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# Epidemiologic studies on diabetes, non-diabetic glycemic levels, insulin resistance and cardiovascular diseases

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ACADEMIC DISSERTATION

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*To my family*

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# LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following original publications.

I. Ning F, Pang ZC, Dong YH, Gao WG, Nan HR, Wang SJ, Zhang L, Ren J, Tuomilehto J, Hammar N, Malmberg K, Andersson SW, Qiao Q; Qingdao Diabetes Survey Group. Risk factors associated with the dramatic increase in the prevalence of diabetes in the adult Chinese population in Qingdao, China. Diabet Med. 2009; 26:855-863.

II. Ning F, Pang ZC, Laatikainen T, Gao WG, Wang SJ, Zhang L, Tuomilehto J and Qiao Q for the Qingdao Diabetes Survey Group and FINRISK 2002 Study. Joint effect of family history of diabetes with obesity on prevalence of type 2 diabetes among Chinese and Finnish men and women. Can J Diabetes. 2013; 37:65-71.

III. Ning F, Qiao Q, Tuomilehto J, Hammar N, Ho SY, Söderberg S, Zimmet PZ, Shaw JE, Nakagami T, Mohan V, Ramachandran A, Lam TH, Andersson SW, Janus ED, Boyko EJ, Fujimoto WY, Pang ZC; DECODA Study Group. Does abnormal insulin action or insulin secretion explain the increase in prevalence of impaired glucose metabolism with age in populations of different ethnicities? Diabetes Metab Res Rev. 2010; 26:245-253.

IV. Ning F, Tuomilehto J, Pyörälä K, Onat A, Söderberg S, Qiao Q; DECODE Study Group. Cardiovascular disease mortality in Europeans in relation to fasting and 2-h plasma glucose levels within a normoglycemic range. Diabetes Care. 2010; 33:2211-2216.

V. Ning F, Zhang L, Dekker JM, Onat A, Stehouwer CDA, Yudkin JS, Laatikainen T, Tuomilehto J, Pyörälä K, Qiao Q on behalf of the DECODE Finnish and Swedish study Investigators. Development of coronary heart disease and ischemic stroke in relation to fasting and 2 hour plasma glucose levels in the normal range. Cardiovasc Diabetol. 2012; 11(1):76.

# ABBREVIATIONS

| | |
|---|---|
| ADA | American Diabetes Association |
| BMI | body mass index |
| CHD | coronary heart disease |
| CI | confidence interval |
| CIMT | carotid intima-media thickness |
| CVD | cardiovascular disease |
| DECODA | Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Asia |
| DECODE | Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe |
| ERFC | Emerging Risk Factors Collaboration |
| FPG | fasting plasma glucose |
| FHD | family history of diabetes |
| HbA1c | glycated hemoglobin |
| 2hPG | 2-hour plasma glucose |
| HR | hazard ratio |
| IDF | International Diabetes Federation |
| IFG | impaired fasting glucose |
| IGT | impaired glucose tolerance |
| OGTT | oral glucose tolerance test |
| OR | odds ratio |
| RR | relative risk |
| SD | standard deviation |
| WC | waist circumference |
| WHO | World Health Organization |

# ABSTRACT

The objectives of this study were to investigate: 1) what the major risk factors are that have contributed to the rise in prevalence of type 2 diabetes in Chinese adults, and whether the joint effect of a family history of diabetes along with obesity on the risk of diabetes in the Chinese differs from that in the Finns; 2) the impact of the homeostasis model assessment of insulin resistance and beta cell function on glucose metabolism in relation to aging in people of Asian origin; 3) the relative risk for cardiovascular disease (CVD) mortality and morbidity associated with fasting plasma glucose (FPG) and 2-hour plasma glucose (2hPG) within the normoglycemic range in European populations.

This study was based on datasets of the Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Asia (DECODA) and in Europe (DECODE) studies comprising 10307 men and 13429 women aged 30 to 74 years from 11 Asian cohorts, and 12566 men and 10874 women aged 25 to 90 years from 19 European cohorts. Type 2 diabetes and intermediate hyperglycemia in this study were determined by a 2-h 75g oral glucose tolerance test according to the World Health Organization/International Diabetes Federation criteria of 2006. The odds ratios for the prevalence of type 2 diabetes and intermediate hyperglycemia were estimated using logistic regression analysis. Cox proportional hazards analysis was performed to estimate the association between plasma glucose and CVD mortality and morbidity, adjusting for conventional cardiovascular risk factors.

Between 2001 and 2006, the age-standardized prevalence of type 2 diabetes increased from 5.2% to 14.2% in men and from 7.2% to 14.5% in women in rural areas, from 12.6% to 19.4% in men and from 10.2% to 16.6% in women in urban areas in Qingdao, China. Age, family history of diabetes and waist circumference was independent risk factors for diabetes in both sexes and in both urban and rural areas ($P < 0.01$ for all). A high level of education and a high income were inversely associated with the increased prevalence in all populations except in rural men ($P < 0.05$). Obesity and a family history of diabetes were major risk factors for type 2 diabetes in men and women from China and Finland. Their synergetic effect on type 2 diabetes was significant in Finnish men, but not in Finnish women or the Chinese. The prevalence of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) increased with age in populations of Asian origin except IFG in the Indians living in India and in African men living in Mauritius. The age-related increase was more prominent for IGT than for IFG in both men and women. Adjustment for insulin resistance and beta cell function reduced the differences

among age groups for all ethnic groups, but the risk gradient between age groups still remained significant for IGT. Within normoglycemic range, individuals whose baseline 2hPG did not return to FPG levels (Group II, 2hPG > FPG) were older and had higher baseline body mass index (BMI), blood pressure and fasting insulin levels compared with those whose baseline 2hPG did (Group I, 2hPG ≤ FPG) in Europeans. Hazard ratios (95% confidence intervals) for CVD mortality were 1.22 (1.05-1.41) in men, and 1.40 (1.03-1.89) in women for Group II versus Group I, adjusting for age, study cohort, BMI, FPG, total serum cholesterol, smoking status and hypertension status. The corresponding hazard ratios for the incidence of coronary heart disease, ischemic stroke and composite CVD events were 1.13 (0.93-1.37), 1.40 (1.06-1.85) and 1.20 (1.01-1.42) in men, and 1.33 (0.83-2.13), 0.94 (0.59-1.51) and 1.11 (0.79-1.54) in women, respectively. The increasing trends for CVD mortality and morbidity did not change substantially after additional adjustment for fasting insulin concentrations.

In conclusion, this study confirmed the impact of established risk factors of age, obesity and a family history of diabetes on the risk of diabetes among the Chinese, which is consistent with literature, but the interaction between the risk factors might be different between ethnicities and requires further investigation. This study also disclosed the deleterious effect of high normal 2hPG levels on CVD mortality and morbidity, which has not been widely investigated previously. The findings further support the view that the CVD risk extends well below the diabetes diagnostic value based on the post-challenge glucose levels, and may have certain clinical implications regarding diabetes diagnosis and glycemic management targets.

# TIIVISTELMÄ

Tämän tutkimuksen tavoitteena oli: 1) tutkia keskeisiä riskitekijöitä, jotka vaikuttivat tyyppin 2 diabeteksen esiintyvyyden nousuun kiinalaisilla aikuisilla, sekä kuinka diabeteksen perhehistorian ja lihavuuden yhdysvaikutus erosi Kiinassa ja Suomessa; 2) tutkia insuliiniresistenssin sekä beeta-solujen toiminnan vaikutusta glukoosiaineenvaihduntaan suhteessa ikääntymiseen aasialaisissa väestöissä; sekä 3) tutkia sydän- ja verisuonitautikuolleisuutta ja -sairastavuutta suhteessa veren paastoglukoosiin ja 2-tunnin glukoosirasitusarvoihin ei-diabeetikoilla eurooppalaisissa väestöissä.

Tutkimuksessa hyödynnettiin kahta laajaa tutkimusaineistoa eli DECODA ja DECODE projekteja, joihin on koottu tietoa aasialaisista ja eurooppalaisista väestöistä. Yhteensä aineistoissa on tietoa 10307 miehestä ja 13429 naisesta ikävälillä 30-74 vuotta 11 aasialaisesta maasta sekä 12566 miehestä ja 10874 naisesta ikävälillä 25-90 vuotta 19 eurooppalaisesta maasta. Tyypin 2 diabetes mitattiin 2-tunnin glukoosirasituskokeella käyttämällä 75 gramman glukoosiannosta mikä noudattaa WHO:n ja Kansainvälisen diabetesjärjestön suosituksia vuodelta 2006. Logistista regressioanalyysiä käytettiin laskettaessa riskitulosuhteita tyypin 2 diabeteksen esiintyvyyden ja korkean veren glukoosipitoisuuden välillä sekä Coxin suhteellisten vaarojen mallia arvioimaan veren glukoosiarvojen yhteyttä sydän- ja verisuonitautikuolleisuuteen ja –sairastavuuteen.

Vuosien 2001 ja 2006 välillä tyypin 2 diabeteksen ikävakioitu esiintyvyys nousi 5,2 prosentista 14,2 prosenttiin miehillä ja 7,2 prosentista 14,5 prosenttiin naisilla maaseudulla ja 12,6 prosentista 19,4 prosenttiin miehillä ja 10,2 prosentista 16,6 prosenttiin naisilla kaupunkialueilla kiinalaisessa Qingdaon maakunnassa. Ikä, diabeteksen perhehistoria ja vyötärön ympärysmitta olivat itsenäisiä riskitekijöitä diabetekselle molemmilla sukupuolilla sekä kaupungissa että maaseudulla ($p<0,01$). Korkea koulutus ja tulot olivat käänteisesti yhteydessä kohonneeseen diabeteksen esiintyvyyteen kaikissa muissa ryhmissä paitsi maaseudulla asuvilla miehillä ($p<0,05$). Lihavuus ja diabeteksen perhehistoria olivat keskeisiä riskitekijöitä tyypin 2 diabetekselle kiinalaisilla ja suomalaisilla miehillä ja naisilla. Näiden yhdysvaikutus oli myös tilastollisesti merkitsevä suomalailla miehillä, mutta ei suomalaisilla naisilla tai kiinalaisilla miehillä tai naisilla. Kohonnut paastoglukoosi ja glukoosirasituskokeen jälkeinen glukoosi lisääntyivät iän mukana aasialaisissa väestöissä lukuun ottamatta paastoglukoosia intialaisilla sekä Mauritiuksella asuvilla afrikkalaisilla miehillä. Paastoglukoosin kohoaminen oli voimakkaammin yhteydessä ikään verrattuna glukoosirasituskokeen jälkeiseen glukoosiin

miehillä ja naisilla. Insuliiniresistenssin ja beeta-solujen toiminnan vakioiminen heikensi ikäryhmittäisiä eroja kaikissa etnisissä ryhmissä, mutta yhteys iän ja glukoosirasituskokeen jälkeisen glukoosin välillä säilyi tilastollisesti merkitsevänä. Ei-diabeetikot joiden veren glukoosiarvo ei palannut paastoglukoosin tasolle kahden tunnin glukoosirasituskokeen jälkeen olivat vanhempia, heillä oli korkeampi painoindeksi, verenpaine ja veren paastoinsuliini verrattuna muihin eurooppalaisissa väestöissä. Tässä ryhmässä sydän- ja verisuonitautikuolleisuuden vaarasuhteet ja näiden 95 prosentin luottamusvälit olivat 1,22 (1,05-1,41) miehillä ja 1,40 (1,03-1,89) naisilla kun ikä, tutkimuskohortti, painoindeksi, veren paastoglukoosi, kokonaiskolesteroli, tupakointi ja korkea verenpaine olivat vakioituja. Vastaavat vaarasuhteet sepelvaltimotaudille, aivoverisuonitukokselle ja kaikille sydän- ja verisuonitautitapahtumille olivat 1,13 (0,93-1,37), 1,40 (1,06-1,85) ja 1,20 (1,01-1,42) miehillä sekä 1,33 (0,83-2,13), 0,94 (0,59-1,51) ja 1,11 (0,79-1,54) vastaavassa järjestyksessä. Sydän ja verisuonitautikuolleisuuden ja –sairastavuuden lisääntyminen ei muuttunut olennaisesti kun tulokset vakioitiin paastoinsuliinilla.

