Publication of Public Health M203

Early detection of type 2 diabetes mellitus in Chinese and Indian adult population

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ACADEMIC DISSERTATION

To be presented, with the permission of the Faculty of Medicine of the University of Helsinki, for public examination in the Auditorium IV, University main building, Unioninkatu 34, 2nd floor on the 27th of April, 2010, at 12 o'clock

Helsinki 2010

ISSN 0355-7979
ISBN 978-952-10-4865-4 (pbk)
ISBN 978-952-10-4866-1 (PDF)

Helsinki University Printing House
Helsinki 2010

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ABSTRACT

Objectives of this study were to determine secular trends of diabetes prevalence in China and develop simple risk assessment algorithms for screening individuals with high-risk for diabetes or with undiagnosed diabetes in Chinese and Indian adults. Two consecutive population based surveys in Chinese and a prospective study in Mauritian Indians were involved in this study. The Chinese surveys were conducted in randomly selected populations aged 20-74 years in 2001-2002 (n=14 592) and 35-74 years in 2006 (n=4416). A two-step screening strategy using fasting capillary plasma glucose (FCG) as first-line screening test followed by standard 2-hour 75g oral glucose tolerance tests (OGTTs) was applied to 12 436 individuals in 2001, while OGTTs were administrated to all participants together with FCG in 2006 and to 2156 subjects in 2002. In Mauritius, two consecutive population based surveys were conducted in Mauritian Indians aged 20-65 years in 1987 and 1992; 3094 Indians (1141 men), who were not diagnosed as diabetes at baseline, were reexamined with OGTTs in 1992 and/or 1998. Diabetes and pre-diabetes was defined following 2006 World Health Organization/ International Diabetes Federation Criteria.

Age-standardized, as well as age- and sex-specific, prevalence of diabetes and pre-diabetes in adult Chinese was significantly increased from 12.2% and 15.4% in 2001 to 16.0% and 21.2% in 2006, respectively. A simple Chinese diabetes risk score was developed based on the data of Chinese survey 2001-2002 and validated in the population of survey 2006. The risk scores based on β coefficients derived from the final Logistic regression model ranged from 3 – 32. When the score was applied to

the population of survey 2006, the area under operating characteristic curve (AUC) of the score for screening undiagnosed diabetes was 0.67 (95% CI, 0.65-0.70), which was lower than the AUC of FCG (0.76 [0.74-0.79]), but similar to that of HbA_{1c} (0.68 [0.65-0.71]). At a cut-off point of 14, the sensitivity and specificity of the risk score in screening undiagnosed diabetes was 0.84 (0.81-0.88) and 0.40 (0.38-0.41).

In Mauritian Indian, body mass index (BMI), waist girth, family history of diabetes (FH), and glucose was confirmed to be independent risk predictors for developing diabetes. Predicted probabilities for developing diabetes derived from a simple Cox regression model fitted with sex, FH, BMI and waist girth ranged from 0.05 to 0.64 in men and 0.03 to 0.49 in women. To predict the onset of diabetes, the AUC of the predicted probabilities was 0.62 (95% CI, 0.56-0.68) in men and 0.64(0.59-0.69) in women. At a cut-off point of 0.12, the sensitivity and specificity was 0.72(0.71-0.74) and 0.47(0.45-0.49) in men; and 0.77(0.75-0.78) and 0.50(0.48-0.52) in women, respectively.

In conclusion, there was a rapid increase in prevalence of diabetes in Chinese adults from 2001 to 2006. The simple risk assessment algorithms based on age, obesity and family history of diabetes showed a moderate discrimination of diabetes from non-diabetes, which may be used as first line screening tool for diabetes and pre-diabetes, and for health promotion purpose in Chinese and Indians.

TIIVISTELMÄ

Tämän tutkimuksen tarkoituksena oli tutkia miten diabeteksen esiintyvyys on muuttunut Kiinassa ja kehittää kiinalaista ja intialaista alkuperää olevaa aikuisväestöä varten yksinkertaiset riskinarviointialgoritmit, joiden avulla voidaan tunnistaa henkilöt, joilla on suuri riski sairastua diabetekseen tai aiemmin diagnosoimaton diabetes.
Tutkimus koostui kahdesta peräkkäisestä väestötutkimuksesta Kiinassa sekä Mauritiuksen intialaisväestön prospektiivisesta tutkimuksesta. Kiinalaisissa väestötutkimuksissa tehtiin satunnaisotanta 20-70 vuotiaista kiinalaisista vuosina 2001-2002 (n=14592) ja 35-74 vuotiaista vuonna 2006 (n=4416). Seulonta suoritettiin kaksivaiheisena 12436 henkilölle vuonna 2001. Ensisijainen seulontatesti oli kapillaariverinäytteestä tehty paastoglukoosin määritys, jota seurasi normaali kahden tunnin 75g glukoosirasituskoe,. Glukoosirasituskoe ja kapillaarinäytteestä tehty paastoglukoosin määritys tehtiin kaikille tutkittaville vuonna 2006 ja 2156 tutkittavalle vuonna 2002.Mauritiuksen 20-65-vuotiaassa intialaisperäisessä väestössä toteutettiin kaksi peräkkäistä väestötutkimusta vuosina 1987 ja 1992. Niille 3094 intialaiselle (1141 miestä), joilla ei todettu olevan diabetesta lähtötilanteessa, tehtiin glukoosirasituskokeet vuosina 1992 ja/tai 1998. Diabetes ja sen esiasteet määriteltiin vuoden 2006 World Health Organization/ International Diabetes Federation kriteerien mukaisesti.
Ikävakioitu, ikä- ja sukupuolispesifinen diabeteksen ja sen esiasteiden vallitsevuus kiinalaisessa aikuisväestössä kasvoi merkitsevästi vuosien 2001 ja 2006 välillä; diabeteksen osalta 12.2 %:sta 16.0 %:iin ja esiasteiden osalta 15.4 % :sta 21.2 %:iin. Yksinkertainen kiinalainen diabeteksen riskitesti kehitettiin pohjautuen kiinalaiseen 2001–2002 väestötutkimukseen ja sen osuvuus varmennettiin vuoden 2006 väestötutkimusaineistolla.

Logistisen regressiomallin kertoimiin (β) perustuvat riskipisteet vaihtelivat välillä 3-32. Kun riskipisteitä testattiin vuoden 2006 tutkimuksen väestöön, riskipisteiden AUC (ROC-käyrän alle jäävä pinta-ala) pistemäärä diagnosoimattomalle diabetekselle oli 0.67 (95% CI, 0.65-0.70), tulos, joka oli alempi kuin kapillaarinäytteestä tehdyn paastoglukoosin määrityksen AUC (0.76 [0.74-0.79]), mutta samankaltainen kuin HbA_{1c}:n AUC (0.68

[0.65-0.71]). Kun katkaisukohtana oli 14 riskitestipistettä, sen herkkyys aiemmin diagnosoimattoman diabeteksen toteamiselle oli 0.84 (0.81-0.88) ja herkkyys 0.40 (0.38-0.41).

Mauritiuksen intialaisväestön tutkimuksessa painoindeksi (BMI), vyötärön ympärys, suvussa esiintynyt diabetes ja glukoosi ennustivat itsenäisesti tulevaa diabetesta..Coxin regressiomallista johdetut diabeteksen kehittymisen todennäköisyysennusteet, kun mallissa selittäjinä olivat sukupuoli, suvussa esiintynyt diabetes, BMI ja vyötärön ympärys, vaihtelivat välillä ,0.05-0.64 miehillä ja 0.03-0.49 naisilla. Ennustettaessa diabeteksen alkamisajankohtaa, ennustetun todennäköisyyden AUC oli 0.62 (95% CI, 0.56-0.68) miehillä ja 0.64(0.59-0.69) naisilla. Käytettäessä katkaisupisteenä 0.12:a, herkkyys oli 0.72(0.71-0.74) ja tarkkuus 0.47(0.45-0.49) miehillä. Vastaavat luvut naisilla olivat 0.77(0.75-0.78) ja 0.50(0.48-0.52).

Yhteenvetona voidaan todeta, että diabeteksen esiintyvyys kasvoi nopeasi Kiinassa vuodesta 2001 vuoteen 2006. Yksinkertainen riskinarviointialgoritmi oli mahdollista kehittää. Se perustui ikään, lihavuuteen ja suvussa esiintyneeseen diabetekseen, osoitti kohtalaista erottelukykyä diabeteksen ja normaalin glukoosiaineenvaihdunnan välillä. Sitä voidaan käyttää terveyden edistämistarkoituksiin sekä ensisijaisena työkaluna seulottaessa diabetesta ja sen esiasteita kiinalaista ja intialaista alkuperää olevilla henkilöillä.

ABBREVIATIONS

ADA	American Diabetes Association
AUC	Area under receiver operating characteristic curve
BMI	body mass index
BP	blood pressure
CI	confidence interval
FH	family history of diabetes
FPG	fasting plasma glucose
FCG	fasting capillary plasma glucose
HbA_{1c}	glycated hemoglobin A_{1c}
IDF	International Diabetes Federation
2hPG	post-challenge 2 hour plasma glucose
Qd-DPP	Qingdao Diabetes Prevention Program
ROC	receiver operating characteristic curve
SE	standard error
SD	standard difference
WHO	World Health Organization

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I. Dong Y, Gao W, Nan H, Yu H, Li F, Duan W, Wang Y, Sun B, Qian R, Tuomilehto J, Qiao Q. Prevalence of Type 2 diabetes in urban and rural Chinese populations in Qingdao, China. Diabet Med 2005; 22 (10): 1427-1433. (Corresponding author)

II. Gao WG, Dong YH, Nan HR, Tuomilehto J, Qiao Q. The likelihood of diabetes based on the proposed definitions for impaired fasting glucose. Diab Res Clin Pract. 2008; 79: 151-155.

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1. INTRODUCTION

During the past few decades, the number of patients with diabetes mellitus has been seen a dramatic increase in the world, which was about 175 million in 2000 and will continue to rise up to 366 million in 2030 (Wild et al. 2004). As the International Diabetes Federation (IDF) and World Health Organization (WHO) estimated, the epidemic of diabetes casts a heavy burden to the human society (http://www.idf.org/human-social-and-economic-impact-diabetes, accessed18 June 2009). The devastating effects on the human health and social-economic development are alarming both in developed and developing countries, particularly in China and India, which hold the largest number of diabetic patients in the world (Wild et al. 2004). According to the WHO estimate, China will lose the national income about $ 555.7 billion from the year of 2005 to 2015, and Indian $ 333.6 billion, which is definitely a heavy burden for their developing society and economy.

Under the pressure of the increasing burden of the disease, diabetes research has become important during the past decades. With the evidence accumulated, it is clear that both diabetes and its complications can be delayed or prevented with appropriate lifestyle intervention and/or drug treatment (Reichard et al. 1993; The Diabetes Control and Complications Trial Research Group 1995; Pan et al. 1997; United Kingdom Prospective Diabetes Study (UKPDS) Group 1998; United Kingdom Prospective Diabetes Study (UKPDS) Group 1998; Tuomilehto et al. 2001; Chiasson et al. 2002; Knowler et al. 2002; Ramachandran et al. 2006; Gerstein et al. 2008; Patel et al. 2008; Duckworth et al. 2009; Nathan et al. 2009; Turnbull et al. 2009). Early detection applying a simple, sensitive and acceptable screening tool is, therefore, crucial to enable early identification and

interventions (Tabák et al. 2009). Blood glucose test, both a diagnostic test and a screening tool, has been widely used in the past to screen for type 2 diabetes, which has a moderate to high sensitivity and specificity in spite of which type of blood glucose tests were applied (Bortheiry et al. 1994; Husseini et al. 2000; Daniel et al. 2002; Bennett et al. 2007). Because blood glucose test is invasive, relatively expensive, time consuming, and requires fasting status and/or glucose ingestion, attempts have been made to assess the diabetes risk according to diabetes risk factors such as age, obesity, physical inactivity, diet, family history of diabetes, blood pressure, blood lipids, history of intermediate hyperglycaemia, gestational diabetes, and hypertension, etc. Different risk assessment algorithms have been developed recently and approved to be used in different screening programs. Most of those risk assessment tools was reported to have a moderate discrimination (Schwarz et al. 2009). However, a few risk assessment tools have been developed and evaluated in Chinese and Indian populations.

Based on two population-based surveys in Qingdao, China, we have estimated the prevalence of type 2 diabetes and its secular increasing trend in Chinese adults. A simple risk score for screening diabetes was developed and its ability to discriminate diabetes from non-diabetes defined by 2-hour 75 gram oral glucose tolerance test (OGTTs) was evaluated and compared with that of fasting capillary plasma glucose (FCG) and glycated hemoglobin A_{1c} (HbA_{1c}) tests. A simple risk score was also derived for Mauritian Indians based on prospective studies of two random population-based surveys.

2. REVIEW OF THE LITERATURE

2.1 Definition, classification and diagnostic criteria for type 2 diabetes mellitus

2.1.1 Definition and classification of diabetes mellitus

As in the 1999 WHO technical report for *Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications*, diabetes mellitus was defined as "a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both" (W.H.O Consultation 1999). If it is not well treated, diabetes might result in a long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, etc. The typical symptoms for diabetes are increased thirst, increased hunger, frequent urination, unexplained weight loss, fatigue, etc. But, these symptoms are usually not present in all patients with type 2 diabetes, which makes the diseases undiagnosed for a long time (Harris et al. 1992; Thompson et al. 1996).

Based on the clinical stages and aetiological types, there are two major forms of diabetes, type 1 and type 2. Patients with type 1 diabetes usually have an absolute deficiency of insulin secretion, which is caused by destructive lesions of islet beta-cells. They are prone to ketoacidosis and need insulin supplement for survival. Individuals with type 2 diabetes frequently have an insulin resistance and insufficient insulin secretion. Insulin treatment is not required for most of the patients at least at the onset of the disease. The most common form of diabetes is type 2, which accounts about 90% of all diabetic patients and is the subject of the present study.

2.1.2 Diagnostic criteria for type 2 diabetes

The first widely accepted classification and diagnostic criterion for diabetes was proposed by National Diabetes Data Group (NDDG) in 1979 (National Diabetes Data Group 1979), which were adopted with minor modification by the WHO in 1980 and modified in 1985 (World Health Organization 1980; World Health Orgnization 1985). Since then, OGTTs has been considered as the "golden standard test" for diabetes for about 20 years, and the glucose cut-off points for a positive test were set at fasting plasma glucose (FPG) $\geq$ 7.8 mmol/l and/or 2-hour post-challenged glucose (2-hPG) $\geq$ 11.1mmol/l. Impaired glucose tolerance (IGT), defined as FPG < 7.8 mmol/l and 2hPG 7.8 - 11.1 mmol/l, was first introduced to denote a state which conveys an increased risk for diabetes and cardiovascular disease.

In 1997, an expert committee sponsored by American Diabetes Association (ADA) proposed new diabetes diagnostic criteria (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997) (Table 1). The major changes include 1) lowering the cut-off point of FPG from 7.8 mmol/l to 7.0 mmol/l for diagnosing diabetes; 2) introducing impaired fasting glucose (IFG), which is defined as FPG of 6.1-6.9 mmol/l, as an analogous of IGT; and, 3) recommending FPG, not OGTTs, as the standard diagnostic test for epidemiological studies and routine clinical practice. Most of these revisions were adopted by WHO Consultation in 1999 (W.H.O Consultation 1999). But in the 1999 WHO Consultation, OGTTs was retained as the "golden" standard diagnostic test and individuals with IFG were recommended receiving an OGTTs to determine glucose tolerance status (Table 1).

Table 1. The clinical stages of type 2 diabetes

Stage of type 2 diabetes		Plasma glucose (mmol/l)	Evident symptoms
Normoglycaemia		FPG < 6.1 and 2hPG < 7.8	No
Intermediate hyperglycaemia	Impaired fasting glucose	FPG 6.1-6.9 and 2hPG <7.8 if measured	No
	Impaired glucose tolerance	FPG < 7.0 and 2hPG 7.8-11.0	
Diabetes	Undiagnosed	FPG ≥ 7.0 and/or 2hPG ≥ 11.1	No
	Clinically diagnosed	FPG ≥ 7.0 and/or 2hPG ≥ 11.1	Yes/no

The difference between ADA and WHO diagnostic criteria evoked a hot debate. Many analysis were performed to examine the equivalence of the FPG and 2hPG to predict the risk of diabetes, mortality and morbidity from cardiovascular disease, and diabetic retinopathy (Barrett-Connor et al. 1998; de Vegt et al. 1998; Harris et al. 1998; de Vegt et al. 1999; Hanefeld et al. 1999; Shaw et al. 1999; Shaw et al. 1999; Tominaga et al. 1999; Vaccaro et al. 1999; Gabir et al. 2000; Gabir et al. 2000; Hanefeld et al. 2000; Ito et al. 2000; Larsson et al. 2000; Shaw et al. 2000; Temelkova-Kurktschiev et al. 2000; The DECODE Study Group 2001; Unwin et al. 2002; Qiao et al. 2003; The DECODE Study Group 2003; Blake et al. 2004; Qiao et al. 2004; Qiao et al. 2004). Both the ADA and WHO expert committee had re-evaluated their recommendations several times since 1997. In 2003, ADA recommended lowering the FPG cut-off point for IFG from 6.1 mmol/l to 5.6 mmol/l (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 2003). However, this was not adopted by the WHO Expert Consultation Committee; and, the FPG cut-off point for IFG is remained at 6.1 mmol/l until now (WHO/IDF Consultation 2006).

