the prevalence of overweight and obesity is increasing in children and adolescents with the prevalence being highest among high SES urban boys. One hypothesis is that the high SES urban boys' parents can afford to feed them more foods than others. As discussed in section 3.2 and 3.3, foods in urban areas tend to be more affected by westernization; increased kcal content due to raised fat- and GI content in the food. The excess body weight that western foods might give the boys is a sign of accomplishment, maybe triggering parents to overfeed their children.

In addition to differences seen between urban and rural areas, there are differences between north and south, where more overweight is seen north of the Yangtze River, called the north-south gradient [123, 206].

3.7 There are geographical differences within China

Until now, China has been considered as one, although there are differences within China. These are mainly seen through the north-south gradient; division by the Yangtze River (figure 1.21), and will be further outlined in the preceding section.

An InterASIA-study comparing overweight and obesity in northern and southern China found higher prevalence in the north (figure 3.44) [123]. Figure 3.44 indicates that citizens in northern parts of China are more prone to CVDs as excess weight is a MetS risk factor.
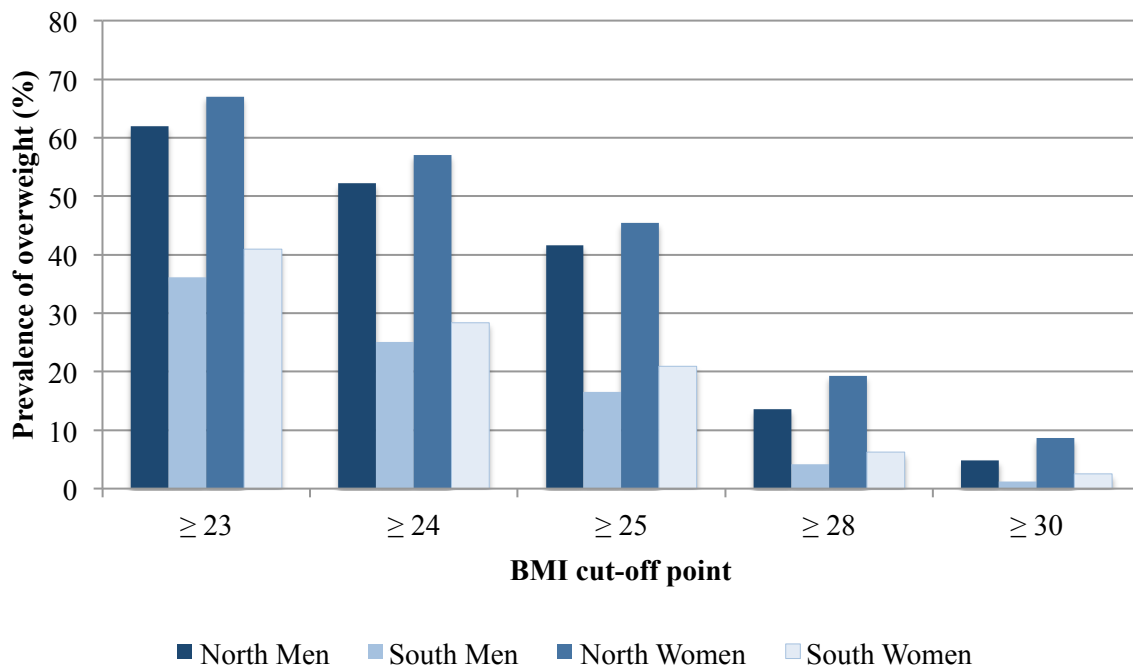
Figure 3.44 Prevalence of overweight in China is higher in the north than the south, independent of BMI cut-off points. Numbers collected from [206].

As abdominal measurements might be a better indicator on obesity in the Chinese population, this might be a better indicator on MetS. People in the northern parts of China also show higher prevalence of abdominal obesity than people in the southern parts (figure 3.45).
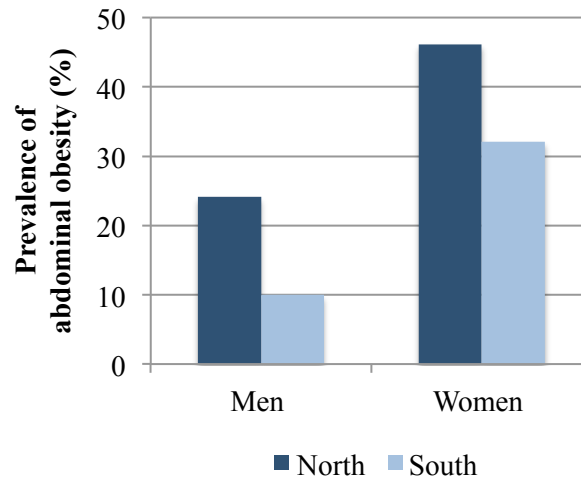
Figure 3.45 There is higher prevalence of abdominal obesity in northern China than southern China. Cut-off points were 80 and 90 cm for women and men, respectively. Numbers collected from [206].

