Jianjun Wang

Assessment of the Metabolic Syndrome in Predicting Incident Type 2 Diabetes in a Chinese Population

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ASSESSMENT OF THE METABOLIC SYNDROME IN PREDICTING INCIDENT TYPE 2 DIABETES IN A CHINESE POPULATION

ACADEMIC DISSERTATION

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ABSTRACT

During the past decade Chinese people have gradually changed their lifestyles following the rapid development of the economy. Lifestyle changes in the population have increased the prevalence of type 2 diabetes and obesity, especially in urban areas. However, no study has been conducted on relationship between the metabolic syndrome and incident diabetes in China.

This study was designed to evaluate the ability of the five definitions, major components and changes in features of the metabolic syndrome with respect to the prediction of type 2 diabetes in a Chinese population.

The Beijing Project of National Diabetes Survey was carried out in 1994, and a follow-up study of 627 high-risk non-diabetic individuals at baseline was untaken in 1999. A total of 146 subjects developed diabetes during the 5-year follow-up.

The definitions of the metabolic syndrome defined by the National Cholesterol Education Program (NCEP) Expert Panel and the European Group for the Study of Insulin Resistance (EGIR) were somewhat insensitive for predicting incident diabetes (especially in men), only detecting about 27% of Chinese men with incident diabetes. Both impaired fasting glucose and impaired glucose tolerance combined were associated with a 9-fold increased risk of incident diabetes in both men and women. Isolated impaired glucose tolerance was also associated with a 7.8-fold increased risk of future diabetes in Chinese men. Factor analysis revealed four factors, rather than only one factor, in non-diabetic and diabetic subjects. Blood pressure was not linked to insulin resistance. The urinary albumin excretion rate was associated with the glucose factor in diabetic subjects. The obesity and glucose factors strongly predicted the development of diabetes. An increase in the prevalence of obesity was associated with a 2.2-fold increased risk of the development of impaired glucose regulation or incident diabetes after adjustment for the confounding factors.

The results suggest that further studies on the definition of the metabolic syndrome should focus on the potential ethnic differences in obesity and insulin resistance. In Chinese men, isolated impaired glucose tolerance is a better predictor of incident diabetes than impaired fasting glucose. Different physiological processes associated with various components of the metabolic syndrome contain unique information about diabetes risk. Microalbuminuria is more likely to be a complication of diabetes or hypertension than a marker of the metabolic syndrome. Obesity may be a more important risk factor for the development of impaired glucose regulation or diabetes than other features of the metabolic syndrome.

Keywords: metabolic syndrome, definition, type 2 diabetes, insulin resistance, incidence

CONTENTS

ABBREVIATIONS

AACE	American Association of Clinical Endocrinologists
APC	Asia-Pacific criteria
BP	blood pressure
BMI	body mass index
CNHS	China's Nutrition and Health Survey
CVD	cardiovascular disease
DBP	diastolic blood pressure
DPP	Diabetes Prevention Program
DPS	Finnish Diabetes Prevention Study
EGIR	European Group for the Study of Insulin Resistance
Fin	fasting insulin
FPG	fasting plasma glucose
HDL	high-density lipoprotein
HOMA-IR	homeostasis model assessment of insulin resistance
IDF	International Diabetes Federation
IFG	impaired fasting glucose
I_2/G_2	2-h insulin/2-h glucose
IGR	impaired glucose regulation
IGT	impaired glucose tolerance
InterASIA	International Collaborative Study of Cardiovascular Disease in Asia
IRAS	Insulin Resistance Atherosclerosis Study
ISI	insulin sensitivity index
LDL	low-density lipoprotein
MetS	the metabolic syndrome
MONICA	Monitoring of Trends and Determinants in Cardiovascular Disease
NEFAs	non-esterified fatty acids
NCEP	National Cholesterol Education Program
NFG	normal fasting glucose
NGT	normal glucose tolerance
OGTT	oral glucose tolerance test
OR	odds ratio
PPARγ	peroxisome proliferator-activated receptor gamma
2-h PG	2-h post glucose load
QTL	quantitative trait loci
QUICKI	quantitative insulin sensitivity check index
RR	relative risk
SAHS	San Antonio Heart Study
SAT	subcutaneous abdominal tissue
SBP	systolic blood pressure
TC	total cholesterol
TG	triglycerides
VLDL	very-low-density lipoprotein
WC	waist circumference
WHO	World Health Organization
WHR	waist-to-hip ratio
UAER	urinary albumin excretion rate
VAT	visceral abdominal tissue
VLDL	very-low-density lipoprotei

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles referred to in the text by their Roman numerals. Some unpublished data is also presented

I. Wang JJ, Hu G, Miettinen ME, Tuomilehto J. The metabolic syndrome and incident diabetes: Assessment of four suggested definitions of the metabolic syndrome in a Chinese population with high post-prandial glucose. Horm Metab Res 36:708-715. 2004

II. Wang JJ, Yuan SY, Zhu LX, Fu HJ, Li HB, Hu G, Tuomilehto J. Effects of impaired fasting glucose and impaired glucose tolerance on predicting incident type 2 diabetes in a Chinese population with high post-prandial glucose. Diabetes Res Clin Pract 66:183-191, 2004.

III. Wang JJ, Qiao Q, Miettinen ME, Lappalainen J, Hu G, Tuomilehto J. The Metabolic syndrome defined by factor analysis and incident type 2 diabetes in a Chinese population with high post-prandial glucose. Diabetes Care 27:2429-2437, 2004.

IV. Wang JJ, Hu G, Lappalainen J, Miettinen ME, Qiao Q, Tuomilehto J. Changes in features of the metabolic syndrome and incident impaired glucose regulation or type 2 diabetes in a Chinese population. Diabetes Care 28: 448-450, 2005.

1. INTRODUCTION

The clustering of hypertension, dyslipidaemia, glucose intolerance, insulin resistance, hyperinsulinemia, microalbuminuria, and obesity (particularly central obesity) was termed the metabolic syndrome (MetS). An important feature of the syndrome is insulin resistance, characterized by increased serum fasting insulin levels among non-diabetic individuals in epidemiological studies. Thus, it has been called syndrome X or insulin resistance syndrome. Despite the fact that the underlying mechanism of the syndrome is not completely understood, obesity and sedentary lifestyle coupled with an unbalanced diet and still largely unknown genetic factors, interact to produce the syndrome. It has been proposed that this syndrome is a powerful determinant of type 2 diabetes and cardiovascular disease (CVD).

To aid in the clinical application and research of the syndrome, the World Health Organization (WHO) consultation for the classification of diabetes and its complications published the first definition of the syndrome and named it MetS. Subsequently, the European Group for the Study of Insulin Resistance (EGIR), the National Cholesterol Education Program (NCEP) Expert Panel, the American Association of Clinical Endocrinologists (AACE), and the International Diabetes Federation (IDF) also proposed different definitions. However, almost all the cut-off points for abdominal obesity used in the definitions of the WHO, the NCEP and the EGIR were based on the results obtained in a Caucasian populatio. It has been unknown whether or not the definitions are suitable for a Chinese population. Although three studies have assessed the association of MetS defined by the NCEP and the WHO criteria with the development of diabetes in Finns, Pima Indians, Mexican Americans, and non-Hispanic whites, none of them addresses the association of MetS based on the other definitions with the risk of type 2 diabetes both in men and women.

It is now commonly agreed that no more controlled trials are needed to prove that type 2 diabetes can be prevented, and it is now more important to find high-risk non-diabetic individuals and to assess their relations to the risk of diabetes and death. Evidence from many prospective studies has indicated that subjects with impaired glucose tolerance (IGT) have markedly higher risk for the development of type 2 diabetes and for all-cause and cardiovascular mortality than subjects with normal glucose. A few studies have assessed the risk of progression to diabetes in subjects with impaired fasting glucose (IFG) and normal fasting glucose (NFG) in white, Pima Indian, and other populations. The development of type 2 diabetes in high-risk non-diabetic individuals is less known in China.

Factor analysis, a statistical technique for studies including interrelating variables, has been applied to investigate the risk factor clustering in MetS and to predict coronary heart disease or total and CVD mortality. However, little information is presently available on the mechanism with which the major components of MetS including urinary albumin excretion rate (UAER) relate to each other in non-diabetic and diabetic individuals. Furthermore, few prospective studies evaluate the extent to which MetS or its individual components predict the development of type 2 diabetes using factor analysis.

The current understanding of the pathogenesis of type 2 diabetes is mainly based on a large number of cross-sectional and prospective studies. In these studies non-diabetic individuals are followed for several years in order to determine incident cases of diabetes without repeating assessment of other metabolic characteristics, except for an assay of plasma glucose during follow-up. In fact, only the studies in the Pima Indian population have examined the changes in anthropometric characteristics,

insulin secretion, and insulin action during the progression from normal glucose tolerance (NGT) to IGT, to diabetes. Thus far, no study has directly addressed the effects of changes in the components of MetS on the transition to diabetes in other populations.

In this study, a screening survey for type 2 diabetes was conducted in 1994 and a follow-up study for high-risk non-diabetic individuals was carried out in 1999. The study first evaluated the ability of the WHO, the EGIR, the NCEP, the AACE and the IDF definitions for MetS in relation to the prediction of type 2 diabetes both in men and women. Second, it compared the relative risk of the development of diabetes between normal glucose homeostasis and isolated IFG, isolated IGT, and both IFG and IGT. Third, it applied factor analysis to investigate how the major components of MetS related to each other and to the development of diabetes in the Chinese population. Finally it investigated the changes in the features of MetS during the transition from one state of glucose homeostasis to another, and understood the relative contributions of these changes to the development of impaired glucose regulation (IGR) or type 2 diabetes.

2. LITERATURE REVIEW

2.1 What is MetS?

In 1923 Kylin first described the clustering of hypertension, hyperglycemia, and gout as a syndrome[1]. In 1988 Reaven reintroduced the concept of syndrome X for the clustering of cardiovascular risk factors, including resistance to insulin-stimulated glucose uptake, glucose intolerance, hyperinsulinemia, increased very-low-density lipoprotein (VLDL) triglycerides, decreased high-density lipoprotein (HDL) cholesterol, and hypertension[2]. Subsequently, several other components to the syndrome, such as obesity and especially its central distribution, microalbuminuria, hyperuricaemia, and abnormalities in haemostatic factors have been added [3-7]. However, controversies still exist as to whether or not microalbuminuria is a component of the syndrome[8-10]. In addition, the syndrome has been given several different names like the deadly quartet, the insulin resistance syndrome, the metabolic cardiovascular syndrome, the insulin resistance-dyslipidaemia syndrome, and plurimetabolic syndrome [11-15]. The name "insulin resistance syndrome" has been widely used and refers to insulin resistance as a common denominator of the syndrome[16]. In 1999, the WHO proposed a unifying definition for the syndrome and chose to call it MetS rather than the insulin resistance syndrome[17]. The reason was mainly that it was not considered established that insulin resistance was the cause of all the components of the syndrome.

2.2 Five definitions of MetS

Despite abundant research on the subject of MetS, the criteria used for diagnosing MetS are different across studies, causing confusion when assessing prevalence rates across countries. To aid in the clinical practice and research of the syndrome, the WHO, the EGIR, the NCEP, the AACE and the IDF have proposed different definitions[17-22]. The new IDF definition emphasizes the importance of central obesity defined by ethnic specific values (Table 2.2).

Table 2.2. WHO, EGIR, NCEP, AACE and IDF definitions of MetS

WHO definition
Diabetes (fasting plasma glucose ≥7.0 mmol/l and/or 2-hour plasma glucose ≥11.1 mmol/l), or impaired glucose regulation (fasting plasma glucose 6.1-6.9 mmol/l and/or 2-hour plasma glucose 7.8-11.0 mmol/l), and/or insulin resistance (below lowest quartile of glucose uptake in the euglycaemic clamp), and two or more of the following: ▪ Raised triglycerides (≥1.7 mmol/l) and/or low HDL-cholesterol (<0.9 mmol/l in men, < 1.0 mmol/l in women) ▪ Central obesity (waist-to-hip ratio >0.90 in men, >0.85 in women) and/or body mass index (BMI) >30 kg/m^2 ▪ Raised blood pressure (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) ▪ Microalbuminuria (urinary albumin excretion rate ≥20 µg/min or albumin/creatinine ratio ≥30 mg/g)
EGIR definition for non-diabetic individuals
Hyperinsulinaemia (fasting insulin concentrations in the highest quartile) and at least two of the following: ▪ Hyperglycaemia (fasting plasma glucose ≥6.1 mmol/l) ▪ Central obesity (waist circumference ≥94 cm in men, ≥80 cm in women)

- Hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or treated for hypertension)
- Dyslipidaemia (triglycerides >2.0 mmol/l or low HDL-cholesterol < 1.0 mmol/l or treated for dyslipidaemia)

NCEP definition

Three or more of the following:

- Abdominal obesity (waist circumference >102 cm in men, >88 cm in women)
- Triglycerides ≥1.7 mmol/l
- HDL-cholesterol < 1.03 mmol/l in men, <1.29 mmol/l in women
- Systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg
- Fasting plasma glucose ≥6.1mmol/l

AACE definition for non-diabetic individuals

Two or more of the following:

- Triglycerides ≥1.7 mmol/l
- HDL-cholesterol < 1.03 mmol/l in men, <1.29 mmol/l in women
- Systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg or current use of antihypertensive medications
- 2-hour plasma glucose 7.8-11.0 mmol/l or fasting plasma glucose 6.1-6.9 mmol/l (IFG) (IFG was added in updated AACE criteria)

IDF definition

Central obesity defined as ethnicity specific values of waist circumference (≥ 90cm for Chinese men and ≥80cm for Chinese women) and at least two of the following:

- Raised triglycerides levels (≥1.7 mmol/l), or specific treatment for this lipid abnormality
- Reduced HDL-cholesterol (< 1.03 mmol/l in men, <1.29 mmol/l in women), or specific treatment for this lipid abnormality
- Raised blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg), or treatment of previously diagnosed hypertension
- Raised fasting plasma glucose (≥5.6 mmol/l), or previously diagnosed type 2 diabetes.
  If above 5.6 mmol/l, OGTT is strongly recommended but is not necessary to define presence of the syndrome