In July 2009, an International Expert Committee appointed by the ADA, the European Association for the Study of Diabetes (EASD), and the IDF proposed to diagnose diabetes by $HbA_{1c} \geq 6.5$ % and high risk individuals by HbA_{1c} 6.0-6.4%, and recommended to abandon the FPG and OGTTs as diagnostic test if the resources are available (The International Expert Committee 2009). More recently, HbA_{1c} range of 5.7-6.4% was recommended as identifying individuals with high risk for future diabetes in a new ADA report (American Diabetes Association 2010).

2.2 Epidemiology of type 2 diabetes mellitus

2.2.1 Prevalence of diabetes

Over the past few decades, numerous studies had performed in different populations and regions all over the world to determine the prevalence of diabetes. The results suggested that type 2 diabetes has become one of the major health threats globally. Although it is still lower than 4% in communities in traditional societies or in remote areas such as in a few of African and Asian countries, the prevalence of diabetes was about 4% - 10% in the adults aged 20-79 years in most regions of the worlds such as in Europe, Australia, most of Asian and American countries (Figure 1) (prevalence of diabetes worldwide, http://www.who.int/diabetes/facts/world_figures/en/print.html, Accessed 8 October, 2009) (Qiao et al. 2003; The DECODE Study Group 2003; International Diabetes Federation 2009). In Bahrain, Saudi Arabia, United Arab Emirates, Singapore, Poland, Kirbati, and Nauru, the rate even caught 15% - 30% (International Diabetes Federation 2006; International Diabetes Federation 2009). Globally, it was estimated that there are about 285 million adults (aged 20-79 years) with diabetes in the world in 2010, given a prevalence of 6.6% (International Diabetes Federation 2009).

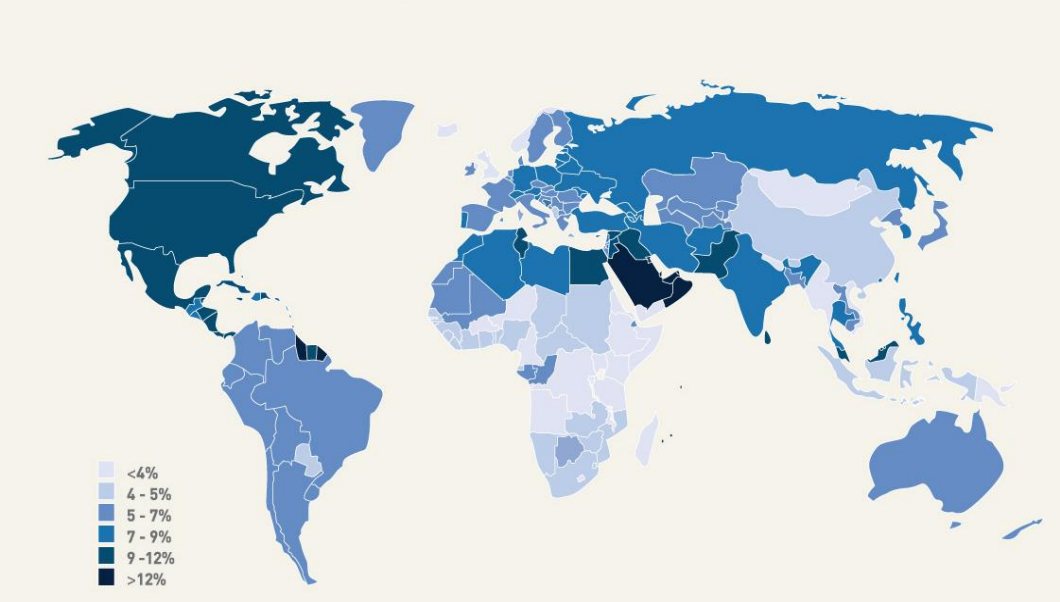

Figure 1 Prevalence estimates of diabetes (age 20-79 years), 2010. Adopted from Diabetes Atlas fourth edition (International Diabetes Federation 2009).

There is an evident increasing trend in the prevalence of diabetes all over the world. As summarized in Table 2, this increasing trend can be observed in either developed or developing countries. In the United State, for example, the National Health and Nutrition Examination Surveys revealed that the prevalence of diabetes was more than doubled from 1976 -1980 (5.3%) to 2005-2006 (12.6%). In Greece and Mauritius, the prevalence rate increased almost 0.5% each year. As shown by several modeling studies, the prevalence of diabetes will keep increasing and the number of diabetic patients will increase to 472 millions in 2030 in the world (McCarty DJ 1994; Amos et al. 1997; Wild et al. 2004; International Diabetes Federation 2006; International Diabetes Federation 2009).

Table 2. Secular increasing trend in prevalence of diabetes in different regions

Region	Prevalence (%)	Methodology	Reference
United States			
1976-1980	5.3	Series of cross-sectional population-	(Gregg et al. 2004)
1988-1994	7.5	based surveys	(Cowie et al. 2009)
1999-2000	8.2		
2005-2006	12.6		
Western Samoa			
1978	7.2	Series of cross-sectional population-	(Collins et al. 1994)
1991	11.4	based surveys	
Poole, United Kingdom			
1983	0.8	Series of surveys based on whole	(Gatling et al. 1998)
1988	0.9	population diabetes registration	
1996	1.5		
Netherlands			
1998	2.2	Series of surveys based on whole	(Ubink-Veltmaat et al.
2000	2.9	population diabetes registration	2003)
Nord-Trøndelag, Norway			
1984-1986	2.9	Series of whole population surveys	(Midthjell et al. 1999)
1995-1997	3.2		
Ontario, Canada			
1995	5.2	Serious of surveys based on whole	(Lipscombe et al.
2005	8.8	population diabetes registration	2007)
Skaraborg, Sweden			
From 1991 to 1995	Increased by 6% each year	Series of surveys based on whole population diabetes registration	(Berger et al. 1999)
Laxå, Sweden			
1988-1992	2.8 in women	Serious of surveys based on whole	(Jansson et al. 2007)
	2.6 in men	population diabetes registration	
1993-1997	4.5 in women		
	4.6 in men		
1998-2001	4.4 in women		
	4.5 in men		
Salamis, Greece			
2002	8.7	Series of cross-sectional population-	(Gikas et al. 2008)
2006	10.3	based surveys	

Mauritius			
1987	12.8	Series of cross-sectional population-	(Soderberg et al. 2005)
1992	15.2	based surveys	
1998	17.9		
Singapore			
1992	8.6	Series of cross-sectional population-	(Lee 2000)
1998	9.0	based surveys	

It has been recognized that the low- and middle-income countries face the greatest burden of diabetes. Population based studies in India conducted around 2000 showed that the prevalence of diabetes ranged from 6.1% to 19.5% (Shah et al. 1999; Zargar et al. 2000; Ramachandran et al. 2001; Gupta et al. 2003; Menon et al. 2006). And, Chennai Urban Rural Epidemiology Study (CURES) revealed that the prevalence of diabetes increased by 72.3% from 1989 (8.3%) to 2004 (14.3%) (Ramachandran et al. 1992; Ramachandran et al. 1997; Ramachandran et al. 2001; Mohan et al. 2006). As called "world diabetes capital", India holds above 50 million people with diabetes (International Diabetes Federation 2009), which is the largest number in the world.

Similarly, the prevalence of diabetes in China also experienced a dramatically increase since 1970s (Figure 2) (Shanghai Diabetes Research Cooperative Group 1980; National Diabetes Co-operative Study Group 1981; Beijing Diabetes Research Cooperative Group 1982; Pan et al. 1997; Wang et al. 1998; Dong et al. 2005; Yang et al. 2010). The national surveys showed that the prevalence of diabetes increased markedly from 1% in the earlier 1980s to 4.5% in the middle 1990s, to 5.5% in the later 1990s, and 9.7% about 2008 (National Diabetes Co-operative Study Group 1981; Wang et al. 1998; Jia et al. 2002; Gu et al. 2003; Yang et al. 2010). The prevalence increased more in big cities like Beijing and Shanghai than the average increase in the whole country (Shanghai Diabetes

Research Cooperative Group 1980; Beijing Diabetes Research Cooperative Group 1982; Diabetes research cooperation group of national 'the ninth five' major research plan 2002; Jia et al. 2002). IDF predicted that there will be 43.2 million patients in 2010 in China (International Diabetes Federation 2009).

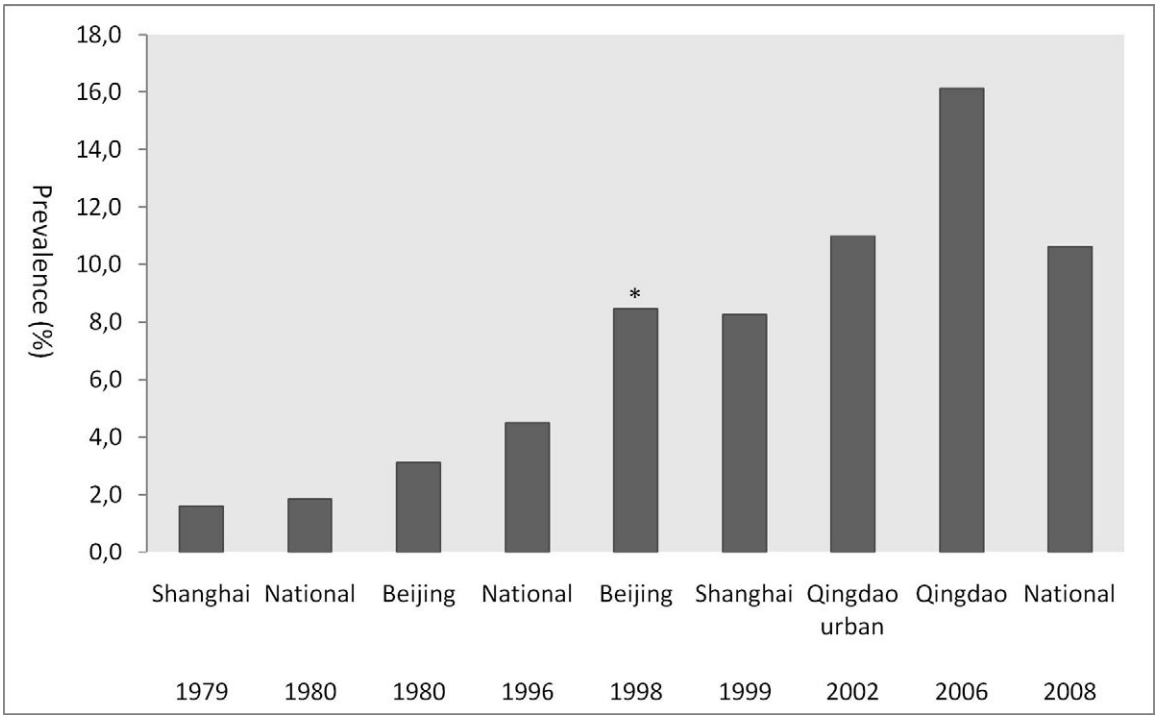

Figure 2. The age-standardized prevalence of diabetes in Chinese adults (aged 30 – 74 years old) from the early 1980s to 2008 in different regions

* The age of the subjects was 40 – 74 years old.

Diabetes was defined according to FPG ≥ 7.8 mmol/l and/or 2hPG ≥ 11.1 mmol/l in the surveys made before 1996; and FPG ≥ 7.0 mmol/l and/or 2hPG ≥ 11.1 mmol/l for the surveys made since 1999 in Shanghai, Qingdao, and national.

2.2.3 Risk determinant of type 2 diabetes mellitus

It is generally agreed that type 2 diabetes is a poly etiological disorder. The genetic background, environmental factors, and the interaction between these all influence the development of the disease.

2.2.3.1 Genetic predisposition

Type 2 diabetes is a genetic predisposed disease. Individuals with a history of diabetes in their parents or siblings were observed to have 2-6 folds high risk for diabetes (Knowler et al. 1981; Mitchell et al. 1993; Shaten et al. 1993; Lin et al. 1994; Burchfiel et al. 1995; Karter et al. 1999; Bjornholt et al. 2000; Meigs et al. 2000; Sargeant et al. 2000; Thorand et al. 2001; Harrison et al. 2003; Valdez et al. 2007). The monozygotic twin concordance rate in type 2 diabetes might be 70-80% (Barnett et al. 1981; Newman et al. 1987; Kaprio et al. 1992; Matsuda et al. 1994; Ghosh et al. 1996). The prevalence of diabetes is higher in certain ethic groups than in others, which also suggests the genetic predisposition (Dowse et al. 1990; Lee 2000). More recently, with the advanced technology, the genome-wide association studies suggested that dozens of gene variants might associate with a high risk for type 2 diabetes (Florez et al. 2007; Zeggini et al. 2007; Gaulton et al. 2008; Lango et al. 2008; Zeggini et al. 2008; Grant et al. 2009).

2.2.3.2 Age

Both the prevalence and incidence of type 2 diabetes increase with age in most of populations but the age at peak varies among different ethnic groups. In Chinese and Caucasians, the incidence of diabetes increased with age up to 65-74 years (Blanchard et al. 1996; Leibson et al. 1997; Ubink-Veltmaat et al. 2003; Liu et al. 2007), but to 40-50 years in Pima and Asian Indian (Pavkov et al. 2007; Mohan et al. 2008). After the age at peak the incidence and prevalence started to decline. These phenomenon might be caused

by the declining glucose utility (Davidson 1979; Ruiz-Torres et al. 1996) and increasing mortality after the age at peak. However, it is not clear whether the glucose metabolic deterioration accompanied with age is the natural processing of aging or secondary to age-related factors such like decreased physical activity and increasing obesity.

2.2.3.3 Obesity

Type 2 diabetes is strongly associated with obesity and weight gain. The measurements of obesity, such as, body mass index (BMI), waist circumference, waist hip ratio, whole or visceral fat mass etc, are positively associated with both the prevalence and incidence of diabetes in different populations (Ramachandran et al. 1997; Haffner 1998; Chang et al. 1999; Goodpaster et al. 2003; Meisinger et al. 2006; Ni Mhurchu et al. 2006). In a US study, for instance, each unit increase in BMI was associated with a 12% increased risk of diabetes (Ford et al. 1997); and in Chinese, the conversion rate from IGT to diabetes in subjects with a high baseline waist circumference was about 3 fold higher than in those with a low one (Wat et al. 2001). Weight gain during the follow-up and duration of obesity was also positively relate to the onset of diabetes (Everhart et al. 1992; Colditz et al. 1995; Wannamethee et al. 1999; Koh-Banerjee et al. 2004; Wannamethee et al. 2005; Schienkiewitz et al. 2006). As reported by Everhart et al, in Pima Indians who attained a BMI 30 kg/m^2, the risk of NIDDM increased from 24.8 per 1,000 person-years in those who were obese for <5 years, to 35.2 per 1,000 for obesity of 5-10 years, to 59.8 per 1,000 for >10 years of obesity (Everhart et al. 1992). Strong evidence from clinical trials have confirmed that the weight reduction can prevent or delay the onset of diabetes (Tuomilehto et al. 2001; Knowler et al. 2002; Li et al. 2008). The risk for diabetes was reduced by 57% in subjects who achieved the weight reduction goal in Finnish Diabetes

Prevention Study (DPS) (Lindstrom et al. 2006). It is noticeable that not all obese people develop diabetes, and not all patients with type 2 diabetes are obese at the onset of the disease. Given the same degree of obesity defined by either BMI or waist circumference, the prevalence of diabetes varied largely among different ethnic groups, which is highest in Indians and lowest in Caucasians (Figure 3) (Nakagami et al. 2003; Nyamdorj et al. 2009). It is still not decided whether diabetes is a consequence of obesity or a parallel disorder caused by the same pathogen.