A study using Beijing and Shanxi as representatives for the northern parts of China and Guangxi for the south found that both SBP and DBP were higher in the north; SBP of 123.7 against 116.3 mmHg and DBP of 75.5 against 68.6 mmHg [207]. This study was small, but others have exposed the same pattern [208]. Higher blood pressure among northerners indicates that they have higher probability of developing T2D. Studies show that people diagnosed with T2D have higher SBP and DBP than people with normal fasting glucose levels; high SBP is an especially important risk factor [209]. Moreover, Hu et al. [209] found that T2D prevalence was higher in north China than in the south; 6.1% against 4.83%. Another study, using Beijing and Shanghai as representatives for north and south regions, respectively, found the same trend (figure 3.46) [210].
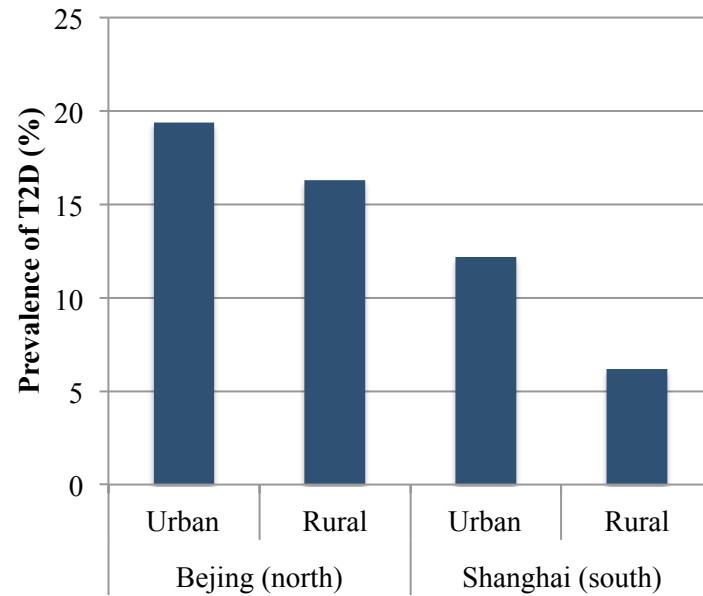
Figure 3.46 The prevalence of T2D is highest in the urban north area of China and lowest in the rural south, using Beijing and Shanghai as representatives for north and south, respectively. Numbers collected from [210].

Another study testing blood pressure in the Chinese population divided China into six parts. Higher prevalence of hypertension was seen in the north and northeast while southwest had lowest prevalence (figure 3.47) [211].
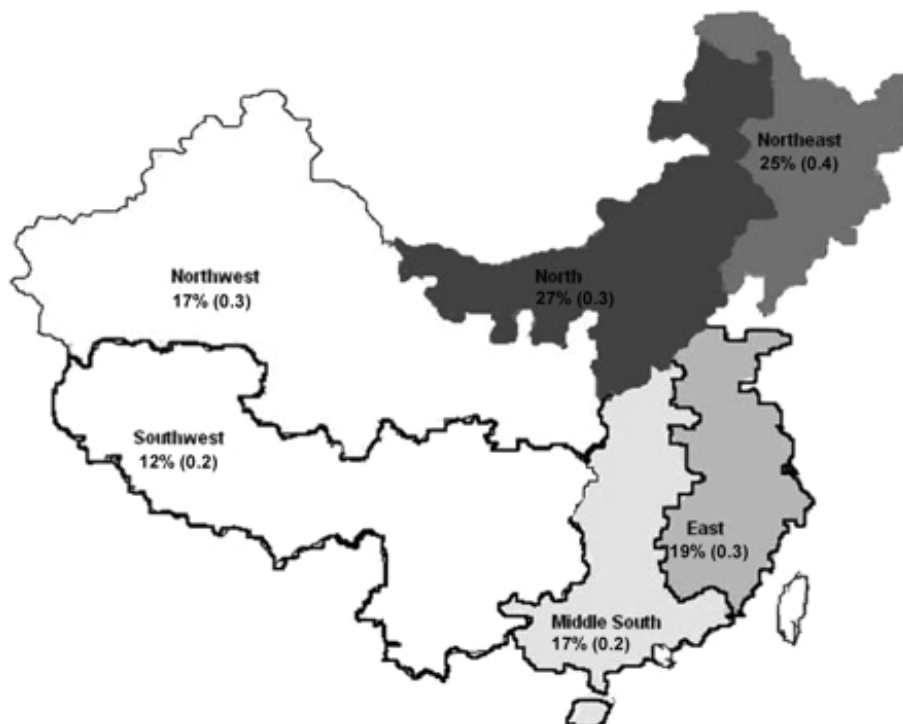
Figure 3.47 Prevalence of hypertension in China is highest in north and northeast, intermediate in east, middle south and northwest, while lowest in southwest [211].