Johtopäätöksenä voidaan todeta, että tämä tutkimus vahvisti tunnettujen riskitekijöiden eli iän, lihavuuden ja diabeteksen perhehistorian vaikutuksen diabeteksen riskiin kiinalaisilla, mikä on sopusoinnussa aikaisemman tutkimuksen kanssa. Kuitenkin näiden riskitekijöiden mahdollinen yhdysvaikutus etnisyyteen vaatii lisää tutkimusta. Tutkimus myös paljasti korkean glukoosirasituskokeen jälkeisen glukoosin yhteyden kohonneeseen verisuonitautikuolleisuuteen ja –sairastavuuteen, mitä ei ole tutkittu aikaisemmin. Tulokset tukevat näkemystä että kohonnut glukoosirasituskokeen jälkeinen glukoosi on yhteydessä kohonneeseen sydän- ja verisuonitautien riskiin, vaikka se olisi alempi kuin diabeteksen nykyinen diagnostinen määritelmä. Tällä on tärkeää kliinistä merkitystä diabeteksen diagnostiikkaan ja veren glukoosiarvojen seurantaan.

# 1 INTRODUCTION

The prevalence of diabetes is increasing at an alarming rate worldwide. In 2011, an estimated 366 million adults aged 20-79 years had diabetes; this number is predicted to rise to 552 million by 2030 (Whiting et al., 2011). Diabetes and its complications impose a large economic burden on diabetic individuals, their families and social health system (World Health Organization, 2005).

Major risk factors for diabetes include increasing age, family history of diabetes (FHD), unhealthy diet, insulin resistance, obesity, physical inactivity and genetic factors (Wild et al., 2004). Obesity is a common risk factor for type 2 diabetes and other non-communicable diseases. Reduction in weight and increase in physical activity have been approved to be able to prevent or delay the progress to diabetes from impaired fasting glucose (IFG) (Saito et al., 2011) or impaired glucose tolerance (IGT) (Gillies et al., 2007; Knowler et al., 2002; Kosaka et al., 2005; Pan et al.,1997a; Ramachandran et al., 2006; Tuomilehto et al., 2001). Lifestyles, such as physical activity and eating habits, are commonly shared by a family. Individuals with a positive FHD in their parents or siblings had 2 to 4 times higher risk of diabetes than those without (Annis et al., 2005; Hilding et al., 2006; Yang et al., 2010). There is a synergetic effect between a positive FHD and obesity on the development of type 2 diabetes in Caucasians (Knowler et al., 1981; Hilding et al., 2006; Sargeant et al., 2000). However, the issue has not been well investigated in the Chinese population. Studies have shown that the strength of the association of obesity with diabetes is similar, but the prevalence of diabetes was higher in Asians than in Europeans at any given body mass index (BMI) or waist circumference (WC) cut-off value (Nyamdorj et al., 2008; Nyamdorj et al., 2010). It suggests that there might be other important biological factors rather than obesity that cause a predisposition for a higher risk of diabetes in Asians.

The prevalence of type 2 diabetes and intermediate hyperglycemia increases with age. The process from normality to IGT and type 2 diabetes is characterized by progressive insulin resistance or the deterioration of beta cell function (Haffner et al., 1997; Weyer et al., 1999). Experimental studies on human beings have shown that insulin resistance is attributed to age-related changes in body composition and level of physical activity, rather than age per se (Boden et al., 1993; Coon et al., 1992; Ferrannini et al., 1996). Among individuals without diabetes, insulin resistance increases progressively with increasing age in some studies (Gayoso-Diz et al., 2011; Qiao et al., 2005), but not in others (Esteghamati et al., 2009;

Ferrannini et al., 1996). The prevalence of IGT increased linearly with age, but not IFG, both in Asian and in European populations (DECODE Study Group, 2003a; Qiao et al., 2003). Studies among non-diabetic Europeans have also shown that age is more strongly associated with IGT than with insulin resistance, estimated by homeostasis model assessment, but whether this is the case among Asians is not well known.

Both diabetes and intermediate hyperglycemia have been convincingly shown to increase cardiovascular disease (CVD) mortality and morbidity (Emerging Risk Factors Collaboration et al., 2010; Huxley et al., 2006). Recent studies have further demonstrated that fasting plasma glucose (FPG) and/or 2h plasma glucose (2hPG) even at a higher normal range could convey an increased risk for having type 2 diabetes (Abdul-Ghani et al., 2006; Park et al., 2006; Reynolds et al., 2006; Tirosh et al., 2005) and atherogenic profiles (Succurro et al., 2009) as compared with the glucose concentrations at the lower normal range. However, little is known about the impact of normal FPG and normal 2hPG on cardiovascular mortality and morbidity.

# 2 REVIEW OF THE LITERATURE

## 2.1 Epidemiology of type 2 diabetes and intermediate hyperglycemia

### 2.1.1 Definition and classification of type 2 diabetes and intermediate hyperglycemia

Type 2 diabetes is characterized by insulin resistance and relative insulin deficiency, either of which may be present at the time that diabetes becomes clinically manifest (WHO Expert Committee, 1999). Type 2 diabetes can remain undetected, i.e. asymptomatic, at the early stage and the diagnosis is often made from diabetic complications or through glucose tests. Over the past decades, different laboratory assays for glucose measures have been developed, and diagnostic criteria for diabetes have also been revised (American Diabetes Association, 1997; National Diabetes Data Group, 1979; WHO Expert Committee, 1999; World Health Organization, 1980). Fasting plasma glucose and 2hPG concentrations after oral glucose tolerance tests (OGTT) have been recommended to define diabetes and IGT since 1979 (National Diabetes Data Group, 1979). Glycated hemoglobin (HbA1c), reflecting an average plasma glucose over the previous 8 to 12 weeks, has also been used as a diagnostic test for diabetes (Nathan et al., 2007a). Current diagnostic criteria for diabetes are classified by FPG ≥ 7.0 mmol/L and/or 2hPG ≥ 11.1 mmol/L and/or HbA1c ≥ 6.5% (WHO, 2011; World Health Organization & International Diabetes Federation consultation, 2006). Intermediate hyperglycemia, i.e, IFG and IGT, refers to an intermediate state between normal and diabetic glucose homeostasis. Studies indicate that IGT is associated with muscle insulin resistance and defective insulin secretion, resulting in a less efficient disposal of the glucose load during the OGTT, while IFG is associated with impaired insulin secretion and impaired suppression of hepatic glucose production (Abdul-Ghani et al., 2006). The current diagnostic interpretations for diabetes and intermediate hyperglycemia are summarized in Table 1.

Table 1 Definitions of normoglycemia, intermediate hyperglycemia and diabetes according to WHO and ADA criteria

| | NGT | IFG | IGT | Diabetes |
|---|---|---|---|---|
| FPG (mmol/L) | ≤ 6.0 (WHO)<br>≤ 5.5 (ADA) | 6.1–6.9 (WHO)<br>5.6–6.9 (ADA) | < 7.0 | ≥ 7.0 |
| 2hPG (mmol/L) | < 7.8 | < 7.8 (if measure) | 7.8–11.0 | ≥ 11.1 |
| HbA1c (%) | ≤ 5.6 (ADA) | 5.7–6.4 (ADA) | 5.7–6.4 (ADA) | ≥ 6.5 |

ADA, American Diabetes Association; FPG, fasting plasma glucose; 2hPG, 2-hour plasma glucose; HbA1c, glycated hemoglobin; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; WHO, World Health Organization.

### 2.1.2 Prevalence of type 2 diabetes and intermediate hyperglycemia

Over the past decades, the number of people with diabetes mellitus has more than doubled globally. It is projected to rise from 366 million in 2011 to 552 million in 2030; 90% of these have type 2 diabetes (Whiting et al., 2011). Diabetes patients aged between 40 and 59 accounts for 50% of total diabetic individuals (International Diabetes Federation, 2009). Estimations for 2011 and 2030 show little sex difference in the number of people with diabetes (Whiting et al., 2011). There are more people with diabetes living in urban than in rural areas. Remarkably, 80% of people with diabetes worldwide live in low- and middle-income countries. The age-standardized prevalence of diabetes in China has increased substantially from less than 2.3% in 1994 (Pan et al., 1997b), to 5.5% in 2000 (Gu et al., 2003; Hu et al., 2009), and to 9.7% in 2008 (Yang et al., 2010). With the development of urbanization and aging, changes in human behavior and a sedentary lifestyle have resulted in a dramatic increase in the incidence of diabetes (Ramachandran et al., 1999; Shai et al., 2006; Zimmet et al., 2001).

People with IGT and IFG are at an increased risk of developing diabetes. It is estimated that 6.5% of adults aged 20-79 years had IGT in 2011, and the figure will increase to 6.7% in 2030 according to the 5th edition IDF Diabetes Atlas (International Diabetes Federation, 2012). The prevalence of IFG and IGT is different across the sexes and ethnicities. The age-standardized prevalence of IFG (FPG, 5.6-6.9 mmol/L) in adults aged 20 years or above was 26% based on the National Health and Nutrition Examination Survey (NHANES) 1999-2002. The prevalence was significantly higher in men than in women in the total population (32.8% vs. 19.5%, $P < 0.001$) and in non-Hispanic whites (33.1% vs. 19.6%, $P < 0.001$) (Cowie et al., 2006). Similarly, the isolated IFG (FPG, 6.1-6.9 mmol/L) was more common in men than in women at 30-69 years of age in European and Asian populations, but not in Indians living in India (DECODE Study Group, 2003a; Qiao et al., 2003). There was no difference in IGT prevalence between the non-Pima and the Pima Indians living in Mexico, but IGT was more prevalent in the U.S. Pima Indians than in the two Mexican groups ($P = 0.02$) (Schulz et al., 2006). A recent study including 46239 Chinese adults aged 20 years or above estimated the age-standardized prevalence of intermediate hyperglycemia (IFG or IGT) was 148.2 million, accounting for 15.5% of the total population. The age-standardized prevalence did not differ significantly between men and women ($P = 0.08$) (Yang et al., 2010). Lifestyle modification is the cornerstone of diabetes prevention, with evidence of a 40-70% relative risk reduction among individuals with intermediate hyperglycemia (Gillies et al., 2007). However, the increasing

trends of obesity and physical inactivity are prominant due to increasing urbanization and sedentary lifestyles. Exposure to the high prevalence of obesity and physical inactivity will increase the risk of developing type 2 diabetes and its complications.

## 2.2 Risk factors for type 2 diabetes

Genes interact with the environment to produce type 2 diabetes. There are several potential factors for developing type 2 diabetes, such as increasing age, ethnicity, FHD, obesity, unhealthy diet and physical inactivity. The role of the major risk factors on type 2 diabetes will be discussed in greater detail below.

### 2.2.1 Age

The risk of type 2 diabetes increases with age, it is most common in people above the age of 40. As a consequence of aging populations, increasing urbanization and sedentary lifestyles, it is projected that there will be 188 million people with diabetes aged 40-59 years by 2030 (International Diabetes Federation, 2009). The age peaks of diabetes prevalence vary across levels of economic development. Most people with diabetes are aged 60 years or above in high-income countries, whereas most people with diabetes in low- and middle-income countries are between 40 and 60 years old (Whiting et al., 2011). Remarkably, the onset of type 2 diabetes has shifted to younger age groups due to increasing obesity in adolescents and young adults (Dabelea et al., 1998; Pavkov et al., 2007). The unfavorable metabolic risks in young people will impose the further burden of type 2 diabetes.