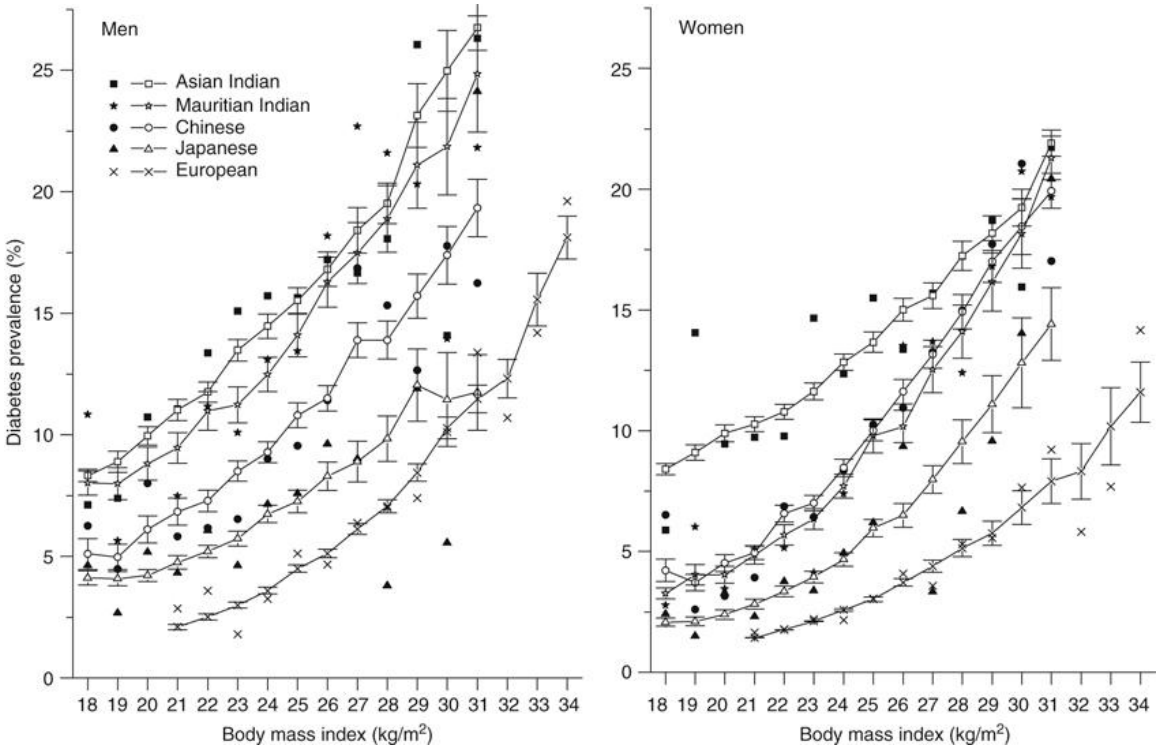

Figure 3. Crude (filled markers) prevalence and estimated (open markers with 95% CIs) probability of undiagnosed diabetes according to BMI categories by ethnicity. Adapted from the article of (Nyamdorj et al. 2009).

2.2.3.4 Physical inactivity

Peoples with sedentary lifestyle have been consistently shown to have a high risk for diabetes in different populations (Villegas et al. 2006; Jeon et al. 2007; Chien et al. 2009; Gimeno et al. 2009). Prolonged television watching, as a surrogate of sedentary lifestyle, was reported to be positively associated with diabetes risk (Hu et al. 2001; Hu 2003; Krishnan et al. 2009). In men, for example, the risk increased progressively to 187% higher incidence among those watching TV > 40 hour per week than among those spending 0-1 hour per week (Hu et al. 2001); while in women, every 2 hour per day increment in television watching was associated with 14% increase in risk of diabetes (Hu 2003). Higher level of physical activity is associated with a lower risk of diabetes. Results from a number of studies showed a dose-response relationship between levels of physical activity and diabetes incidence (Helmrich et al. 1991; Manson et al. 1991; Schranz et al. 1991; Manson et al. 1992; Burchfiel et al. 1995; Lynch et al. 1996; Haapanen et al. 1997; Folsom et al. 2000; Fretts et al. 2009). And, several clinical trials have shown that moderate physical activity might reduce the progression of IGT to diabetes by 30-58% (Eriksson et al. 1991; Pan et al. 1997; Tuomilehto et al. 2001; Knowler et al. 2002; Yamaoka et al. 2005; Ramachandran et al. 2006; Li et al. 2008). The results of Malmö, Daqing and DPS study even suggested that the protecting effect of physical activity was independent of diet and weight loss (Eriksson et al. 1991; Pan et al. 1997; Hu et al. 2004). There's no doubt that physical inactivity is an important modifiable risk factor of type 2 diabetes. However, it is noticeable that the physical activity data based on a questionnaire might be not reliable (Rennie et al. 1998; Shephard et al. 2003; Prince et al. 2008). There is still a need to have a valid, accurate and reliable measure of physical activity.

2.2.3.5 Diet

For a long time, diet has been considered as an important risk factor for diabetes. Excess caloric intake, which results in a positive energy balance, promotes the onset of both obesity and diabetes. The westernized dietary pattern, which is rich in saturated fat and simple carbohydrate, and scarce in fibres, was suggested to associate with a high risk of type 2 diabetes (van Dam et al. 2002; Hodge et al. 2007; McNaughton et al. 2008; Liese et al. 2009). On the contrary, a low risk for diabetes was observed in people consuming lot of vegetables, fruits, whole grain products, and fish, etc, which are characterized by low energy density and low glycemic index but high fibre and unsaturated fat acid (Hodge et al. 2004; Liu et al. 2004; Montonen et al. 2005; de Munter et al. 2007; Villegas et al. 2008; Patel et al. 2009). The antioxidant such as vitamin C and E, unsaturated fat acid, flavonoid etc, might also have protecting effect (Tuomilehto et al. 2004; Montonen et al. 2005; Harding et al. 2008; Stote et al. 2008). Diet intervention, plus moderate or intensive physical activity have been proved to be effective on the prevention of diabetes (Tuomilehto et al. 2001; Knowler et al. 2002; Li et al. 2008). However, since dietary pattern depends on the local food resource and the cooking procedure, which is closely related to the folk custom, religion, and culture, etc, the results from different studies were not always consistent.

2.2.3.6 Smoking, alcohol consuming and other environmental risk factors

A numerous studies have conducted to determine the association between smoking and the risk of type 2 diabetes. The results, however, are not consistent. Recently, a meta-analysis including 25 perspective studies showed that current smoking associated with a 44% increased risk of diabetes (Willi et al. 2007). The authors concluded that there is an

association between smoking and diabetes; but, whether the association is causal needs to be further studied. As for alcohol consumption and the risk of diabetes, a U-shaped relationship was found (Baliunas et al. 2009). Compared with abstainers, moderate alcohol consumers had about 30% reduced risk of diabetes (Koppes et al. 2005; Beulens et al. 2008; Crandall et al. 2009; Imamura et al. 2009). However, high daily consumption of alcohol beverage has no protecting effect and might reversely increase the risk for diabetes (Beulens et al. 2005; Hodge et al. 2006).

Urbanization in the developing countries is observed to relate to an increasing prevalence of diabetes (King et al. 1998). In China, a consistent urban-rural difference was observed in the different surveys (National Diabetes Co-operative Study Group 1981; Pan et al. 1997; Wang et al. 1998; Gu et al. 2003; Dong et al. 2005). In India, the urban population had a 2-5 times higher prevalence of diabetes than the rural (Ramachandran et al. 1999; Mohan et al. 2007; Mohan et al. 2008). Although the social-economic status has been suggested to modify the risk of diabetes, the affects are different in developing and developed regions. In Qingdao city, for example, low socio-economic classes associated with a higher prevalence of diabetes in urban areas but a lower prevalence in rural areas (Ning et al. 2009).

2.3 Screening for type 2 diabetes mellitus

2.3.1 Rational for screening diabetes

In the WHO guideline of **Screening for Type 2 Diabetes**, screening was defined as "the process of identifying those individuals who are at sufficiently high risk of a specific disorder to warrant further investigation or direct action" (World Health Orgnization 2003). "It (screening) is systematically offered to a population of people who have not

sought medical attention on account of symptoms of the disease for which screening is being offered and is normally initiated by medical authorities and not by a patient's request for help on account of a specific complaint".

The rationales to screen for type 2 diabetes are:

- Diabetes, which has a rising prevalence world-wide, is now one of the major threats to the human health and hinders the social-economic development;
- In the natural history of diabetes, there is a long, latent, and asymptomatic period in which the disease may be detected (Harris et al. 1992; Thompson et al. 1996);
- Accumulating evidences support that diabetes and its complications are preventable with appropriate intervention and/or treatment;
- There are some screening tools which have been shown to be effective in screening diabetes;
- Although not consistent, there are some evidences showing that screening for diabetes might be cost-effective (The C. D. C. Diabetes Cost-Effectiveness Study Group 1998; Chen et al. 2001; Hoerger et al. 2004; Hoerger et al. 2007; Gillies et al. 2008);

2.3.2 Screening tools and their performance

The screening tools for diabetes include **biochemical tests** such as blood glucose, HbA_{1c} and urinary glucose test, **genetic markers**, and **risk assessment questionnaires or scores,** which are briefly reviewed as following**.**

2.3.2.1 Biochemical markers

Urinary glucose test is now not in use where the blood glucose tests are available. Although the specificity may be higher than 98%, the sensitivity of urinary glucose test was only around 20% to 64% (Davies et al. 1993; Friderichsen et al. 1997; Engelgau et al. 2000). The renal threshold for re-absorption of glucose varies between individuals, and, the presence of glucose in the urine is more likely positive in individuals with a low threshold than those with a high threshold. Urinalysis, therefore, has limited use as a solitary tool for diabetes screening.

Fasting/Random finger capillary blood glucose test is the easiest and simplest way of blood glucose testing. As shown in Table 3, the sensitivities of the capillary blood glucose at the optimal cut-off points were about 80% and specificities above 70% in most of studies. It is noticeable that the optimal cut-off points varied from 5.0mmol/l to 7.9mmol/l in different studies. According to Engelgau et al, different optimal cut-off points were required to account for the age and postprandial period (Engelgau et al. 1995). And, the performance was poor in the Finnish women, with a sensitivity about 40% (Qiao et al. 1995). The other concern with the portable blood glucose meter measured readings is the accuracy of the result (Sacks et al. 2002).

Table 3. Sensitivity and specificity of finger capillary blood glucose in detecting diabetes

Studies	Metabolic state	Diagnostic test	Cut-off point (mmol/l)	Sensitivity (%)	Specificity (%)
(Murphy et al. 1993)	Fasting	OGTTs	6.7	75.0	93.0
(Bortheiry et al. 1994)	Fasting	OGTTs	5.6	In men 89.4, in women 85.3	In men 67.7, in women 74.4
(Engelgau et al. 1995)	Random	2hPG	6.1-7.2, depending on age	76.0 – 81.0, depending on age	75.0 – 80.0, depending on age
(Qiao et al. 1995)	Random	OGTTs	6.2	In men 79.0, in women 40.0	in men 93.0, in women 92.0
(Husseini et al. 2000)	Fasting	OGTTs	5.0	83.3	79.0
(Rolka et al. 2001)	Random	OGTTs	6.7	75.0	88.0
(Herdzik et al. 2002)	Fasting	OGTTs	5.8	85.4	94.9
(Zhang et al. 2005)	Random	OGTTs	6.7	68.0	89.0
(Somannavar et al. 2009)	Random	OGTTs	7.9	78.6	83.9

Glycated haemoglobin A_{1c} (HbA_{1c}) is a good and stable marker of mean blood glucose in 4-8 weeks preceding the test. At a value of 5.9% and 6.1%, the sensitivity of HbA_{1c} was reported ranging from 76% to 95%, and specificity from 67% to 86% (Tavintharan et al. 2000; Tanaka et al. 2001; Bennett et al. 2007). However, in an USA population, it is reported that 60% of individuals with screen-detected diabetes based on FPG had a normal value of HbA_{1c} (Davidson et al. 1999; Davidson et al. 2001). And the biology variation of hemoglobin limits the usage of HbA_{1c} in certain situation such as women in pregnancy, individuals with anemia or with abnormal hemoglobin, etc. Also, the assay of HbA_{1c} is most expensive.

2.3.2.2 Genetic markers

To establishing a genetic score, which adds up a number of genetic markers, to predict diabetes was reported in several studies recently. It has been shown that genetic score may improve the performance over clinical predictors of prevalent diabetes (Lyssenko et al. 2008; Meigs et al. 2008; Cornelis et al. 2009; Lin et al. 2009); but, the improvement was very limited, and was not found in other studies (Balkau et al. 2008; Schulze et al. 2009).

2.3.2.2 Risk assessment questionnaires or scores

Blood sample is needed for all the blood glucose test and HbA_{1c}. They are invasive, relatively expensive, time consuming, and not easy to apply in large population screening programs. Dozens of risk scores, risk predicting models or risk assessing questionnaires without biochemical measurements have been developed to serve as screening tests (Table 4). Most of these were developed and validated in the Caucasians, and a few in Indians and other Asians. In general, the areas under the receiver operating characteristic curve (AUC) of these risk assessment tools, varied from 70% to 80%. The sensitivities of these tools in predicting diabetes were above 70%; but, the specificities were relatively low or moderate, about 50-60% at the optimal cut-off points.

Table 4. Risk predicting or assessment algorithms in different populations

Risk assessment scores	Risk factors involved	Diagnostic test	Optimal cut-off point (range)	Area under the ROC curve (95% CI), %	Sensitivity (95% CI) at the optimal cut-off point, %	Specificity (95% CI) at the optimal cut-off point, %
Cambridge risk model (Griffin SJ. et al. 2000)	Age, sex, drug-treated hypertension, corticosteroids treatment, family history of diabetes, BMI and smoking	2h 75g OGTTs	0.199	80.0 (68-91)	77.3 (54.6-92.2)	72.0 (68.0-76.0)
Danish Risk score (Glumer C. et al. 2004)	Age, sex, BMI, known history of hypertension, diabetes in parents, physical activity at leisure time	2h 75g OGTTs	29(0-60)	80.4 (76.5-83.8)	79.3 (71.4-86.3)	68.7 (67.1-70.3)
Indian risk score (Ramachandran A. et al. 2005)	Age, sex, family history of diabetes, BMI, waist circumference, physical activity	2h Post load blood Glucose ≥ 11.1 mmol/l	21(0-42)	73.2 (70.2-76.1)	76.6 (70.9-81.7)	59.9 (58.5-61.3)
Indian Diabetes risk score (Mohan et al. 2005)	Age, waist circumference, physical activity, family history of diabetes	2h venous plasma glucose ≥ 11.1 mmol/l	60(0-100)	69.8 (66.3-73.3)	72.5	60.1
Rotterdam study (Baan CA. et al. 1999)	Age, sex, drug-treated hypertension, BMI	2h 75g OGTTs	6(0-22)	68.0 (64-72)	78.0	55.0
Finnish Risk Score (Lindström J. et al. 2003)	Age, BMI, waist, drug-treated hypertension, physical inactivity, daily consuming vegetable, fruit, or berries	Drug-treated diabetes	9(0-20)	85.0	78.0 (71.0-84.0)	77.0 (76.0-79.0)
DESIR Risk Score	Waist circumference, smoking,	Clinical	Not available	73.3 in men..	-	-

(Balkau B. et al. 2008)	hypertension, family history of diabetes	diagnosed diabetes or FPG	(0-5)	83.9 in women		
Thai Risk Score (Aekplakorn W. et al. 2006)	Age, sex, BMI, waist circumference, hypertension, family history of diabetes	2h 75g OGTTs	6 (0-17)	74.0 (71-78)	77.0	60.0
ADA recommendation (ADA. 2000) *	Delivery of a baby weighing > 9 pounds, diabetes in parents or siblings, BMI, age, physical activity	2h 75g OGTTs	10(0-27)	71.0	80.0	34.6
QDScore (Hippisley-Cox et al. 2009)	Age, BMI, family history of diabetes, smoking, history of treated hypertension, history of cardiovascular disease, use of corticosteroids, social deprivation, ethnicity	Clinically diagnosed diabetes	Not available	85.3 (85.0-85.6) in women 83.4 (83.1-83.6) in men	-	-
Oman risk score (Al-Lawati et al. 2007)	Age, waist circumference, BMI, family history of diabetes, hypertension	2h post load serum glucose ≥ 11.1 mmol/l	10 (0-25)	76(74-79)	62.8(54.3-70.6)	78.2(75.8-80.4)
German risk score (Schulze et al. 2007)	Waist, height, age, hypertension, physical activity, smoking, consumption of red meat, whole-grain bread, coffee and moderate alcohol,	Self-reported diabetes	500(118-983)	82	94.4	66.7

SUNSET study (Bindraban et al. 2008)	Ethnicity, BMI, waist circumference, resting heart rate, family history of diabetes, hypertension, history of cardiovascular disease	FPG	Not available (0-19)	74 (70-79) in Hindustani Surinamese, 79(76-85) in African Surinamese, 79 (75-87) in Dutch	79,5(69.0-87.3) in Hindustani Surinamese, 78.1(66.6-86.6) in African Surinamese, 71.9(53.0-85.6) in Dutch	47.4(41.0-53.8) in Hindustani Surinamese, 60.7(56.3-65.0) in African Surinamese, 71.2(66.7-75.3) in Dutch
Canary Islands survey (Cabrera de Leon et al. 2008)	Age, waist/height ratio, family history of diabetes, systolic blood pressure, gestational diabetes	FPG	100	83.7(80.3-87.1)in men 87.4(84.7-90.1) in women	93 in men 95 in women	54 in men 48 in women
ARIC study (Kahn et al. 2009)	Parental history of diabetes, hypertension, race, age, smoking, waist circumference, height, resting pulse, weight	FPG, 2hPG or clinical diagnosis	38(0-100)	71(69-73)	69	64
(Bang et al. 2009)	Age, sex, family history of diabetes, personal history of hypertension, obesity, and physical activity	FPG	5(0-9)	79	79	67
AUSDRISK (Chen et al. 2010)	Age, sex, ethnicity, parental history of diabetes, history of high blood glucose level, use of antihypertension medications, smoking, physical inactivity, waist circumference	FPG, 2hPG or on treatment of diabetes	12(0-35)	78(76-81)	74.0	67.7

3. AIMS OF THE STUDY

I. **To determine the prevalence of type 2 diabetes and secular trend in prevalence of diabetes in Chinese adults in Qingdao, China (Paper I, II, III)**

II. **To construct a simple risk score for the presence of undiagnosed diabetes in Chinese adults in Qingdao, China (Paper IV)**

III. **To evaluate the performance of fasting capillary plasma glucose (FCG) and glycated haemoglobin A_{1c} (HbA_{1c}) as screening tests for detecting diabetes and pre-diabetes (Paper IV and V)**

IV. **To develop a simple risk predicting model for developing diabetes in Mauritian Indian adults (Paper VI)**

4. STUDY POPULATION AND METHODS

4.1 Study population

4.1.1 Qingdao Diabetes Survey 2001-2002

Qingdao city locates in the eastern coastline of China facing Yellow Sea. There are 12 administration regions in Qingdao city, four urban districts (Shinan, Shibei, Sifang, Licang) and 8 rural counties (Laoshan, Chengyang, Jiaozhou, Jimo, Pingdu, Jiaonan, Huangdao, Laixi). According to the 2000 census, there were about 7.02 million residents living in Qingdao city, about 4.7millions in the rural areas and 2.3 in urban. About 99% of the total population are Han Chinese. During the past three decades, the city had experienced a rapid urbanization, modernization and industrialization. For example, its urban area doubled from 1980 to 2000. The gross domestic product of the city has increased from 479.21 million Chinese Yuan ($57.89 million) to 11 500.73 million ($1389.48 million) during the same period.