Not just CVD risk factors, such as increased BMI and hypertension, are higher in north China; incidences of CVDs are also higher (figure 3.48). Furthermore, the increase is likely to continue as China is urbanizing and urban citizens have higher prevalence of CVD (figure 3.13) [212].
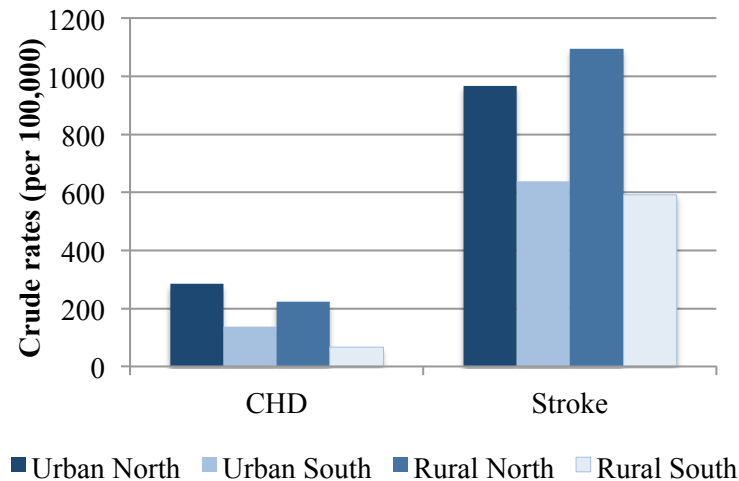
Figure 3.48 Prevalence of CHD and stroke is higher in north China than south China. Numbers collected from [212].

There are no clear reasons to the north-south gradient. However, one explanation might be the different diets. In studies by Yap et al. [208] and Zhao et al. [207] some differences between nutrition in north and south China were listed; parts of their results are presented in table 3.3. Both studies showed a difference in total energy intake, something that may explain the higher BMI and WC values in the north (figure 3.44 and 3.45). Total available carbohydrate is also higher, along with starch intake. All these factors affect insulin secretion and might partly explain the higher prevalence of T2D and CVDs in north China. Both studies also found higher pro-inflammatory SFA intake in the northern parts. Vegetable consumption differed as well, most likely due to the production difficulties in the north, especially during winter time [213]. Little difference was seen in sugar, fiber, and PUFA intake [207, 208].

Table 3.3 People living in north China consume more energy per day, carbohydrates, starch, and SFA than south Chinese people.

	North	South
Energy kcal/d [208]	2,080	1,962
Energy kcal/d [207]	2,078	1,956
Total available carbohydrate, %kcal [207]	67.4	60.2
Starch, %kcal [207, 208]	58.8	51.6 – 51.9
SFA, %kcal [207, 208]	4.5	6.1

Using 2002 China National Nutrition and Healthy Survey, Li et al. [214] found that 36.1% of Chinese people live on a traditional southern diet "*characterized by high intakes of rice, vegetables, seafood, pork, and poultry*". 28.1% live on a traditional northern diet "*characterized by high intakes of wheat, flour products and (sweet) potato, combined with low consumption of protein products such as pork, beef, poultry, seafood, or milk and milk products*". The remaining 35.8% live on a western diet, characterized by a "*high consumption of beef, fruit, eggs, poultry, seafood, tofu, milk products, cake, fruit juice, beverages, nuts, beer, and wine*". The southern diet was least associated with stroke. Furthermore, both the north and western diet were positively associated with stroke, proving that diet may play a part in the CVD risk in China.

Other factors, such as the large difference in activity level or the amounts of smoking may also contribute to the T2D and CVD prevalence being higher in northern parts of China than the southern parts. The cooler winter in the north may also explain parts of the gradient; in addition to this affecting vegetable production, it makes the north population stay indoors, which results in less physical activity than normal. In the southern parts, temperatures are higher and they keep up outdoor activity and thereby maintain physical activity [123].