The age-specific prevalence of IFG and IGT varied according to ethnicity and sex. The DECODA study reported that the age-specific prevalence of impaired glucose regulation increased with age up to 70-89 years in most ethnic groups, but not in the Indian residents (Qiao et al., 2003). The Indian residents reached the peak prevalence of intermediate hyperglycemia at an age 10 years younger than the Chinese and the Japanese. The prevalence of IGT in Asians increased linearly with age, but not IFG, which is consistent with the data in Europeans (DECODE Study Group, 2003a; Qiao et al., 2003). Data from the NHANES 2005-2006 demonstrated that the prevalence of IFG increased with age, doubling between the ages of 20-39 and 40-59, and then remained constant at above the age of 60 years. Similarly, the prevalence of IGT steadily increased with age, peaking at 35.1% at above the age of 75 years (Cowie et al., 2009). The prevalence of IGT was significantly higher in women than in men aged between 30 and 69 years old in Europeans, between 40-49 years old in the Chinese and the

Japanese, but between 30-39 years old in the Indian residents.

Aging characterized by deterioration in the maintenance of homeostatic processes over time, is arguably the most universal contributor to the etiologies of metabolic decline and its related diseases, including type 2 diabetes and CVD (Ford et al., 2002). The prevalence of obesity and physical inactivity increases with age. An age-associated increase in body visceral fat, pro-inflammatory cytokines and a decline in mitochondrial and endocrine function, may explain an age-related decline in beta cell function and glucose homeostasis (Barzilai et al., 2012). However, it is not clear whether the glucose intolerance accompanied with age is a natural process associated with aging or secondary to age-related obesity and physical inactivity.

### 2.2.2 Obesity

The increased prevalence of type 2 diabetes is correlated with a comparably steep increase in the prevalence of obesity. Studies have shown that the strength of the association of obesity with diabetes is similar but the prevalence of diabetes is higher in Asians than in Europeans at any given BMI or WC cut-off value (Nyamdorj et al., 2008; Nyamdorj et al., 2010). The higher risk of metabolic diseases at a lower degree of obesity in Asians than in Europeans was partly due to unfavorable body composition (Ramachandran et al., 2012; Wulan et al., 2010). In addition, common variations in the *FTO* (fat mass and obesity-associated) gene have been found to be strongly associated with obesity and type 2 diabetes in adult Europeans (Frayling et al., 2007; Zeggini et al., 2007), but inconsistency exists in Asians (Chang et al., 2008; Karasawa et al., 2010; Li et al., 2008; Li et al., 2012). Other factors rather than obesity might have contributed to a higher diabetes risk in certain ethnic groups.

Weight gain is an independent risk factor for diabetes (Chan et al., 1994; Colditz et al., 1995; Ford et al., 1997; Wannamethee & Shaper, 1999; Willett et al., 1995). One prospective study including 1929 overweight participants identified 251 diabetic patients, has demonstrated that for each kilogram of weight gain there was a 49% increase in the risk of developing diabetes during a 10-year follow-up period as compared with stable weight (Resnick et al., 2000). This is consistent with the findings that weight gain is associated with insulin resistance and deterioration in glucose tolerance (Swinburn et al., 1991). Findings from the clinical trials have confirmed that weight reduction could prevent or delay the onset of diabetes among individuals with IFG/IGT (Knowler et al., 2002; Kosaka et al., 2005; Lindstrom et al., 2013; Ramachandran et al., 2006; Tuomilehto et al., 2001).

There is increasing evidence that obese people with type 2 diabetes can benefit substantially from bariatric surgery. A meta-analysis of 621 clinical studies involving 135246 adult patients showed that, after bariatric surgery, diabetes was improved or resolved in 86.6% of the patients with an overall weight loss of 55.9% (Carlsson et al., 2012). Calorie restriction and subsequent weight loss after bariatric surgery can have more potent effects on an increase in insulin sensitivity (Lee et al., 2010; Lim et al., 2011; Perugini & Malkani, 2011) or beta cell function (Bradley et al., 2012; Dixon et al., 2012; Taylor, 2012). However, another study found that greater insulin resistance, lower insulin secretion, persistent adiposopathy and chronic subclinical inflammation exists in the no remission of diabetes group despite a similar level of weight loss as compared with the remission group (Hirsch et al., 2012). The reason for these differences in patients with similar clinical profiles and surgically-induced weight loss could be related to a different genetic background or some unknown factors. A better understanding of the endocrine changes following bariatric surgery is becoming increasingly important. Moreover, the long-term benefits, cost-effectiveness and risk of bariatric surgery in individuals with type 2 diabetes should be studied in well-designed controlled trials with optimal medical and lifestyle therapy as the comparator.

The hypotheses or candidate mechanisms of obesity in the pathogenesis of insulin resistance and type 2 diabetes has been reviewed extensively (Cnop et al., 2002; Item & Konrad, 2012; Kahn et al., 2006). Obesity is defined as excess fat in the subcutaneous and visceral tissue. The distribution of body fat is a critical determinant of insulin sensitivity. The accumulation of intra-abdominal fat correlates with insulin resistance (Item & Konrad, 2012), whereas subcutaneous fat deposition correlates with circulation leptin levels (Cnop et al., 2002). Adipose tissue modulates the metabolism by releasing non-esterfied fatty acids (NEFAs) and glycerol, hormone and pro-inflammatory cytokines (Boden, 1997). In addition to adipocyte-derived factors, an increased release of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1) and additional products of macrophages and other cells might result in the regulation of potential mediators of inflammation that could lead to insulin resistance and impaired glucose homeostasis (Kahn et al., 2006; Wang et al., 2013; Wellen & Hotamisligil, 2005). In addition, the lipid metabolic pathway (Amati, 2012; Unger, 2003) and oxidative stress (Evans et al., 2005; Henriksen et al., 2011) may also explain the underlying mechanisms of the obesity-insulin resistance relationship. Lipotoxicity is a metabolic syndrome that results from the accumulation of lipids, particularly fatty acids, leading to resistance to an insulin-stimulated glucose metabolism (Unger, 2003). The view that oxidative stress is a

causative factor in the development of insulin resistance has been supported by several studies that showed that reversal of the imbalance between reactive oxygen sepecies and antioxidants improves insulin resistance in animals and humans (Fridlyand & Philipson, 2006; Henriksen et al., 2011; Houstis et al., 2006; Qatanani & Lazar, 2007).

### 2.2.3 Genetic background and Ethnicity

Linkage studies, candidate gene approaches, and genome-wide association studies have identified several gene variants associated with type 2 diabetes (Ahlqvist et al., 2011; Barroso, 2005; Billings & Florez, 2010; Dupuis et al., 2010; Jing et al., 2012; Ribel-Madsen et al., 2012; Saxena et al., 2012; Voight et al., 2010). Meta-analysis has confirmed strong associations between common polymorphisms of the transcription factor 7-like 2 (*TCF7L2*) gene variants and type 2 diabetes in Europeans, African Americans, Mexican Americans, and East Asians (Luo et al., 2009; Tong et al., 2009). Genome-wide association analysis has identified more than 40 genetic variants associated with blood glucose levels, highlighting important biological pathways involved in glucose regulation (Dupuis et al., 2010; Voight et al., 2010). However, in aggregate these variants account for only about 10% of the heritability of diabetes (Ahlqvist et al., 2011; Stolerman & Florez, 2009).

Global studies on ethnic groups and the rising incidence of diabetes have revealed ethnicity can increase or decrease one's risk of developing diabetes. Recent data from the U.S. national survey 2007-2009, indicated that the risk of diabetes was 18% higher among Asian Americans, 66% higher among Hispanics, and 77% higher among non-Hispanic blacks as compared with non-Hispanic white adults aged 20 years or above (Sentell et al., 2012). Furthermore, a population-based study including 4688 Europeans and 1352 south Asians showed that HbA1c as well as FPG and 2hPG levels, were higher in south Asians independently of the conventional risk factors than in Europeans across the glucose tolerance categories (Mostafa et al., 2012). It indicated that Asian Indians are more insulin resistant and had a higher risk of developing metabolic syndrome than other ethnic groups (Abate et al., 2004; Banerji et al., 1999; Tan et al., 1999). Compared with Europeans, the higher amount of truncal fat and the large dysfunctional subcutaneous fat cells were strongly related to insulin resistance in Asians (Chandalia et al., 2007).

Family history of diabetes plays an important role in its development. In comparison with individuals without a FHD, those with a positive FHD had a 2 to 4 times higher risk of developing diabetes (Bjørnholt et al., 2000; Knowler et al., 1981; Meigs et al., 2000; Ohlson et

al., 1988). Moreover, numerous studies found that a positive FHD was associated with a decline in insulin sensitivity and/or insulin secretion (Arslanian et al., 2005; Haffner et al., 1996; Isomaa et al., 2010; Martin et al., 1992). Considering the strong association of obesity and insulin resistance, the joint effect of a positive FHD and obesity on the risk of diabetes was also widely investigated. Either cross-sectional studies or prospective studies indicated that the synergistic effect was strongly associated with diabetes as compared with FHD or obesity alone (Annis et al., 2005; Chen et al., 2010; Hilding et al., 2006; Isomaa et al., 2010; Knowler et al., 1981; Nakanishi et al., 2003; Sargeant et al., 2000; Valdez et al., 2007). However, this was not confirmed in a Japanese study (Fujimoto et al., 1991) or in a Dutch study (Boer et al., 1996). The synergistic effect of a positive FHD and obesity on type 2 diabetes has, however, not been well investigated in the Chinese.

### 2.2.4 Physical inactivity

Experimental designs and clinical interventions have found that physical activity increases total energy expenditure and promotes weight loss (Donnelly et al., 2009; Hollenbeck et al., 1985; Rosenthal et al., 1983). Short-term clinical interventions, 6 months or less in duration, have reported that exercise alone has a vital impact on body weight loss (National Heart, Lung, and Blood Institute, 1998; Ross et al., 2000; Ross et al., 2004). Moreover, exercise contributes to the long-term maintenance of weight loss (Jakicic et al., 2002; Jakicic et al., 2003; Klem et al., 1997; Wood et al., 1988). Experimental studies have demonstrated that exercise training results in a higher rate of insulin-stimulated glucose disposal at a defined insulin dose through hyperinsulinemic-euglycemic clamp (Hollenbeck et al., 1985; Rosenthal et al., 1983). Previous studies provided clear evidence that weight training has been beneficial to diabetes reduction, which are likely to be mediated through increased muscle mass and improved insulin sensitivity (Davis et al., 2012; Grøntved et al., 2012). A meta-analysis including 47 randomized controlled clinical trials with 8538 diabetic patients, showed that individuals participating in structured exercise training is associated with a 0.67% (0.49%-0.84%) decline in HbA1c level compared with those in the control group (Umpierre et al., 2011).

An increase in physical activity is associated with a reduction of the risk of diabetes. The evidence of physical activity on the prevention of type 2 diabetes in people with IFG/IGT was well established in several clinical trials (Gillies et al., 2007). Prospective studies have supported strongly an inverse association between daily physical activity and the risk of developing diabetes, with a 15%-60% reduction of risk (Hu et al., 1999; Hu et al., 2004; Jeon et

al., 2007). In a meta-analysis including 10 prospective studies it was shown that individuals who regularly engaged in moderate physical activity had a 17% lower risk of type 2 diabetes than those who were sedentary, adjusting for BMI (Jeon et al., 2007). Similarly, the Health Professionals Follow-up Study including 32002 men indicated that engaging in weight training for at least 150 minutes per week was independently associated with a lower risk of type 2 diabetes of 34% (7%-54%) in a multivariate adjusted model (Grøntved et al., 2012). On the other hand, another recent meta-analysis including 794577 participants, confirmed that higher levels of sedentary behavior are associated with increased risk of the development of diabetes, with a relative risk (RR) of 2.12 (1.61-2.78) (Wilmot et al., 2012).