From April 2001 to July 2002, a cross-sectional population-based survey for diabetes prevalence was conducted in Qingdao. Stratified random cluster sampling was employed in the survey to recruit the subjects (Figure 4). Three urban districts (Shinan, Shibei, and Sifang) and four rural counties (Jiaonan, Pingdu, Chengyang, and Laoshan) were first randomly selected (Dong et al. 2005). Streets and towns were, then, randomly drawn from each selected urban and rural area. From the selected streets and towns, street blocks and/or villages were then randomly drawn. About 400-800 residents, aged 20-74 years old and lived in Qingdao for at least 5 years, from each of the street blocks and/or villages were randomly selected and invited to participate in the survey. According to the

urban to rural ratio of 1:2, 4900 individuals from the urban areas and 10000 from the rural areas were randomly selected. In addition, 2 600 urban citizens from one community were recruited at the end of the 2001-2002 survey (Gao et al. 2008). Thus, a total of 17 500 citizens invited and 14 592 participated the survey, with an overall response rate of 83.4%.

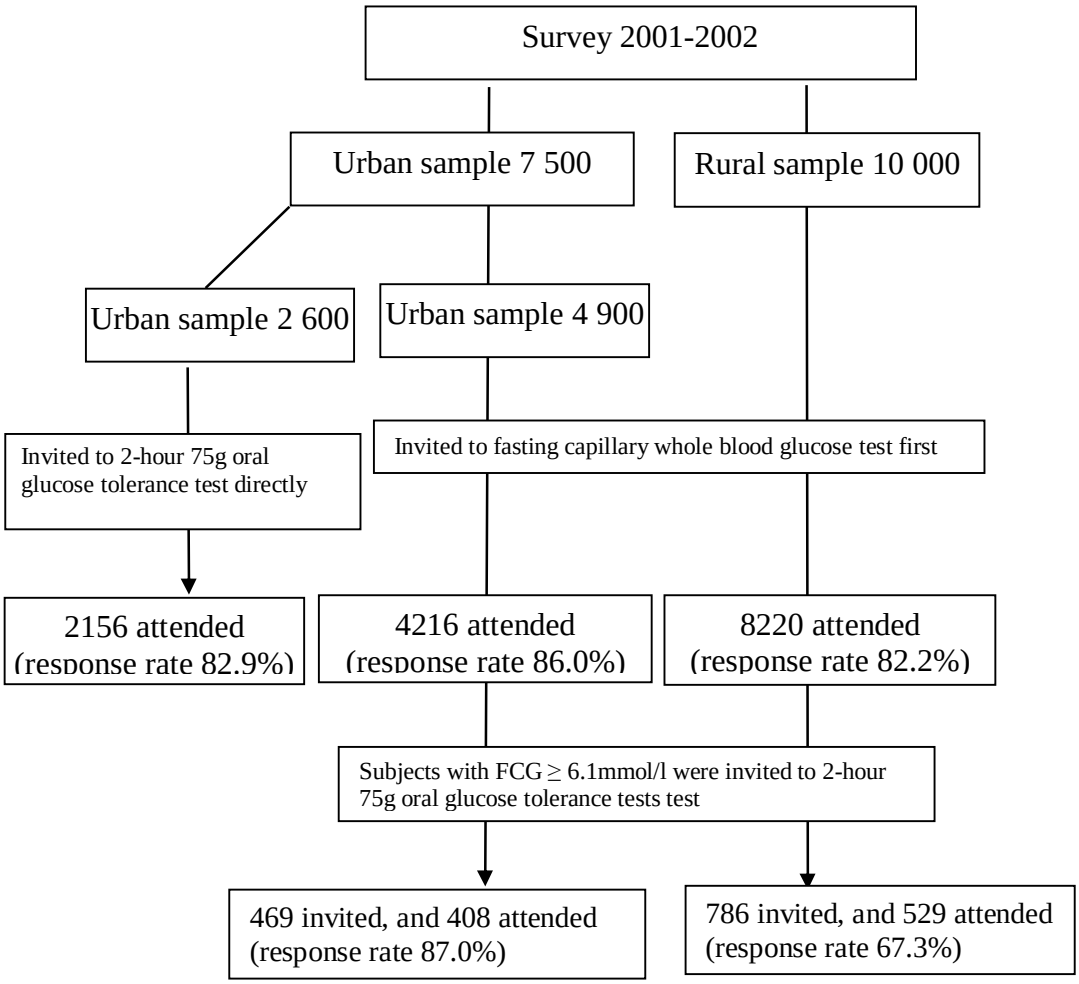

Figure 4. The sampling procedures, participating rates and screening strategies in the Qingdao diabetes survey 2001-2002

4.1.2 Qingdao Diabetes Survey 2006

The Qingdao Diabetes survey 2006 was aimed to investigate the baseline diabetes prevalence before the Qingdao Diabetes Prevention Program (Qd-DPP) was started to implement. The prevention project targeted at the entire population of two urban districts (Shinan and Shibei) and two rural counties (Jiaonan and Huangdao), which were randomly selected. In addition, one urban district (Sifang) and one rural county (Jimo) was selected as geographically matched control area. Therefore, the 2006 survey was conducted in the six districts mentioned above from February to May 2006. Five residential communities (or villages) from each district and 200-250 residents aged 35 - 74 years and lived in Qingdao for at least five years from each residential community (or village) were randomly selected. A total of 6 100 individuals were invited and 5 355 individuals took part in the survey, giving a response rate of 87.8%.

The two surveys were approved by Qingdao Municipal Health Bureau and local ethics committee. Verbal or written consent were obtained from all participants before the survey.

4.1.3 Mauritian Non-Communicable Disease Surveys

The subtropical island of Mauritius locates in the southwestern Indian Ocean with a population about 1.2 million. About 70% of the population are Indians, who were migrated from south Asia to the island in 19th centuries. Creoles (28%) and migrant Chinese (2%) comprise the rest 30% of the population. Since the World War II, Mauritius has experienced industrializations accompanying with a rise in living standards and in the prevalence of non-communicable disease (Dowse et al. 1990).

In 1987, 1992, and 1998, population-based surveys to inform the prevention and control of diabetes and other non-communicable disease were conducted in Mauritius. The target population for the surveys was Mauritian adults aged 25-74 years. Two-stage cluster sampling schemes based on the existing census was used to randomly select the subjects. In 1987, ten randomly selected population clusters (with probability proportional to cluster size) were selected. All residents aged 25-74 years from those clusters (about 500-600 individuals in each cluster) were invited to participate the survey. In 1992 and 1998, the same clusters were invited again to re-examinations, and three additional clusters were recruited from 1992 and onwards. The response rates of the three surveys were 86%, 89%, 87% in 1987, 1992 and 1998, respectively.

Four cohorts (1987-1992, 1987-1998, 1987-1992-1998, and 1992-1998) were identified according to the dates of baseline survey and dates of re-examinations. Participants with both known diabetes and newly diagnosed diabetes at the baseline survey were excluded from the current study and incident cases were defined as diabetes diagnosed after the baseline survey. After excluding individuals with missing data and participants over 65 years of age (small numbers of people in this age group), data for analysis were available for 1 441 men and 1 653 women aged 25-64 years.

4.2 Methods

4.2.1 Qingdao Diabetes Surveys

4.2.1.1 The demographic and anthropometric measurements

Similar survey approach was followed by the two surveys except the questionnaire used in survey 2006 contains more questions. All eligible individuals were invited to a survey

site near their residential communities. Participants were interviewed by trained doctors or nurses. Every participant was asked whether he/she had been previously diagnosed with diabetes. If the answer was 'yes', the glucose level at the diagnosis and the treatment for diabetes was checked and reviewed by a doctor. Information about the diabetes in parents, siblings and/or offspring was collected with questionnaires. The leisure time physical activity during the last 12 months was recorded as: 1) sedentary (no leisure time physical activity), 2) light (relaxing walking outside, taiji, etc.), 3) moderate (jogging, brisk walking, bowling, social dancing, etc.); and, 4) strenuous (running, gymnastics, swimming, badminton, tennis ball, table tennis, etc.). In the survey 2006, information on frequency and duration of the exercise was also asked and recorded. Participants were divided into non-smokers including never and ex-smokers, and current smokers if smoking daily regardless of the amount and type of smoking for at least half a year.

Height and weight was measured with participants wearing light clothes and without shoes. BMI was then calculated by dividing weight (Kg) by height (m) squared. Waist circumference was measured at the middle of the rib cage and iliac crest, and the hip circumference at the maximal horizontal girth between the waist and thigh. Waist-hip-ratio (WHR) was calculated by dividing the waist girth (cm) by the hip (cm). Three consecutive blood pressure readings, apart for at least 30 second, were taken from the right arm of seated subjects, and the average of the three readings was used in subsequent data analysis.

4.2.1.2 Screening strategies for undiagnosed diabetes in the 2001-2002 survey

Two screening strategies for detecting undiagnosed diabetes were applied in the 2001-2002 survey (Figure 4). From April 2001 to February 2002, two-step screening strategies using FCG test as first line screening, followed by a standard 2-hour 75g OGTTs to those with a FCG $\geq$ 6.1mmol/l, was applied in 12 436 participants who did not have a prior history of diabetes. From March to July of 2002, standard 2h 75g OGTTs were administrated directly to all participants (n = 2156) (Figure 4).

4.2.1.3 Screening test for undiagnosed diabetes in the 2006 survey

The standard 2h 75g OGTTs was administrated to all participants (n = 5355). FCG was also tested in the same morning in all participants in order to compare the data with those collected in 2001-2002 survey.

4.2.1.4 Laboratory assays

Blood samples were collected locally. All participants were instructed not to eat after 20:00 h and not to drink after 22:00 h in the night before the blood sampling. In next morning, fasting blood samples were collected from 07:00 to 09:30 h and post-load samples from 09:00 to 11:30 h. FCG were determined in the same morning immediately after the fasting blood sample was taken using Lifescan one Touch II glucose testing system in the survey 2001-2002, and, Bayer Brio Meter Kit in the survey 2006. The assays of plasma glucose and lipids of the two surveys were done in the central laboratory of Hiser Medical Centre. Plasma glucose was determined by the glucose oxidase method, and fasting plasma triglycerides, total and high density lipoprotein cholesterol (HDL-c) with enzymatic method. In the 2001-2002 survey, fasting and 2-hour serum insulin was measured in a sub-sample with radioimmunoassay (ket

purchased from North Biotechic Institute, Beijing); while in 2006 survey, serum insulin was measured with chemiluminescent immunoassay (Abbott, Axsym, USA). Homeostasis model assessment insulin resistance (HOMA IR) index was calculated as: fasting insulin (μIU/l) multiplied by fasting glucose (mmol/l), divided by 22.5. HbA_1c was determined in the participants of 2006 survey with Olympus AU640 Automatic analyzers using immunoturbilimetric assay (Tina-quant Hemoglobin A_{1c}, BM/Hitachi reagent kit, Roche, Germany).

4.2.2 Mauritian Non-Communicable Disease Surveys

The same study protocol was used for all surveys in Mauritian. All eligible residents were invited to attend a survey site after an overnight fast. Trained nurses administered a questionnaire to all participants, in which the self-reported family history of diabetes in first-degree relatives (parents, sibling and/or offspring), smoking and alcohol habits, treatment for hypertension, prior history of diabetes, years of full-time education, and monthly household income of the family were recorded. Height and weight was measured in light clothing without shoes, and body mass index (BMI) was calculated. Waist circumference was measured as the minimum circumference between iliac crest and the lowest rib.

All subjects had fasting blood samples taken, and plasma total cholesterol, triglyceride, and high density lipoprotein cholesterol (HDL-c) were measured by enzymatic methods. Standardized 75-g OGTTs was administered to all participants not taking diabetes medication. Fasting and 2-hour post-challenge plasma glucose was determined on-site in 1987 and 1992 using YSI glucose analyzers (Yellow Springs Instruments, OH, USA)

within 3 hours of collection with quality controls measured several months later in Newcastle upon Tyne, UK, at the reference laboratory. In 1998, plasma sample was frozen immediately and glucose was measured within 4 months in Newcastle upon Tyne, UK. The 1998 glucose values were adjusted to account for delay in analysis of blood samples using an equation (adjusted glucose = 0.0288 + 1.037 × measured glucose) based on the difference between on-site values and quality controls from the 1987 and 1992 surveys (Soderberg et al. 2004).

Data pertaining to occupational and leisure physical activities over the past year were collected by interview-administered questionnaire. Using a prepared guideline, occupational and leisure physical activity level was categorized into four patterns: sedentary (1), light (2), moderate (3), and heavy (4) (Dowse et al. 1991). Occupational activity was graded as 'sedentary' for office workers and 'heavy' for building laborers, while leisure activity varied from 'sedentary' for those house-bound with no regular outside activity to 'heavy' for individuals who undertook vigorous sports (e.g. tennis, volleyball, jogging, etc.) for 30 min or more on at least 3 days per week. Since there were few participants with 'heavy' physical activity, their data were pooled with those reporting 'moderate' physical activity in the current study.

4.3 Diagnosis of diabetes and pre-diabetes

Previously diagnosed diabetes was made if a prior history of diabetes was reported and confirmed by a doctor according to previous fasting plasma glucose (FPG) level of ≥ 7.0 mmol/l and/or information on treatment regardless of the FPG level.

Those without a prior history of diabetes were classified according to the 2006 WHO /IDF criteria for diabetes (WHO/IDF Consultation 2006). Undiagnosed diabetes was defined by a FPG level of ≥ 7.0 mmol/l and/or 2h PG of ≥ 11.1mmol/l. Individuals who had a FPG of 6.1-6.9mmol/l and/or 2hPG of 7.8-11.0 mmol/l were defined as impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT). Both IFG and IGT were considered as pre-diabetes in the current study.

4.4 Statistical analyses

4.4.1 The calculation of prevalence in Qingdao Diabetes Surveys

The prevalence of previously diagnosed diabetes was calculated by dividing the number of subjects with confirmed history of diabetes by the total number of participants returning valid questionnaire. The prevalence of undiagnosed diabetes was calculated in two different ways among individuals without a prior history of diabetes. Because only subjects with FCG ≥ 6.1 mmol/l were invited to have OGTTs from April 2001 to February 2002, the prevalence of undiagnosed diabetes was calculated according to the equation: (total number invited to the OGTTs × prevalence [%] of diabetes in the participants attending in the OGTTs) / number of the entire study population without diagnosed diabetes. Among the participants who participated the survey from March to July in 2002 and from February to May in 2006, the prevalence of undiagnosed diabetes was calculated as number of diabetes detected by the OGTTs divided by the total number of participants attending in the OGTTs. According to the 2000 census in Qingdao the age- and sex-standardized prevalence was calculated for population aged 35 to 74 years. The Chi-square test was used to test the difference in prevalence among age groups, sexes and areas.