2.3 Prevalence of MetS in some countries

Applying the NCEP definition of MetS in a representative U.S. sample of 8,814 men and women aged 20 years and older from the Third National Health and Nutrition Examination Survey (1988-1994), the unadjusted and age-adjusted prevalence of MetS was 21.8% and 23.7%, respectively. The prevalence increased from 6.7% among participants aged 20 through 29 years to 43.5% and 42.0% for participants aged 60 through 69 years and aged at least 70 years, respectively. Mexican Americans had the highest age-adjusted prevalence of MetS (31.9%). The age-adjusted prevalence was similar for men (24.0%) and women (23.4%). However, African American women had a 57% higher prevalence than African American men did, and Mexican American women had a 26%

higher prevalence than Mexican American men did. Using 2000 census data, about 47 million U.S. residents have MetS[23]. The data from eight European studies, which included 8,200 men and 9,363 women, showed that in non-diabetic subjects the frequency of the WHO-defined syndrome varied between 7% and 36% for men aged 40 to 55 years, and for women of the same age, between 5% and 22%; the EGIR-defined syndrome was less frequent than the WHO-defined syndrome (1% to 22% in men, 1% to 14% in women 40-55 years)[24]. In another study based on 11 prospective European cohort studies comprising 6,156 men and 5,356 women without diabetes and aged from 30 to 89 years, the age-standardized prevalence of MetS defined by the modified WHO definition was slightly higher in men (15.7%) than in women (14.2%). The overall prevalence of the WHO-defined MetS in non-diabetic adult Europeans is 15%[25]. In Omani adults aged 20 years and over, living in the city of Nizwa, the age-adjusted prevalence of the NCEP-defined MetS was 21.0% (men: 19.5%, women: 23.0%) [26]. Among 40,698 Korean metropolitan subjects (26,528 men, 14,170 women) aged 20-82 years, the age-adjusted prevalence of the NCEP-defined MetS was 6.8% in total (5.2% male, 9.0% female). Using the Asia-Pacific criteria (APC) for abdominal obesity based on waist circumference (WC) (APC-WC: ≥ 90 cm in men, ≥ 80 cm in women), the prevalence rates of MetS increased to 10.9% (9.8% male, 12.4% female). The subjects over 70 years of age had a 14-fold increased risk for MetS than those aged 20-29 years, and females had higher prevalence rates than males in age groups older than 50 years[27]. The 1998 Singapore National Health Survey involving 4,723 men and women of Chinese, Malay, and Asian-Indian ethnicity aged 18-69 years, demonstrated that the age-adjusted prevalence rates of the NCEP-defined MetS were 9.4, 18.7, and 20.4% for Chinese, Malays, and Asian-Indians, respectively. Using the APC criteria, the analogous prevalence rates increased to 14.8, 24.2, and 28.8% for the three ethnic groups, respectively[28].

2.4 Prevalence of MetS or individual components of MetS in China

According to the fourth China's Nutrition and Health Survey (4th CNHS), which was carried out between August and December 2002 among population-based samples of 272,023 individuals from 31 provinces, the prevalence of obesity (BMI ≥30) in Chinese adults aged 18 years and older was 7.1%, while in some large cities 12.3% of adults and 8.1% of children were classified as obese and 30% of adults were overweight (BMI ≥25). About 19% of Chinese adults had hypertension or dyslipidaemia[29]. The International Collaborative Study of Cardiovascular Disease in Asia (InterASIA) was conducted in China and Thailand between 2000 and 2001, including a nationally representative sample of 15,540 individuals from ten provinces of China. The study displayed that 19.4% of Chinese adults aged 35-74 years had hypertension, 24.8% had raised triglycerides levels and 33.9% had low HDL cholesterol. The age-standardized prevalence of the NCEP-defined MetS was 9.8% in men and 17.8% in women[30-32] (Table 2.4).

2.5 Epidemiology of type 2 diabetes

2.5.1 Definition, classification, and diagnosis of diabetes

The term diabetes mellitus describes a metabolic disorder of multiple aetiologies characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion and/or insulin action. The 1999 WHO criteria proposed four major classes of diabetes and named them, type 1, type 2, other specific types, and gestational diabetes. 90% of people with diabetes have type 2 diabetes[17]. According to the 1999 WHO criteria, the

present study only discussed type 2 diabetes and classified the participants into five categories of glucose status based on fasting plasma glucose (FPG) and 2-h postload glucose (2-h PG) (Table 2.5.1). In addition, the American Diabetes Association (ADA) has suggested that IFG should be redefined as an FPG of 5.6-6.9 mmol/l[33].

Table 2.4 The prevalence of obesity, hypertension, and dyslipidaemia in China based on 4th CNHS and InterASIA

Study (year)	Area	n	Age (years)	Prevalence (%) 25≤BMI<30	BMI ≥30	hypertension	dyslipidaemia
4th CNHS (2002)	31 provinces	272,023	≥18	22.8	7.1	18.8	18.6
	Large cities		≥18	30.0	12.3		
			≤12		8.1		
InterASIA (2000)	10 provinces	15,540	35-74			19.4	24.8 (TG ≥ 1.7mmol/l) 33.9 (HDL< 1.0mmol/l in men; <1.3 mmol/l in women)
		7,526 (M)		21.8*	5.0**		
		8,014 (F)		23.4 *	7.7**		

Hypertension: blood pressure ≥140/90 mmHg or antihypertensive medication.

Dyslipidaemiais defined as at least one of the following: HDL< 0.91 mmol/l; total cholesterol ≥ 5.21 mmol/l; triglycerides ≥ 1.7 mmol/l.

M: male; F: female.

* 25≤BMI<29. ** BMI ≥29.

Table 2.5.1 The categories of glucose status based on the 1999 WHO criteria

	NFG and NGT	Isolated IFG	Isolated IGT	Combined IFG and IGT	Diabetes
FPG mmol/l	<6.1	6.1 - 6.9	<6.1	6.1 - 6.9	≥7.0
	and	and	and	and	and/or
2-h PG mmol/l	<7.8	<7.8	7.8-11.0	7.8-11.0	≥11.1

2.5.2 Prevalence of type 2 diabetes

In 2003, it was estimated that approximately 194 million people worldwide, or 5.1% in the age group 20-79, have diabetes, and around two-third of these people lived in developing countries. This estimate is expected to increase to some 333 million, or 6.3% in the adult population, by 2025. The European Region with 48 million and Western Pacific Region with 43 million currently have the highest number of people with diabetes. However, the prevalence rate of 3.1% for the Western Pacific Region is significantly lower than 7.9% in the North American Region and 7.8% in the European Region. By 2025, the region with the greatest number of persons with diabetes is expected to change to the South-East Asian Region with about 82 million. The region's prevalence of 7.5% will however continue to be lower than that of North America, estimated at 9.7%, and

Europe[34]. The 10 countries[35] estimated to have the highest numbers of people with diabetes in 2000 and 2030 are listed in table 2.5.2.

Table 2.5.2 List of countries with the highest numbers of estimated cases of diabetes for 2000 and 2030

Ranking	2003		2030	
	Country	People with diabetes (millions)	Country	People with diabetes (millions)
1	India	31.7	India	79.4
2	China	20.8	China	42.3
3	U.S.	17.7	U.S.	30.3
4	Indonesia	8.4	Indonesia	21.3
5	Japan	6.8	Pakistan	13.9
6	Pakistan	5.2	Brazil	11.3
7	Russia	4.6	Bangladesh	11.1
8	Brazil	4.6	Japan	8.9
9	Italy	4.3	Philippines	7.8
10	Bangladesh	3.2	Egypt	6.7

2.5.3 Age, gender and urban/rural distributions

According to the previous two references, the 40-59 age group currently has the greatest number of persons with diabetes. By 2025, because of the aging of the world's population, there will be 146 million aged 40-59 and 147 million aged 60 or older with diabetes. The estimates for both 2003 and 2025 showed a female predominance in the number of persons with diabetes. The female numbers were about 10% higher than for male. In developing countries, the majority of people with diabetes are in the 45- to 64-year age range. In contrast, the majority of people with diabetes in developed countries are older than 64 years of age. In 2003, the number of people with diabetes in urban areas was 78 million, compared to 44 million persons with diabetes in rural areas in countries not considered to be established market economies or former socialist economies. By 2025 it is expected that this discrepancy will increase to 182 million urban and 61 million rural persons with diabetes.

2.5.4 Prevalence of type 2 diabetes in China

In 1980 the first National Diabetes Survey (1st NDS) investigated 300,000 people in 14 provinces and cities. The results showed that the prevalence of type 2 diabetes in the subjects aged 30 years or older was 0.9% in China[36]. In 1986 the Da Qing IGT and Diabetes Study investigated 10,660 men and women from 33 health care clinics in the city of Da Qing. The prevalence of type 2 diabetes was reported to be about 1% among subjects aged 25 to 64 years living in this urban community[37]. In 1994 the second National Diabetes Survey (2nd NDS) from 19 provinces and areas found that the prevalence of type 2 diabetes in subjects aged 25 years or older increased to 3.1%[38]. In this survey, the prevalence in the Beijing area in subjects aged 25 years or older was higher than the

overall prevalence, reaching 3.4%[39]. The results from the InterASIA reported that China's prevalence of type 2 diabetes in 2000 was six times that in 1980 and the prevalence among residents living in urban was higher than those living in rural areas[40]. Recently, 4th CNHS showed that the overall prevalence of type 2 diabetes in subjects aged 18 years and older was 2.6%, but the prevalence in residents aged 20 years and older in the big cities reached 6.4% (Table 2.5.4).

Table 2.5.4 The prevalence of type 2 diabetes or IGT or IFG in China

				Prevalence		
Study (year)	Area	n	Age (years)	Diabetes (%)	IGT (%)	IFG (%)
1st NDS (1980)	14 provinces	107,954	≥30	0.9	0.8	
Da Qing (1986)	Da Qing	109,629	25-64	1.0	0.7	
		110,660	>25	1.3	0.8	
2nd NDS (1994)	19 provinces	213,515	25-64	2.5	3.2	
		224,251	>25	3.1	4.0	
	Beijing	20,682	≥25	3.4	3.3	
InterASIA (2000)	10 provinces	15,540	35-74	5.5		7.3
	Urban	7,893	35-74	7.8		7.7
	Rural	7,647	35-74	5.1		7.4
4th CNHS (2002)	31 provinces	272,023	≥18	2.6		1.9
	Big cities		≥20	6.4		

2.6 Incidence of type 2 diabetes

An analysis of six prospective studies have reported cumulative incidences of type 2 diabetes ranging from 23% to 62% among persons with IGT during a 2- to 27- year follow-up[41]. The incidence was higher among Hispanic, Mexican-American, Pima, and Nauruan populations compared with the incidence among white populations. However, less is known about the incidence of diabetes among persons with IFG and normal NFG. In addition to the Hoorn study in a Dutch population and a cohort study in Hong Kong Chinese[42,43], a Finnish study, the Bruneck study in an Italian population and the population-based surveys in Mauritius, also reported the incidence of type 2 diabetes from different stages of glucose during the follow-up[44-46] (Table 2.6). In the Hoorn study, the Finnish study, and the Bruneck study, the individuals with both IGT and IFG combined had the highest incidence of diabetes, while subjects with isolated IFG appeared to have a lower incidence than those with isolated IGT, except for those participants in the Bruneck study. However, the Bruneck study defined incident diabetes as FPG ≥7.0 mmol/l or clinical diagnosis. This might explain why subjects with isolated IFG had a higher incidence of diabetes instead of those with isolated IGT in the study.

Table 2.6 Incidence of type 2 diabetes in five studies based on different stages of glucose

Author (Population)	n	Category of glycemic status	Period	Mean follow-up duration (years)	Cumulative Incidence (%)	Incidence rate per 1000 person years
de Vegt et al. 2001 (Dutch)						
	1125	NFG and NGT		6.47	4.5	7.0
	106	IFG and NGT		6.42	33.0	51.4
	80	NFG and IGT		5.83	33.8	57.9
	31	IFG and IGT		5.75	64.5	112.2
Ko et al. 2001 (Hong Kong Chinese)						
	264	NFG		0.87-8.54	4.9	
	55	IFG		0.87-8.54	25.5	
Qiao et al. 2003 (Finland)			1987-1997			
	2129	NFG and NGT				2.0
	104	IFG and NGT				4.6
	322	NFG and IGT				10.8
	38	IFG and IGT				49.9
Soderberg et al. 2004 (Mauritius)						
		NGT				

	1176 (M)		1987-1992	14.6 (M)
	1268 (F)			5.8 (F)
	1169 (M)		1992-1998	12.9 (M)
	1413 (F)			10.3 (F)
		IFG		
	92 (M)		1987-1992	54.1 (M)
	57 (F)			35.1 (F)
	153 (M)		1992-1998	60.5 (M)
	100 (F)			74.7 (F)
		IGT		
	221 (M)		1987-1992	60.7 (M)
	379 (F)			47.9 (F)
	227 (M)		1992-1998	119.6 (M)
	435 (F)			81.0 (F)
Bonora et al. 2004 (Italian)			1990-2000	
	710	NFG and NGT		4.3
	55	IFG and NGT		37.0
	53	NFG and IGT		17.0
	19	IFG and IGT		49.2

M: male; F: female

2.7 MetS and incident diabetes

2.7.1 Components of MetS and incident diabetes

There have been many prospective studies on the association between the components of MetS, e.g. IFG, IGT, insulin resistance, overweight/obesity, hypertension, and dyslipidaemia, and incident diabetes. Among these individual risk factors, the most important and consistent are IGR, obesity, and insulin resistance. However, studies in relation to prediction of other risk factors such as hypertension and dyslipideamia, to incident diabtes showed conflicting results due to differences in covariates or definition of diabetes. Little information is available on whether or not microalbuminuria is an independent predictor of incident diabetes.

2.7.1.1 Impaired glucose regulation

Although there is evidence that other factors such as age, family history of diabetes, waist-to-hip ratio (WHR), BMI, blood pressure (BP), and lipid levels are independently associated with the development of diabetes, none taken singly is as good at discriminating who will progress to diabetes as measuring glucose levels. IGT had been found to be a strong predictor of incident diabetes before IFG was also created as a new category of abnormal glucose metabolism[41 47]. Since the WHO approved new diagnostic criteria for the diagnosis of diabetes in 1999, the Hoorn Study has demonstrated that after adjustment for age, sex, and follow-up duration, the relative risks (RR) of incident diabetes were 10.0 and 10.9 for isolated IFG and isolated IGT, respectively, compared to normal glucose levels, while combined IFG and IGT were associated with a 39.5-fold increased risk of future diabetes[42]. Furthermore, another study showed that the sensitivity for predicting progression to type 2 diabetes was 26% for IFG and 50% for IGT. Only 26% of subjects that progressed to type 2 diabetes were predicted by their IFG values, but a further 35% could be identified by also considering IGT. The results implicate that IGT identifies more high-risk subjects than IFG[48].