### 2.2.5 Socioeconomic status

With the development of urbanization and nutritional change, the prevalence of type 2 diabetes has had a dramatic increase, particularly in low- and middle-income countries (Chan et al., 2009; World Health Organization, 1994). Socioeconomic status (SES) plays different roles in the development of diabetes across all levels of economic status. In developed countries, high SES is positively associated with a reduction in type 2 diabetes (Connolly et al., 2000; Robbins et al., 2000; Robbins et al., 2001). Individuals with higher SES were more likely to do exercise and have access to a healthy diet, whereas those with lower SES were prone to unhealthy lifestyles in developed countries (Roos et al., 1998; Wardle & Steptoe, 2003). A meta-analysis including 21978 cases of diabetes, demonstrated that low SES in terms of education (41%), occupation (31%) and income (40%) increased the risk of diabetes incidence as compared with those high levels of determinants in high-income countries ($P < 0.05$ for all) (Agardh et al., 2011). However, a reversed association between SES and risk of diabetes were presented in some low- and middle-income countries, such as China (Pan et al., 1997b; Xu et al., 2006), India (Corsi & Subramanian, 2012; Ebrahim et al., 2010; Kinra et al., 2010; Mohan et al., 2008; Ramachandran et al., 2002) and Bangladesh (abu Sayeed et al., 1997). A population-based study including 29340 Chinese participants aged 35 years or above, showed that participants in the higher and middle average family income categories were more than twice as likely to have type 2 diabetes as those in the lower category, adjusting for conventional risk factors (Xu et al., 2006). A prospective study including 46382 African American women confirmed the evidence for an association of individual SES with the risk of diabetes may be partly mediated by BMI (Krishnan et al., 2010).

### 2.2.6 Diets, cigarette smoking and alcohol consumption

Enormous studies have widely have demonstrated that diets with a high glycemic index or glycemic load were significantly associated with the development of type 2 diabetes (Salmeron et al., 1997; Salmeron et al., 1997; Schulze et al., 2004; Villegas et al., 2007), but no significant effect was observed in other studies (Marshall et al., 1997; Meyer et al., 2000; Stevens et al., 2002). A high-fat dairy, red or processed meat intake increased the risk of type 2 diabetes and vascular diseases (van Dam et al., 2002; Song et al., 2004; Micha et al., 2010), whereas dietary patterns made up of fruit or vegetables reduced the risk of metabolic disorders (Harding et al., 2008; Nettleton et al., 2008; Carter et al., 2010; Zhou et al., 2011). The randomized controlled clinical trials have supported the hypothesis that dietary intervention, plus moderate or intensive physical activity, is associated with reduction of type 2 diabetes in individuals with IFG/IGT (Gillies et al., 2007; Knowler et al., 2002; Pan et al., 1997a; Saito et al., 2011; Tuomilehto et al., 2001).

The relationship between cigarette smoking and type 2 diabetes has been widely evidenced. Some prospective cohort studies demonstrated that active smoking increased the risk of type 2 diabetes by 31% (Yeh et al., 2010) and 44% (Willi et al., 2007), whereas a protective effect of smoking on type 2 diabetes was observed in another study (Onat et al., 2007). Moreover, there was a dose-response relationship between the number of cigarettes smoked and the risk of diabetes. The biological mechanism between cigarette smoking and diabetes was not well understood.

Alcohol consumption as a lifestyle factor has also been suggested to be relevant to the risk of type 2 diabetes. Several studies on the association between alcohol consumption and incidents of type 2 diabetes have been published during the last few years. A U-shaped relationship was found between alcohol consumption and risk of type 2 diabetes in recent meta-analysis studies (Baliunas et al., 2009; Koppes et al., 2005). Compared with lifetime abstainers, moderate alcohol comsumption had a protective effect on type 2 diabetes in both men (consuming 22 g/day alcohol) and women (consuming 24 g/day alcohol) (Baliunas et al., 2009). Possible mediators of the benefical effecs of moderate alcohol consumption include improved insulin sensitivity, increased high density lipoprotein cholesterol and adiponectin and the anti-inflammatory effect of alcohol (Hu, 2011; Koppes et al., 2005). However, heavy drinking has no effect and might increase the risk of diabetes (Beulens et al., 2005; Hodge et al., 2006; Koppes et al., 2005).

## 2.3 Insulin resistance and beta cell dysfunction

Insulin is a peptide hormone secreted by the beta cells of the pancreatic islets of langerhans and maintains glucose homeostasis and promotes efficient glucose utilization. Insulin synthesis and insulin secretion is influenced by genetic susceptibility and environmental factors (Wilcox, 2005), which require the coordinated action of several mechanisms, some of which are only partially defined. Age, ethnicity, obesity, physical activity, and inflammation are potential risk factors influencing insulin secretion and insulin action.

Experimental methods for the assessment of insulin sensitivity and insulin secretion have been widely described (Bergman et al., 1985; DeFronzo et al., 1979; Muniyappa et al., 2008). Hyperinsulinemic-euglycemic clamp and hyperglycemic clamp are considered as the gold standards for measuring insulin sensitivity and insulin secretion, respectively (DeFronzo et al., 1979). Alternatively, the indirect measurement of insulin sensitivity on the basis of glucose and insulin is assessed using a frequently sampled intravenous glucose tolerance test (FSIVGTT) (Bergman et al., 1979). Measurements of plasma glucose and insulin concentrations under fasting conditions and during the OGTT have been used to derive indexes of insulin sensitivity, which correlates reasonably with hyperinsulinemic-euglycemic clamp. However, the OGTT is time consuming and labor intensive, which limits its application in routine clinical practices or large scale epidemiological studies. Surrogate markers for insulin sensitivity have been introduced as potential alternatives, i.e., Homeostasis model assessment (HOMA) (Matthews et al., 1985), Quantitative insulin sensitivity check index (QUICKI) (Katz et al., 2000), 1/(Fasting insulin) (Laakso,1993) and the Matusda index (Matsuda & DeFronzo,1999). Although certain limitations exist compared with the gold standard methods (Boyko & Jensen, 2007; Buchanan et al., 2010; Hockaday et al., 2007; McAuley et al., 2007), HOMA has been widely used as a convenient surrogate marker of insulin resistance and beta cell function (Matthews et al., 1985). The fasting plasma glucose and insulin concentrations were employed in mathametical equations of the HOMA model (Matthews et al., 1985).

Insulin resistance is a condition where insulin is not able to ensure adequate peripheral tissue glucose utilization, especially in muscle and liver. Impaired beta cell function is manifested most commonly by decreased early insulin release and the inability of beta cells to compensate appropriately for insulin resistance. Insulin resistance and beta cell dysfunction are the hallmarks of intermediate hyperglycemia (Reaven, 1988). However, features of glycemic disorder differ from hepatic and peripheral tissues (Abdul-Ghani et al., 2007). An isolated IFG

is associated with reduced hepatic insulin sensitivity and decreased first-phase insulin secretion (DeFronzo, 2004), while the isolated IGT is associated with peripheral insulin resistance and impairment of both first- and second-phase insulin secretion (Bogardus et al., 1984).

It has been well documented that the prevalence of type 2 diabetes and IGT increases with age, but the pathogenesis underlying age-related deterioration in glucose metabolism is not fully understood. Both type 2 diabetes and glucose intolerance are more common in older individuals than in younger individuals. Many (Chen et al., 1985; Coon et al., 1992; Defronzo, 1979; Ferrannini et al.,1996; Qiao et al., 2005; Rowe et al., 1983), but not all studies (Ahren & Pacini, 1998; Basu et al., 2003; Boden et al., 1993; Broughton et al., 1991; Pacini et al., 1988) have demonstrated that older individuals are more insulin resistant than younger individuals. Similarly, a reverse association between beta cell function and age was shown in some studies (Chen et al., 1985; Chiu et al., 2000; Clausen et al., 1996; Fritsche et al., 2002; Iozzo et al., 1999; Roder et al., 2000; Scheen et al., 1996; Shimizu et al., 1996), but not in others (Bourey et al., 1993; Defronzo, 1979). The progressive deterioration of glucose metabolism in healthy elderly individuals is attributed to a decrease in both insulin secretion and insulin action with a severity of dysfunction in insulin action being explained by the degree of obesity and the level of physical activity rather than age per se (Basu et al., 2003; Boden et al., 1993; Coon et al., 1992; Ferrannini et al., 1996). To what extent aging contributes to the deterioration of insulin action and insulin secretion observed in the elderly population remains uncertain. It will be of considerable interest to determine the effect of aging on insulin secretion and insulin resistance and their relationship with the deterioration of glucose intolerance in the elderly population.

## 2.4 Glycemic levels and cardiovascular outcomes

### 2.4.1 Association of diabetes and cardiovasular mortality and morbidity

Both macro- and micro-vascular complications increase premature deaths in people with diabetes. Cardiovascular disease is the name for the group of disorders of heart and blood vessels, which accounts for 80% of deaths in people suffering from diabetes. Diabetes as an independent risk factor for cardiovascular mortality has been widely evidenced. Individuals with previously diagnosed diabetes have a 2- to 4-fold higher risk of CVD than non-diabetic individuals (DECODE Study Group, 2003b; Howard et al., 1996; Huxley et al., 2006; Magliano et al., 2010; Taylor et al., 2013). However, data from the International Collaborative Project, which included 11 prospective studies, failed to find a relationship between asmptomatic

hyperglycemia and mortality from coronary heart diease (CHD) based on coronary arteries narrowing or becoming blocked (The International Collaborative Group, 1979). A meta-analysis of 37 prospective studies has shown that the rate of fatal CHD was greater in patients with diabetes than in those without diabetes, with a RR of 1.99 (1.69-2.35) in men and 3.12 (2.34-4.17) in women (Huxley et al., 2006). Another meta-analysis of Emerging Risk Factors Collaboration (ERFC) studies including 264353 participants with 11848 CHD events has shown a HR of 2.10 (1.85-2.39) for CHD after adjusting for age, sex and smoking status in participants versus those without diabetes; the figure did not change substantially after adjustment for other conventional risk factors (Emerging Risk Factors Collaboration et al., 2010).

Cerebrovascular disease, as well as CHD, is the leading cause of death and disability in diabetic patients. It has been shown that patients with diabetes are 2 to 5 times more likely to develop stroke compared to those without diabetes (Tuomilehto et al., 1996; Barrett-Connor & Khaw, 1988; Berger et al., 1998; Emerging Risk Factors Collaboration et al., 2010). In the ERFC study including 157315 participants with 2858 stroke cases accumulated, the multivariate-adjusted HR was 2.59 (2.16-3.09) for ischemic stroke in patients with diabetes versus those without diabetes (Emerging Risk Factors Collaboration et al., 2010). Data from 18360 Finns and Swedes aged 25 to 90 showed the HRs for ischemic stroke incidence were 2.20 (1.48-3.29) for previously diagnosed diabetes and 1.48 (1.08-2.02) for newly diagnosed diabetes defined using the FPG criteria, and corresponding figures of 2.26 (1.51-3.38) and 1.60 (1.18-2.16) for the diabetes category defined using the 2hPG criteria, as compared with normal fasting or 2h glucose levels (Hyvarinen et al., 2009).