4.4.2 The development and validation of the diabetes risk score in Chinese

The risk score was derived based on the data of the Qingdao diabetes survey 2001-2002. Candidate risk factors including age, family history of diabetes, smoking status, physical activity, BMI, waist circumference, and systolic blood pressure were fitted into a Logistic regression model one by one. Those came out to be statistically significant ($p<0.05$) in the univariate analysis were further fitted into the final multivariate Logistic regression model using backward stepwise LR method. The Hosmer-Lemeshow test was used to examine how well the predicted prevalence matches the observed prevalence. A large p-value indicates a good match. The net reclassification improvement (NRI) was also calculated according to Pencina MJ et al to quantify the improvement in the right reclassification of models (Pencina et al. 2008). According to the estimated probability of having diabetes, individuals were classified into categories of ≤ 10.9%, 11.0-15.2%, 15.3-19.7% and ≥ 19.8% in men and of ≤ 7.5%, 7.6-11.9%, 12.0-17.7% and ≥ 17.8% in women. These categories were used in NRI analysis. The log-likelihood ratio test was performed to check whether adding a variable to a model will improve the model prediction. Beta coefficients derived from the final multivariate Logistic regression model was used to calculate the diabetes risk score.

The validation of the risk score derived based on the data of the survey 2002 was examined in the population of the 2006 survey. Receiver operating characteristic curve (ROC) was plotted for the score against the presence of the undiagnosed diabetes. The optimal cut-off point was identified as the co-ordinate closest to the y intercept (0, 1) of

the ROC curve, and it is at this point that the sum of the sensitivity and the specificity is maximum. C-statistics was used to compare AUC.

4.4.3 The development and validation of the diabetes risk predicting models in Mauritian Indians

Since the diabetic status was only assessed in each of the three surveys in five-years interval approximately, the actual date of a diagnosis of diabetes was not available. Therefore, the Cox proportional hazard model for interval censored data using age as the time scale was applied to estimate the regression coefficients of the risk factors and the baseline hazards (Carstensen 1996) with assumption that diabetes were developed just prior to the follow-up survey. The R program (version 2.5.1) (http://www.r-project.org/) was used to establish the Cox regression models for interval censored data.

Data from half of the participants were randomly selected to establish the risk predicting models and the remaining data were used to assess the validation. Due to the small sample size, the data derived for certain age group in women was less reliable as indicated by a wide confidence interval. Nevertheless the risk predictors identified were similar for men and women. To increase the statistical power, data from men and women were pooled together when developing the predicting model, where sex was considered as a co-variable. However, the predicting model was assessed separately for men and for women to see whether the model derived based on the whole study population is valid when it is applied to men or to women separately.

The potential risk predictors such as BMI, waist, family history of diabetes, and FPG etc. were first tested in separate models adjusting for sex and cohort. The final full model was

fitted with risk factors which were statistically significant ($P < 0.05$) in each of the separate models. In order to get a simple prediction model based on only demographic and physical examination data, FPG, systolic blood pressure and triglycerides, which require blood sampling and clinical measure were excluded from the simple model. The probabilities of diabetes (given the age at entry) were calculated with regression coefficient and baseline hazard derived from the simple model and plotted in the risk chart. Akaike's information criterion (AIC) values, a measure of goodness-of-fit of the regression models, were calculated for each of the models (Clayton et al. 1993)]. The lower ACI value indicates a better fit to the data.

To evaluate the discriminatory ability of the models in the prediction of developing diabetes, receiver operating characteristic curves (ROC) were plotted using estimates of the simple model and the simple model plus FPG; C-statistics were used to compare the areas under the receiver operating characteristic curves (AUC) using STATA 8.2 (Stata Corporation, College Station, Texas, USA).

5 RESULTS

5.1 Baseline characteristics of the participants of the Qingdao diabetes surveys

The population mean of BMI, waist and hip circumference, blood pressure, glucose, lipids and the proportion of individuals who were current smoker, had a positive family history of diabetes and different levels of physical activity was calculated in the participants aged 35 – 74 years old and presented in Table 5. In both surveys, the urban participant reported more often a positive family history of diabetes than the rural individuals did. In the survey 2001-2002, participants in the urban areas were more obese, and practised less vigorous physical activity than those in the rural areas. In the survey 2006, the urban men tended to be more obese than the rural men, but the urban women were slender than the rural women. And, rural residents were more sedentary than urban individuals. The prevalence of current smoker was higher in rural participants than in urban in both surveys.

Compared with the participants in the survey 2001-2002, the subjects of the survey 2006 had a higher level of blood pressure, blood glucose, and a lower physical activity levels (Table 5). BMI, waist and hip circumference were larger in 2006 survey than in 2001 in the rural participants, whereas this was not observed in the urban. The prevalence of current smoker was significantly higher in male subjects of the survey 2006 than in those of the survey 2001-2002.

Table 5. Baseline characteristics of the participants (aged 35-74 years) who had no a prior history of diabetes

	Survey 2001-2002		Survey 2006		P value between surveys in urban	P value between surveys in rural
	Urban	Rural	Urban	Rural		
Men						
No of subjects	2048	2331	707	1007	-	-
Age, years	53.8(53.3-54.2) †	50.5(50.0-50.9)	51.2(50.4-51.9)	50.1(49.4-50.7)	< 0.001	0.32
Body mass index, kg/m^2	25.9(25.7-26.0) †	23.9(23.8-24.1)	25.8(25.6-26.1)	25.6(25.4-25.8)	0.70	< 0.001
Waist, cm	89.3(88.9-89.7) †	84.4(84.0-84.8)	88.9(88.2-89.6) ‡	86.8(86.2-87.4)	0.36	0.02
Hip, cm	99.4(99.1-99.7) †	96.8(96.4-97.1)	100.1(99.6-100.6) ‡	98.0(97.5-98.4)	0.01	< 0.001
Systolic blood pressure, mmHg	129(128.4-130.0)	128(127.5-129.1)	134(132.9-135.7)	136(134.7-137.1)	< 0.001	< 0.001
Diastolic blood pressure, mmHg	84(83.3-84.4) †	82(81.7-82.7)	88(86.9-88.6)	87(86.5-88.1)	< 0.001	< 0.001
Fasting capillary glucose, mmol/l	5.32(5.27-5.37) †	5.12(5.08-5.16)	5.68(5.60-5.75) ‡	6.06(5.99-6.13)	< 0.001	< 0.001
Fasting plasma glucose, mmol/l	5.47(5.39-5.56) *	-	6.14(6.04-6.25) ‡	5.24(5.16-5.31)	< 0.001	< 0.001
2-hour post-load glucose, mmol/l	5.90(5.71-6.09) *	-	7.07(6.83-7.31) ‡	6.38(6.23-6.53)	< 0.001	< 0.001
Physical activity (%)					< 0.001	< 0.001
Sedentary	23.6	23.7	51.6†	77.1	-	-
Light	58.3	52.6	34.9	17.1	-	-
Moderate or intensive	18.0†	23.7	13.6†	5.9	-	-
Family history of diabetes, (yes, %)	14.5†	3.7	19.5	11.4	< 0.001	< 0.001
Current smoker (%)	40.6†	47.6	47.1	58.3	< 0.001	< 0.001
Women						
No of subjects	2874	3601	1259	1443		
Age, years	53.2(52.9-53.6) †	50.4(50.1-50.7)	50.3(49.8-50.9) ‡	48.9(48.3-49.4)	< 0.001	< 0.001
Body mass index, kg/m^2	25.8(25.7-26.0) †	24.7(24.6-24.8)	25.6(25.4-25.7) ‡	26.3(26.1-26.4)	0.03	< 0.001

Waist, cm	83.7(83.4-84.1) †	82.7(82.3-83.0)	81.6(81.1-82.0) ‡	83.6(83.1-84.1)	< 0.001	0.003
Hip, cm	99.2(98.9-99.5) †	97.3(97.1-97.6)	99.5(99.1-99.9)	99.1(98.7-99.5)	0.32	< 0.001
Systolic blood pressure, mmHg	128(127.3-128.7)	128(127.3-128.7)	131(129.7-131.8) ‡	136(135.5-137.7)	< 0.001	< 0.001
Diastolic blood pressure, mmHg	82(81.5-82.3) †	80(79.5-80.3)	84(83.4-84.7)	85(84.5-85.8)	< 0.001	< 0.001
Fasting capillary glucose, mmol/l	5.37(5.32-5.42)	5.33(5.29-5.36)	5.61(5.55-5.67) ‡	6.21(6.14-6.28)	< 0.001	< 0.001
Fasting plasma glucose, mmol/l	5.47(5.42-5.53) *	-	5.85(5.79-5.91) ‡	5.30(5.24-5.37)	< 0.001	-
2-hour post-load glucose, mmol/l	6.05(5.93-6.18) *	-	7.13(6.99-7.28)	6.86(6.73-7.00)	< 0.001	-
Physical activity (%)					< 0.001	< 0.001
Sedentary	20.5	24.6	53.8‡	77.8	-	-
Light	63.7	53.5	35.2	17.6	-	-
Moderate or intensive	15.8†	21.9	11.0‡	4.6	-	-
Family history of diabetes, (yes, %)	15.8†	3.3	25.5‡	11.6	< 0.001	< 0.001
Current smoker (%)	1.8	2.2	1.6	2.8	0.70	0.25

Data are mean (95% CI) or percentage.

*Data for 661 urban men and 1130 urban women attending oral glucose tolerance tests directly in the 2001-2002 survey.

$p < 0.005$, † for the difference between the subjects of the urban areas and of the rural in the survey 2001-2002; ‡ for the difference between the subjects of the urban areas and of the rural in the survey 2006

5.2 Prevalence of diabetes and pre-diabetes in Qingdao city

5.2.1 Prevalence in the survey 2001-2002 (Paper I and II)

With the two-step screening approach, the age-standardized prevalence of diabetes was 6.0% (4.0% for undiagnosed and 2.0% for previously known diabetes) in the adults aged 20 to 74 years. The prevalence of diabetes, both previously undiagnosed and known, increased with aging (Figure 5). It reached 10% in subjects older than 50, and about 89% of the cases were 40 to 74 years old. The mean age of those with previously undiagnosed diabetes was 54.6±10.8 (rural 53.8±11.2, urban 55.6±10.2).

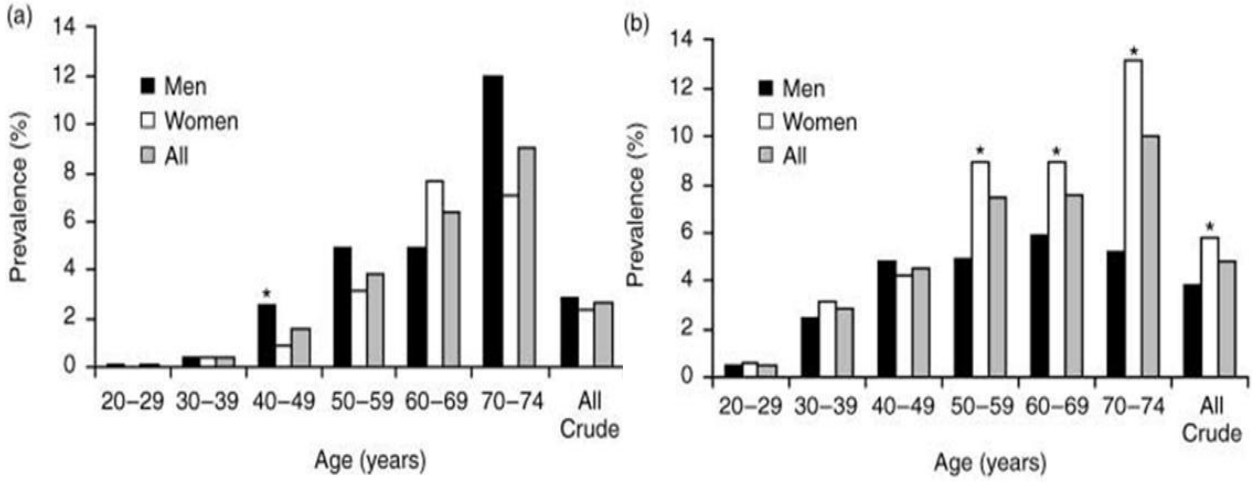

Figure 5. Prevalence of diagnosed (a) and previously undiagnosed diabetes (b) in men and women in Qingdao city, China. P<0.05, * for difference between the men and women in the same age stratum.

Men tended to have a higher prevalence of known diabetes than women, whereas, prevalence of previously undiagnosed diabetes was higher in women than in men, particularly in elder population (50-74 years old). The prevalence of diabetes was higher in urban men than in rural men (9.2% vs 5.1%, X^2=14.4 and 20.0, df=1, p<0.05). The proportion of previously undiagnosed

cases among all diabetic subjects was higher in the rural than in the urban residents (70.4% vs 58.0%, X^2=15.4, df = 1, p<0.05).

The age-standardized prevalence of diabetes and pre-diabetes in 2156 urban participants, who underwent OGTTs directly, was 8.9% (6.5% for undiagnosed and 2.4% for previously known diabetes) and 13.8%, respectively. The prevalence of diabetes and pre-diabetes increased with aging and above 10% in participants older than 40 years. There's no significant difference in the prevalence of diabetes (10.8% VS 7.8%, X^2 = 3.38, df=1, p = 0.07) and pre-diabetes (16.1% VS 12.4%, X^2 = 0.08, df=1, p = 0.78) between men and women.

5.2.2 Prevalence in the survey 2006 (paper III)

The age-standardized prevalence of diabetes and pre-diabetes was 16.0% (10% for undiagnosed diabetes and 6.0% for diagnosed diabetes) and 23.9% in the population aged 35 to 74 years, respectively. Similar as in the 2001-2002 survey, the prevalence of diabetes and pre-diabetes raised with aging; and higher in the urban participants than in the rural (Table 6). The prevalence did not differ between men and women, and the proportion of undiagnosed diabetes was similar in rural and in urban areas (60.8% vs 64.4%, df =1, X^2=0.96, P=0.33).

5.2.3 Increasing secular trends in prevalence of diabetes (Paper III)

Applying the same diagnostic approach and in the same age range (35-74 years), the age- and sex-specific prevalence of diabetes increased remarkably in the population of survey 2006 than in the survey 2001-2002 (Table 6 and Table 7). According to the results of the direct OGTTs test, the age-standardized prevalence was 12.2% in the urban population (aged 35-74 years) in survey 2001-2002, whereas they were18.8% in the urban (X^2 = 32.2, df = 1, p < 0.001) and 14.1% (X^2 = 9.1, df =1, P = 0.003) in the rural populations in 2006, a significant increase from 2002 to 2006.

The prevalence of pre-diabetes was also higher in both men and women in the survey 2006 than in 2001-2002 in each age band (Table 6). The age-standardized prevalence of pre-diabetes in the urban population was almost doubled from 2002 to 2006 (28.7% in 2006 vs 15.4% in 2002, X^2=96.6, df = 1, P < 0.001).

Table 6. The age- and sex-specific prevalence of pre-diabetes, undiagnosed, and previously diagnosed diabetes based on one-step standard 2-h 75g oral glucose tolerance test results in participants aged 35-74 years

	Survey 2001-2002				Survey 2006			
	No of subjects	Prevalence (%)			No of subjects	Prevalence (%)		
		Pre-diabetes	Undiagnosed diabetes	Diagnosed diabetes		Pre-diabetes	Undiagnosed diabetes	Diagnosed diabetes
Urban Men								
35-44	112	11.6	6.3	3.3	222	32.0	11.3	1.4
45-44	204	12.7	11.3	4.3	232	33.3	13.7	5.7
55-64	226	20.8	11.9	6.4	158	27.6	12.8	11.6
65-74	159	23.3	12.6	7.5	95	27.2	21.4	19.8
Age-standardized	-	15.1	9.6	4.7	-	31.0	13.6	6.8
Urban Women								
35-44	197	9.1	5.1	0.5	400	24.1	6.2	0.8
45-44	403	16.4	6.7	3.3	487	26.3	9.5	3.5
55-64	379	21.9	12.7	6.5	248	36.6	17.1	12.7
65-74	206	24.3	11.2	6.0	124	28.7	18.9	20.4
Age-standardized	-	15.6	7.7	3.1	-	27.5	10.8	6.4
Rural Men*								
35-44	-	-	-	-	363	16.8	6.1	2.8
45-44	-	-	-	-	317	15.4	11.9	6.5
55-64	-	-	-	-	214	24.5	11.3	4.8
65-74	-	-	-	-	113	24.6	11.5	8.0
Age-standardized	-	-	-	-	-	18.7	9.5	4.9
Rural Women*								

35-44	-	-	-	-	569	17.7	2.2	1.6
45-44	-	-	-	-	490	21.6	9.8	5.1
55-64	-	-	-	-	269	28.0	12.6	10.4
65-74	-	-	-	-	115	21.5	16.3	15.3
Age-standardized	-	-	-	-	-	21.1	8.2	6.1

* There were no direct OGTTs administrated to the rural subjects in the survey 2001-2002, and they could not be classified.