2.7.1.2 Obesity

Overweight, obesity, or weight gain has shown to be an important risk factor for the development of type 2 diabetes. In a cohort study of 51,529 U.S. male health professionals aged 40-75 years, a strong positive association between overall obesity as measured by BMI and risk of incident diabetes was observed during the 5-year follow-up[49]. In this study men with a BMI of at least 35 kg/m^2 had a multivariate RR of 42.1, compared to men with a BMI of less than 23 kg/m^2 (P<0.001). Fat distribution, measured by WHR, was a good predictor of diabetes only among the top 5%, while WC was positively associated with the risk of diabetes among the top 20% of the cohort. Recently, the Health Professionals Follow-Up Study of 27,270 American men reported that both overall and abdominal adiposity strongly and independently predicted the risk of type 2 diabetes, and WC was a better predictor than WHR[50]. In a national cohort of 8,545 U.S. adults from the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study, 5- < 8 kg, 11- < 20 kg and over 20 kg weight gains were associated with a 2.1-fold, 2.6-fold, and 3.9-fold increased risk of incident

diabetes during the 9-year follow-up, respectively, compared with participants whose weights remained relatively stable[51]. The authors found no evidence that the results differed by age, sex, or race. They estimated that the population attributated risk was 27% for weight increases of 5 kg or more. Of an age- and sex-stratified random sample of 1,000 individuals aged 40-79 years, the Bruneck Study confirmed that BMI was a predictor of incident diabetes, independently of other components of MetS such as IFG, IGT, insulin resistance, hypertension, and dyslipidaemia[45].

2.7.1.3 Insulin resistance

In a prospective study of Pima Indians the 90th percentile of fasting insulin level was associated with a 15.8-fold increased risk of incident diabetes compared with the 10th percentile adjusted only for gender[52]. The San Antonio Heart Study (SAHS) of Mexican Americans and non-Hispanic whites reported that after adjustment for age, sex, ethnicity, BMI, and centrality, the top quartile of fasting insulin levels were significantly associated with a 2.3-fold increased risk of the development of diabetes over an 8-year follow-up[16]. Using combined prospective data from the SAHS, the Mexico City Diabetes Study (MCDS), and the Insulin Resistance Atherosclerosis Study (IRAS), the authors found that in adjusting for age, sex, systolic blood pressure (SBP), HDL-cholesterol and BMI models with all subjects pooled as well as separately glucose tolerance status (NGT versus IGT), study and ethnic group, insulin resistance predicted type 2 diabetes independently of these covariates. However, there were substantial differences between published IR indices in the prediction of diabetes. Among the indices of insulin resistance such as fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR), quantitative insulin sensitivity check index (QUICKI), insulin sensitivity index (ISI), and 2-h insulin/2-h glucose (I_2/G_2), Gutt et al.'s ISI at 0 and 120 min (ISI (0,120)) displayed the strongest prediction[53]. After adjustment of age, sex, alcohol, smoking, physical activity, IFG, IGT, BMI, hypertension, and dyslipidaemia, the Bruneck Study also showed that insulin resistance measured as HOMA predicted the development of diabetes independently.

2.7.1.4 Dyslipidaemia

The results from the Norwegian population-based Finnmark Study showed that HDL cholesterol was inversely related to incident diabetes in women, but not in men, controlling for other risk factors such as BMI, diastolic blood pressure (DBP), glucose and ethnicity. However, triglycerides were positively related to the incidence of diabetes in men and women adjusted for age[54]. The MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study also displayed an inverse association between HDL-cholesterol and incident diabetes in both genders[55]. In a prospective study in Swedish women, triglycerides (TG) carried a steeply increased multiple-adjusted (adjusted for age, physical activity, BMI, SBP and total cholesterol) risk for incident diabetes with hazard ratio 3.0 already at TG 1.0-1.4 mmol/l, 3.7 at TG 1.5-1.9 mmol/l and 4.5 at TG $\geq$2.0 mmol/l, compared with TG < 1.0 mmol/l ($P<0.001$)[56]. However, the Bruneck Study did not demonstrate a significant association between dyslipidaemia and incident diabetes in multivariate logistic regression analysis (adjusted for age, sex, alcohol, smoking, physical activity, IFG, IGT, BMI, insulin resistance, and hypertension).

2.7.1.5 Hypertension

A questionnaire survey in the Netherlands among 5,700 men and women aged 20 to 65 showed that after adjusting for age and BMI, SBP and DBP were still associated with the incidence of diabetes (defined as the current use of oral hypoglycemic drugs and /or insulin) in men. For women, only the relative risk associated with the use of diuretics remained statistically significant[57]. The MONICA Augsburg Cohort Study demonstrated that in multivariate analysis (controlling for age, BMI, HDL cholesterol, uric acid, alcohol intake, physical activity and survey), SBP predicted the development of diabetes in men also[55]. A study reported that the Swedish women whose SBP was at least 145 mmHg had a risk to diabetes over 2.2 times that of women with a SBP of less than 145 mmHg, after adjusting for age, BMI, physical activity, TG, and total cholesterol[56]. However, the Bruneck Study displayed that after further control for alcohol, smoking, physical activity, IFG, IGT, BMI, insulin resistance, and dyslipidaemia, there was no association between hypertension and incident diabetes. However, hypertension was associated with a 2.3-fold increased risk of future diabetes adjusted for only age and sex.

2.7.1.6 Microalbuminuria

Microalbuminuria is a well-established marker for incipient nephropathy in patients with diabetes[58]. In addition, microalbuminuria is associated with increased CVD in both diabetic and non-diabetic subjects[59,60]. Previous studies reported that microalbuminuria in non-diabetic subjects was associated with MetS, and suggested that microalbuminuria might be a feature of MetS[61]. However, multiple logistic regression analyses in diabetic and non-diabetic subjects separately showed that microalbuminuria was independently associated only with hypertension, diabetes and WHR, but not with other variables of MetS in a Caucasian population. It is therefore likely that microalbuminuria is a complication of hypertension and diabetes, and not an integral part of MetS[62]. Thus far, there has been only a Finnish study on the association between the microalbuminuria factor derived from factor analysis and incident diabetes[63]. However, the microalbuminuria factor did not predict incident diabetes in the study.

2.7.2 The WHO-defined or the NCEP-defined MetS and incident diabetes

There have been three prospective studies on association between the WHO-defined or the NCEP-defined MetS and incident diabetes[64-66]. These results showed that both the WHO-defined and the NCEP-defined MetS were predictors of incident diabetes. The WHO-defined MetS seemed to be more sensitive for predicting the development of diabetes than the NCEP-defined MetS, except for the inverse results from the SAHS. However, IGT was not included as a component of the WHO-defined MetS in the SAHS (Table 2.7.2).

Table 2.7.2 Three studies on comparisons of ability of the NCEP-defined or WHO-defined MetS to predict type 2 diabetes

Author (year)	Duration of follow-up (years)	Population	Odds Ratio		Sensitivity	
			NCEP-defined MetS	WHO-defined MetS	NCEP-defined MetS	WHO-defined MetS
Laaksonen et al. (2002)	4	1005 middle-aged Finnish men	8.0	8.8	41	67
Hanson et al. (2002)	4.1	890 Pima Indians aged at least 20 years	2.09 (1.49-2.92) †	3.58 (2.56-5.00) †	43	58
Lorenzo et al. (2003)	7-8	1734 Mexican Americans and Hispanic whites aged 25-68 years	3.30 (2.27-4.80)		53	43*

†Incidence rate ratio (IRR); *IGT was excluded as a component of the WHO-defined MetS

2.8 Mechanism of MetS

Although the underlying mechanism of the syndrome is not completely understood, environmental factors such as obesity, physical inactivity, and unbalanced total energy intake, together with still largely unknown genetic triggers, increase susceptibility to the syndrome[67,68].

2.8.1 Environmental factors

2.8.1.1 Birth weight, childhood obesity, smoking, alcohol, coffee, tea, social status and age

Birth weight

Low birth weight and thinness at birth are correlated with abnormal glucose tolerance, dyslipidaemia and hyperinsulinaemia in later adulthood[69-71]. In 34 studies of more than 66,000 people, almost all results showed that an increase in birth weight was associated with a fall in blood pressure, and there was no exception to this in the studies of adults which included total nearly 8,000 men and women[72]. The odds ratio (OR) for diabetes, after adjusting for current body mass, was 3.8 in men whose birth weights were less than 2.5 kg compared with those who weighed 3.2-3.9 kg[73]. Of 64-year-old men whose birth weights were 2.95 kg or less, 22% had MetS. Their risk of developing MetS was more than 10 times greater than that of men whose birth weights were more than 4.31 kg[74].

Childhood obesity

It has been suggested that the origins of adulthood risk of CVD and type 2 diabetes can be related to somatic growth as a child, not necessarily to intrauterine growth. In westernized countries, the relative proportion of underweight newborn children is decreasing; thus, considering the entire population's low birth weight has lost its theoretical role in the aetiology of type 2 diabetes and CVD[75]. Conversely, as obesity is known to be increasing in the industrialized countries among all age groups, the association between weight gain in childhood and MetS in adulthood is more than noteworthy. The risk of MetS was lower among obese adults who had not been obese as children compared to obese adults who had also been obese as children[76]. A population study in Finland found that among

obese children at the age of seven (BMI in the highest quartile), the OR for MetS in adulthood was 4.4 (95% CI 2.1-9.5) as compared to the other children (the three other quartiles combined). After adjustment for age, sex and current obesity, the risk of the syndrome still was 2.4 (95% CI 2.1-9.5)[75].

Smoking

The results of 54 published studies displayed that overall, smokers had significantly higher serum concentrations of cholesterol, TG, VLDL cholesterol, and low-density lipoprotein (LDL) cholesterol, and lower serum concentrations of HDL cholesterol and apolipoprotein AI compared with non-smokers[77]. It was shown that the measures of insulin sensitivity were significantly lower in smokers when the degree of insulin-mediated glucose uptake (insulin sensitivity) was compared in smoking and non-smoking men[78]. Among those who smoked at least two packs per day at baseline, men had a 45% higher diabetes rate than men who had never smoked; the comparable increase for women was 74%. Quitting smoking reduced the rate of diabetes to that of non-smokers after five years in women and after ten years in men[79]. Recently, a study on Koreans reported that smoking (more than 20 pack-years) was associated with a 1.4-fold and 1.9-fold increased risk of high triglycerides and low HDL-cholesterol. The relative risk of developing NCEP-defined MetS in smokers (more than 20 pack-years) was 1.9-fold higher compared with non-smokers although there was no significant difference in blood pressure in the smoking group[80].

Alcohol

Epidemiological studies have shown an association between light to moderate alcohol consumption and reduced risk of MetS and developing type 2 diabetes. Some of the biological mechanisms reported to explain this observation include an improvement of the lipid profile, especially HDL cholesterol[81] and increasing insulin sensitivity[82,83]. Recently, a cross-sectional analysis on data from 8,125 participants in the U.S. showed that after adjustment for age, sex, race/ethnicity, education, income, tobacco use, physical activity, and diet, subjects who consumed 1-19 and $\geq$ 20 drinks of alcohol per month had ORs for the prevalence of the NCEP defined- MetS of 0.65 and 0.34, respectively ($P < 0.05$), compared with current nondrinkers. These findings were particularly noteworthy for beer and wine drinkers. Alcohol consumption was significantly and inversely associated with the prevalence of the following four components of MetS: low serum HDL cholesterol, elevated serum triglycerides, high WC and hyperinsulinemia[84]. Although alcohol consumption had a significant inverse relation with the OR for low HDL cholesterol in all alcohol groups, and lower alcohol consumption had a favorable effect on MetS, an increasing dose-response relation was found between alcohol consumption and the OR for MetS in a Korean population. In this population, heavy alcohol consumption of at least 30 g per day was associated with significantly higher ORs for high blood pressure, and high triglycerides in men and high fasting blood glucose and high triglycerides in women. ORs for the NCEP-defined MetS and its components tended to increase with increasing alcohol consumption[85].

Coffee

Intake of coffee is often reported as a cardiovascular risk factor[86]. However, no clear association between coffee and the risk of hypertension, total cholesterol, LDL-C levels, myocardial infarction, or other cardiovascular diseases has been demonstrated[87,88]. Furthermore, coffee consumption was related to improved insulin sensitivity[89]. Several studies on Dutch, Japanese, American, and Swedish population have shown that coffee consumption was associated with a substantially lower risk of clinical type 2 diabetes[90-93], although the reasons for this risk reduction remain unclear. A Finnish study reported that in 6,974 Finnish men and 7,655 women aged 35 to 64 years during a mean follow-up of

12 years, after adjustment for confounding factors (age, study year, BMI, SBP, education, occupation, commuting, leisure-time physical activity, alcohol and tea consumption, and smoking), the hazard ratios of diabetes associated with the amount of coffee consumed daily (0-2, 3-4, 5-6, 7-9, ≥10 cups) were 1.00, 0.71 (95% CI, 0.48-1.05), 0.39 (0.25-0.60), 0.39 (0.20-0.74), and 0.21 (0.06-0.69) in women, and 1.00, 0.73 (0.47-1.13), 0.70 (0.45-1.05), 0.67 (0.40-1.12), and 0.45 (0.25-0.81) in men, respectively. In both sexes combined, the multivariate-adjusted inverse association was significant and persisted when stratified by younger and older than 50 years; smokers and non-smokers; healthy weight, overweight, and obese participants; alcohol drinkers and non-drinkers; and participants drinking filtered and nonfiltered coffee[94].

Tea

The results of experimental studies have shown the protective effect of tea in improving lipid and glucose metabolism and enhancing insulin sensitivity[95-97]. A study from Taiwan showed that Oolong tea significantly decreased plasma glucose (from an initial concentration of 229±53.9 to 162.2±29.7 mg/dl), whereas water did not (from 208.7± 61.0 to 232.3±63.1 mg/dl). Fructosamine concentration decreased significantly (from 409.9± 96.1 to 323.3±56.4 μmol/l with the tea treatment) but did not change significantly with water treatment (from 368.4±85.0 to 340.0±76.1 μmol/l). This study supports the concept that Oolong tea is effective in lowering the plasma glucose levels of subjects who have type 2 diabetes[98]. However, the epidemiological evidence, data released from recent the cohort study of diverse countries (i.e. the Netherland, the U.S., Sweden and Finland), failed to show the same association as coffee on the risk of type 2 diabetes[92-94].