This section has showed that there are differences within China and that the northern population is more likely to develop T2D and CVDs. This might be explained through nutrition as the southern diet is more varied and have fewer kcal than the western and northern diet. One hypothesis is that people previously living on the typical southern diet are among those that are changing their diet due to the westernization process, as some of the

larger cities, such as Shanghai and Hong Kong, are placed in the southern parts. Exchanging the southern diet with a western diet contributes to an increase in T2D development.

Even though the disease pattern in China is a greater problem in the northern parts, it is a national problem. Two important factors to the disease development appear to be genetic predisposition and the dietary changes seen due to urbanization and westernization.

3.8 Genetic predisposition and changes in dietary patterns may contribute to increased development of type 2 diabetes in the Chinese population

The nutritional patterns seen in China the last years can at least partly explain the rise in T2D and CVD cases. According to the topics discussed in this paper there seem to be two main reasons to the disease pattern in China. The urbanization and westernization processes in China the last decades may explain some of the disease development as it has resulted in changed dietary patterns. An increased consumption of fat has been observed, resulting in increased kcal intake, which may eventually trigger overnutrition. Furthermore, an increased intake of high GI carbohydrates has also been observed. This diet contributes to increased metabolic inflammation in addition to overweight, which is characterized by constant inflammation.

According to the timeline in figure 3.49, it seems as urbanization started the development of T2D in China. Increased fat intake triggers overweight that escalates progression of T2D. So far, this pretty much equals the trend in the western world. It would be interesting to see if abdominal obesity might have affected the development, but figures older than 1993 were difficult to find.
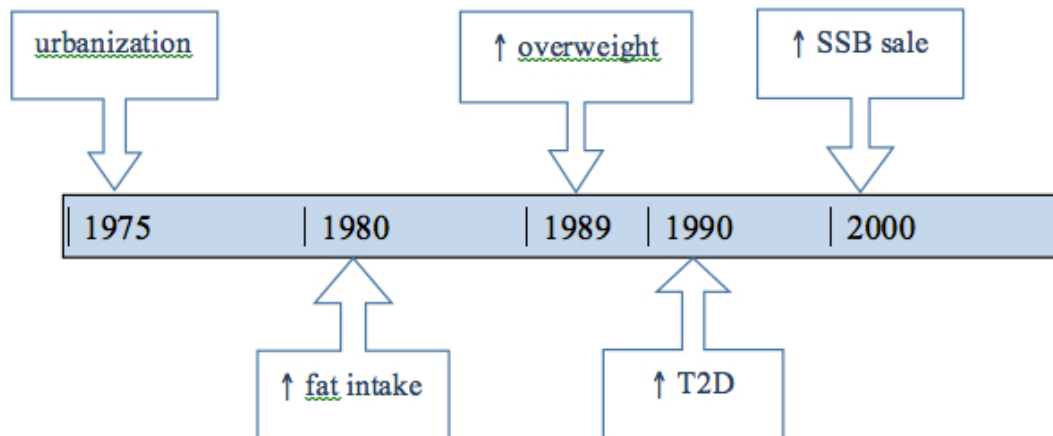
Figure 3.49 Some of the relationships between lifestyle and T2D development discussed in this paper are placed on a timeline to display relationships between the different events. Increased fat intake is most likely related to the urbanization and westernization during the 1970s. From the timeline, it seems that the increased overweight prevalence might come as a result of the increased fat intake; the T2D rates started to increase a decade after increased fat intake. In the year 2000 the SSB sale started to raise, which indicates that China might be looking at an even higher prevalence of T2D today.

China has lower prevalence of overweight than western populations, but similar prevalence of T2D. Thus, there must be other explanations to the increasing T2D rates than the westernization process. The second explanation to the T2D development in China found in this thesis is the genetic predisposition. Chinese people have higher PAI-1 and lower adiponectin concentrations compared to other ethnic groups. This makes them more prone to inflammation, which strengthens development of T2D. However, this is just a small part of the inflammatory system and there might be several other factors differing in ethnic groups.

Even though this paper cannot give conclusive explanations to the T2D and CVD development in China, it is obvious that the diseases arising today are a problem. It is not just a problem among Chinese adults, but also among children and adolescents. The high prevalence among young Chinese age groups indicates the importance around preventable strategies, as well as implementing strategies to reduce the diseases already occurring; *what actions are seen from the governments to slow development of overweight and T2D? Are there more that can be done?*

3.9 Governmental strategies are important to prevent and reduce disease development

Several problems around overweight, T2D, and CVDs have been presented within this thesis, all with a nutritional focus. Parallel to the nutrition transition it is important that the government realizes the arising problems and makes adjustments in food recommendations, in addition to organizing educational campaigns for the population.