Table 7. The age- and sex-specific prevalence of undiagnosed and previously diagnosed diabetes based on two-step screening approach* in participants aged 35-74 years

	Survey 2001-2002			Survey 2006		
	No of subjects	Prevalence (%)		No of subjects	Prevalence (%)	
		Undiagnosed diabetes	Diagnosed diabetes		Undiagnosed diabetes	Diagnosed diabetes
Urban Men						
35-44	334	5.4	1.8	222	7.6	1.9
45-44	467	7.8	3.6	232	8.6	5.6
55-64	372	6.4	6.8	158	9.8	11.6
65-74	280	6.4	12.3	95	15.8	18.7
Age-standardized	-	6.4	4.6	-	9.3	6.9
Urban Women						
35-44	417	2.5	0.7	400	4.0	1.0
45-44	634	6.8	2.0	487	5.4	3.5
55-64	423	8.2	6.0	248	11.2	12.4
65-74	332	11.1	11.7	124	9.0	18.4
Age-standardized	-	5.9	3.6	-	6.3	6.2
Rural Men						
35-44	710	2.0	1.1	363	3.6	2.8
45-44	777	3.7	3.3	317	10.3	6.5
55-64	481	5.2	4.1	214	7.7	4.8
65-74	312	5.0	4.2	113	9.0	8.0
Age-standardized	-	3.5	2.7	-	7.0	4.9
Rural Women						

35-44	1193	3.7	0.6	569	1.7	1.6
45-44	1282	7.3	1.6	490	8.3	5.1
55-64	687	8.9	4.2	269	9.7	10.4
65-74	523	10.1	5.5	115	13.3	15.3
Age-standardized	-	6.6	2.2	-	6.7	6.1

* OGTTs administrated to those with fasting capillary plasma glucose (FCG) ≥ 6.1mmol/l, and the classification made based on the OGTTs results only.

5.3 Performance of FCG and HbA_{1c} as a screening test for diabetes in Chinese adults (paper IV and V)

FCG

There were 3948 participants (1555 males) in the survey 2006 who had both FCG and OGTTs results, but no prior history of diabetes. Based on the data of these subjects, the AUC in predicting undiagnosed diabetes was 76.9% (72.9-80.9%) in men and 76.0% (72.2-79.8%) in women for FCG (Figure 6). They were 62.4% (59.0-65.7%) in men and 63.2% (60.5-65.8%) in women in predicting pre-diabetes. The sensitivity and specificity of FCG at different cut-off point for predicting diabetes was presented in Table 10.

Validation of two-step screening strategy using FCG as first line screening test

The two-step screening approach, i.e. using FCG test as first line screening and followed by a standard 2-hour OGTTs, missed both undiagnosed diabetes and pre-diabetes who would have been detected by OGTTs. In the participants of the Qingdao survey 2006, for example, there were about 670 men (42.5%) and 849 (34.7%) women with a FCG $\geq$ 6.1mmol/l. Among them, the number of undiagnosed diabetes was 140 in men and 174 in women. However, the total number of undiagnosed diabetes in the entire study population defined by the direct OGTTs was 193 in men and 253 in women. The two-step screening approach, thus, missed about 27.5% ([193 – 140] / 193) of undiagnosed diabetes in men and 32.3% in women. The corresponding figures for pre-diabetes were 48.1% in men and 46.2% in women, respectively. When FCG of 5.5 mmol/l was set as the cut-off point for the first line screening, there were still 10.5% men and 13.1% women with undiagnosed diabetes unidentified (26.7% men and 26.2% women for pre-diabetes).

HbA_{1c}

A total of 3132 participants in the 2006 survey had both HbA_{1c} and OGTTs results. In these participants, the AUC of HbA1c in predicting undiagnosed diabetes was 68.0% (63.6-72.4%) in men and 67.5% (63.6-71.4%) in women (Figure 6). The optimal cut off point was 5.90% in men and 5.44% in women (Table 10). The HbA_{1c} values did not distinguish between people with pre-diabetes from those who were normal because the AUC was about 50% in both men and women.

Comparison between FCG and HbA_{1c}

This was done in 2332 participants in the survey 2006, who have no missing data in HbA_{1c}, FCG, FPG, 2hPG, BMI, triglyceride, and high density lipoprotein cholesterol. The AUC was lower for HbA_{1c} than for FCG for detecting undiagnosed diabetes (0.67 vs. 0.77, $P < 0.01$, in men; and 0.67 vs. 0.75, $P < 0.01$, in women) and pre-diabetes (0.47 vs. 0.64, $P < 0.001$, in men; and 0.51 vs. 0.65, $P < 0.001$, in women). For undiagnosed diabetes plus pre-diabetes the AUC for HbA_{1c} were also lower than that for FCG (0.53 vs. 0.69, $P < 0.001$, in men; and 0.55 vs. 0.68, $P < 0.001$, in women). At the optimal HbA_{1c} cut-off point of 5.6% for undiagnosed diabetes, the sensitivity was 64.4% in men and 62.3% in women, whereas they were 72.0% and 65.1% at the optimal FCG cut-off point of 6.3 mmol/l for men and 6.6 mmol/l for women.

5.4 Risk score and its performance in Chinese (Paper IV)

Development of risk score

Age, waist circumference, and diabetes in parents and/or siblings were independently associated with the presence of undiagnosed diabetes in both men and women (Table 8). Waist circumference appeared to be a strong modifiable risk factor for type 2 diabetes in this study population as shown by the log likelihood ratio test. Systolic blood pressure (SBP) was associated with the presence of undiagnosed diabetes in females only, but SBP did not improve

the model reclassification (net gain in reclassification proportion of 0.023 in men [p = 0.75] and 0.015 in women [p = 0.89] calculated using NRI) when it was added to the model with age, family history of diabetes and waist circumference. SBP was thus not included in the final model in order to make the final model similar in women as in men and easy to apply by a lay person. Hosmer-Lemeshow test showed the predicted risk of the final model matched up well with the observed risk (X^2 = 6.23, p = 0.62 in men; and X^2 = 10.36, p = 0.24 in women). Based on the beta coefficient of the final model (Table 8), the risk score was constructed and shown in the Table 9. The optimal cut-off point of the risk score for undiagnosed diabetes was 17 in men and 14 in women. Among all the participants with undiagnosed diabetes in the survey 2002, 97.5% of men and 86.8% of women had a risk score ≥ 14; and 85.0% in men and 69.5% in women had a score ≥ 17, respectively.

Validation of the risk score

The risk score derived based on the data of the survey 2002 was evaluated by applying the score to the population of the 2006 survey. The ROC curves for the risk score, the FCG and HbA1c tests were plotted in Figure 6 and the discrimination of the score was compared with other two. The score gave an AUC of 63.5% (95% CI, 59.1-67.9%) in men and 68.9% (63.6-72.4%) in women for detecting undiagnosed diabetes, which was slightly lower than that of the FCG test (p < 0.001) but not different from that of the HbA_{1c} (p > 0.20). Given the same sensitivity, the specificities of the FCG test were highest; however, there was no significant difference between the HbA1c and the risk score (Table 10).

The AUC of the risk score for pre-diabetes were 61.2% (57.9-64.5%) in men and 63.2% (60.7-65.7%) in women. At a cut-off point of ≥ 14, the sensitivity and specificity of the risk score to screen pre-diabetes were 85.6% (83.9-87.4%) and 21.1% (19.0-23.1%) in men, and 75.5% (73.8-77.2%) and 43.6% (41.6-45.6%) in women, respectively.

Comparison of the Chinese risk score with other existing ones

We applied also other previously published scores which were derived from other populations to our study population of the 2006 survey. Eight such risk scores (Baan et al. 1999; American Diabetes Association 2000; Griffin et al. 2000; Lindstrom et al. 2003; Glumer et al. 2004; Ramachandran et al. 2005; Aekplakorn et al. 2006; Balkau et al. 2008) were applicable to the data and thus, validated. The performance of these scores was poorer in Chinese population of the 2006 survey than in their original populations as shown by the lower AUCs (Table 11). None of the existing risk scores had a significantly larger AUC than the simple risk score developed in this study.

Table 8. The risk factors and the beta coefficient derived from the Logistic regression analyses based on the data of Qingdao 2001-2002 survey

	Univariate model		Final model	
	B coefficient (SE)	Odds ratio (95%CI)	B coefficient (SE)	Odds ratio (95%CI)
Men				
Age (year)	0.03(0.01)	1.03(1.01-1.05)	0.03(0.01)	1.03(1.01-1.05)
BMI (Kg/m^2)	0.06(0.03)	1.06(1.01-1.12)	-	
Waist (Chinese Chi) *	0.12(0.03)	1.12(1.05-1.20)	1.09(0.33)	2.98(1.56-5.68)
Systolic blood pressure, (mmHg)	0.01((0.00)	1.01(1.00-1.02)	-	-
Diabetes in parents or siblings	0.60(0.23)	1.82(1.16-2.84)	0.73(0.24)	2.07(1.30-3.29)
Leisure time physical activity (moderate)	-	1	-	-
Sedentary	0.16(0.32)	1.18(0.63-2.20)	-	-
Light	0.50(0.27)	1.66(0.97-2.83)	-	-
Current smoker (vs non-smoker)	-0.09(0.21)	0.91(0.60-1.38)	-	-
Women				
Age (year)	0.05(0.01)	1.05(1.03-1.06)	0.04(0.01)	1.04(1.02-1.06)
BMI, (Kg/m^2)	0.07(0.02)	1.07(1.03-1.11)	-	-
Waist, (Chinese Chi)*	0.14(0.03)	1.15(1.09-1.20)	0.86(0.28)	2.36(1.35-4.12)
Systolic blood pressure (mmHg)	0.02(0.00)	1.02(1.02-1.03)	-	-
Diabetes in parents or siblings	0.51(0.19)	1.67(1.15-2.42)	0.82(0.20)	2.27(1.53-3.38)
Leisure time physical activity (moderate)	-	1	-	-
Sedentary	-0.05(0.28)	0.95(0.55-1.65)	-	-
Light	0.10(0.21)	1.11(0.73-1.69)	-	-
Current smoker (vs non-smoker)	0.60(1.04)	1.83(0.24-14.18)	-	-

*1 Chinese Chi ≈ 33 cm.

Table 9. The risk score based on the age, sex, waist girth and diabetes in parents or siblings

Waist (Chinese Chi *)			
Men	Score	Women	Score
≤2.3	1	≤2.0	1
2.4-2.6	4	2.1-2.3	3
2.7-2.9	8	2.4-2.6	6
≥3.0	12	≥2.7	9
Age (years)	Score		
≤35	1		
36-45	3		
46-55	6		
56-65	9		
≥65	12		
Diabetes in parents and/or siblings			Score
Negative			1
Positvie			8
Score range			3-32

* 1 Chinese Chi ≈ 33 cm

Table 10. Sensitivity (%), specificity (%) and positive predictive value (%) of the risk score, as compared with fasting capillary plasma glucose (FCG) and glycated hemoglobin A_{1c} (HbA_{1c}) tests at different cut-off points, for predicting undiagnosed diabetes

	Number (%)	Sensitivity (95% CI)	Specificity (95% CI)	Positive predict value (95% CI)
Men				
Risk score ≥ 14	1266(75%)	87.0(82.2-91.7)	27.4(25.0-29.7)	14.4(12.4-16.3)
Risk score ≥ 17 *	773(46%)	64.1(57.3-70.8)	56.7(54.1-59.3)	17.2(15.5-18.9)
FCG ≥ 6.25 mmol/l *	645(35%)	71.0(64.3-77.7)	69.7(67.2-72.2)	24.7(22.4-27.1)
FCG ≥ 6.10 mmol/l	648(42%)	74.0(67.8-80.2)	62.9(60.3-65.4)	21.8(20.0-23.7)
FCG ≥ 5.60 mmol/l	963(62%)	86.5(81.6-91.3)	41.5(38.9-44.1)	17.2(16.2-18.2)
HbA_{1c} ≥ 5.90% *	399(26%)	50.0(42.6-57.4)	76.9(74.6-79.2)	23.3(20.1-26.5)
Women				
Risk score ≥ 14 *	1462(55%)	80.7(75.7-85.7)	47.5(45.4-49.6)	15.3(13.4-17.2)
Risk score ≥ 17	883(33%)	55.0(48.7-61.4)	69.0(67.0-70.9)	16.9(15.1-18.8)
FCG ≥ 6.55 mmol/l *	1003(26%)	65.9(59.5-72.3)	76.4(74.5-78.3)	24.3(22.0-26.5)
FCG ≥ 6.10 mmol/l	1009(42%)	71.8(66.1-77.6)	61.1(59.1-63.2)	17.5(16.1-18.9)
FCG ≥ 5.60 mmol/l	1489(62%)	84.5(79.9-89.1)	40.2(38.2-42.3)	14.0(13.2-14.7)
HbA_{1c} ≥ 5.44% *	1089(47%)	72.0(66.0-78.0)	55.3(53.1-57.5)	15.6(14.4-16.8)

* The optimal cut-off points.

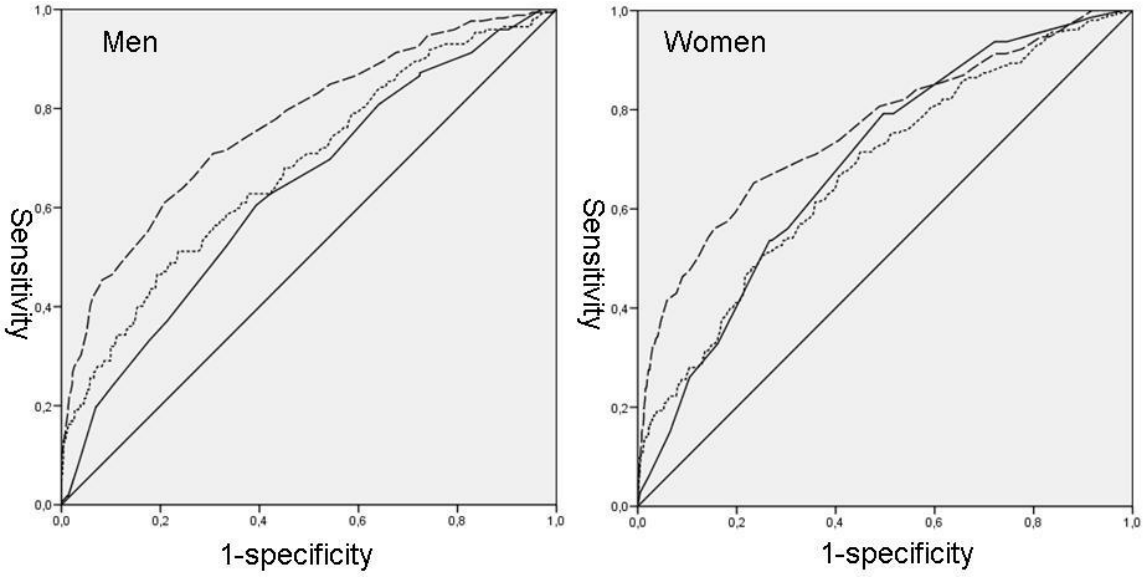

Figure 6. Receiver operating characteristic (ROC) curve of the risk score (——), fasting capillary blood glucose test (FCG,— —) and glycated hemoglobin A_{1c} (HbA_{1c}, ·····) in predicting undiagnosed diabetes in men and women.

The area under the ROC curve was 63.5% (95% CI, 59.1-67.9%) in men, and 68.9% (63.6-72.4%) in women for the questionnaire, 76.9% (72.9-80.9%) in men and 76.0% (72.2-79.8%) in women for the FCG, and 68.0% (63.6-72.4%) in men and 67.5% (63.6-71.4%) in women for the HbA_{1c}.