Socioeconomic status

Individual components of MetS have been related to socioeconomic factors. Low socioeconomic position is associated with increased risk for the metabolic clustering of risk factors[99,100]. The Whitehall II study of 4,978 men and 2,035 women showed the age-adjusted OR for having clustering of MetS comparing the lowest with the highest employment grade was 2.2 (95% CI 1.6-2.9) in men and 2.8 (1.6-4.8) in women adjusting for menopausal status (Brunner et al. 1997). In Swedish women, after adjustment for age, the lowest (≤ 9 years) education was associated with a 2.7-fold increased risk of the presence of MetS compared with the highest (college/university) education. This association persisted after controlling for menopausal status, family history of diabetes, and behavioral risk factors[101]. A Korean study also found that RR of the NCEP-defined MetS was 2.0 in Koreans with no or an elementary school education versus university graduation adjusted for age, sex, BMI, and exercise[80].

Age

Aging is associated with increased insulin resistance and declining glucose tolerance, an increase in visceral adipose tissue, and a trend towards increased blood pressure[102-104]. Epidemiological studies have demonstrated a marked increase in prevalence of MetS with age[105,106]. Park et al. found that the prevalence of MetS increased steeply after the third decade and reached a peak in the sixth decade for men and in the seventh decade for women. In some ethnic groups prevalence rates declined in the eighth decade for men and women[106].

2.8.1.2 Diet

Dramatic changes in the prevalence or incidence of type 2 diabetes have been observed in communities where there have been major changes in the type of diet consumed, from a traditional indigenous diet to a typical ‘Western’ diet, e.g. Pima Indians in Arizona, Micronestans in Nauru and Aborigines in Australia[107-109]. For the Pima Indians in Arizona, the transition from an agrarian to a modern society

was associated with the consumption of increasing amounts of dietary fat, decreasing amounts of dietary carbohydrates, and a deterioration in insulin sensitivity[110]. Most developing countries have experienced a shift in the overall structure of its dietary pattern with related disease patterns over the last few decades. Major dietary change includes a large increase in the consumption of fat and added sugar in the diet, often a dramatic increase in animal food products contrasted with a fall in total cereal and fiber intake[111]. The traditional lifestyle of Chinese has changed markedly over two decades with rapid development of its economy. According to 4th CNHS, fat consumption in the diet increased from 28% in 1992 to 35 % of total energy intake in 2002 in urban areas, while carbohydrate consumption decreased from 57% in 1992 to 47% of total energy intake in 2002. In contrast, the analogous values of fat intake were 19%, 28% (carbohydrate: 72%, 61%), respectively, in rural areas. In developed countries, i.e. in the U.S., a demographic shift toward an overall positive energy balance that has increased over the past few decades has been observed. It has been estimated that Americans consumed an average of 340 kcal/day more in 1994 than in 1984 and 500 kcal/day more than in 1977[112].

Animal models have shown high-fat diets and increased levels of non-esterified fatty acids (NEFAs) to cause insulin resistance in hepatocytes, adipose cells and skeletal muscle in vitro[113-115], and to be involved in the pathogenesis of type 2 diabetes[116]. In humans, intakes high in total fat and saturated fat, and intakes low in carbohydrates or starches and fiber, correlated with higher fasting insulin concentrations[117-119]. High total fat intake has also been associated with a lower insulin sensitivity index[120]. In both Pima Indians and Caucasians, glucose-mediated glucose disposal, beta-cell function, and glucose tolerance deteriorated in the modern diet (carbohydrate, 30%; fat, 50%; protein, 20%) [121]. A high fat intake has been shown to predict development of IGT in a group of healthy subjects and progression from IGT to type 2 diabetes in a group of subjects with IGT[122,123]. Higher proportions of saturated fatty acids in serum lipids/muscle phospholipids have been associated with higher fasting insulin levels, lower insulin sensitivity, and a higher risk of developing type 2 diabetes[124,125]. A high intake of trans-fatty acids was also associated a higher risk of diabetes[126]. However, higher vegetable fat (unsaturated fat) and polyunsaturated fatty acids (PUFAs) intake have been associated with a lower risk of type 2 diabetes, as well as lower fasting and 2-hour glucose concentrations[127,128]. A whole-grain diet resulted in higher concentrations of insulin sensitivity and lower concentrations of fasting insulin than did a refined-grain diet[129], while increasing intakes of refined carbohydrates (corn syrup) concomitant with decreasing intakes of fiber paralleled the upward trend in the prevalence of type 2 diabetes[130].

2.8.1.3 Physical inactivity

Low levels of physical activity are associated with most components of MetS, especially with an increased risk of obesity. Advances in technology and transportation have reduced the need for physical activity in daily life. Labor-saving devices have eliminated many of back-breaking tasks of agricultural- and industrial-sector occupations and reduced the time it takes to complete them. The appeal of television, electronic games, and computers has increased the time spent in sedentary pursuits among children and adults[131]. The average person in England watched over 26 hours of television a week in the 1990s, compared with 13 hours in the 1960s[132]. In the United States the prevalence of obesity increased by 2% for each additional hour of television viewed among 12-to17-year-old adolescents[133]. The adjusted odds of overweight incidence were 8.3 times greater for youths watching more than 5 hours of television per day compared with those watching for 0 to 2 hours, and more than 60% of overweight incidence can be linked to excess television viewing time[134]. A cohort study (1989 to 1997) from 2,485 adults aged 20 to 45 years from eight provinces in China found that after adjustment of age, work, leisure activity, energy intake, smoking status, alcohol consumption, income, education, household ownership of a computer and TV, and urban

residence, the odds of being obese were 70% higher for men and 85% higher for women in households who owned a motorized vehicle compared with those who did not own a vehicle[135].

Insulin resistance plays a central role in MetS, being associated with most of the other metabolic abnormalities in the syndrome[136]. Physical training has mostly been shown to improve insulin sensitivity in healthy humans regardless of age, in obese non-diabetic subjects, and in patients with type 2 diabetes [137,138]. Exercise also has pronounced effects upon the metabolism of glucose because exercising muscle may increase glucose uptake 7- to 20-fold[139]. The Finnish Diabetes Prevention Study (DPS) and the Diabetes Prevention Program (DPP) in the United States revealed a 58% reduction in the risk of diabetes in high-risk subjects who enhanced physical activity[140,141]. The DPS also found that the intervention group had a significant decrease in serum concentrations of 2-h postload insulin and TG, and a marked increase in HDL colesterol levels compared with the control group. Physical activity has been positively associated with HDL cholesterol concentrations among men and women[142,143]. A cross-sectional survey in an urban area of the city of Tianjin, China, found that daily walking or cycling to and from work was inversely associated with serum total cholesterol, LDL cholesterol, and TG concentrations among men, and was positively associated with HDL cholesterol concentrations among women as compared to traveling to and from work by bus[144]. A meta-analysis of 25 longitudinal studies examining the antihypertensive effect of exercise showed reductions in resting SBP and DBP of 11 and 8 mmHg, respectively. However, the decrement in BP evoked by exercise was not sufficient to produce normotension in many studies[145]. The overall impression from the published studies is that regular exercise training provides a modest antihypertensive effect, and the use of exercise therapy for the treatment of hypertension is most beneficial in the early stages of hypertension, as well as for the prevention of hypertension[146-148].

2.8.1.4 Obesity

Obesity is becoming increasingly common worldwide due to adoption of a more sedentary lifestyle and an increased intake of energy-rich diets[149]. It is well accepted that obesity, as the core of MetS, promotes glucose intolerance, insulin resistance, hypertension, and dyslipidaemia, and is associated with the development of type 2 diabetes and coronary heart disease[150]. The prevalence of serious obesity doubled in Britain between 1980 and 1991 and is continuing to increase[151]. In the United States, the age-adjusted prevalence of obesity was 30.5% in 1999-2000, compared with 22.9% in 1988-1994. The prevalence of overweight also increased during this period from 55.9% to 64.5%. Extreme obesity (BMI $\geq$ 40) also increased significantly in the population, from 2.9% to 4.7%[152]. A gradient of increasing prevalence of abdominal obesity (WC $\geq$102cm in men; $\geq$88cm in women) from 1960 to 2000 was also observed in men and women in the U.S.. In men, the overall age-adjusted prevalence of abdominal obesity was 12.7%, 29%, and 38.3% in 1960–1962, 1988–1994 and 1999–2000, respectively. In women, the analogous values were 19.4%, 38.8% and 59.9%, respectively. The 4th CNHS showed that the prevalence of obesity (BMI $\geq$30) and overweight (BMI $\geq$25) has increased by 97% and doubled, respectively, between 1992 and 2002 in Chinese adults[153].

Obesity and weight gain are important determinants of clustering of the individual traits of MetS. A study in Hong Kong Chinese men showed, after adjustment for age, smoking, and insulin resistance, increasing BMI and WHR remained closely associated with increased concentrations of TG and apo B, increased ratios between LDL and HDL (LDL/HDL) cholesterol, and between apo B and LDL (apo B/LDL), increased fasting and 2-h plasma glucose and insulin, as well as decreased concentrations of HDL, HDL_2 and apolipoprotein A-I (apo A-I)[154]. The relationship between insulin sensitivity and overall obesity is well established[155]. Furthermore, visceral abdominal tissue

(VAT) and subcutaneous abdominal tissue (SAT), which were measured from computed tomography scans performed at the L4/L5 vertebral region, and their joint interactions were each inversely and significantly associated with ISI, adjusting for age, sex, ethnicity, and BMI. SAT, but not VAT, was positively associated with acute insulin response (AIR). Thus, fat distribution is an important determinant of both insulin resistance and insulin secretion[156]. The NHANES II (National Health and Nutrition Examination Survey II) study found obese women to be four times more likely to develop diastolic hypertension than non-obese women[157]. In the Framinghan population, weight gain had a stronger relationship with blood pressure in males than in females[158]. There appears to be a consensus that obesity is an important risk factor of type 2 diabetes[159]. Besides, researchers reported that the RR for IGT increased more than 4-fold among obese subjects, compared with normal-weight subjects in a Swedish population[160]. In an Italian population, obese subjects had a frequency of IGR three times that of subjects with normal weight[161].

2.8.2 Genetic factors

Racial differences in risk[162], familial clustering of case[163], twin studies[164] have provided grounds for the argument that genetic factors contribute to MetS.

2.8.2.1 Candidate gene studies

There is clearly a multitude of genes responsible for the regulation of the manifold phenotypes that comprise MetS. Among these genes contributing to MetS, genes regulating lipolysis and thermogenesis still remain prime candidates[165-168] (Table 2.8.2.1).

In addition, the genetic basis of MetS as a composite phenotype has been systematically explored. Polymorphisms in eight genes, including low density lipoprotein receptor (LDLR), glucan (1,4-alpha)-branching enzyme 1 (GBE1), interleukin 1 receptor, type 1 (IL1R1), transforming growth factor-{beta}1 (TGFB1), interleukin 6 (IL6), collagen, type V, alpha 2 (COL5A2), E-selectin (SELE), and hepatic lipase (LIPC) have been found to be associated with the NCEP-defined MetS[169].

Table 2.8.2.1 Candidate genes related to MetS (in alphabetical order)

Adiponectin	Insulin receptor
Angiotensinogen	Insulin receptor substrate-1 (IRS-1)
β_2- and β_3- adrenergic receptors	Leptin and leptin receptor
CD36	Insulin
Cytokine interleukin-6 (IL-6)	Insulin receptor
Cytokine tissue necrosis factor alpha (TNF-α)	Peroxisome proliferator-activated receptor gamma (PPARγ)
Glucocorticoids	Plasminogen activator inhibitor-1 (PAI-1)
Glycogen synthase	Plasma cell membrane glycoprotein 1 (PC-1)
11β hydroxysterol dehydrogenase type 1 (11 β HSD-1)	Sterol regulatory element binding protein-1C (SREBP-1C)
Insulin	Uncoupling proteins

2.8.2.2 Genome-wide scans

Genome scans have identified various chromosomal regions with suggestive linkage to clusters of specific metabolic traits in Caucasian families: a quantitative trait locus (QTL) on chromosome 3 (3q27) strongly linked to six traits such as BMI, WC, hip circumference, weight, insulin, insulin/glucose, and QTL on chromosome 17 (17p12) exhibited significant linkage with plasma leptin levels[170]. A susceptibility locus for coronary heart disease on chromosome 16p13 and replicates linkage with MetS on 3q27 were also observed in Indo-Mauritians[171]. In whites, promising evidence for linkage was found for MetS phenotypes (2 markers on 10p11.2, a marker on 19q13.4), while in blacks promising linkage was found for MetS phenotypes on 1p34[172].

2.9 Prevention of MetS and diabetes

The previous clinical trials of lifestyle-intervention in Sweden[173], China[174], Finland[140], and the United States[141] demonstrated that the combination of weight loss, diet intervention and increased physical activity could significantly decrease the development of type 2 diabetes in high-risk individuals. The four studies provide the most dramatic evidence of the beneficial effects of lifestyle intervention on prevention of diabetes and MetS.

2.9.1 Lifestyle intervention

In the Da Qing IGT and Diabetes Study, for subjects assigned to the diet-only intervention, the participants with BMI $\geq$ 25 kg/m^2 were encouraged to reduce their calorie intake so as to gradually lose weight at a rate of 0.5-1.0 kg per month until they achieved a BMI of 23 kg/m^2. The participants with BMI < 25 kg/m^2 were prescribed a diet containing 25-30 kal/kg body weight, 55-65% carbohydrate, 10-15% protein, and 25-30% fat. For subjects assigned to the exercise-only intervention, the participants were taught and encouraged to increase the amount of their leisure physical activity by at least 1U/day, i.e., faster walking at least 20 minutes per day and by 2 U/day if possible for those < 50 years of age with no evidence or CVD or arthritis. For subjects assigned to the diet-plus-exercise intervention, the participants received instruction and counseling for both diet and exercise interventions that were similar to those for the diet-only and the exercise-only intervention group. The diet-plus-exercise intervention was associated with a 42% reduction in risk of incident diabetes[174]. In the DPS, 25-47% of the subjects in the intervention group succeeded in achieving the goals of the lifestyle intervention during the first year, which were a reduction in total intake of fat to less than 30% and in the intake of saturated fat to less than 10%, an increase in fiber intake to at least 15 g per 1000 kcal, a weight reduction of at least 5% of initial body weight, and moderate excise for at least 30 minutes per day. As a result, the risk of diabetes was reduced by 58% in the intervention group after four years. In contrast, only 11-26% of the subjects in the control group achieved these goals. The DPP tested a goal of intervention including physical activity of moderate intensity, such as brisk walking for at least 150 minutes per week, a reduction in total intake of average fat to less than 32%, and a weight reduction of at least 7% of initial body weight. There was also a 58% reduction in the rate of progression in the lifestyle intervention group in the study (Table 2.9.1).