### 2.4.2 Association of non-diabetic glycemic levels with cardiovascular diseases

The relationship between glucose levels and CVD has been investigated in order to find whether there is a threshold or a change point in the glucose distribution that can be used to define diabetes according to the changes in CVD risk. In the ERFC study, the HR for CHD risk corresponding to per 1 mmol/L increase in FPG was 1.12 (1.08-1.15) within the range of FPG concentrations greater than 5.6 mmol/L (Emerging Risk Factors Collaboration et al., 2010). In another meta-analysis including 38 cohorts, the CVD risk started to increase at the FPG threshold of $\geq$ 5.6 mmol/L (Levitan et al., 2004). In the DECODE study including 29714 individuals aged 30-89 years, a J-shaped relationship between FPG levels and CVD mortality was observed among Europeans who did not have a prior history of diabetes, with the lowest

risk of CVD mortality observed in individuals with a FPG of 4.5-5.0 mmol/L (DECODE Study Group, 2003b). In the AusDiab (Australian Diabetes, Obesity, and Lifestyle) study, the HR for CHD corresponding to one standard deviation (SD) (mmol/L) decrease in FPG concentrations was 4.0 (2.1-7.6) for FPG < 5.1mmol/L, while to one SD increase (mmol/L) the HR was 1.3 (1.1-1.4) for FPG ≥ 5.1mmol/L in the multivariate-adjusted models (Barr et al., 2009). The causes of an increased CVD mortality risk associated with low FPG level remains unclear, but the low BMI has been considered as a potential risk factor (Wandell & Theobald, 2007; Wei et al., 2000). Different from the FPG-CVD relationship, a linear or graded rather than a J-shaped relationship between post-challenge glucose levels and CVD risk has been reported in many studies (Barr et al., 2009; Coutinho et al., 1999; DECODE Study Group, 2003b; Levitan et al., 2004).

A number of studies have demonstrated that hyperglycemia was associated with an increased risk of stroke (Danaei et al., 2006; Eguchi et al., 2007; Selvin et al., 2010; Wannamethee et al., 1999), but not other studies (Haheim et al., 1993; Lawlor et al., 2007). Recently, a systematic review of epidemiological studies and surveys from 52 countries showed that 13% deaths from stroke were attributable to a higher-than-optimum FPG (Danaei et al., 2006). In the Goettingen Risk Incidence and Prevalence Study with 5790 men aged 40-60 years who were followed for 10 years, the RR for stroke incidence was 1.6 (1.1-2.2) in individuals with FPG > 6.2 mmol/L compared to those with FPG < 4.8 mmol/L (Cremer et al., 1997). In another study of 28477 non-diabetic individuals, compared with fasting blood glucose < 5.6 mmol/L at the baseline, a 24% increased risk of stroke or transient ischemic attack was observed in the fasting blood glucose over 5.6 mmol/L (Nielson & Fleming, 2007). The Northern Manhattan study found distinct ethnic differences regarding the FPG-stroke relationship. In a multivariate-adjusted model, FPG is a better predictor for ischemic stroke in African Americans, but not in Hispanics or white Americans, where the corresponding HRs were 1.38 (1.09-1.74), 0.97 (0.70-1.34) and 0.81 (0.47-1.40), respectively (Eguchi et al., 2007). Data from 3246 British women aged 60 to 79 years free of baseline CHD, stroke and diabetes did not, however, show a positive relationship between a linear form of FPG and an incidence of stroke (Lawlor et al., 2007).

Increasing evidence has shown that the CHD risk is higher among individuals with IFG and/or IGT than among those with normal glucose levels. In the AusDiab study, IFG but not IGT were an independent predictor for CVD mortality after adjustment for conventional factors, as compared with normal glucose tolerance, where the corresponding HRs were 2.6 (1.2-5.1) and

1.2 (0.7-2.2), respectively (Barr et al., 2007). The multivariate adjusted OR for CHD was 1.7 (1.0 to 3.0) among women with IFG defined by a FPG of 5.6-6.9 mmol/L, as compared with those with a FPG of < 5.6 mmol/L, while the OR was 2.2 (1.1-4.4) in women with IFG defined according to a FPG of 6.1-6.9 mmol/L as compared with those with FPG < 6.1 mmol/L in the Framingham Heart Study (Levitzky et al., 2008). Although IFG and IGT are associated with risk of type 2 diabetes, IGT is more strongly associated with CVD outcomes than IFG. The Bedford Cohort Study with a 10-year follow-up found that IGT carried an excess risk of CHD mortality in women but not in men (Jarrett et al., 1982). As shown in the DECODE study, individuals with IGT had survival profile falling between diabetic and normal subjects according to the 2-h glucose criteria; while those with IFG had survival profile similar to that of subjects with normoglycemia based on the fasting glucose criteria alone (DECODE Study Group., 2001). Outcomes from the DECODE study cohort further showed that baseline IGT was an independent risk predictor for cardiovascular morbidity and mortality, and the prediction was not explained by the subsequent development of overt diabetes (Qiao et al., 2003). Recently, a meta-analysis of 15 prospective studies demonstrated a 21% increased risk of stroke (1.21[1.02-1.44]) for intermediate hyperglycemia defined as a FPG of 6.1-6.9 mmol/L after adjusting for established cardiovascular risk factors, whereas no significance observed for the intermediate hyperglycemia defined as a FPG of 5.6-6.9 mmol/L. Moreover, the IGT or the combination of IFG and IGT independently increased the risk of stroke (Lee et al., 2012).

The CVD mortality in relation to both FPG and 2hPG were compared in some studies. Findings from the DECODE and the DECODA studies showed that fitting the 2hPG to a model based on the FPG significantly improved the prediction of the CVD mortality; but no fundamental change was observed when the FPG was adjusted into the model based on the 2hPG (DECODE Study Group., 2001; Nakagami et al., 2004). This was further supported by data from the Cardiovascular Health Study including 4014 adults, where 2hPG criteria appeared to be better than FPG criteria in predicting incidents of CVD among older adults (Smith et al., 2002); and from other studies that showed the relationship between 2hPG and CVD was independent of FPG (DECODE Study Group, 1999; Hyvarinen et al., 2009). A number of studies have shown that IFG and IGT reflect different pathophysiological mechanisms of abnormal glucose homeostasis (Laakso et al., 2008; Nathan et al., 2007b). The individuals with isolated IGT are markedly more insulin resistant than those with isolated IFG (Festa et al., 2004; Meyer et al., 2006). The difference in insulin resistance might partly explain the differences in CVD risk between IFG and IGT.

Both insulin resistance and reduced beta cell function occurred during the normoglycemic stage as shown by the Québec Family Study among 643 participants aged 18 to 71 years (O'Malley et al., 2010; Piche et al., 2005). Another cross-sectional study, including a multi-ethnic sample of 1020 obese youths (with a mean age of 12.9 years) with normal FPG levels (FPG < 5.6 mmol/L), showed that insulin sensitivity declines when moving from low to high glucose levels within the normal range, independent of age, BMI, sex and ethnicity (O'Malley et al., 2010). Recently, it has been shown that among individuals with normal fasting and 2-h plasma glucose, those with 2hPG who did not return to their FPG levels during an OGTT had an increased risk of type 2 diabetes (Abdul-Ghani et al., 2006) and higher carotid intima-media thickness (CIMT) (Succurro et al., 2009) as compared with those whose 2hPG returned to their fasting glucose levels. However, in the Bruneck Study including subjects with normoglycemia, neither 2hPG nor FPG independently predicted the carotid atherosclerosis assessed by the intima-media thickness during a 5-year follow-up (Bonora et al., 1999). Whether or to what extent the insulin resistance contributes to the increased CVD mortality in individuals with normal glucose levels requires further investigation.

### 2.4.3 Intensive glycemic control and CVD outcome

In spite of the strong evidence from large observational epidemiological studies showing the deleterious effects of hyperglycemia on CVD outcomes, intensive glycemic control has not convincingly shown CVD benefit among either patients with type 2 diabetes (Duckworth et al., 2009; The ACCORD study group., 2008; The ADVANCE Collaborative Group., 2008; R. Wilcox et al., 2008) or individuals with IGT (ORIGIN Trial Investigators et al., 2012; The NAVIGATOR study group., 2010). The United Kingdom Prospective Diabetes Study (UKPDS)(Holman et al., 2008; UKPDS Study Group, 1998), the Action to Control Cardiovascular Risk in Diabetes (ACCORD)(The ACCORD study group., 2008), the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE)(The ADVANCE Collaborative Group., 2008), the Veterans Affairs Diabetes Trial (VADT) (Abraira et al., 2003; Duckworth et al., 2009) and the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) (Charbonnel et al., 2004; Dormandy et al.,2005; Wilcox et al., 2008) including patients with diabetes, all showed a reduction in either single or composite CVD events in intensive treatment arms as compared with the control arms, but the risk reduction was borderline significant or insignificant in most of the individual trials. Meta-analysis based on five randomized controlled clinical trials

demonstrated a significant risk reduction in non-fatal myocardial infarction (-17%) and in CHD (-15%), but not in stroke and all-cause deaths (Ray et al., 2009). The discrepancy between observational studies and interventional trials needs to be further investigated regarding the trial designs, patient populations, outcomes defined and drugs applied.

# 3 AIMS OF THE STUDY

1) To investigate risk factors for the increased prevalence of type 2 diabetes among Chinese adults (Study I),
2) To evaluate the joint effect of a positive family history of diabetes and obesity on the prevalence of type 2 diabetes in the Chinese and the Finns (Study II),
3) To estimate the impact of age-related insulin resistance and insulin secretion on prevalence of intermediate hyperglycemia in people of Asian origin (Study III),
4) To study cardiovascular mortality in relation to fasting and 2-hour plasma glucose within normoglycemia in European men and women (Study IV),
5) To examine the impact of normoglycemia on the incidence of coronary heart disease and ischemic stroke in European men and women (Study V).

# 4 STUDY POPULATION AND METHODS

## 4.1 Study population

### 4.1.1 Qingdao Diabetes Survey 2001-2002 and 2006

Qingdao is located on the eastern coast of China and comprises four urban (Shinan, Shibei, Sifang and Licang) and eight rural areas (Laoshan, Chengyang, Jiaonan, Jiaozhou, Jimo, Huangdao, Laixi and Pingdu). From April 2001 to July 2002, a population-based cross-sectional survey for the prevalence of diabetes was conducted in Qingdao. The stratified random cluster sampling was employed to recruit individuals aged 35-74 years and living in Qingdao city for over 5 years (Figure 1). Three urban districts (Shinan, Shibei and Sifang) and four rural areas (Chengyang, Laoshan, Jiaonan and Pingdu) were randomly selected (Dong et al., 2005; Gao et al., 2009). A total of 14500 individuals were invited to attend the survey and 11393 individuals participated in the survey, with an overall response rate of 78.6% (Gao et al., 2009).

Qingdao Diabetes Survey 2006 was carried out in six randomly selected urban and rural areas of Shinan, Shibei, Sifang, Jiaonan, Huangdao and Jimo. Five communities (or villages) from each of the six districts and 200-250 residents aged 35-74 years from each community or village were randomly selected (Figure 1). A total of 6100 individuals were invited and 5355 individuals participated in the survey, with a response rate of 87.8%. Both of the diabetes surveys were approved by the Qingdao Health Bureau and local ethics committees. Verbal or written consents were obtained from all participants.

After excluding individuals with missing information (Table 2), data from 2915 men and 4338 women in the survey of 2001-2002, and 1683 men and 2688 women in the survey of 2006 were included in the study I. The age ranged from 35 to 74 years.