Great economic growth is accomplished in China due to the rural reforms implemented in the late 1970s. After the Great Leap Forward; "*a collapse in grain production and a widespread famine in China between 1959 and 1961, is found attributable to a systematic failure in central planning*" [215], it was important to increase agricultural production to provide people with enough food. The rural reforms gave farmers better conditions through the household-responsibility system, which was a contract between farmers and the government lasting up to 15 years. Previously, land was shared between 20-30 neighborhoods. Land was now divided into private households and production increased since farmers now were responsible for their own land. Increasing food prices probably resulted in the largest economical growth. From before, there were two pricing systems in China: the quota price and the above-quota price. The latter price type for crops sold excess to obligations. Quota price on grain, oil cops, cotton, sugar crops, and pork were raised by an average of 17.1% in 1979. Above-quota price for grain and oil crops were raised from 30% to 50% of the quota price. This raised the above-quota prices by 40.7%. Retail prices also increased, mainly in pork, fish, and eggs; urban residents received 5-8 Yuan subsidy per month as a compensation for the increase. After some time, this subsidy became too expensive for the government over time and the quotas were removed. Contracts between farmers and the government replaced the quotas and the price was an average of quota price and above quota price. In total, price paid to the farmers was then reduced [216]. Still, agricultural growth is seen in China from late 1970 up till today (figure 3.50), most likely due reforms helping farmers.
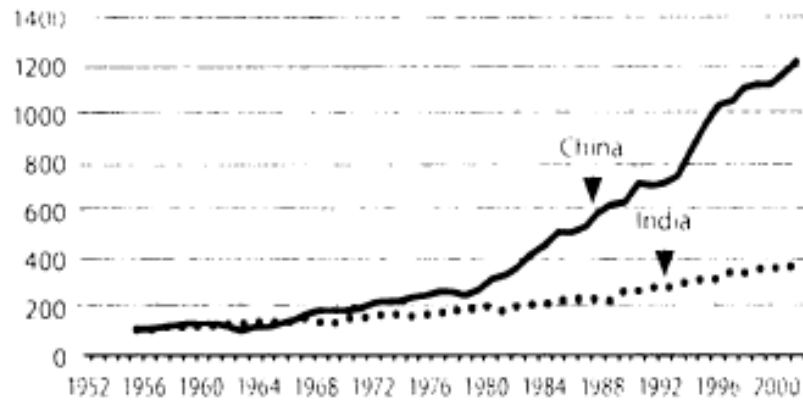
Figure 3.50 Agricultural output and productivity has increased in China (whole line) from the 1950s to 2002 [217].

The challenge today is different form the challenge seen in the 1970s and 80s when the rural reforms were implemented. In much of Asia, the dual burden households represent a challenge for the government (section 3.1.3). This is primarily a problem among low-income households and the challenge is to avoid a "*one size fits all*" solution. Kohr [218] suggests improvements of income through agricultural productivity and biodiversity. In some Asian countries, a diversification into horticultural crops has increased income due to a worldwide increase in fruit and vegetable demand as health benefits are becoming clearer. Government can help small farmers improve productivity by changing economical and agricultural policies, just as the Chinese government did in the late 1970s. However, this will not help urban poor people; they need a job. If both parents in a household have jobs where they are likely to work many hours it may result in older siblings babysitting younger siblings. They often lack food knowledge, something affecting food quality. Also, if the parents work many hours they tend to resort to ready-to-eat foods, as they are cheap and convenient. If the parents have improved access to coursing they might get access to better paid jobs where they do not have to work such long hours; thus, government can help by increasing access to training programs [218].

The dual burden is not as great a challenge in China as in other Asian countries; in most Chinese households overweight is a greater problem than undernutrition and underweight [144, 219]. The overweight problem is probably due to the nutrition transition triggering overnutrition. The government has to implement changes in the society to reduce intake of energy-dense and high-GI foods, especially among overweight people. The Chinese population seems to change their macronutrient intake when price of various foods is altered [220]. Using CHNS 1989, 1991, and 1993, increased price and corresponding intake of six food groups; rice, wheat flour, coarse grains, pork, eggs, and oils were compared. Significant