2.9.2 Pharmacologic therapies

Given the difficulty in changing lifestyle, and the probable limits of its efficacy in many individuals, it could be argued that treatment of MetS would be a drug(s) that could significantly enhance insulin sensitivity, as well as the other manifestations of MetS. Although metformin does not seem to act by directly improving insulin sensitivity, there is evidence that metformin administration can lower circulating insulin levels and improve glucose and lipid metabolism in patients with characteristics of MetS[175]. The findings of the DPP, where a 31% reduction in the rate of progression was observed in patients taking metformin (850mg twice daily), provide evidence that metformin can also delay progression of IGT to diabetes. Thus, the drug may offer potential benefit for treatment of MetS. In addition, acarbose can decrease resistance to insulin in patients with IGT, and significantly decrease the postprandial rise in plasma glucose[176]. The results of the STOP-NIDDM Trial showed that treating IGT patients with acarbose (100mg three times daily) was associated with a 49% reduction in the development of cardiovascular events, a 34% reduction in the incidence of new cases of hypertension and a 25% reduction in the progression of type 2 diabetes compared with those taking placebo[177,178]. In the troglitazone in the prevention of diabetes (TRIPOD) trial, the average incidence of diabetes was 12.1% in women randomized to placebo and 5.4% in women taking the PPARγ agonist troglitazone during a median follow-up of 30 months [179]. Given the importance that obesity plays in the development of MetS in susceptible individuals, pharmacological treatment of obesity may play an important role in the management of overweight individuals with MetS. If overweight/obese patients with MetS cannot lose weight with simple caloric restriction, both orlistat and sibutramine have been shown to be more effective than diet alone in the treatment of obesity. Furthermore, administration of both drugs to appropriately selected individuals has been shown to result in attenuation of the manifestations of MetS[180]. In the absence of evidence that there is one drug capable of addressing the entire cluster of abnormalities associated with MetS, pharmacological treatment at this point is by necessity directed to the individual manifestations of MetS, i.e. hypertension, dyslipidaemia, etc., which persist despite appropriate changes in lifestyle. Patients with MetS also have elevations in fibrinogen and other coagulation factors leading to a prothrombotic state. Thus aspirin may be beneficial for primary prevention in these patients[181].

Table 2.9.1 The goals of lifestyle intervention in Da Qing IGT and Diabetes Study, DPS and DPP

			Goals for the lifestyle intervention group				
Study	Duration of follow-up (year)	Reduction in risk of diabetes (%)	Weight reduction (%)	Fat intake of energy intake (%)	Saturated-fat intake of energy intake (%)	Fiber intake (g/1000kcal)	Moderate exercise (min/week)
Da Qing	6	42	≤23*	25-30			≥140
DPS	4	58	>5	<30	<10	≥15	≥210
DPP	2.8	58	≥7	<32			≥150

*BMI≤23

3. AIMS OF THE STUDY

The overall aim was to obtain new information about the relationship between MetS and incident diabetes in a Chinese population. The follow-up data collected in the Beijing Project survey provides unique possibilities for such an evaluation. More specifically, the aims of the study were to address the following questions:

- Are the WHO, EGIR, NCEP, AACE and IDF definitions of MetS sensitive for predicting type 2 diabetes in Chinese men and women?
- Which state of impaired glucose homeostasis at baseline best predicts the conversion to type 2 diabetes?
- How do the major components of MetS defined by factor analysis relate to each other and to the development of diabetes in the Chinese population?
- Are there differences in changes in the features of MetS during the transition of glucose tolerance, and what are the relative contributions of these changes to the development of impaired glucose regulation or type 2 diabetes?

4. MATERIALS AND METHODS

4.1 The second National Diabetes Survey

China has 31 administrative provinces, cities, and autonomous areas with a total population of 1.3 billion people. The first national diabetes survey was carried out in 1980. The second National Diabetes Survey, involving a population of 250,000 aged 25 and older in 19 provinces and areas, was launched in 1994. The survey included cities and rural areas in the eastern, southern, western, northern parts of China. A total of 224,251 subjects aged 25 and over participated in the survey (89.7%), of whom 213,515 (men 113,002; women 100,513) were aged 25-64 years. In April 1994, a workshop was held in order to standardize the protocol and methodology, and a three-day training course took place for the investigators in each location before the baseline survey. The results from the previous Da Qing IGT and Diabetes Study on 2,692 subjects with 2-h post-prandial plasma glucose 6.67-7.70 mmol/l showed 9 cases of diabetes (0.3%) and 31 cases of IGT (1.2%) based on the WHO - 1985 criteria[37]. Thus, the subjects with 2-h post-prandial capillary glucose < 6.67 mmol/l would be expected to have an extremely low percentage of diabetes or IGT. In this context, a fingerstick pre-screening using a One Touch II glucose meter after a breakfast containing at least 80g of carbohydrates was used in the present screening survey in order to maximize the yield of abnormal glucose tolerance at 75g oral glucose tolerance test (OGTT). In the participants whose 2-hour post-prandial capillary blood glucose was ≥6.67 mmol/l the OGTT was performed. Of 224,251 subjects, 21,851 (9.7%) had a 2-h finger blood glucose level ≥6.67 mmol/l after breakfast and 15,918 of them (73%) participated in the OGTT.

4.2 The Beijing Project

4.2.1 Baseline survey

The Beijing Project, as part of the National Diabetes Survey, was carried out between July 1994 and January 1995. 76 units in the Beijing area including 33 villages, 15 factories, 11 military camps, and 17 urban communities were randomly ascertained with a multi-stage sampling method. In these units, 20,682 inhabitants aged 25 – 82 years (64% of them aged 25 - 44 years) participated in the finger blood glucose screening survey. The participation rate was 92%. A total of 2,499 participants aged 25 – 80 years who at the screening had a 2-hour capillary blood glucose of ≥6.67 mmol/l were invited to participate in the OGTT. Among them, the OGTT was performed in 1,566 subjects (62.7%). Of these 1,566 subjects, after excluding 106 with known diabetes and 221 currently taking antihypertensive or hypolipidemic drugs, 305 with newly diagnosed diabetes and 934 without diabetes were included in the baseline study (article III).

4.2.2 Follow-up survey

From October 1999 to January 2000, the 5-year follow-up survey was carried out in subjects who participated in the OGTT at baseline. Of the initial 1,566 subjects, 483 had moved out of Beijing and 181 persons could not be followed up because of logistical reasons. The remaining 902 persons (57.6%) participated in the follow-up examination. The non-participants did not differ significantly

from participants in age, sex, BMI, WHR, FPG, 2-h PG, serum fasting and 2-hour postload insulin, TG, total cholesterol, timed 2-hour UAER, and the frequency of diabetes, hypertension, and obesity at baseline. Of the 902 subjects who participated in the follow-up study, 275 had diabetes at baseline, 68 currently took antihypertensive or hypolipidemic drugs and 129 developed type 2 diabetes (61 men, 68 women) during the 5-year follow-up. Thus, 559 subjects without diabetes at baseline and without antihypertensive or hypolipidemic treatment were included in the study (article III); 627 subjects without diabetes at baseline were included in the study (article I, II, IV). The enrolment and examinations of subjects were conducted in accordance with the Helsinki Declaration.

4.3 Measurements

The anthropometric and laboratory measurements were carried out at baseline and follow-up separately. The assay conditions, such as storage of the blood samples, experimental methods, kit producers, technicians, laboratory and instruments, in the two surveys were identical. The specifically trained physicians performed face-to-face interviews using a standardized questionnaire, which included questions about past medical history, family histories of diabetes, history of pharmacological treatment, smoking habits, occupation, and education. Family histories of diabetes, and antihypertensive and hypolipidaemic medication were dichotomized. Smoking status included current smokers and non-smokers. Occupation was classified as white collar or blue collar work. Three education categories were created according to the total number of years in school: 0–6, 7–12, and ≥13 years.

Body weight of the subjects wearing light clothing without shoes was measured with 0.1 kg precision. Height was measured to the nearest 0.5 cm. BMI was calculated as the weight in kilograms divided by the square of the height in meters. WC was defined as the average of two measurements taken after inspiration and expiration at the midpoint between the lowest rib and iliac crest. Hip circumference was measured at the point of trochanter major. WHR was defined as WC to hip circumference. After each subject had been seated for five minutes, BP was measured twice to the nearest two mmHg from the left arm of the participant using a standard sphygmomanometer. The average of the two measurements was used for all analyses. DBP was recorded at the fifth Korotkoff sound.

After 10 to 12 hours of an overnight fast each subject voided and then the fasting blood sample was collected. A 75 g anhydrous glucose dissolved in 300 ml of water was given orally over the course of five minutes and a second blood sample was drawn two hours later for the glucose and insulin determination, respectively. A urine sample was collected immediately after the 2-hour blood collection to quantify timed 2-hour UAER. Blood samples were immediately centrifuged and processed further. Plasma glucose was detected in duplicate within 2 hours by a glucose oxidase method at the Laboratory Center of Beijing Tongren Hospital. The blood samples for other assays had been kept in –80° C freezer for 2-8 months until they were analyzed. Serum insulin was determined by a double-antibody radioimmunoassay. Urinary albumin concentration was measured by radioimmunoassay. Their intra- and interassay CVs were <6% and <8% for insulin, <5% and <7% for urinary albumin. Serum total cholesterol and TG levels were measured by enzymatic methods.

4.4 Statistical analyses

The analysis of variance (one-way ANOVA for linear trends, univariate ANOVA and repeated-measures ANOVA) and paired *t* tests were used to assess the continuous variables, while Chi-square, the Mantel-Haenszel method and McNemar test were performed in categorical variables. Individual associations between variables were assessed using Pearson's correlation coefficients. Factor analysis was conducted to examine how the major components of MetS relate to each other in article III. Logistic regression models were used to determine risk factors or risk factor clusters for the development of diabetes or IGR. All statistical analyses were done using SPSS 11.5 software.

5. RESULTS

5.1 Assessment for the sensitivity of four definitions (Article I) and the new IDF definition

The AACE definition of MetS had the highest sensitivity for incident diabetes compared with the other three definitions both in men and women, respectively (0.61 and 0.58). Using the updated AACE criteria (AACEN) for analyses in which IFG as a component is included, the highest sensitivity still remained in men and women (0.69 and 0.66) despite the highest false positive rate (men: 0.39; women: 0.36). The sensitivity of the WHO definition of MetS was a little lower than that of the AACE definition in men (0.53) and women (0.42). The NCEP definition with a WC of 102 cm in men had the lowest sensitivity among all definitions. However, it had the lowest false positive rate as well (0.09). Similarly, the EGIR definition was most insensitive (both men and women: 0.28) despite the lowest false positive rates (men: 0.09; women: 0.13). In addition, the NCEP definition has almost the same sensitivity as that of the WHO definition in women (0.41 and 0.42, respectively), but the former had a lower false positive rate than the latter (0.16 vs 0.29).

According to the recommended standards of obesity for Asians (BMI ≥25; WC ≥90 cm for men and ≥80 cm for women) (Steering Committee of the Western Pacific Region of the World Health Organization 2000), the analyses were repeated by using the modified NCEP definition with WC ≥90 cm in men and ≥80 cm in women (NCEPA). The sensitivity of the NCEPA definition for new-onset diabetes was improved to 0.40 (false positive rate: 0.20) in men and 0.49 (false positive rate: 0.24) in women. Using the modified WHO definition with WHR >0.90 (women >0.85) or BMI ≥25 kg/m^2 (WHOA), the sensitivity of the WHOA definition was also improved (men: 0.58; women: 0.49), although the false positive rate rose a little (men: 0.31; women: 0.32). The recently suggested IDF definition was significantly associated with a 1.9-fold increased risk of developing diabetes in men and a 2.4-fold increased risk in women after adjustment for age, education, occupation, smoking, family history of diabetes, and total cholesterol (model 2). Interestingly, the definition was insensitive for predicting incident diabetes in men while it had better sensitivity in women (0.31 vs. 0.61). However, men had a lower false positive rate than women (0.20 vs. 0.34) (Figure 5.1). If using a modified IDF definition, in which IGT was included and central obesity was as one of the parallel components rather than as a requirement in the definition, the sensitivity could be improved to 0.49 in men and to 0.70 in women. In addition, a BMI of ≥25 kg/m^2 and a WHR of >0.90 (women: >0.85) were associated with a 2.3- to 2.5-fold increased risk of incident diabetes in men and a 2.2- to 3.0-fold increased risk in women in the model 2. However, a WC of ≥90 cm (women: ≥80cm) did not predict incident diabetes in the model (Table 5.1).

5.2 Effects of IFG and IGT on predicting diabetes in men and women combined (Article II)

When men and women were combined for analyses, subjects with both IFG and IGT had a OR of 9.40 (95% CI, 4.58-19.29) for incident diabetes, compared with those with both NFG and NGT after adjustment of age, sex, smoking, SBP, BMI, family history of diabetes, total cholesterol, triglycerides, antihypertensive medication, occupation, education, and UAER. When fasting insulin was added into the model, however, the OR decreased to 8.91 (95%CI, 4.32-18.38). Subjects with

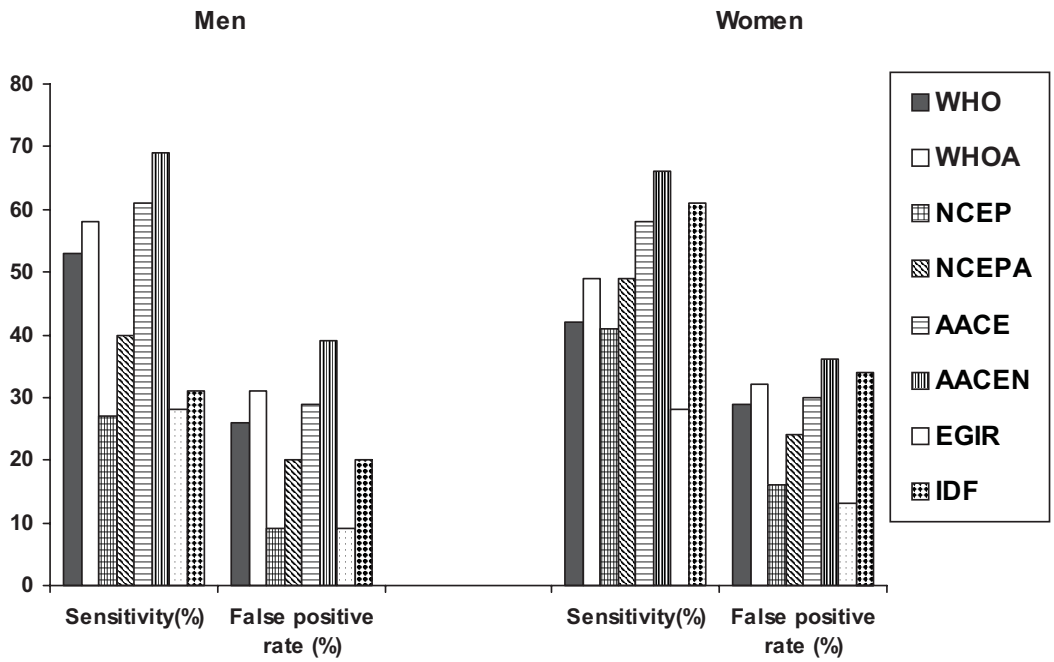

Figure 5.1 Sensitivity and false positive rate of the NCEP, NCEPA, WHO, WHOA, AACE, AACEN, EGIR and IDF definitions of MetS for incident diabetes in men and women. NCEPA: the modified NCEP criteria based on Asian criteria of obesity (WC ≥90cm in men; ≥80 cm in women); WHOA: the modified WHO criteria based on Asian criteria of obesity (BMI ≥25); AACEN: updated AACE criteria in which FPG 6.1-6.9 mmol/l was also included.