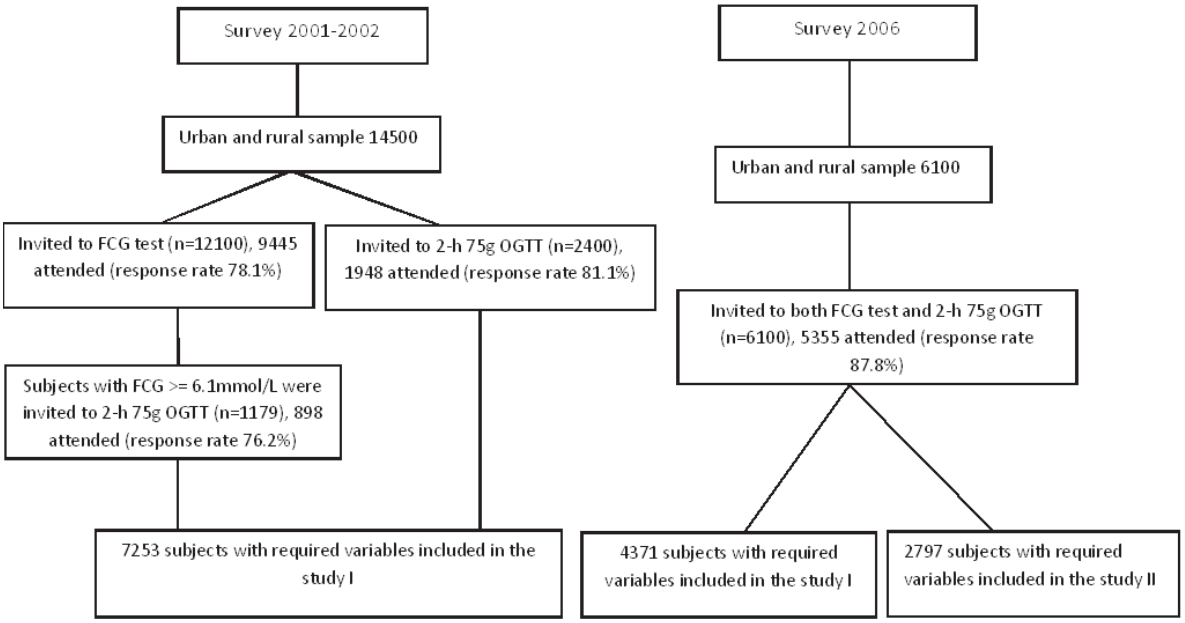



Figure 1. The sampling procedures, participation rates and screening strategies in Qingdao Diabetes Survey 2001-2002 and 2006. FCG, fasting capillary glucose; OGTT, oral glucose tolerance test.

### 4.1.2 FINRISK Study 2002

The FINRISK study is a chronic disease risk factors survey that has been carried out since 1972 in every fifth year using a random sample of the middle-aged Finnish population. The entire study procedure followed the recommendations of WHO-Multinational MONItoring of trends and determinants in CArdiovascular disease (WHO-MONICA) project protocol (WHO MONICA Project Principal Investigators, 1988) and the European Health Risk Monitoring Project (Tolonen et al., 2007). The Coordinating Ethics Committee of Helsinki University Hospital District approved the study protocol and the participants provided their written consent. In 2002, a random sample form the age range of 25-64 years, stratified by sex and age, was drawn from six Population Register Regions; the age group 64-74 years was also included in Helsinki/Vantaa, North Karelia, and Lapland. A total of 13437 individuals were invited and 9581 attended, which gave a response rate of 71.3%.

All participants from the Qingdao Diabetes Survey 2006 were administrated to a standard 2-h OGTT, while only participants aged 45-74 years underwent the OGTT in the FINRISK Study 2002. To make it comparable between the two studies in paper II, only individuals aged 45-74 years from both studies were analyzed. Thus, a total of 1091 men and 1706 women from the Qingdao Diabetes Survey 2006 (Figure 1), and 1472 men and 1694 women from the FINRISK Study 2002 who had all variables required for the data analysis were included in paper II.

### 4.1.3 DECODE and DECODA studies

The DECODE and the DECODA studies were initiated in 1997 and 1998 respectively (Qiao et al., 2000; The DECODE Study Group, 1998). Briefly, researchers who had carried out population-based or large occupational epidemiological studies on diabetes in Europe or in Asia, using a standard 75g glucose load, were invited to participate. From each centre crude original data on sex, age, height, weight, known status of diabetes, date of the start and end of survey, blood specimens used and the method of glucose assay were collected. Individual data on FPG and 2hPG concentrations as well as total cholesterol, fasting insulin and a number of other variables were sent to the National Institute for Health and Welfare in Helsinki, Finland for collaborative data analysis.The informed consent of participants complying with the Declaration of Helsinki or other ethical standards was obtained in all studies. The Ethics Committee of the National Institute for Health and Welfare had approved the data analysis plans for both the DECODE and the DECODA studies. The two studies consisted of 64 cohorts made up of subjects from 24 countries and regions around the world, with about 84000 Europeans and 84207 Asians comprising Chinese, Japanese, Indians, Mongolians and Filipinos. The age ranged from 25 to 99 years. Of the 23 European cohorts they provided the follow-up data on the vital status with 5811 CVD deaths and 12283 all-cause deaths accumulated in Europeans. The existing database has been updated continuously for mortality/morbidity outcomes.

For study III, data from 11 cohorts of the DECODA study including 6610 men and 7664 women aged 30-69 years were analyzed; study IV was restricted to normoglycemic individuals whose FPG < 6.1 mmol/L and 2hPG < 7.8 mmol/L, comprising 12566 men and 10874 women aged 25 to 90 years from 19 European cohorts. A total of 9 cohorts from Finland and Sweden including 3743 men and 3916 women aged 25 to 90 years were included in the study V.

Table 2 Inclusion/Exclusion criteria of the study populations

| | Study population | Inclusion criteria | Exclusion criteria |
|---|---|---|---|
| Study I | Qingdao Diabetes Survey 2001-2002 and 2006/DECODA | 1) Participants aged 35-74 years; 2) Undergoing a standard 2h 75g OGTT test; 3) The availabity of BMI,WC, family history of diabetes, education, personal income, occupation, leisure time physical activity, triglycerides, smoking, drinking and hypertension status. | Missing required variables |
| Study II | Qingdao Diabetes Survey 2006/DECODA and FINRISK 2002/DECODE | 1) Participants aged 45-74 years; 2) Undergoing a standard 2h 75g OGTT test; 3) The availabity of BMI, WC, family history of diabetes, education, personal income, occupation, leisure time physical activity, smoking, drinking and hypertension status. | Missing required variables |
| Study III | 11 study cohorts / DECODA | 1) Participants aged 30-69 years; 2) Undergoing a standard 2h 75g OGTT test; 3) The availabity of BMI and fasting insulin data. | Missing required variables |
| Study IV | 19 study cohorts / DECODE | 1) Cohort study with data on cause-specific mortality; 2) Undergoing a standard 2h 75g OGTT test at baseline; 3) Normoglycemia defined by a FPG < 6.1 mmol/L and a 2hPG < 7.8 mmol/L; 4) Baseline measurement of FPG, 2hPG, total cholesterol, BMI, blood pressure and smoking status | 1) Previously diagnosed diabetes at baseline; 2) a FPG ≥ 6.1 mmol/L and/or a 2hPG ≥ 7.8 mmol/L at baseline |
| Study V | 9 study cohorts / DECODE | 1) Cohort study with data on cause-specific morbidity; 2) Undergoing a standard 2h 75g OGTT test at baseline; 3) Normoglycemia defined by a FPG < 6.1 mmol/L and a 2hPG < 7.8 mmol/L; 4) Baseline measurement of FPG, 2hPG, total cholesterol, BMI, blood pressure and smoking status | 1) A prior history of diabetes and/or CVD at baseline; 2) a FPG ≥ 6.1mmol/L and/or a 2hPG ≥ 7.8 mmol/L at baseline |

## 4.2 Methods

### 4.2.1 Anthropometric and demographic measurements

In all DECODE and DECODA studies, anthropometric measurements were performed by trained doctors or nurses. Height and weight were measured and recorded with participants wearing light clothes and without shoes. Waist circumference was measured at the mid-point between the rib cage and the iliac crest to the nearest 0.1 cm. Body mass index was defined as the individual's body weight divided by the square of his height ($kg/m^2$). Individuals with a BMI ≥ $30kg/m^2$ were considered to be obese according to the criteria of the WHO Expert Consultation (WHO consultation, 2000). Abdominal obesity was classified according to the criteria of National Cholesterol Education Program expert panel, i.e. WC ≥ 102 cm for men and WC ≥ 88 cm for women (Adult Treatment Panel III, 2001). Two consecutive blood pressure readings, at least 30 seconds apart, were taken from the right arm of seated individuals, and the

average of the two readings was recorded. A person with a history of hypertension defined by a physician or having a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg was classified as hypertension (World Health Organization, 1999).

In studies I and II, a positive FHD was defined as having at least one first degree family member (father, mother or siblings) with diabetes. Socioeconomic status (SES) was measured according to two dimensions: education and personal income (Krieger et al., 1997). Occupational status was categorized into white collar, blue collar and not working outside the home. Leisure time physical activity was classified into three levels: (1) Sedentary: taking no regular exercise; (2) Slightly active: relaxing walk after supper or doing Tai Chi; (3) Moderately to vigorously active: jogging, walking briskly, dancing, bowling etc. or engaged in an intensive exercise program (e.g. running, playing basketball, playing football). Smoking status was classified as current smokers (smoking every day) or non-smokers (including ex-smoking, occasional smoking and never smoking). Alcohol consumption status was defined as currently regular drinkers and non-drinkers (including ex-drinking, occasional drinking and never drinking).

### 4.2.2 Blood glucose and insulin assays

Blood samples of the Qingdao Diabetes Surveys 2001-2002 and 2006 were collected at local test centers. From April 2001 to February 2002, a two-step screening approach using a fasting capillary glucose (FCG) test as first-line screening test, followed by a 2-h 75g OGTT as a diagnostic test of newly diagnosed diabetes was applied (Figure 1). For the period of March to July 2002, the OGTTs were directly administered to all participants in one urban community. From February to April 2006, the OGTTs together with the FCG tests were administered to all participants in the survey 2006.

In all DECODE and DECODA cohorts, blood samples were collected after overnight fasting. Plasma glucose was measured in each of the studies with an oxidase- or dehydrogenase-based method. Fasting insulin concentrations were determined by different assays across the study cohorts included in this study. Homeostasis model assessments of insulin resistance (HOMA-IR) and beta cell function (HOMA-B) were calculated by the following equation: HOMA-IR= [(fasting insulin (μIU/ml)* FPG (mmol/L) /22.5], and HOMA-B=20*fasting insulin (μIU/ml) / [FPG (mmol/L) -3.5] (Matthews et al., 1985). Detailed information on glucose, total cholesterol and insulin assays in each study were shown in the Appendix.

### 4.2.3 Classifications of diabetes and intermediate hyperglycemia

A person with a prior history of diabetes or receiving any anti-diabetes therapy at the time of the

surveys was classified as having previously diagnosed diabetes according to the WHO/IDF diagnosis criteria of 2006 (World Health Organization & International Diabetes Federation consultation, 2006). Participants without previously diagnosed diabetes were given a standard 2-h 75g OGTT. Individuals with a FPG ≥ 7.0 mmol/L and/or a 2hPG ≥ 11.1 mmol/L were classified as having newly diagnosed diabetes, a FPG 6.1-6.9 mmol/L and/or a 2hPG 7.8-11.1 mmol/L was classified as IFG and/or IGT. Both IFG and IGT were considered as intermediate hyperglycemia in this study. Normoglycemia was defined as individuals with a FPG < 6.1 mmol/L and a 2hPG < 7.8 mmol/L. In the studies IV and V, the normoglycemic individuals were further classified into Group I if the 2hPG after a 75g oral glucose load was equal to or less than the FPG (2hPG ≤ FPG), or Group II if the 2hPG was greater than FPG (2hPG > FPG).

### 4.2.4 Definition of fatal and non-fatal cardiovascular events

For the cardiovascular mortality in the study IV, vital signs were assessed and recorded for each of the individuals attending the baseline examination. Individuals who had emigrated and for whom the vital status could not be confirmed were treated as censored at the time of emigration. The follow-up was almost complete, from 98% in the Newcastle Heart Project to 100% in most of the other studies (DECODE Study Group, 1999). Causes of death were coded according to the International Classification of Diseases (ICD), 9th Revision (10th Revision) (World Health Organization, 1994). Total CVD death was defined as ICD codes 401-448 (I10-I79).