Table 11. Risk assessment scores (questionnaires) developed in Caucasians or other Asian populations, and their performance in the Chinese population of the Qingdao survey 2006

Risk assessment scores	Risk factors involved	Optimal cut-off point (range)	Area under the Roc curve (95% CI), %			Sensitivity (95% CI) at the optimal cut-off point, %		Specificity (95% CI) at the optimal cut-off point, %	
			In Original population	In Chinese in Qingdao	P value[†]	In original population	In Chinese in Qingdao	In original population	In Chinese in Qingdao
Cambridge risk model (Griffin SJ. et al. 2000)	Age, sex, drug-treated hypertension, corticosteroids treatment, family history of diabetes, BMI and smoking	0.199	80.0 (68-91)	67.6 (65.2-69.3)	0.91	77.3 (54.6-92.2)	42.2 (37.8-46.6)	72.0 (68.0-76.0)	79.5 (78.3-80.8)
Danish Risk score (Glumer C. et al. 2004)	Age, sex, BMI, known history of hypertension, diabetes in parents, physical activity at leisure time	29(0-60)	80.4 (76.5-83.8)	69.0 (66.6-71.3)	0.10	79.3 (71.4-86.3)	55.1 (50.6-59.5)	68.7 (67.1-70.3)	72.1 (70.7-73.6)
Indian risk score (Ramachandran A. et al. 2005)	Age, sex, family history of diabetes, BMI, waist circumference, physical activity	21(0-42)	73.2 (70.2-76.1)	67.5 (65.1-70.0)	0.91	76.6 (70.9-81.7)	96.1 (94.3-97.9)	59.9 (58.5-61.3)	18.7 (17.4-19.9)
Rotterdam study (Baan CA. et al. 1999)	Age, sex, drug-treated hypertension, BMI	6(0-22)	68.0 (64-72)	63.1 (60.5-65.8)	0.002	78.0	18.8 (15.3-22.3)	55.0	90.4 (89.5-91.3)
Finnish Risk Score (Lindström J. et al. 2003)	Age, BMI, waist, drug-treated hypertension, physical inactivity, daily consuming vegetable, fruit, or berries	9(0-20)	85.0	66.5 (63.7-69.3)	0.92	78.0 (71.0-84.0)	39.5 (34.6-44.4)	77.0 (76.0-79.0)	80.4 (79.0-81.7)
DESIR Risk Score (Balkau B. et al. 2008)	Waist circumference, smoking, hypertension, family history of diabetes	Not available (0-5)	73.3 in men, 83.9 in women	55.4 in men, 67.9 in women	< 0.001 in men, 0.13 in women	-	-	-	-
Thai Risk Score (Aekplakorn W. et al. 2006)	Age, sex, BMI, waist circumference, hypertension, family history of diabetes	6 (0-17)	74.0 (71-78)	66.2 (63.7-68.6)	0.15	77.0	86.8 (83.7-89.8)	60.0	32.6 (31.1-34.1)

ADA recommendation (ADA. 2000) *	Delivery of a baby weighing > 9 pounds, diabetes in parents or siblings, BMI, age, physical activity	10(0-27)	71.0	66.1 (63.6-68.6)	0.18	80.0	39.3 (34.9-43.7)	34.6	80.1 (78.9-81.4)
Qingdao diabetes risk score	Age, waist circumference, diabetes in parents or siblings	14(3-32)	64.2 (60.3-68.0)	67.3 (64.9-69.7)	-	88.7 (84.2-93.1)	84.2 (81.0-87.5)	27.1 (25.0-29.2)	39.8 (38.2-41.3)

* ADA. American Diabetes Association

† Compared with Qingdao diabetes risk score

5.5 Risk prediction models and its performance in Mauritian Indians (Paper VI)

Diabetes developed in 511 out of 3094 Mauritian Indians during follow-up. The baseline characteristics of participants by sex and diabetes status at the end of follow-up were shown in Table 12. From the whole 3094 participants, 1544 were randomly selected to establish the Cox regression model; and, the remaining 1550 were used to validate the models. There were no statistically significant differences in the mean age, BMI, waist, blood pressure, blood glucose level, lipids, and, in the proportion of sex, physical activity, education levels, and family history of diabetes (FH) between the two groups. The incidence of diabetes was 17.2% in the group used to establish the models and 15.8% ($X^2 = 1.13$, df = 1, P = 0.29) in those used to validate the models.

Development of risk predicting models

Among the risk factors tested, obesity (BMI and waist circumference), blood pressure, plasma glucose, triglyceride, and family history of diabetes came out to be significant predicators of diabetes and were, thus, included in the full model (Table 13). A simple model fitted with BMI, waist circumference and FH, and the simple model plus the FPG were also constructed. The Akaike's information criterion value of the full model, simple model and simple model plus the FPG were 1284, 1363, and 1287, respectively. A risk chart was constructed with the estimated risk probabilities derived from a simple model fitted with FH and obesity (Figure 7).

Table 12. The baseline characteristic of the participants who were free of diabetes at baseline stratified by diabetes status at the end of the follow-up

	Indian Men			Indian Women		
	Non diabetes	Diabetes	P value	Non diabetes	Diabetes	P value
No of cases	1182	259	-	1401	252	-
Age (year)	39(38.1-39.3)	43(41.5-44.1)	< 0.001	39(37.8-39.9)	43(41.6-44.2)	< 0.001
BMI (kg/m^2)	22.7(22.5-22.9)	24.9(24.5-25.4)	< 0.001	23.7(23.5-24.0)	26.5(25.9-27.0)	< 0.001
Waist (cm)	79.0(78.5-79.5)	84.6(82.5-85.6)	< 0.001	74.8(74.3-75.4)	80.8(79.5-82.0)	< 0.001
Systolic blood pressure (mmHg)	122(120.7-122.5)	128(125.7-129.5)	< 0.001	118(117.2-118.7)	123(121.4-125.1)	< 0.001
Diastolic blood pressure (mmHg)	76(75.4-76.7)	80(79.0-81.8)	< 0.001	73(72.0-73.1)	75(73.9-76.5)	< 0.001
Total cholesterol (mmol/l)	5.30(5.22-5.37)	5.49(5.32-5.65)	0.04	5.00(4.94-5.06)	5.05(4.89-5.20)	0.59
HDL cholesterol (mmol/l)	1.26(1.24-1.28)	1.18(1.14-1.22)	0.001	1.34(1.33-1.36)	1.26(1.22-1.30)	< 0.001
Triglyceride (mmol/l)	1.58(1.51-1.65)	2.20(2.06-2.35)	0.001	1.11(1.07-1.14)	1.37(1.29-1.45)	< 0.001
Fasting glucose (mmol/l)	5.19(5.17-5.22)	5.62(5.56-5.68)	< 0.001	5.07(5.04-5.09)	5.48(5.42-5.54)	< 0.001
2-h postchallenged glucose (mmol/l)	5.74(5.65-5.82)	7.08(6.89-7.26)	< 0.001	6.38(6.31-6.46)	7.77(7.60-7.93)	< 0.001
Current smoker (%)	52.9	53.3	0.97	0.8	0.8	0.80
Alcohol consumption (%)	67.4	76.1	0.03	33.3	35.7	0.62
Leisure time physical activity (%)			0.001			0.04
Sedentary	25.0	36.7	-	67.1	70.6	-
Light	57.0	52.1	-	32.3	27.8	-
Moderate or heavy	15.8	9.7	-	0.6	1.2	-
Occupational physical activity (%)			0.10			0.91
Sedentary	17.8	13.5	-	4.1	3.6	-
Light	29.3	26.6	-	75.7	76.2	-
Moderate or heavy	22.4	22.0	-	8.6	9.5	-
Education (years, %)			<0.001			0.001

0	8.5	8.1	-	27.5	30.3	-
1-6	43.0	56.4	-	47.5	55.8	-
≥ 7	48.5	35.5	-	25.1	13.9	-
Income (Mauritian Rupee, %)			0.17			0.01
< 2500	30.1	31.4	-	45.6	54.4	-
2600-5000	50.3	51.2	-	40.7	34.9	-
> 5000	19.5	17.4	-	12.7	9.1	-
Current occupation (%)			0.88			0.02
Professions *	19.9	16.6	-	5.9	2.8	-
Workers	71.1	73.7	-	29.4	25.8	-
Not work outside †	9.1	9.7	-	64.7	71.4	-
Positive Family history of diabetes (%)	24.9	21.6	0.27	22.3	32.5	< 0.001
Drug treated hypertension (yes, %)	2.7	5.0	0.15	3.9	8.3	0.002

Data were mean (95%CI) or %.

* Professions: business managers, technicians, clericals, etc.

† Not work outside: unemployed, retired, or housewife, etc.

Table 13. Regression coefficients and hazard ratio for predicting the development of diabetes in Mauritian Indians

	Full model *		Simple model		Simple model with FPG	
	β coefficient (SE)	Hazard ratio (95% CI)	β coefficient (SE)	Hazard ratio (95% CI)	β coefficient (SE)	Hazard ratio (95% CI)
Age (years)						
20-29	0.0028(0.0010)	-	0.0031(0.0011)	-	0.0032(0.0011)	-
30-44	0.0038(0.0004)	-	0.0044(0.0005)	-	0.0042(0.0042)	-
45-54	0.0054(0.0006)	-	0.0079(0.0008)	-	0.0062(0.0007)	-
55-65	0.0042(0.0007)	-	0.0068(0.0010)	-	0.0051(0.0008)	-
Sex, men	-0.0213(0.1660)	0.98(0.71-1.35)	0.4331(0.1199)	1.48(1.14-1.93)	0.2637(0.1247)	1.30(1.02-1.66)
Body mass index (Kg/m^2)						
< 23	-	1.00	-	1.00	-	1.00
23-24.99	0.3720(0.2424)	1.45(0.90-2.33)	0.5059(0.2349)	1.63(1.02-2.59)	0.4377(0.2414)	1.55(0.96-2.49)
≥ 25	0.6412(0.2487)	1.90(1.17-3.09)	0.7943(0.2419)	2.12(1.31-3.43)	0.7517(0.2464)	2.12(1.31-3.43)
Waist circumference (cm)						
<80 in men, or < 70 in women	-	1.00	-	1.00	-	1.00
80-89 in men, or 70-79 in women	0.7550(0.2411)	2.12(1.33-3.41)	0.8681(0.2211)	2.57(1.65-4.01)	0.8463(0.2271)	2.33(1.49-3.63)
≥ 90 in men, or ≥ 80 in women	0.9390(0.2904)	2.56(1.45-4.51)	1.0870(0.2684)	3.33(1.95-5.70)	1.0276(0.2742)	2.79(1.63-4.78)
Family history of diabetes (yes vs no)	0.3249(0.1410)	1.38(1.05-1.82)	0.3284(0.1351)	1.40(1.07-1.83)	0.2652(0.1370)	1.30(1.00-1.70)
Fasting glucose (mmol/l)						
< 5.60	-	1.00	Not included	Not included	-	1.00
5.60-6.09	0.7233(0.1580)	2.06(1.51-2.81)	Not included	Not included	0.7592(0.1553)	2.14(1.58-2.89)

≥ 6.10	1.5529(0.1760)	4.72(3.34-6.67)	Not included	Not included	1.6431(0.1706)	5.17(3.70-7.22)
Triglyceride ≥ 1.7 mmol/l	0.3607(0.1461)	1.43(1.08-1.91)	Not included	Not included	Not included	Not available
Systolic blood pressure, ≥ 130 mmHg	0.2703(0.1410)	1.31(1.00-1.73)	Not included	Not included	Not included	Not available

Including all variables with a P value of < 0.05 in the full model.

Validation of the risk predicting model

When applying the simple model to the rest of the population in reserved for validation purpose, the AUC for the estimated risk probabilities to predict the onset of diabetes was 0.62 (95% CI, 0.56-0.68) in men and 0.64 (0.59-0.69) in women (Figure 8). Using a cut-off point of 0.12, the sensitivity and specificity of the risk probabilities was 0.72 (0.71-0.74) and 0.47 (0.45-0.49) in men and 0.77 (0.75-0.78) and 0.50 (0.48-0.52) in women, respectively. With increasing the estimated risk probability from ≤ 0.07, 0.08-0.13, 0.13-0.25 to ≥ 0.26, the incident of diabetes rose from 13.5% (8.2-18.9%), 10.7% (6.5%-15.0%), 17.5% (11.5-23.5%), to 28.3% (22.0%-34.6%) in men and from 6.0% (3.0-9.1%), 10.4% (6.0-14.8%), 20.0% (14.9-25.1%), to 21.1% (15.3-26.8%) in women, respectively. In addition, among those with a risk probability of ≥ 0.12, 25.6% of the men and 30.6% of the women who had normal FPG and normal 2hPG at baseline survey developed IFG/IGT by the end of follow-up; while in individuals with a score of < 0.12, the incidence of IFG/IGT was 18.9% in men [$X^2 = 3.43$, df = 1, P = 0.06] and 15.5% in women [$X^2 = 19.4$, df = 1, $P < 0.05$]).

Adding FPG to the simple model improved the prediction of the model. The area under the ROC curve increased from 0.62 (0.56-0.68) to 0.70 (0.64-0.75) in men and from 0.64(0.59-0.69) to 0.71 (0.66-0.76) in women (c-statistic, $p < 0.001$) (Figure 8). Further addition of systolic blood pressure and triglyceride to the model, i.e. the full model, improved the risk prediction slightly over the model with FPG in men (with AUC of 0.71 [0.66-0.77], P = 0.003), but not in women (0.71 [0.66-0.76], P = 0.21).

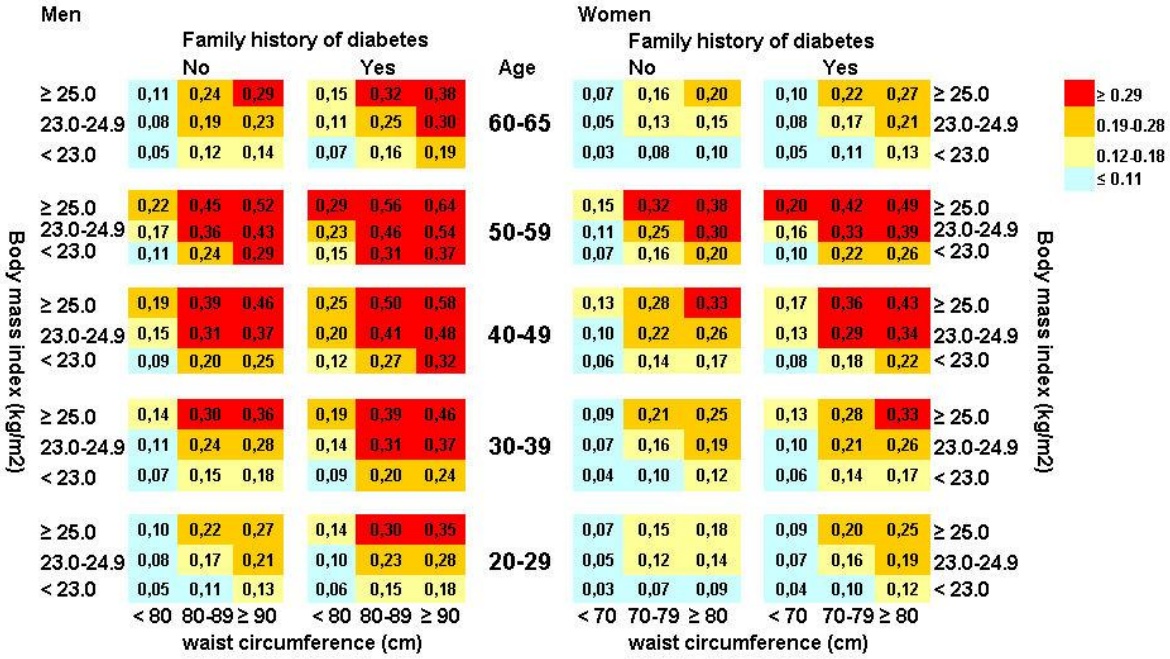

Figure 7. Absolute risk probabilities of developing diabetes estimated with regression coefficients, derived from the simple model fitted with body mass index, waist circumference and family history of diabetes

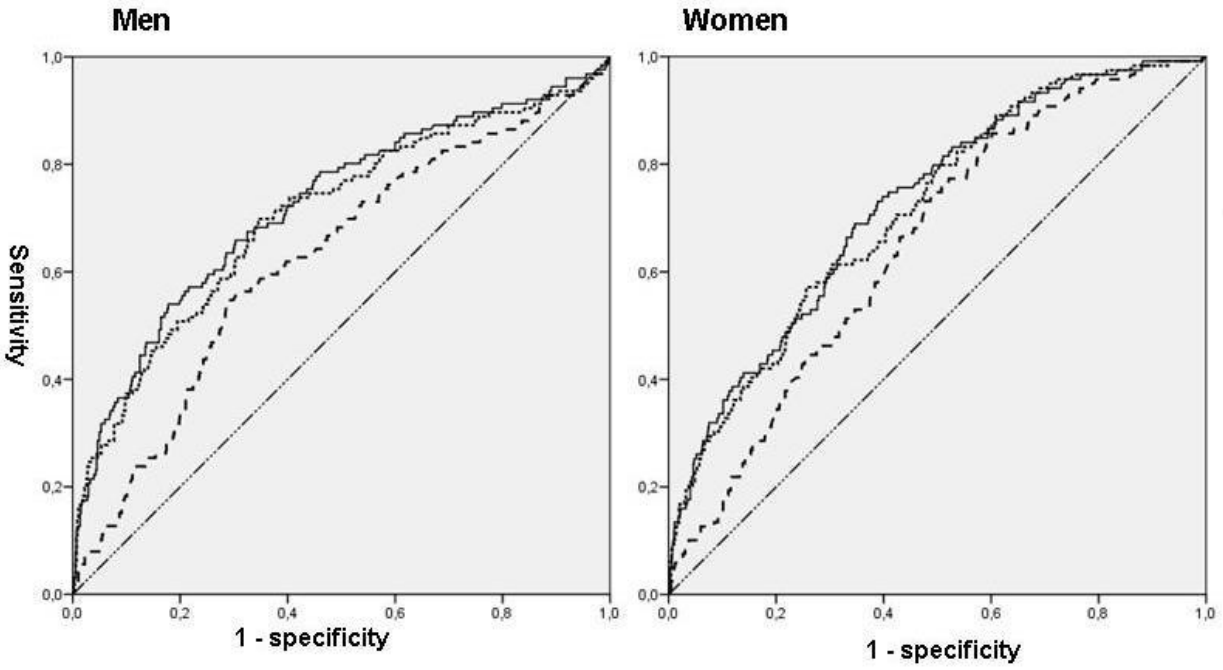

Figure 8. Receiver operating characteristic (ROC) curve for men and women showing predicted probabilities of developing diabetes derived from 1) Simple model (— —): fitted with BMI, waist girth, and family history of diabetes, adjusting for cohorts; 2) Simple model + FPG (·····); 3) Full model (——): Simple model + FPG + systolic blood press and triglyceride.