Table 5.1 Relative risks of incident diabetes from the new IDF definition of MetS or some individual components during the five-year follow-up

	RR (95% CI)*			
	Men (n=308)		Women (n=319)	
	Model 1	Model 2	Model 1	Model 2
The metabolic syndrome				
IDF definition	1.83 (1.01-3.33)	1.86 (1.01-3.60)	2.83 (1.62-4.96)	2.42 (1.30-4.49)
The individual components of the metabolic syndrome				
Waist circumference ≥ 90 cm (women: ≥ 80 cm)	1.44 (0.84-2.49)	1.24 (0.69-2.26)	1.84 (0.94-3.59)	1.98 (0.94-4.18)
Waist–to-hip ratio > 0.90 (women: > 0.85)	2.55 (1.45-4.50)	2.51 (1.36-4.66)	3.01 (1.63-5.55)	2.95 (1.46-5.93)
BMI ≥ 25 kg/m^2	2.17 (1.23-3.83)	2.26 (1.22-4.18)	2.36 (1.37-4.07)	2.14 (1.17-3.93)

*Model 1: Adjusted for age; model 2: adjusted for age, education. occupation, smoking, diabetic family history, and total cholesterol.

Table 5.2 Adjusted odds ratios (95% CI) for incident diabetes in 627 subjects with normal and abnormal glucose levels during 5- year follow-up*

			Odds Ratio (95% CI)				
	Subjects	Cumulative Incidence NO. (%)	Model 1	Model 2	Model 3	Model 4	Model 5
n=627							
NFG and NGT	358	51(14.2)	1.00	1.00	1.00	1.00	1.00
IFG and NGT	112	28 (25.0)	1.99 (1.18-3.37)	1.93 (1.08-3.45)	2.03 (1.12-3.67)	2.01 (1.11-3.66)	2.00 (1.15-3.71)
IGT and NFG	95	31 (32.6)	2.78 (1.64-4.69)	2.75 (1.54-4.90)	2.83 (1.56-5.11)	2.68 (1.45-4.96)	2.64 (1.47-5.03)
IFG and IGT	62	36 (58.1)	8.39 (4.66-15.12)	8.30 (4.25-16.22)	8.74 (4.39-17.40)	9.40 (4.58-19.29)	8.91 (4.32-18.38)
n=627							
New IFG criteria							
NFG and NGT	209	26(12.4)	1.00	1.00	1.00	1.00	1.00
IFG and NGT	261	53 (20.3)	1.77 (1.06-2.95)	1.71 (0.95-3.06)	1.88 (1.03-3.43)	1.86 (1.01-3.42)	1.80 (0.98-3.33)
IGT and NFG	48	13 (27.1)	2.54 (1.18-5.43)	2.59 (1.13-5.94)	2.98 (1.28-6.97)	2.92 (1.21-7.05)	2.90 (1.19-7.05)
IFG and IGT	109	54 (49.5)	6.72 (3.83-11.78)	6.8 (3.31-11.91)	6.67 (3.45-12.86)	6.54 (3.33-12.83)	6.34 (3.21-12.51)

*Adjusted for sex.

Model 1: adjusted for age.

Model 2: adjusted for age, smoking, SBP, BMI, family history of diabetes, total cholesterol, and triglycerides.

Model 3: education, occupation and antihypertensive medication were added to model 2.

Model 4: UAER was added to model 3.

Model 5: fasting insulin was added to model 4.

isolated IGT had a higher OR than those with isolated IFG (2.64 vs. 2.00) after adjustment for the confounding factors in model 5 (Table 5.2). Based on the updated FPG value between 5.6-6.9 mmol/l for IFG, the number of individuals with IFG alone or with both IGT and IFG combined, increased dramatically compared with a reduction in the number of individuals with isolated IGT and with normoglycaemia. However, subjects with isolated IGT had a higher OR for incident diabetes than those with isolated IFG (2.90 vs. 1.80). Subjects with both IGT and IFG combined still had the highest OR (6.34) after adjustment for the confounding factors in the model 5 (Table 5.2).

5.3 MetS defined by factor analysis and incident diabetes (Article III)

5.3.1 Partial correlations between variables at baseline

Among non-diabetic subjects, BMI and WHR correlated with SBP, DBP, and fasting and 2-h insulin both in men and women, after adjustment for age. Fasting and 2-h insulin correlated with most other variables, especially in men. Serum cholesterol had low correlations with most other parameters. Both SBP and DBP correlated significantly with UAER in men, but not in women. While among diabetic subjects, UAER correlated with FPG and 2-h PG in men and women. Serum cholesterol and triglycerides correlated strongly with 2-h PG in both sexes. Significant correlations were found between insulin and glucose in diabetic men and women (Table 5.3.1).

5.3.2 Factor patterns in participants with NGT and with IGR

Subjects with NGT had similar factor patterns to those with IGR (Figure 5.3.2). Factor loadings after varimax rotation showed that the first factor correlated with BMI, WHR, and fasting insulin levels; the second factor with SBP and DBP, the third factor with FPG, 2-h PG and 2-h insulin; and the fourth factor with serum cholesterol and triglycerides. In men FPG also loaded on the first factor. These four factors were interpreted as obesity/insulin resistance, BP, glucose/2-h insulin, and lipid factor, respectively.

5.4 Changes in features of MetS and incident IGR or diabetes (Article IV)

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5.4.1 Baseline and follow-up characteristics

Baseline characteristics

The subjects who retained IGR and who progressed from IGR to diabetes were older than those who retained NGT during follow-up. The subjects with IGR at baseline had higher FPG values than those with NGT at baseline, while those who progressed from NGT to IGR or diabetes during follow-up had higher 2-h PG values than those who retained NGT. Mean values of 2-h PG, BMI, triglycerides and 2-h insulin, and prevalence of obesity and dyslipidaemia were significantly correlated with glycemic deterioration during follow-up. Mean fasting insulin values and prevalence of hypertension in subjects with NGT at baseline, and prevalence of insulin resistance in subjects with IGR at baseline were significantly correlated with further glycemic deterioration.

Table 5.3.1 Partial correlations between variables at baseline in non-diabetic and diabetic subjects by sex

	Men/women										
N	BMI	WHR	SBP	DBP	Log UAE	TC	Log TG	Log Fin	Log 2-h insulin	FPG	2-hPG
Non-diabetic subjects (men = 449 Women = 485)											
BMI		0.33***	0.14*	0.30***				0.30***	0.21**	0.24***	
WHR	0.33***		0.21**	0.23***				0.35***	0.27***	0.19**	
SBP	0.24**	0.15**		0.51***	0.16*				0.18**		0.21**
DBP	0.20***	0.20***	0.70***		0.26***		0.17*	0.16*	0.16*	0.17*	0.17*
Log UAER			0.18***				0.18*	0.15*	0.23**		
TC				0.13*			0.24***		0.20**		
Log TG				0.15**		0.18**		0.17*	0.20**	0.13*	
Log Fin	0.26***	0.23***	0.29***	0.18**					0.30***	0.18**	
Log 2-h insulin	0.18**	0.18***	0.12*	0.21***				0.26***		0.18**	0.47***
FPG			0.13*	0.15**					0.13*		0.24***
2-h PG	0.16**		0.22***	0.22***					0.35***	0.12*	
Diabetic subjects (men = 132 Women = 173)											
BMI		0.22***	0.19**					0.30***			
WHR	0.24***						0.12*	0.12*			
SBP	0.22***			0.56***	0.30***			0.12*			
DBP	0.12*		0.58***		0.17**	0.13*					

Log UAER			0.27***	0.17**			0.15**	0.18**		0.13*	0.26***
TC				0.13*			0.13*		0.13*		0.21***
Log TG		0.12*			0.11*	0.14**					0.16**
Log Fin	0.30***	0.16**			0.16**				0.31***		
Log 2-h insulin								0.28**			
FPG					0.14**						0.21***
2-h PG					0.22***	0.20**	0.11*			0.35***	

Correlations for men are shown in the upper right corner of the matrix and for women in the lower left corner. The values of $P>0.05$ are omitted.

*$P<0.05$, **$P<0.01$, ***$P<0.001$. All variables are adjusted for age.

BMI, body mass index; WHR, waist-to- hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; UAER, urinary albumin excretion rate; TC, total cholesterol; TG, triglycerides; Fin, fasting insulin; FPG, fasting plasma glucose; 2-hPG, 2-h postload glucose.

Table 5.4.1 Baseline and follow-up characteristics by glucose status at baseline and during follow-up in 627 subjects

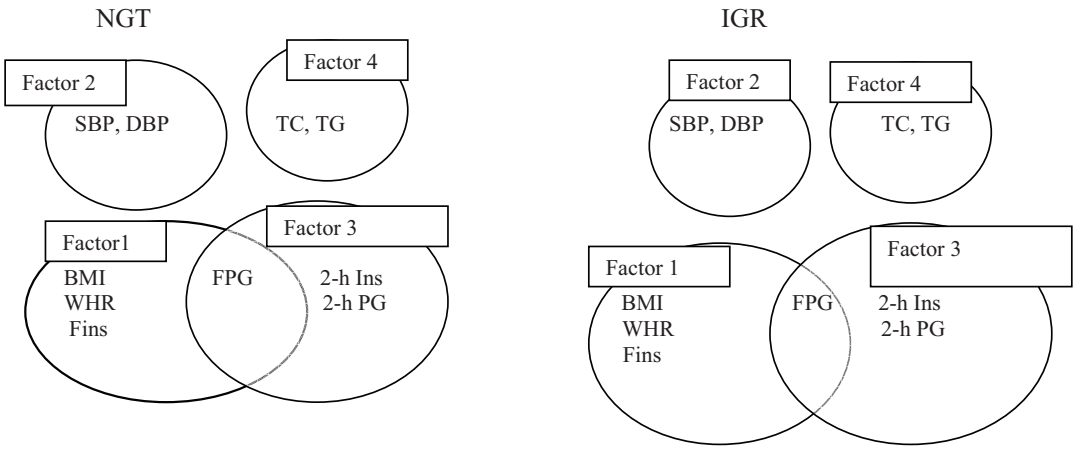
	At baseline	NGT				IGR				*P* value**
	At follow-up	NGT	IGR	DM	*P* trend*	NGT	IGR	DM	*P* trend*	
n	B	213	94	51		90	84	95		
	F	213	94	51		90	84	95		
Age (yr)	B	47 ± 11	48 ± 10	49 ± 11	NS	47 ± 11	51 ± 10	50 ± 10	NS	0.013
	F	52 ± 11	53 ± 10	54 ± 11	NS	52 ± 11	56 ± 10	55 ± 10	NS	0.005
Sex (M/F)	B	96/117	53/41	22/29	NS	44/46	45/39	48/47	NS	NS
FPG (mmol/l)	B	5.2 ± 0.6	5.4 ± 0.5	5.4 ± 0.6	NS	6.0 ± 0.7	6.0 ± 0.7	6.2 ± 0.7	NS	<0.001
	F	5.0 ± 0.7	6.0 ± 0.7	7.3 ± 1.9	<0.001	5.0 ± 0.7	6.0 ± 0.6	7.9 ± 2.0	<0.001	<0.001
2-h PG (mmol/l)	B	5.6 ± 1.1	6.0 ± 1.2	6.2 ± 1.2	<0.001	7.2 ± 1.8	7.4 ± 1.8	8.4 ± 1.6	0.002	<0.001
	F	5.6 ± 1.1	7.9 ± 1.6	12.3 ± 4.1	<0.001	5.8 ± 1.2	8.6 ± 1.6	12.8 ± 3.1	<0.001	<0.001
BMI (kg/m^2)	B	23.7 ± 3.2	24.9 ± 3.2	25.2 ± 3.7	<0.001	24.6 ± 3.3	24.9 ± 3.0	26.2 ± 3.5	0.002	<0.001
	F	24.6 ± 3.4	26.2 ± 5.2	26.1 ± 3.5	0.002	25.0 ± 3.5	26.1± 3.1	26.6 ± 3.2	0.001	<0.001
SBP (mmHg)	B	123 ± 22	126 ± 23	128 ± 23	NS	129 ± 23	129 ± 21	134 ± 22	NS	0.009
	F	124 ± 18	129 ± 17	129 ± 17	0.015	128 ± 17	129 ± 17	133 ± 18	NS	0.017
DBP (mmHg)	B	76 ± 12	79 ± 11	79 ± 12	NS	80 ± 13	80 ± 12	82 ± 11	NS	0.008
	F	79 ± 12	83 ± 10	82 ± 11	NS	81 ± 11	82 ± 12	85 ± 13	NS	NS
Cholesterol (mmol/l)	B	4.7 ± 1.8	4.7 ± 1.7	4.8 ± 1.1	NS	4.7 ± 1.7	4.5 ± 1.6	5.1 ± 1.7	NS	NS
	F	4.7 ± 1.1	4.8 ± 1.1	5.0 ± 1.0	NS	4.6 ± 1.0	5.2 ± 1.0	5.0 ± 1.0	0.003	0.002
Triglycerides (mmol/l)	B	1.3 ± 0.9	1.5 ± 1.1	1.7 ± 1.0	0.015	1.5 ± 0.9	1.7 ± 0.9	1.9 ± 1.0	0.001	<0.001
	F	1.3 ± 0.8	1.5 ±1.3	1.9 ± 1.3	<0.001	1.4 ± 0.8	1.8 ± 1.4	2.0 ± 1.1	<0.001	<0.001
Fasting insulin (pmol/l) †	B	42 (39-44)	49 (44-53)	48 (42-55)	0.014	50 (46-56)	50 (45-56)	56 (51-62)	NS	<0.001
	F	51 (46-57)	61 (52-72)	54 (41-57)	0.042	49 (41-57)	53 (44-62)	70 (59-82)	0.001	0.008
2-h Insulin (pmol/l) †	B	134 (122-147)	185 (159-211)	205 (169-249)	<0.001	172 (150-198)	219 (189-254)	255 (222-294)	<0.001	<0.001
	F	208 (186-234)	375 (315-447)	319 (251-405)	<0.001	207 (174-247)	350 (291-420)	322 (270-383)	<0.001	<0.001
HOMA-B%†‡	B	64 (60-70)	73 (65-83)	69 (59-81)	NS	57 (51-65)	60 (53-69)	62 (55-69)	NS	0.032

	F	104 (91-119)	72 (60-89)	39 (30-51)	<0.001	93 (76-114)	59 (48-72)	47 (39-57)	<0.001	<0.001
Obesity (%)	B	31	45	47	0.002	46	48	64	0.02	<0.001
	F	36	65	61	0.03	46	67	70	0.002	<0.001
Hypertention (%)	B	26	40	55	0.001	47	41	51	NS	<0.001
	F	34	56	67	0.012	57	57	68	0.041	<0.001
Dyslipidemia (%)	B	24	28	45	0.03	37	41	57	0.003	<0.001
	F	24	31	45	0.02	27	44	61	<0.001	<0.001
Insulin resistance (%)	B	20	26	25	NS	24	30	41	0.028	0.012
	F	23	45	41	0.023	31	37	55	0.003	0.02
Antihypertensive drugs (%)	B	4	6	7	NS	5	7	7	NS	NS
	F	4	7	7	NS	4	7	9	0.034	0.014
Hypolipidemic drugs (%)	B	3	4	4	NS	2	3	6	NS	NS
	F	4	4	5	NS	3	3	5	NS	NS

Data are means ± SD or percentages. B, baseline; F, follow-up; obesity, BMI ≥25.0 kg/m^2; hypertension, SBP ≥140 mm Hg and /or DBP ≥90 mm Hg or using antihypertensive drugs; dyslipidemia, serum triglycerides ≥1.7mmol/l or taking hypolipidemic medication; insulin resistance, upper fasting insulin quartile at baseline (B) or upper fasting insulin quartile at baseline cut-point (F).