decrease in consumption was seen in every food group, except coarse grain, when price increased. 10% increase in pork price resulted in 5% decreased intake, 9% decrease in rice consumption, and 3% decreased egg consumption; rice and egg are complementary to pork. Wheat flour intake increased by 2% and oil consumption by 3%; they are substitutions. The increased pork price reduced the total energy intake by 2%, protein intake by 2%, and fat intake by 8%. Among the poor, the increased pork price resulted in 11% decrease in daily fat intake, against 5% among the rich. The protein intake also decreased more among the poor than the rich. The different response in rich and poor is important to keep in mind when altering food prices to change people's nutrition patterns. As increased fat intake is a growing problem in China, increasing pork price would seem to be a solution. In addition to food groups being linked, the increased price reduced protein intake. In this scenario, people were more likely to consume coarse grains, wheat flour, and oils. It would therefore be better to increase oil price, as this only reduced fat intake [220]. As discussed in section 3.3.1, increased intake of oils having a high n-6 content is seen in China. The government could increase price on these oils and reduce price on oils having high n-3 content, to reduce n-6:n-3 ratio.

Plant oil price has decreased in China since the early1990s along with an increased intake. Ng and colleagues [221] studied consumption change of different food groups in the Chinese population after increasing price on the cheapest edible plant oil. Price increase resulted in decreased rice consumption and increased wheat intake. Rice decline was clearest in the north and among the poor. Considering macronutrients, fat intake decreased after oil price increase, while protein and carbohydrate intake increased. However, the carbohydrate increase was not significant. Figure 3.51 shows change in macronutrient intake after the 10% price increase in the cheapest edible oil. The poor were more price-sensitive and had the largest reduction in fat intake. Ng et al. [221] suggest a relocation of funds to avoid affecting the poor in need of high kcal diets. This study did not separate types of fat, and as discussed in section 1.1.2.2; TFA, SFA, and PUFA have different effects on inflammatory responses.
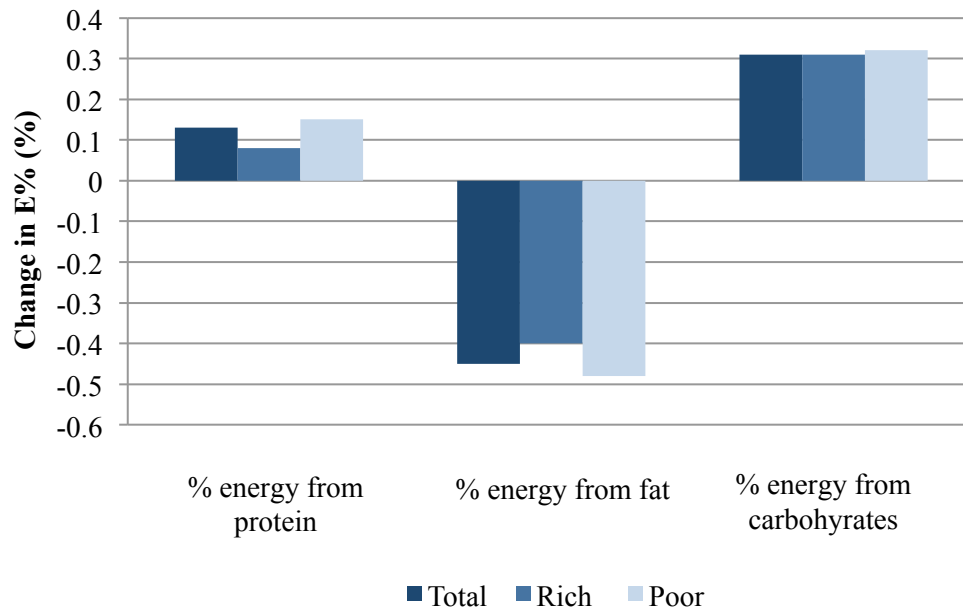
Figure 3.51 Macronutrient intake changed in the Chinese population after a 10% price increase in plant oil. Numbers collected from [221].