6 DISCUSSIONS

6.1 Diabetes increases in China

The results of current studies showed that the prevalence of diabetes in Qingdao City had a remarkable increment in only five years, and reached up to 16% in the adults aged 35-74 years. This is in line with the findings from other studies (Table 2, **4** and Figure 2) and indicates an urgent need to prevent the further increase.

The Qingdao city has undergone a fast social-economic development in the past several years (http://www.stats-qd.gov.cn, accessed July 7, 2008). Due to the mechanized farming less labour works and less farmers are required; an increasing number of farmers have worked in factories in cities. The number of families having cars increased fast in the last 5 years, the sidewalks inside the communities are full of parked cars. This has reduced spaces for outdoor activities in the urban areas, and reduced the number of people who were used to walk alone the sidewalks after the dinner. In addition, entertainments inside the room such as TV, internet, computer games, mahjong, etc. have become popular, people enjoyed to spend spare time on these indoor games in both rural and urban areas. As a consequence of the changes in lifestyle, obesity was prevalent in both urban and rural areas, this plus physical inactivity have to certain extent contributed to the increased prevalence of diabetes. It is noticeable that rural citizens caught up their urban counterparts with both obesity and diabetes. It can be speculated that diabetes will continue to increase in Qingdao with long-term exposure to obesity and physical inactivity if there is no lifestyle interventions.

The knowledge about the diabetes, such as risk factors, treatment, and prevention, etc. was not well-known by the residents of Qingdao city. This can be partly reflected by the high proportion

of newly diagnosed diabetes in both surveys and decreased proportion of individuals doing moderate physical activity. In a response to a multi-choice question on diabetes awareness, half of the participants in the 2006 survey did not know whether obesity or physical inactivity contribute to the development of diabetes; a large proportion of individuals didn't do any leisure time physical exercise. This is alarming and calls for an immediate action to promote healthy lifestyle, in parallel with the economic development.

6.2 HbA_{1c} and FCG as screening test for undiagnosed diabetes

FCG might be a good screening test for undiagnosed diabetes, which had an AUC above 76% and a sensitivity and specificity above 70% at the optimal cut-off point (Bortheiry et al. 1994; Husseini et al. 2000). The FCG test is also available in the most of hospitals and community clinics and not very expensive. With the portable glucose measurement system, FCG test even can be performed at home. Therefore, FCG might be an appropriate screening test in a screening program performed in the hospital or by the healthcare professionals in their routine clinical practice. It is noticeable that the two-step screening strategy with FCG as first line screening test misses cases with undiagnosed diabetes and pre-diabetes. Even if the cut-off point for a positive screening test was set at FCG $\geq$ 5.5 mmol/l, there were still 10% or more patients with diabetes and 26% individuals with pre-diabetes unidentified. This should be taken into account when an optimal cut-off point for a positive screening test was selected.

In previous studies, the sensitivity for detecting diabetes varied from 63.2% to 86.0% and the specificity ranged from 82.8% to 97.4% at a given optimal HbA_{1c} cut-off point (Rohlfing et al. 2000; Colagiuri et al. 2004; Buell et al. 2007), which is higher than the results in the current study. In a study among Hong Kong Chinese who were referred to a hospital for confirmative

testing for glucose intolerance, an optimal HbA_{1c} cut-off point of 6.1% for detecting 2-hPG ≥ 11.1mmol/l was reported, which gave a sensitivity of 77.5% and a specificity of 78.8% (Ko et al. 1998). This study was, however, carried out among a pre-selected high-risk population for which close to one fourth of its participants were diagnosed as having diabetes. Moreover, the diagnostic criteria for diabetes in the Hong Kong study were also different from those used in our study. The inconsistency in performance of the HbA_{1c} test between studies may have been due to the discrepancies in ethnicity, assay methods for HbA_{1c}, the gold standard for diagnosis of diabetes, study design (population-based vs. clinical based) and the prevalence of other risk factors such as obesity. To what extent these factors affect the performance of the HbA_{1c} need to be further investigated. However, our results are consistent with other studies that showed HbA_{1c} test did not detect pre-diabetes (Saydah et al. 2002; Mannucci et al. 2003; Colagiuri et al. 2004).

As compared with glucose test, HbA_{1c} has, however, several advantages. It is an indicator of long-term glycemia. The HbA_{1c} test does not ask examinees to fast and can be tested at any time of a day, has a better reproducibility and is easier to perform than the OGTTs does (Rohlfing et al. 2002; Sacks et al. 2002). The result of the current study, however, did not appreciate the use of the HbA_{1c} as a screening test when compared with FCG. This is consistent with another study conducted in Caucasians (Herdzik et al. 2002). In that study, FCG was more effective than HbA_{1c} in discriminating the individuals with abnormal glucose tolerance from those with normal. Considering it is the most expensive test, HbA_{1c} as a screening test may not be suitable in low income regions with relatively limited resource for medical care unless the cost decreased to an affordable level in the future.

6.3 The risk assessment algorithms for diabetes

India and China are the top two countries with the largest number of patients with diabetes in the world. And, the proportion of undiagnosed diabetes has been reported to be high about 50% to 80% (Gu et al. 2003; Sadikot et al. 2004; Dong et al. 2005; Menon et al. 2006; Jia et al. 2007; Gao et al. 2008). Considering the large number of individuals with diabetes, high medical cost induced by diabetes care, the low diabetes awareness and the low economic status in China and India, it is politically and practically important to find a simple risk assessment tool to identify undiagnosed diabetes and pre-diabetes in order to provide them with early treatment or lifestyle intervention to reduce the burden of the disease.

In the current study, the simple risk score or risk predicting model established on the anthropometric measurements and family history of diabetes yielded moderate discrimination in Chinese and Mauritian Indians. They are simpler than those existing risk scores and the information required are all self-measurable by a layperson. Obesity is a strong modifiable lifestyle related risk factor for diabetes, and inclusion of BMI and/or waist circumference in the risk score can educate people to reduce weight or keep from weight increase. The omitting of the SBP and biochemical measures from the final risk predicting model did not lose much of the prediction but simplify the application of the risk assessment tools in lay populations. Thus, the current risk scores can be widely distributed to the laypersons, and be helpful in raising the public awareness and facilitating the health promotion. Compared with fasting glucose test, the performance of the simple risk score or risk predicting model were slightly inferior. But, the portable glucose meters are less affordable and currently not available to the most of the community dwellers. Most of the glucose tests are performed in hospitals prescribed by a doctor. In addition, difficulties to confirm a fasting status and to perform invasive blood sampling limit

the usage of fasting glucose test as a mass screening tool. It is widely believed in Chinese that drawing a blood sample will damage the essential of the body. Unless necessary, people do not want to have a glucose testing.

Many risk assessment tools had been established on age, BMI, waist circumference, and family history of diabetes (Table 4). Most of those tools were derived from the data of Caucasian populations. The performance of these scores in predicting diabetes is usually moderate, with an AUC about 0.70 - 0.85. This is similar with the results presented in this study. However, it should be cautious to generalize a tool from its original population to others. When the risk assessment tools were applied in a new population, particularly in different races, the performance became poorer than in the original population (Table 11) (Rathmann et al. 2005). This might be due to the facts that both genetic and the environmental determinants differ between different ethnic groups, for example the body size, diet, lifestyle, climate, and response to the same outside changes are all different. Thus, ethnic-specific risk assessment tools are desired. In case that local score is not available, it is recommended to validate and calibrate an existing score according to the data of the local population before adopting it.

In India, two risk scores to screen undiagnosed diabetes were published in 2005 (Table 4) (Mohan et al. 2005; Ramachandran et al. 2005). Both were derived from cross-sectional data based on age, family history of diabetes and physical activity. The merit of current risk assessment model in Mauritian Indian is that it was developed based on prospective data rather than cross-sectional data and that absolute risk rather than relative risk was estimated.

6.4 The methodology considerations

6.4.1 The assessment of secular trends of diabetes in Qingdao city

The secular trend of the prevalence of diabetes in Qingdao city was estimated based on two consecutively conducted population-based cross-sectional studies. The two surveys followed the same procedures for sampling and for anthropometric and biochemical measurements. This is crucial to determine the secular trend of diabetes in a big developing countries like China where the economic development, culture, climate, working condition and dietary habits are different in different regions and the prevalence of diabetes varies largely across the country (Wang et al. 1998; Gu et al. 2003). Otherwise, it is hard to differentiate the regional differences and methodological variances from the true secular changes in prevalence of diabetes.

The surveys included in the current study had both large sample size and high participation rate of above 80%. We checked the data of the non-participants in the OGTTs and found they were similar to the participants in age, BMI, waist, family history of diabetes, and physical activity. Therefore, the non-responders are less likely to bias the estimation of the prevalence of diabetes.

There is a weakness that the FCG was measured with different devices in the two surveys in 2001-2002 and 2006. Since there was no cross validation between the Lifescan one Touch II glucose testing system and the Bayer Brio Meter Kit at the moment, it cannot be precisely estimated what variance will lead to by the two different devices. Despite the different method, an increased prevalence of diabetes was observed in the population who were administrated to OGTTs directly. Another weakness is that the rural counties included in the two surveys are not completely same because the random selection procedure. We compared the prevalence of diabetes in Jiaonan where both surveys were made; the prevalence was 9.8% in the early survey

and 16.9% in the late survey ($X^2 = 21.9$, $P < 0.001$). We also checked the prevalence between the three rural areas of the 2006 survey and found they did not differ from each other ($p>0.05$). Therefore, it is less likely the increased prevalence in rural was due to the difference in the areas selected.

6.4.2 The development of diabetes risk assessment algorithms

Obesity (as measured by BMI, waist circumference or waist to hip ratio, etc.), age, family history of diabetes, physical inactivity, plasma glucose concentration, blood pressure levels etc. was confirmed to be the independent determinant of the risk for diabetes both in Indians and Chinese in the current study. Therefore, they were including in developing the risk assessment algorithms. In the Chinese risk score, BMI was excluded from the final model because it correlated strongly with waist circumference and became non-significant when waist circumference was entered. In the Indian risk predicting models, however, both BMI and waist circumference were included in the same model. This is because that either BMI or waist circumference contributed to the prediction of the model independently. For this reason, BMI and waist circumference were both included in the final model to emphasize the importance to the weight control.

Neither the leisure time physical activity nor the occupational physical activities was included in the current risk assessment algorithms because they were not included in the final Cox or Logistic regression model. This is not surprising because the moderate and heavy leisure time physical exercise was not common in Chinese in Qingdao city (18% in men and 16% in women) and Indians in Mauritian (22% in men and 9% in women) during the survey period. The variable on physical activity, therefore, did not contain informative data to distinguish individuals who did intensive exercise from those who did not. And, the exercise intensity may not the same as

reported in other studies given the same category of physical activities. For example, most Chinese living in urban areas are used to have a relaxing walk around the living areas after dinner, and these individuals were all included in the "light" physical activity group. The occupational physical activities are closely related with the type of jobs and the economic status of the country and might vary between time periods and between living areas; thus, the association of the occupational activities and the diabetes incidence is not easy to assess. Moreover, the physical activity questionnaires used in both Qingdao and Mauritius studies are not evaluated and their reliability is not known. As indicated by Rennie and co-workers that physical activity data based on questionnaire is usually not reliable (Rennie et al. 1998).

6.5 The future prospective

A community-based Qingdao Diabetes Prevention Program (Qd-DPP) is ongoing in close cooperation between the local health care organizations and the University of Helsinki since 2005. As it was planed, the participants of 2006 survey will be re-examined from August 2009 to October 2010, and in 2012-2013. A new cohort (N = 6 000) will be recruited in 2009 and re-examined in 2012-2013. Thus, the secular changes in prevalence of diabetes will be further estimated with the new data. The Chinese diabetes risk score might be further validated with the new data, particularly the prospective data.

The Chinese diabetes risk score has been adopted and applied in the Qd-DPP project since 2006. It is reported to be acceptable, feasible, applicable and useful for health promotion and high-risk identification. Over 912 000 citizens have received the risk assessment questionnaire and 270 911 people with a risk score>=14 have undergone glucose tests and registered to the Qd-DPP for

lifestyle counseling. When the Qd-DPP ends in the December 2012, the benefit and cost of the screening program, particularly using the risk score as first step of screening can be evaluated.

The Indian risk predicting models were developed with the data of Mauritian Indians rather than the Asian Indians. Further validation is needed to determine the usefulness in the Asian Indians. University of Helsinki is now collaborating the Diabetes Epidemiology Collaborative Analysis Of Diagnostic Criteria in Asia (DECODA). There are several Indian Centers participated in the DECODA study and supplied their data collected from Asian Indians. It is, thus, possible to evaluate the performance of the Mauritian Indian risk predicting models in Asian Indians. The Indian risk score can also be evaluated based on mortality data collected in 2008 Mauritius to examine whether the score is also able to identify individuals at increased risk for premature mortality from cardiovascular and non-cardiovascular disease.

7. CONCLUSIONS

I. The prevalence of type 2 diabetes in Chinese was high and increasing in Qingdao city from 2001 to 2006. Action is urgently needed to prevent the epidemic of diabetes.

II. Fasting capillary blood glucose test is an adequate screening test for detecting undiagnosed diabetes in a mass screening program. But, it should be noticed that the two-step screening strategy based on FCG as a first line screening test and followed by a standard oral glucose tolerance test will miss a number of patients with undiagnosed diabetes and pre-diabetes. This should be taken into account when an optimal cut-off point for a positive screening test was selected.

III. The performance of a simple risk score comprising modifiable lifestyle factors is moderate, and it is a good alternative screening test in screening programs covering large population or as a first-step screening tool in a multi-steps screening program. It can also serve as a useful health promotion tool in a prevention program.

ACKNOWLEDGEMENTS

This study was carried out in the Diabetes Unit, Division of Chronic Disease Prevention, National Institute for Health Welfare (THL) and Department of Public Health, University of Helsinki. I wish to thank THL and Department of Public Health for providing me with such excellent research facilities. I am also grateful to Qingdao Endocrinology and Diabetes Hospital, Qingdao Municipal Center for Disease Prevention and Control, Qingdao Health Bureau, the Ministry of Health and Quality of Life, Mauritius and all of those who collected the excellent data for this study.

I owe my deepest gratitude to my supervisors Docent Qing Qiao and Professor Jaakko Tuomilehto for their excellent guidance and support. Docent Qing Qiao, not only my scientific guider but also my best friend, always encourages me, gives me excellent ideas, answers my questions and comments my works quickly. It is her who opened my eyes to the scientific research. Professor Jaakko Tuomilehto gives me intelligent ideas and detailed comments to improve my works. It is a great honor for me working with them and I really cherish the last 7 years experience. I wish to keep our friendship in the future.

The official referees of the dissertation, Docent Ulla Rajala and Professor Mauno Vanhala are gratefully acknowledged for their careful and quick work. I am honored that Professor Peter E.H. Schwarz has agreed to be the opponent of my dissertation on the occasion of its public defense.

I owe my sincerest thanks to all my co-authors of the original publications, who had kindly spent time to read and comments on the manuscripts. I also wish to thank Professor Yanhu Dong, who recommended me to study in Helsinki, Professor Zengchang Pang, Professor Shaojie Wang and the friends in Qingdao Endocrine and Diabetes Hospital and Qingdao Municipal Center for

Disease Prevention and Control for their kind help when I worked in Qingdao. I warmly thank all colleagues Pirjo Saatamoinen, Janne Pitkäniemi, Regzedmaa Nyamdorj, Feng Ning, et.al. in THL and Department of Public Health by accepting me and never turning down my request for help. I thank Lei Zhang, who has worked and studyed together with me during the period of my stay in Helsinki.

I owe my greatest thanks to my parents Zuozhen Zhang and Yusen Gao, my sister Yu Gao and my brother Shujing Li. Without their endless love and kindly support, this work cannot be finished. I would like to share my joy with and dedicate this work to my dear wife Li Zhang. I am sorry that I could not stay beside her while she is in pregnant. I am also eager to see our coming baby.

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