†Geometric means (95% CI); *Linear trend in continuous variables or Chi-square (linear-by-linear association) in categorical variables; **Adjusted for age and sex among six groups. ‡HOMA-B% as an index of pancreatic β–cell function was calculated as 20 × fasting insulin in pmol/l/(fasting glucose in mmol/l – 3.5)

Men



Women

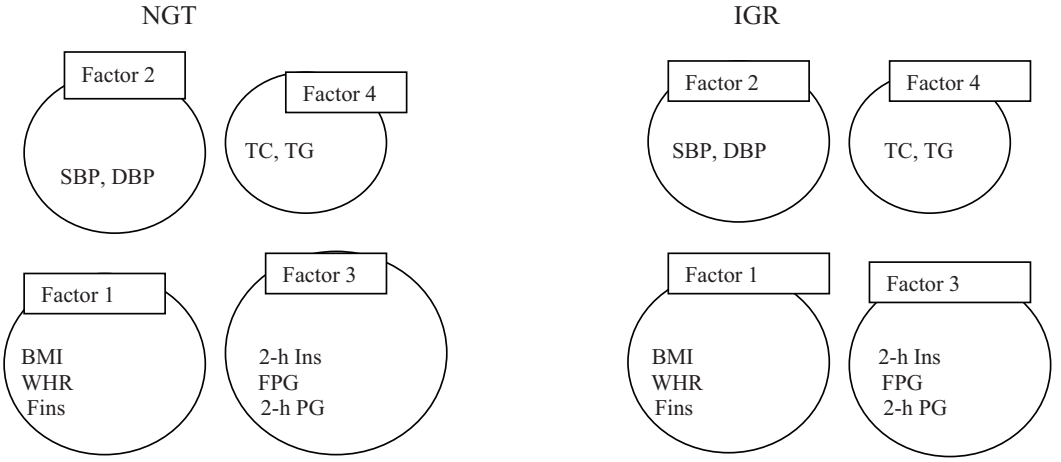


Figure 5.3.2 Clusters of the risk variables of MS in men and women with NGT or IGR. BMI, body mass index; WHR, waist-to- hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; UAER, urinary albumin excretion rate; TC, total cholesterol; TG, triglycerides; Fins, fasting insulin; FPG, fasting plasma glucose; 2-h PG, 2-h postload glucose; 2-h Ins, 2-h postload insulin.

Subjects who retained NGT during the follow-up had a significantly lower prevalence of obesity, hypertension, and dyslipidaemia than those who worsened from NGT to IGR, those who progressed from NGT to diabetes, and those who had IGR at baseline. There was no difference in frequency of taking antihypertensive and/or hypolipidemic drugs between groups (Table 5.4.1).

Follow-up characteristics

No intervention program was carried out during the follow-up. By design, plasma glucose concentrations increased in the progressors. Mean values of BMI, triglycerides, fasting and 2-h insulin, and prevalence of obesity, hypertension, dyslipidaemia, and insulin resistance were significantly correlated with glycemic deterioration during the follow-up. Mean SBP in subjects with NGT at baseline, and mean total cholesterol values in subjects with IGR at baseline were significantly correlated with further glycemic deterioration during the follow-up. In contrast, mean values of HOMA-B% was negatively correlated with glycemic deterioration. More hypertensive subjects who progressed from IGR to diabetes took antihypertensive drugs during follow-up (Table 5.4.1).

5.4.2 The association of changes in features of MetS with the risk of incident IGR or diabetes

Change in obesity was significantly associated with a 2.1-fold increased risk of incident IGR or diabetes in an univariate model after adjustment for age, sex, family history of diabetes, smoking, education, occupation, antihypertensive and hypolipidemic medication, FPG, 2-h PG, SBP, BMI, total cholesterol, triglycerides, and fasting insulin at baseline. After further adjustment for change in hypertension, change in dyslipidaemia and change in insulin resistance, this association did not appreciably change. Change in hypertension, change in dyslipidaemia, or change in insulin resistance was not associated with the risk of incident IGR or diabetes (Table 5.4.2).

Table 5.4.2 Adjusted odds ratios for incident IGR or diabetes in 627 nondiabetic subjects during 5- year follow-up*

	Univariate		Multivariate	
	OR	95%CI	OR	95%CI
Change in obesity (%)	2.11	1.31-3.42	2.20	1.36-3.57
Change in hypertention (%)	1.51	0.87-2.63	1.69	0.95-3.00
Change in dyslipidemia (%)	0.85	0.56-1.27	0.76	0.50-1.15
Change in insulin resistance (%)	0.92	0.62-1.37	0.86	0.57-1.28

*Adjusted for age, sex, family history of diabetes, smoking, education, occupation, antihypertensive and hypolipidemic medication, FPG, 2-h PG, SBP, BMI, total cholesterol, triglycerides and fasting insulin at baseline.

6. DISCUSSION

The aim of the present study was to evaluate the ability of the five definitions of MetS for prediction of type 2 diabetes and investigate how the components of MetS and changes in features of MetS related to the development of type 2 diabetes. The data collected in the National Diabetes Prevention Survey-Beijing Project during 1994-1995 and in the follow-up survey during 1999-2000 offered the unique possibility to do the current study because all assessments of metabolic characteristics at baseline were repeated during the follow-up.

6.1 Materials and methods

China has the largest population in the world and is still a developing country. The prevalence of type 2 diabetes in China has been rising, but it is still lower compared with many Western countries. Therefore, it is of importance to find high-risk non-diabetic individuals in China and among them assess the major determinant factors for the development of type 2 diabetes. The present study introduced a capillary glucose pre-screening for OGTT at baseline for this purpose, while the initial participants at first survey were drawn randomly from a population. This selection procedure has two advantages: first, the yield of abnormal glucose tolerance at OGTT can be maximized in a large population survey; second, the follow-up study may be more efficient because more high-risk cases can be included at baseline only at cost of missing a small number of individuals with diabetes or IGT. Therefore, the study sample in this study represents a population-based high-risk segment identified by raised post-prandial glucose rather than a general population. The limitation of the selection procedure may be that its findings cannot necessarily be applied to the general population. However, the major findings from the study are relevant for health promotion in the general population.

Another limitation in this study is the lack of HDL-cholesterol values, although all other components of MetS in terms of different definitions were included. The lack of HDL-cholesterol would underestimate the prevalence of MetS and weaken the direct association between MetS and risk of type 2 diabetes to some extent. However, triglycerides ≥1.7 mmol/l or current use of hypolipidaemic drugs were defined as dyslipdaemia in the NCEP, the WHO, and the AACE definitions, which may minimize the missing cases of MetS determined by low HDL-cholesterol. Lack of information about physical activity, alcohol consumption, tea or coffee drinking, and dietary patterns is a third limitation. Besides, the relatively low follow-up rate is also a limitation in this study, although no difference in baseline characteristics was found between the participants and non-participants in the follow-up study.

Regarding multifactorial diseases, it has been the epidemiologists' convention to consider the independent weight of each risk factor in turn by multivariate analysis, thus adjusting for bias introduced by confounding variables. Such an approach, however, fails to take into account the manner in which related factors may confer the risk in concert and obscures attempts to gain understanding about the factors[182,183]. Factor analysis provided a method for addressing some of these challenges. It can reduce a large number of correlated variables to fewer uncorrelated factors. Therefore, the statistical technique for studies including interrelating variables was applied to investigate the risk factor clustering of MetS in this study.

6.2 Explanations for the lower sensitivity of some definitions of MetS for predicting diabetes

6.2.1 Impact of cut-off points for obesity on the sensitivity

Since almost all suggested cut-off points for abdominal obesity in the definitions of MetS were derived from the studies on a Caucasian population[184], one of the most controversial aspects of MetS is without doubt the definition of obesity. This study showed that the WHO definition, including WHR >0.90 (women >0.85) or BMI ≥30 kg/m^2, detected 53% of incident diabetes in Chinese men and 42% in women. However, a Finnish study found that the WHO definition identified 67% of incident diabetes in the Finnish men[64]. The NCEP definition, in which central obesity was defined as WC >102 cm was quite specific but insensitive in the Chinese men, detecting only 27% of incident diabetes. In contrast, 41% of incident diabetes was identified in the Finnish men. The lower sensitivity of the definitions for incident diabetes in the Chinese men may be attributable to the anthropometric indicators for classification of obesity. Among the Finnish men 8% (30%) of individuals without diabetes and 31% (59%) of incident diabetic individuals had a WC of >102 cm (94 cm), but only 3% (17%) of the Chinese men without diabetes and 8% (28%) of incident diabetic individuals had a WC of >102 cm (94 cm). Furthermore, only 9% of men and 10% of women without diabetes in the Chinese population at baseline had a BMI of ≥30 kg/m^2. In contrast, 20% of American white men and 21% white women, and 24% of American black men and 44% of American black women without diabetes were obese (BMI ≥30 kg/m^2)[185]. Because these assessments in the present study were based on the Chinese high-risk population, the difference in abdominal obesity between Chinese general populations and Caucasian populations would be expected to be much larger. When using the recommended standards of obesity for Asians, 63% of the Chinese men with incident diabetes and 44% of the men without diabetes were obese (BMI ≥25 kg/m^2), and 43% of the Chinese men with incident diabetes and 34% of the men without diabetes had a WC ≥90 cm. Clearly, these cut-offs were more suitable to detect incident diabetes for Chinese men. When applying the modified NCEP definition with a WC ≥ 90 cm in men and ≥80 cm in women, the sensitivity for incident diabetes was improved to 0.40 in men and to 0.49 in women in this study. Using the modified WHO definition with WHR >0.90 (women >0.85) or BMI ≥25 kg/m^2, the sensitivity was also improved (men: 0.58; women: 0.49). These findings thus confirm that the relation between adiposity and BMI varies by ethnicity[186-188]. The NCEP definition with a waist cut-off of 102 cm or the EGIR definition with a waist cut-off of 94 cm did not seem very useful in Chinese men.

6.2.2 Effect of combinations of different components to define MetS on the sensitivity

Given the fact that insulin resistance appears central to the development of MetS, accurate quantification of insulin's in vivo action, secretion, and disposal is necessary. While a combination of hyperglycemic and euglycemic-hyperinsulinemic clamp studies supplies the gold standard for quantifying these parameters, clamp studies are expensive and difficult tests to perform and require highly trained personnel. For the purpose of epidemiologic studies, several indices of insulin resistance such as ISI, fasting insulin, HOMA, QUICKI, etc., have been developed[189-192]. However, thus far there has been an apparent lack of consistency in the assessment of insulin resistance for

epidemiological studies. As there are different standards for assaying insulin, it is impossible to propose a universal cut-off. The EGIR recommended use of the upper quartile of fasting insulin concentrations, instead of clamp studies, to estimate insulin resistance. It also suggested that the upper quartile of fasting insulin concentrations was an essential requirement in the definition, while the WHO definition included either IGR or insulin resistance as an essential requirement. This study found that 55% of non-diabetic Chinese had IGR at baseline, and only 29% of non-diabetic and 34% of incident diabetic individuals had the highest quartile for fasting insulin concentrations. In contrast, 54% of Italians with incident diabetes were insulin resistant[45]. Clearly, the sensitivity of the EGIR definition was influenced by the essential requirement in the Chinese population. Since the insulin deficiency, rather than insulin resistance, plays a prominent role in the progression of diabetes in non-obese Chinese and Japanese populations compared to European populations[193], the definition based on insulin resistance as a requirement of MetS may miss more incident cases of diabetes in Chinese. Recently, the new IDF definition defined ethnicity-specific central obesity (measured as WC) as a prerequisite for the diagnosis of MetS. IGT was excluded in the definition. However, there has not been a unified cut-off of obesity because of lack of consistent results from varied studies in China[194,195]. It has been controversial which anthropometric index of obesity is the best predictor of CHD or diabetes in Chinese[196,197]. The current study showed that IGT was a better predictor of type 2 diabetes than IFG in men, and a BMI of ≥25 kg/m^2 or a WHR of >0.90 (women: >0.85) other than a WC of ≥90 cm (women: ≥80cm) was a better predictor of incident diabetes. Clearly, central obesity defined as WC ≥90 cm (women: ≥80cm) as a requirement and exclusion of IGT in the IDF definition mainly led to a lower sensitivity of the definition for predicting future diabetes in the Chinese population, especially in men. When using a modified IDF definition in which IGT was included and central obesity was as one of parallel components rather than as a requirement in the definition, this study showed that the sensitivity improved from a previous 0.31 to 0.49 in men.