TFA food labeling became mandatory in Korea in 2007 and premise for "*trans* fat free"-labeling is 0.2 g TFA per serving. A study comparing Korean foods in 2005 and 2008 found a reduction in TFA content. Other types of fat were also included in the study and SFA content ranged from 18.3% to 64.7% of total FA in 2005, while USFA content ranged from 27.9% to 64.5%. FA composition drastically changed in the time period 2005-2008; cream-filled biscuit and cream-stuffed cake had reduced TFA content and increased SFA content (figure 3.52). Although TFA content is reduced, the food is still not *healthy* as SFA is a pro-inflammatory FA. The USFA content barley changed; it would be interesting to see a separation of MUFA and PUFA, and n-3 and n-6 PUFA content. The TFA content was also reduced in French fries and deep-fried chicken; indicating an exchange of frying oils, to *trans* fat free oils. Thus, mandatory TFA labeling of foods in Korea has reduced TFA content in various foods. To achieve this, manufacturers had to adopt alternative technologies [222]. The authors presenting reduction in TFA content in Korea do not mention people's reactions to the labeling. Normally, manufacturers only change food content if sales drops and costumers demand a change. For costumers to act, they need knowledge about the food they buy. Thus, education is important in this type of process. People have to learn how to read the label before buying a product; and when doing so, they must know what to look for. Several studies recommend nutritional labeling as a governmental strategy, along with education of the population [149, 223]. In addition to labeling food in the grocery store, labeling fast food

would also help people make informed decisions. And maybe such labeling would reduce sales, forcing producers to better the product. Alternatively, government could set rules for fast-food making. At last, pricing of unhealthy foods making it cheaper with increased quantity should be avoided [223].
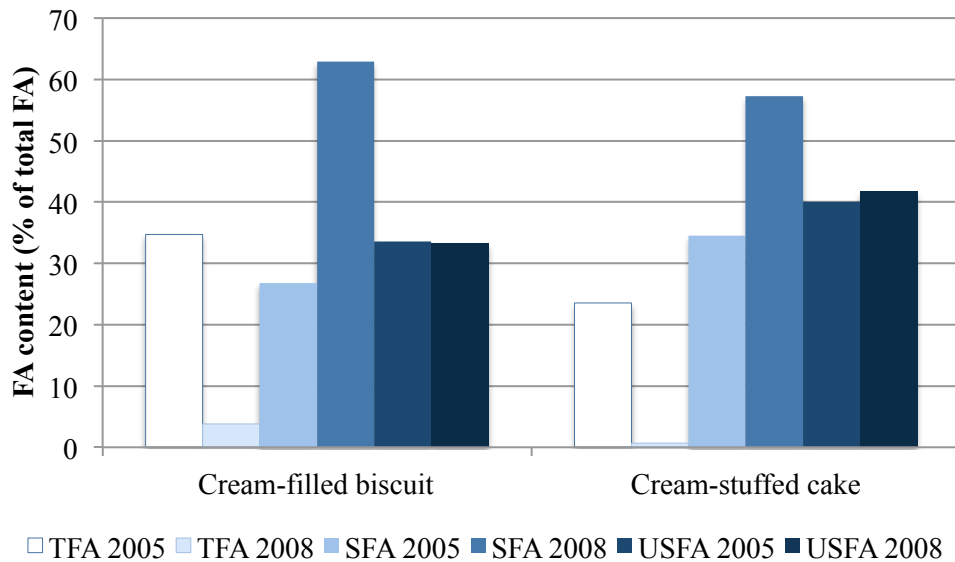
Figure 3.52 TFA content in Korean foods has decreased from 2005 till 2008. SFA content has increased in the same time period, while USFA content has been stable. Numbers collected from [222].

As discussed in section 3.3.2, raised intake of high GI foods is seen in China. This increase is seen partly due to an increased intake of SSBs. A taxation system on SSBs has been discussed in many countries, especially in the US [22, 224]. Brownell et al. [22] propose "*an excise tax of 1 cent per ounce for beverages that have any added caloric sweetener*" to reduce sale and thereby intake; price on a 20-oz soft drink would increase by 15-20%. In a study on the US population, highest response was seen in away-from-home foods and soft drinks; 10% price increase in soft drinks resulted in 8-10% decreased intake [225]. The tax may be put on producers whom most likely would forward the price raise to consumers. Alternatively, sugar used in SSBs could be taxed. Even though taxation of SSBs might not eliminate the overweight problem, it will most likely reduce kcal intake, especially among the poor [22].

As discussed so far, preventable strategies are important to reduce disease patterns. However, strategies for dealing with diseases are also important. In 2006, China's government launched the "*Healthy China 2020 programme*" containing five goals:

1) Medical insurance cover for more than 90% of the Chinese population.
2) Establishment of a national drug system providing people with essential treatment in a safe way.
3) Improvement of medical care and public health service system.
4) Promotion of basic health service.
5) Action plan to launch the pilot reform of public hospital.

The project's ambition is to fulfill all these five goals by the year 2020. The fourth goal includes management of chronic diseases and the provision of screening for major diseases in elderly [76]. An estimated 60.7% of diabetes cases were undiagnosed in China in 2010, showing the importance of screening. Naturally, screening is important for other diseases as well [128].