For the cardiovascular morbidity mentioned in study V, first-ever CHD and stroke events until the end of 2008 were ascertained through a computerized record linkage of the unique national identification numbers of survey participants to the national Causes of Death Registry and the national Hospital Discharge Registry both in Finnish (Mahonen et al., 2000; Tolonen et al., 2007) and in Swedish studies (Stegmayr & Asplund, 1992). Individuals with a prior history of CVD (including a history of CHD, myocardial infarction and stroke) were excluded from data analyses. Incident CHD events were defined as fatal CHD and non-fatal myocardial infarction; ischemic stroke events were defined as fatal and non-fatal ischemic strokes. ICD codes 410 to 414 (I20 to I25) were categorized for fatal CHD; 410 to 411 (I21 to I22, I24) for non-fatal acute myocardial infarction; 433, 434, 436 (I63 to I64) for fatal and non-fatal ischemic strokes, respectively.

### 4.2.5 Statistical analyses

A general linear model of univariate ANOVA was used to estimate mean differences adjusting for age and study cohort. The Chi-square test was employed to calculate the difference in

proportions between study cohorts. All analyses were performed using SPSS 18.0 for Windows (SPSS Inc, Chicago, IL, USA). A probability of less than 0.05 (two tails) was considered statistically significant. The specific statistical methods in each study were described as follows:

**Study I:**

Logistic regression analysis was performed to estimate ORs (95% CIs) for the prevalence of diabetes corresponding to one SD increase in BMI, WC and triglycerides, adjusting for age, survey year, residential districts, FHD, occupational status, school years, income level, leisure time physical activity, smoking status, drinking status and hypertension status.

**Study II:**

Logistic regression analysis was employed to estimate the probability of having diabetes and 95% CI for each BMI or WC category stratified by FHD and sex, adjusting for age, residential areas, occupation, educational level, income level, leisure time physical activity, smoking, drinking and hypertension status. Both observed the prevalence and estimated probability of diabetes were plotted and stratified by FHD and sex. β coefficients corresponding to linear form of BMI or WC were also estimated using logistic regression analysis to examine the slope or the strength of association of BMI (or WC) with the presence of diabetes in individuals with or without a positive FHD adjusting for any confusion.

We employed the synergy index (SI) and relative excess risks due to interaction (RERI) to test whether the joint effect of FHD with obesity was greater than the sum of the independent effects of the single factor on the prevalence of diabetes. The SI was equal to $[OR_{11}-OR_{00}] / [(OR_{01}-OR_{00}) + (OR_{10}-OR_{00})]$, and the RERI was equal to $[OR_{11}- OR_{01}- OR_{10}+1]$ (Rothman, 1986). The OR stands for the odds ratio estimated using logistic regression analysis adjusting for age, residential areas, occupation, school year, income level, leisure time physical activity, smoking status, drinking status and hypertension status for individuals with both FHD and obesity ($OR_{11}$), with FHD but without obesity ($OR_{10}$) and without FHD but with obesity ($OR_{01}$), as compared to those with neither FHD nor obesity ($OR_{00}$). The SI > 1.0 and RERI > 0 indicate the presence of synergistic effect between FHD and elevated BMI (or WC). The synergistic effect of FHD and sex on diabetes was also assessed. The 95% CIs for the SI and RERI were calculated by the method of Hosmer and Lemeshow (Hosmer & Lemeshow, 1992).

**Study III:**

The age-specific prevalence of IFG and IGT by 10-year age groups were calculated for each study included in the DECODA. Logistic regression analysis was used to estimate age-specific

ORs and 95% CIs for IFG and IGT in each ethnic group, subsequently adjusting for BMI, study cohort, HOMA-IR and HOMA-B.

**Studies IV and V:**

The assumption of the proportionality was examined using log minus log survival plots for each categorical variable. None of these indicated departure from the assumption of the proportionality of hazards. Cox proportional hazards analysis was used to calculate HRs and their 95% CIs for CVD mortality (study IV) and morbidity (study V) for the Group II (2hPG > FPG) as compared with Group I (2hPG ≤ FPG). The multivariate models were adjusted for age, study cohort, FPG, BMI, total cholesterol, smoking status and hypertension status at baseline. Fasting insulin concentrations were additionally adjusted in a multivariate model in a subgroup.

The difference between 2hPG and FPG (2hPG-FPG) as a continuous variable was also fitted into a separate multivariate model to examine whether the relationship of normoglycemia and CVD outcomes was linear. In addition, to check whether the "return of the 2hPG to the FPG level" was determined by the FPG levels, the comparison of Group II and Group I was further made in two FPG subgroups: FPG ≤ 5.6 mmol/L and 5.6 mmol/L < FPG < 6.1 mmol/L.

**Z-scores**

To reduce the bias derived from differences in laboratory assays between study cohorts, the cohort-specific Z score transformation was calculated for fasting triglycerides (Study I), FPG, 2hPG (Study II) and fasting insulin concentrations (Studies III, IV and V) in each study cohort before the data was pooled together. The Z score was calculated according to the formula $Z=[\chi-\mu]/\sigma$, where $\chi$ stands for the raw values with mean ($\mu$) and standard deviation ($\sigma$) (Larsen & Marx, 2000).

# 5 RESULTS

## 5.1 Risk factors and the prevalence of diabetes in Qingdao diabetes surveys (Study I)

Characteristics of the study cohorts included in studies I, II and III are summarized in Table 3. Between 2001 and 2006, the age-standardized prevalence of type 2 diabetes increased from 5.2% to 14.2% in men and from 7.2% to 14.5% in women in rural areas, and from 12.6% to 19.4% in men and from 10.2% to 16.6% in women in urban areas in Qingdao, China ($P < 0.05$ for all comparisons). The prevalence increased more in rural than in urban areas, and more in rural men than in rural women. Meanwhile, the prevalence of intermediate hyperglycemia was 17.9% for men and 19.1% for women in urban areas in 2001-2002. The corresponding figures were 21.1% and 23.3% in rural areas, 33.7% and 29.7% in urban areas in 2006, for men and women, respectively.

From 2001 to 2006, age-adjusted mean BMI and WC as well as the prevalence of obesity increased markedly in both men and women in rural areas but remained essentially unchanged in their urban counterparts. Similary, the prevalence of hypertension also increased in rural areas and reached the same level as that in urban areas 5 years previously. The upper level of school years, personal income and the number of people not working outside the home increased in rural areas and in urban women, whereas the frequency of leisure time physical activity reduced substantially in both areas.

Age, FHD and WC were independent risk factors for diabetes and were common in both urban and rural areas, adjusting for conventional risk factors in a multivariate model. High education and high income were significantly associated with a reduced prevalence in all except in rural men. This was closely associated with weight gain. In comparison with 2001-2002, age- and district-adjusted ORs for the prevalence of diabetes in 2006 increased more pronouncedly in rural than in urban areas (men: 5.34 versus 1.85; women: 2.22 versus 1.74). Adjusting for FHD, the ORs decreased moderately in urban women and in rural men and women. A further reduction in the ORs for rural men and women was observed after an additional adjustment for WC, whereas decreased OR was observed only in rural men when SES or WC plus SES were fitted to the model. Further adjustment for occupation, leisure time physical activity, hypertension, smoking and drinking status, the ORs for diabetes prevalence did not change substantially. The corresponding figures were 1.92, 1.79 for urban men and women, 3.33 and 1.70 for their rural counterparts respectively.

Table 3 Characteristics of study cohorts separated by ethnicity/country (studies I, II and III)

| Ethnicity/Country | Studies | Age (year) Mean (range) | No. (% men) | BMI ($kg/m^2$) | FPG (mmol/L) | 2hPG (mmol/L) | Fasting insulin (ρmol/l) | HOMA-IR | HOMA-B | Year of screening |
|---|---|---|---|---|---|---|---|---|---|---|
| Chinese/China | HK-wscvdrf | 41 (30-66) | 1065 (58.5) | 23.8 (0.11) | 4.94 (0.02) | 5.75 (0.05) | 61.5 (1.05) | 13.9 (0.27) | 940.0 (17.66) | 1991 |
| | HK-cvrfps | 45 (30-69) | 1896 (48.7) | 24.0 (0.08) | 5.10 (0.01) | 6.16 (0.04) | 40.5 (0.77) | 9.4 (0.20) | 525.5 (12.91) | 1995-1996 |
| | Qingdao 2001-02 | 52 (35-74) | 7253 (40.2) | 25.5 (0.04) | 6.14 (0.04) | 7.72 (0.08) | NA | NA | NA | 2001-2002 |
| | Qingdao 2006 | 51 (35-74) | 4371 (38.5) | 25.9 (0.05) | 6.02 (0.04) | 8.03 (0.07) | 45.5 (0.69) | 11.1 (0.19) | 575.6 (14.13) | 2006 |
| Finns/Finland | FINRISK 2002 | 58 (45-74) | 3166 (46.5) | 27.9 (0.08) | 5.96 (0.02) | 6.83 (.05) | NA | NA | NA | 2002 |
| African/Mauritius | Mauritius 1987 | 45 (30-69) | 889 (46.7) | 24.1 (0.16) | 5.39 (0.02) | 6.39 (0.06) | 47.1 (1.62) | 11.6 (0.42) | 535.3 (18.72) | 1987 |
| | Mauritius 1992 | 47 (30-69) | 557 (43.3) | 25.5 (0.20) | 5.49 (0.02) | 6.28 (0.07) | 78.1 (2.05) | 19.3 (0.53) | 811.8 (23.73) | 1992 |
| | Mauritius 1998 | 40 (30-68) | 271 (43.2) | 25.0 (0.29) | 5.32 (0.04) | 6.17 (0.10) | 64.5 (2.98) | 15.3 (0.77) | 773.1 (34.41) | 1998 |
| Indian/India | CUPS 1997 | 44 (30-69) | 665 (40.5) | 22.9 (0.16) | 4.38 (0.02) | 5.60 (0.06) | 48.5 (1.74) | 10.0 (0.39) | 1093.0 (45.29) | 1996-1998 |
| | CURES | 42 (30-69) | 1326 (45.1) | 23.3 (0.11) | 4.81 (0.02) | 6.11 (0.04) | 59.6 (1.22) | 12.9 (0.27) | 1050.6 (31.76) | 2001 |
| Indian/Mauritius | Mauritius 1987 | 43 (30-69) | 2196 (46.3) | 23.4 (0.09) | 5.17 (0.01) | 6.39 (0.03) | 52.5 (1.07) | 12.3 (0.27) | 652.4 (12.61) | 1987 |
| | Mauritius 1992 | 46 (30-69) | 1110 (47.8) | 24.9 (0.13) | 5.40 (0.02) | 6.57 (0.05) | 78.3 (1.51) | 19.2 (0.39) | 858.4 (17.82) | 1992 |
| | Mauritius 1998 | 41 (30-68) | 618 (43.0) | 24.4 (0.18) | 5.33 (0.01) | 6.40 (0.07) | 71.6 (2.02) | 17.1 (0.52) | 822.2 (23.88) | 1998 |
| Japanese/Brazil and USA | San Paulo 1992 | 55 (37-69) | 365 (48.5) | 24.5 (0.18) | 5.16 (0.03) | 6.01 (0.09) | 38.4 (2.47) | 8.9 (0.63) | 506.1 (39.70) | 1992-1993 |
| | San Paulo 1999 | 52 (31-69) | 696 (42.5) | 24.0 (0.13) | 6.13 (0.02) | 7.29 (0.06) | 54.8 (1.78) | 15.2 (0.45) | 426.9 (28.56) | 1999-2000 |
| | Seattle | 51 (34-69) | 458 (51.3) | 24.1 (0.16) | 5.27 (0.03) | 7.35 (0.07) | 93.7 (2.20) | 22.3 (0.56) | 1212.5 (35.35) | 2001 |

Data are age-adjusted mean (SE) unless otherwise stated. BMI, body mass index; CUPS1997, Chennai Urban Population Study in 1997; CURES, Chennai Urban Rural Epidemiology Study; FPG, fasting plasma glucose; 2hPG, 2-hour plasma glucose; HK-cvrfps, Hong Kong Cardiovascular Risk Factor Prevalence Study; HK-wscvdrf, Hong Kong Workforce Survey on Cardiovascular Risk Factors; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-B, homeostasis model assessment of beta cell function; NA, not available.