6.3 MetS defined by factor analysis and incident diabetes

6.3.1 Pathophysiological mechanism of MetS

An important feature of MetS is insulin resistance, characterized by increased fasting insulin levels among non-diabetic individuals[2,190]. However, whether insulin resistance really is the unifying underlying abnormality is still debatable[198,199]. Factor analysis has been used for decades to understand relations among psychometric variables, but only since 1994 has this method been used to understand relations among metabolic risk variables[200]. Factor analysis can reveal underlying patterns or structure among variables showing high degrees of intercorrelation. Since insulin resistance has been proposed as the underlying pathophysiological mechanism of MetS, if factor analysis reveals only one underlying factor, it may be interpreted as supporting the unity hypothesis that one unifying physiology (perhaps insulin resistance) underlies and accounts for the metabolic risk variable clustering[201]. However, this study did not just identify a single factor in non-diabetic individuals but a total of four factors that result in the clustering of the basic risk variables: obesity/insulin resistance, blood pressure, glucose/2-h insulin, and lipid factors. Similar results were observed in a study in non-diabetic elderly Japanese-Americans, in which four similar factors to this study were also found[202]. The studies in Korean men, non-Hispanic white, African-American, and Pima Indian populations identified two to four factors as well. In these studies the blood pressure factor was probably the most tenuously linked with other factors[182,203,204]. The results suggest that insulin resistance alone does not underlie all features of MetS, and more than one pathophysiological mechanism are present for the full expression of MetS.

6.3.2 Predictive factors of MetS defined by factor analysis for incident diabetes

Factor analysis, a statistical technique for studies including interrelating variables, has been applied to investigate the risk factor clustering in MetS and to predict coronary heart disease or total and CVD mortality[205,206]. Thus far there have been only two studies relating the clustering of risk factors for MetS to incident diabetes using factor analysis. Neither of these two studies, however, analyzed the data separately by sex, nor included UAER into the variables among diabetic patients. A Finnish study population consisted of 309 siblings of diabetic (DM^+) or non-diabetic (DM^-) probands[63], which showed that factor analyses revealed four significant factors in both the DM^+ and DM^- groups. Of these, factor 1 was characterized by high loadings for BMI, hypertension, glucose area, insulin area (the highest loading), and triglycerides in both the DM^+ and DM^- groups. Therefore, factor 1 can be interpreted as a hyperinsulinemia factor. The hyperinsulinemia factor was similarly associated with the risk of developing diabetes in the two groups. Another study in Pima Indians also identified four factors including insulinemia, body size, blood pressure, and lipid metabolism[65]. The insulinemia factor was strongly associated with diabetes incidence. The body size and lipids factors also significantly predicted diabetes, whereas the blood pressure factor did not. The present study included UAER in the analyses and analyzed data for men and women separately. The results displayed that the glucose/2-h insulin factor and the obesity/insulin resistance factor were strong risk factors for type 2 diabetes, whereas the blood pressure factor and the lipid factor were not associated with the development of diabetes. This implied that different physiological processes associated with various components of MetS contained unique information about the diabetes risk in the Chinese population.

6.3.3 Relationship between MetS and microalbuminuria

A Korean study in a general population found that not only diabetes and hypertension, but also fasting hyperinsulinemia and WHR were independent factors associated with the presence of microalbuminuria. When the normotensive, non-diabetic subjects were analyzed separately, fasting hyperinsulinemia and IGT remained independent variables associated with the presence of microalbuminuria. These results showed that microalbuminuria in the Korean general population was associated with hyperinsulinemia and central obesity, and suggested that microalbuminuria was a feature of MetS independent of hypertension or type 2 diabetes[207]. Nevertheless, the Hoorn study in a Dutch population showed that microalbuminuria was independently associated with hypertension, diabetes, and WHR, with ORs of 3.33, 2.26, and 2.49, respectively. No associations were found between IGT, hyperinsulinaemia, insulin resistance or dyslipidaemia and microalbuminuria. Multiple logistic regression analyses in diabetic and non-diabetic subjects separately showed that microalbuminuria was independently associated only with hypertension (ORs 4.31 and 2.69)[62]. Using factor analysis, the IRAS displayed that the log albumin/creatinine ratio did not significantly load on the BP factor (loading: 0.30) in non-diabetic men[204]. No study thus far has included UAER into the variables among diabetic subjects using factor analysis. The current study showed that although the factor patterns were consistent in the analyses among men and women separately, there was a remarkable contrast in the patterns between subjects with and without diabetes. Among non-diabetic subjects UAER correlated significantly with both SBP and DBP only in men, but did not load on any factors. In contrast, among diabetic subjects UAER significantly loaded on the glucose factor, but UAER did not positively load on the blood pressure factor (loading: 0.39 in men; 0.37 in women). The results provide evidence that microalbuminuria is most likely to be a complication of hyperglycemia or hypertension rather than a marker of MetS.

6.4 The cumulative 5-year incidence of type 2 diabetes in China

Although type 2 diabetes has a genetic predisposition, there is strong evidence that environmental factors such as obesity and physical inactivity play an important role in diabetic etiology. As the economy has quickly grown, traditional lifestyles have changed in China during the past 20 years. Diets are shifting towards higher fat and lower carbohydrate contents. The number of people who are overweight and had low physical activity is increasing rapidly around the country, especially in large cities. From 1989 to 1997 the prevalence of overweight (BMI ≥25) in Chinese men tripled and among women it doubled[208]. The new data from the 4th CNHS showed that the prevalence of obesity (BMI ≥30) and overweight (BMI ≥25) in Chinese adults between 1992 and 2002 has increased by 97% and doubled, respectively. The prevalence of obesity in large cities in China is higher (12.3%) than the overall level of the country (7.1%). In 1994 the prevalence of type 2 diabetes in Beijing was 3.4%, which was four times the overall prevalence of diabetes observed in 1980. In the present study, 45.2% of participants were overweight (BMI≥25) at baseline, five years later the rate of overweight significantly increased to 52.8% adjusted for sexes and ages. The cumulative 5-year incidence of diabetes was 58.1% for participants with both IFG and IGT combined, 25.0% for participants with IFG alone, and 32.6% for those with isolated IGT at baseline in men and women combined analyses. The results were similar to the previous results from the Dutch population and in the Hong Kong Chinese[42,43]. However, the Chinese with NFG and NGT had a higher cumulative incidence of diabetes (14.2%) than the Dutch population (4.5%) and the Hong Kong Chinese (4.9%). Given the fact that the sample in the present study represents a population-based high-risk segment other than a general population, the selection procedure in this study may be a cause of the high cumulative incidence in those with NGT and NFG. Besides, the transition from a traditional lifestyle to a western one that occurred in China may be another cause.

6.5 Impaired glucose tolerance as a predictor of diabetes in men and women

Although many prospective studies has showed that subjects with IGT have markedly higher risk for the development of type 2 diabetes and for all-cause and cardiovascular mortality than subjects with normal glucose[41,209,210], less has been known about the effect of isolated IFG on the development of diabetes by gender. A Finnish study reported that the multivariate adjusted Cox hazard ratio was higher for isolated IGT (3.9, 95% CI 2.4-6.2) than for isolated IFG (2.3, 0.9-5.7) as compared with subjects with neither IFG nor IGT[44]. However, the subjects in the study were not stratified by sex. In the current study the analyses were carried out separately for men and women. Although both IGT and IFG combined were strongly associated with future diabetes in both men and women, isolated IGT appeared to be a stronger predictor for development of diabetes than isolated IFG in men. In contrast, there was no significant difference in ORs for future diabetes between isolated IFG and isolated IGT in women. Recently, the ADA has suggested that the cut-off point for IFG should be lowered from 6.1 mmol/l to 5.6 mmol/l, and that IFG should be redefined as an FPG of 5.6-6.9 mmol/l. Based on the updated cut-off point for IFG, both men and women with both IFG and IGT combined in this study still had the highest OR for the development of diabetes and also isolated IGT was a better predictor of incident diabetes than isolated IFG in Chinese men. Lowering the FPG cut-off point will however double the number of people with isolated IFG without improving the prediction. Thus, lowering the cut-off point of FPG does not resolve the problem that the use of FPG alone leads to false negative cases. Since there was a low participant rate (57.6%) at the follow-up, it was not certain if the finding that IGT was a stronger predictor than IFG in men was due to the bias. However, there were no differences in the baseline

characteristics between nonparticipants and participants. Furthermore, when the logistic regression analyses were performed in both men and women combined after adjustment for sex and the other confounding factors, the highest OR for future diabetes was still observed in those with both IFG and IGT combined, whereas those with isolated IGT had a slightly higher OR than those with isolated IFG (2.64 vs 2.00). This proportion of isolated IGT to isolated IFG in OR was similar to previous findings from the Hoorn Study (10.9 vs 10.0) where the analyses were not stratified for gender[42]. A prospective study on an Italian population, where 76.7% of total subjects were men also found that the OR for diabetes in the subjects with isolated IGT was higher than in those with isolated IFG (6.2 vs1.2)[211]. Whether IGT is a stronger predictor than IFG in men and what mechanism is involved for this sex-difference may need further study.

6.6 The role of obesity in the development of IGR or diabetes

There is consensus that individualized lifestyle modification is appropriate for all patients who are considered at risk for having MetS. Both adiposity and the level of physical activity are powerful modulators of insulin-mediated glucose disposal. More importantly, in contrast to the other factors that affect insulin action, they are modifiable by safe, straightforward lifestyle changes. Thus weight loss of 5-10% of body weight in overweight/obese individuals, who are also insulin resistant, will significantly enhance insulin sensitivity, lower ambient plasma insulin concentrations, and improve the manifestations of MetS[212]. The Da Qing IGT and Diabetes Study, the DPP and the DPS have confirmed that changes in lifestyle aimed at weight loss reduced the incidence of diabetes. The Da Qing IGT and Diabetes Study in China is the first lifestyle-intervention trial for preventing diabetes in the world. It randomized 577 subjects with IGT by clinic into the clinical trial, either to a control group or to one of three active treatment groups: diet only, exercise only, or diet plus exercise. Follow-up evaluation examinations were conducted at 2-year intervals over a 6-year period to identify subjects who developed type 2 diabetes. In a proportional hazards analysis adjusted for differences in baseline BMI and fasting glucose, the diet, exercise, and diet-plus-exercise interventions were associated with 31% ($P < 0.03$), 46% ($P < 0.0005$), and 42% ($P < 0.005$) reductions in risk of developing diabetes, respectively. Compared with the control group which had a reduction of 0.27 kg for weight, the diet, exercise, and diet-plus-exercise groups had a reduction of 0.93, 0.71 and 1.77 kg for weight, respectively. Furthermore, one of the goals for the lifestyle intervention was to achieve and maintain a BMI of 23 kg/m^2 in the participants with BMI $\geq$ 25 kg/m^2. In the present study, the subjects who remained NGT and those who progressed from NGT to diabetes during the follow-up had almost a similar increase in mean BMI. Nevertheless, the former still maintained a mean BMI below 25 kg/m^2 during the follow-up, while the latter had a mean BMI of over 25 kg/m^2. Interestingly, BMI also increased in the subjects who reverted from IGR to NGT during follow-up, but their mean BMI maintained about 25 kg/m^2 and no change in the prevalence of obesity was observed. Furthermore, an increase in obesity, rather than change in other features of MetS, predicted the progression of IGR or diabetes after adjustment of the confounding factors. These results implicate that obesity may be a more important risk factor for development of IGR or diabetes than other features of MetS. The lifestyle intervention aimed at preventing diabetes should place higher importance on obesity than IGR, because even IGR could still revert to a normal glucose state as long as an increase in obesity did not occur or mean BMI was kept below 25 kg/m^2.

7. SUMMARY AND CONCLUSSIONS

This prospective study in China has provided an excellent opportunity to evaluate the sensitivity of different definitions of MetS for predicting diabetes, and to examine the relationship between MetS and incident diabetes.

The NCEP, WHO, EGIR, AACE and IDF definitions of MetS appeared valid, detecting those at a 1.6- to 4.5-fold increased risk of developing diabetes during the follow-up in the Chinese high-risk population. The NCEP definition, in which the cut-off point of central obesity is based on the results obtained in a Caucasian population, did not seem to be sensitive in predicting diabetes in Chinese men. The EGIR definition, which includes insulin resistance as an essential requirement of MetS, missed more incident cases of diabetes in the Chinese. The IDF definition, in which IGT (actually, only fasting glucose is mentioned in the IDF definition) is excluded and central obesity is used as an essential requirement of MetS is insensitive for predicting diabetes in Chinese men.

Both IFG and IGT combined were associated with an 8.8- to 9.4-fold increased risk of development of diabetes in Chinese men and women. Chinese men with isolated IGT had a 7.8-fold increased risk of incident diabetes.

Factor analysis revealed consistent clusters of variables that were different in non-diabetic and diabetic subjects in the Chinese population. UAER was associated with the glucose factor in diabetic subjects. Blood pressure was not linked to insulin resistance. The obesity/insulin resistance factor and the glucose/2-h insulin factor predicted the development of type 2 diabetes.

Although the individuals who remained NGT and those who progressed from NGT to diabetes during the follow-up had an almost similar increase in mean BMI, the former still maintained a mean BMI of below 25 kg/m^2 during the follow-up, while the latter had a mean BMI of over 25 kg/m^2. Subjects who reverted from IGR to NGT had no change in the prevalence of obesity during the follow-up. An increase in obesity, rather than a change in other features of MetS, predicted the progression of IGR or diabetes after adjustment for the confounding factors.

A single worldwide definition of MetS is convenient and useful in clinical practice and epidemiological studies. Since five definitions, especially the new IDF definition, have been released, the most important is to test their ability for predicting incident diabetes and CVD across ethnic groups. More information from different populations is needed for the further refinement of the definition of MetS. In addition, since MetS is not only associated with the elevated risk of diabetes but also with that of CVD, there is an urgent need to develop strategies to prevent the emerging global epidemic of MetS.

In conclusion, further studies on the definition of MetS should focus on the potential ethnic differences in obesity and insulin resistance. Both IFG and IGT combined exhibit the strongest predictor for development of diabetes in both men and women compared with other categories of glucose homeostasis. Isolated IGT is a better predictor of incident diabetes than isolated IFG in Chinese men. Insulin resistance is not the only single unifying factor for the clustering of components of MetS. Different physiological processes associated with various components of MetS contain unique information about diabetes risks. Microalbuminuria is more likely to be a complication of the type 2 diabetes or hypertension than a marker of MetS. Obesity may be a more important risk factor for the development of IGR or diabetes than other features of MetS. The lifestyle intervention aimed at preventing diabetes should place higher importance on obesity than IGR.

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