The most important governmental intervention has to be education. In the study on brown rice consumption in section 3.3.2 [160], few of the participants had knowledge about the nutritional benefits around choosing brown rice; some thought it would trigger stomach problems among elderly. In countries with high human developmental index, such as Norway and the United Kingdom, BMI is negatively associated with SES. In countries with lower human developmental index, such as China and India, the association is positive [226]. Thus, importance of education seems to increase parallel to increase of a country's development. It is often the well educated that make the healthiest life choices; when people know what to look for in food many choose the healthier alternatives [227]. Of course, making the healthiest food the cheapest food will also help people make *right* decisions, with or without knowledge on healthy foods. As mentioned in the previous section, vegetable intake in north China is lower than in the south, especially during winter. To increase intake, the central government has adjusted price in addition to help change plant breeding to enhance production [213].

Governmental strategies are important to make people choose a healthier alternative when putting together a meal. To help the rural population the government may contribute with agricultural technologies and education. Education may also help urban citizens, as it may result in employment. This means better income and more time at home to prepare real food.

During this paper, overnutrition, due to increased fat quantity and SSB intake, and GI has been argued to be the main reasons for the increased T2D rates. It is therefore conceivable that education of the population would be the best strategy, along with reducing price on the healthier foods, as this will make it more available. At last, food labeling is also important, in combination with education.

4 Conclusion

This thesis has reviewed lifestyle changes associated with the increased development of T2D and CVDs in the Chinese population over the last decades, and has attempted to examine and discuss several hypotheses forwarded by various researched explaining this trend. The Chinese Famine in the mid1940s resulted in genetic changes due to phenotypic plasticity. These changes do not correspond to the diet seen in China after the westernization process, as this includes a more energy dense diet. The difference between malnourishment *in utero* or during childhood joined with the affluent diet seen today appears to have resulted in an increased prevalence of T2D and CVDs among people affected by the famine. Thus, the phenotypic changes might explain some of the development of T2D and CVDs in China. However, it does not explain the development seen in the younger age groups. Increased prevalence of both overweight and T2D has been observed in children and adolescents and the one-child family policy has been blamed for this development as it results in more focus and resources on one child. However, studies presented in this thesis do not back-up the hypothesis that the one-child family policy has affected development of overweight and T2D in China.

Prevalence of overweight and T2D is higher in urban areas than rural areas, and also higher in northern parts of China compared to southern parts. These differences might be due to differing nutritional patterns; the southern diet is characterized by lower kcal and GI intake than the northern diet. The relationship is the same in rural and urban areas where urban regions have higher prevalence of overweight and T2D than rural regions. Differences between urban and rural areas can also be related to the nutritional patterns as urban regions are more affected by the westernization and therefore consume a more energy-dense diet. Even though there are differences within China, increasing occurrence of T2D is a problem concerning all parts of the country. This is likely because Asians have higher concentrations of the pro-inflammatory mediator PAI-1 and lower concentrations of the anti-inflammatory mediator adiponectin than other ethnic groups. These differences suggest that Asians may be genetically predisposed to developing metabolic inflammation, most likely amplified by changed nutritional patterns seen due to the urbanization and westernization process. Hence, genetic predisposition and changes in dietary patterns appear to be two important factors contributing to the development of T2D and CVDs in the Chinese population.

5 Recommendations for further work

To further research genetic differences among the Chinese population and other ethnic groups, resistin expression could be explored. Resistin is included in the introduction (section 1.3.2) of this thesis; however, no results are presented. Most studies done on mice show positive associations between resistin levels, inflammation and IR [100, 228]. Still, there are no conclusive evidence in humans [62]. One study published in a Chinese journal show relationships between resistin level, BMI, WC, WHR and blood pressure in humans. Nevertheless, due to missing information about the participants and the study in general the results should not be used as a certainty, in addition to the article not being from a reputable journal [229]. Comparing resistin levels in Chinese and Americans or Europeans would be an interesting future study project that might be able to explain some of the development of T2D in China at lower BMI levels. Further work could also be to study stimulation of cells by different cytokines and adipokines.

To further research the nutritional aspect, more data on fat quality in the Chinese or Asian diet could be collected and discussed. Direct figures on SFA intake in addition to consumption of n-3 and n-6 PUFAs could contribute to the discussion as an unbalance in fat intake may increase inflammation and therefore strengthen development of T2D.

This thesis studied the disease development due to nutrition as a lifestyle factor. If future studies, other lifestyle factors, such as physical activity, smoking and alcohol consumption, could be included. Several of the cited articles include these factors, so data are available.

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