## 5.2 Joint effect of a family history of diabetes with obesity on the prevalence of type 2 diabetes in the Chinese and the Finns (Study II)

Previous studies have demonstrated that a positive FHD and obesity were two major risk factors for type 2 diabetes both in the Chinese and the Finns. Individuals with a positive FHD had greater BMI, WC, FPG and 2hPG than those without in both ethnic groups, except BMI and WC in Chinese women. Age-standardized prevalence of diabetes was significantly higher in individuals with a positive FHD than in those without in both ethnic groups ($P < 0.05$) (Figure 2 and 3). Compared with individuals having BMI < 30 kg/m$^2$, those with BMI ≥ 30 kg/m$^2$ had a higher prevalence of diabetes in all ($P < 0.001$) except Chinese men. The prevalence of obesity defined by either BMI or WC was significantly higher in individuals with a positive FHD than those without ($P < 0.05$) in the Finns. Such a finding was only observed in the BMI category in Chinese men.

A positive FHD was less reported in Chinese men and women than in their Finnish counterparts ($P < 0.05$). In comparison with the reference group, the ORs associated with the FHD alone were approximately equal in men as in women and not different in the Finns from those in the Chinese. Either a positive FHD or obesity was independently associated with an increased OR for type 2 diabetes; obesity plus a positive FHD slightly increased the OR over that for each factor alone. However, the synergistic effect of a positive FHD and obesity on diabetes was statistically significant only in Finnish men. The corresponding figures of SI were 2.4 (1.4-3.9) in the BMI category and 2.2 (1.3-3.6) in the WC category. Considering the cut-offs of the BMI or WC derived from the Europeans may be too high for the Chinese, further analyses were performed by lowering the BMI from ≥ 30kg/m$^2$ to BMI ≥ 28kg/m$^2$ or WC from ≥ 102 cm to WC ≥ 90 cm for men and from ≥ 88 cm to ≥ 80 cm for women. Lowering the BMI or the WC cut-off values did not alter the results in the Chinese. The corresponding SIs were 0.72 (0.31, 1.36) and 0.90 (0.46, 1.58) in the new BMI category, and 1.5 (0.5, 4.0) and 1.1 (0.6, 2.1) in the new WC category, for men and women, respectively.

As compared with women without a FHD, the OR (95%CI) was 2.1 (1.5, 2.9) for men without a FHD, 2.1 (1.5, 2.9) for women with a positive FHD and 5.9 (4.2, 8.3) for men with a positive FHD in the Finns. The corresponding figures were 1.0 (0.8, 1.4), 1.9 (1.4, 2.6), 3.0 (2.0, 4.6) in the Chinese. The SIs (95%CIs) were 2.3 (1.5, 3.5) and 2.2 (1.0, 4.6) for the Finns and the Chinese, respectively.

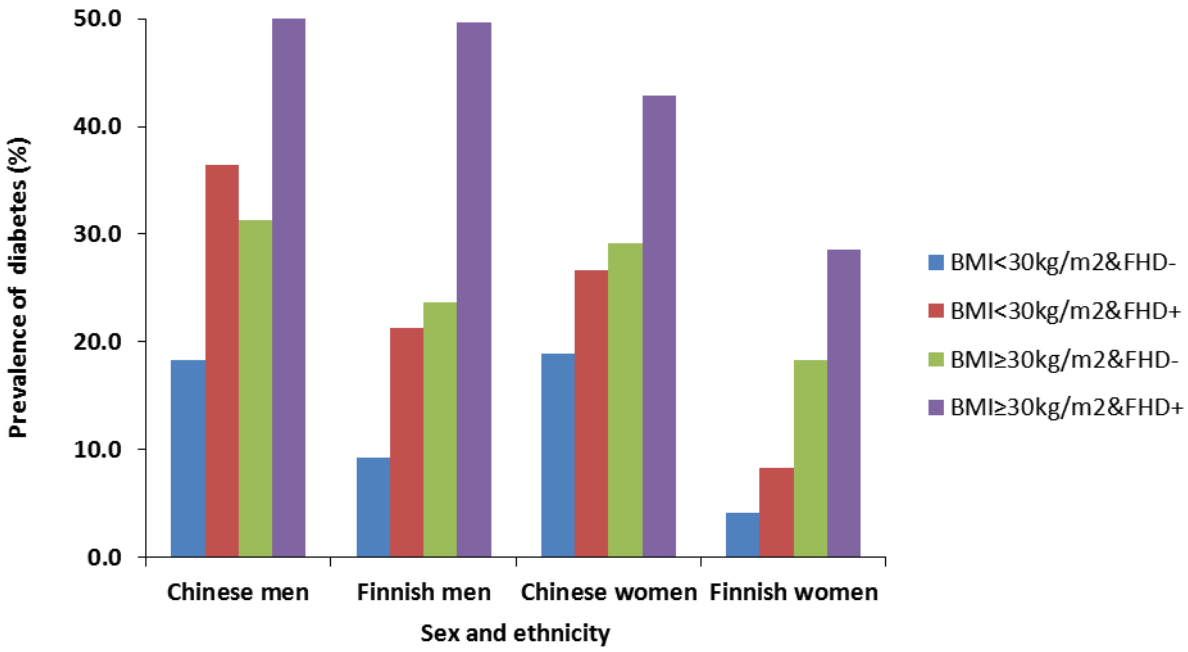



Figure 2 Sex- and ethnic-specific prevalence of type 2 diabetes according to BMI categories and the presence ($FHD^+$) or absence ($FHD^-$) of a family history of diabetes (study II)

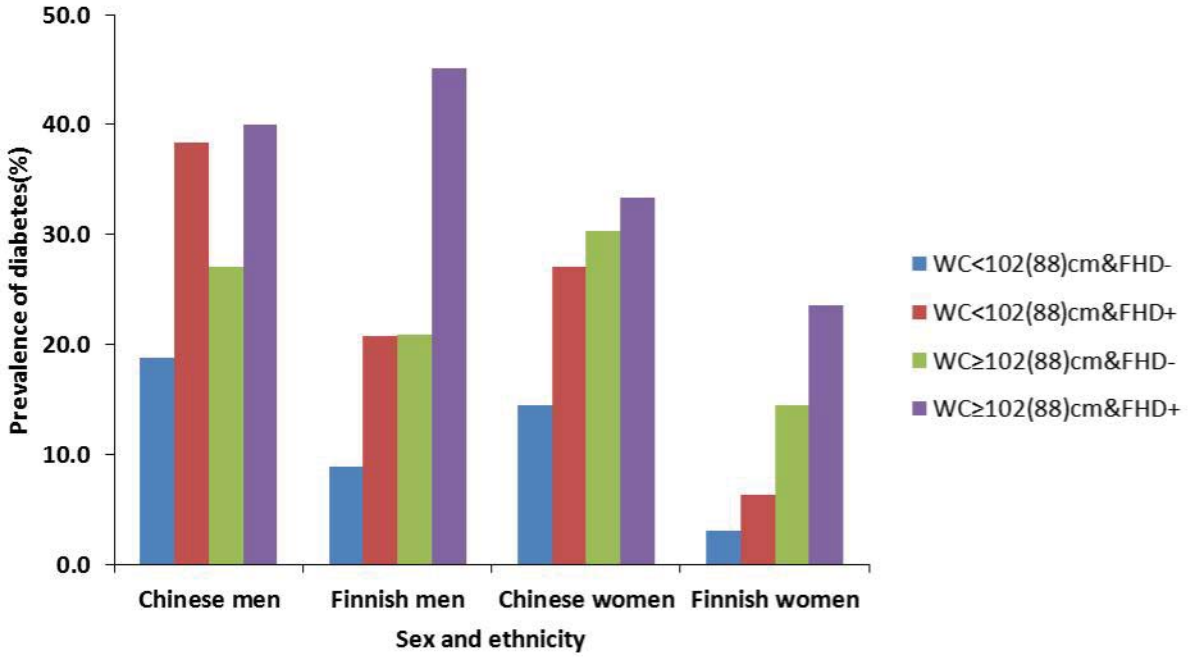
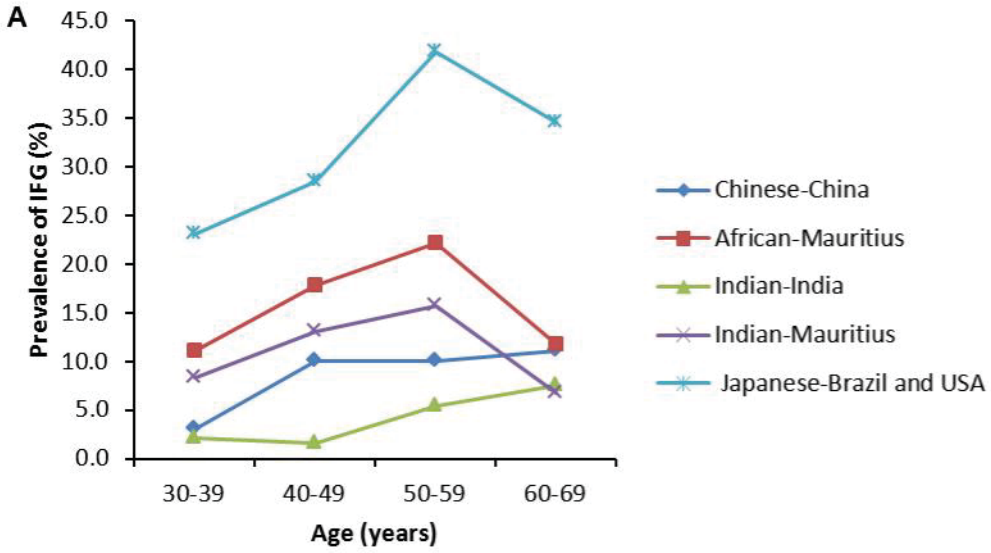



Figure 3 Sex- and ethnic-specific prevalence of type 2 diabetes according to WC categories and the presence (FHD+) or absence (FHD-) of a family history of diabetes (study II)

## 5.3 The impact of insulin sensitivity and insulin secretion on intermediate hyperglycemia in relation to aging (Study III)

The increased prevalence of intermediate hyperglycemia (IFG and IGT) as well as insulin resistance was associated with risk of type 2 diabetes. Along with age, the prevalence of obesity and physical inactivity it increases dramatically, which may accelerate the process of intermediate hyperglycemia and insulin resistance to diabetes. Characteristics of the individuals of Asian origin within non-diabetic hyperglycemia differed slightly among studies of the same ethnicity (Table 3). In all ethnic groups, the mean Z scores of FPG and 2hPG increased with age among men and women ($P < 0.001$ for all comparisons), while beta cell function declined with age, although it did not reach statistical significance in Indians living in India and Japanese men living in Brazil and the USA. However, no consistent trend was observed for mean Z scores of insulin resistance across age groups.

The prevalence of IFG (Figure 4) and IGT (Figure 5) increased significantly with age in men and women of all ethnic groups ($P$ for trends $< 0.05$ for all comparisons), except IFG in Indians living in India and African men living in Mauritius. As shown in Tables 4 and 5, the increase was more prominent for IGT than for IFG in both sexes, and the associations of age with IFG and IGT were not altered after adjustment for BMI and studies. Further adjustment for either insulin resistance, or beta cell function, or both simultaneously reduced the OR for IFG and IGT in all age groups of all ethnic groups. The reduction was slightly larger in the middle (50-59 years) and old (60-69 years) age groups than in the younger (40-49 years) age group for IFG in some ethnic groups but not in others. The results based on pooled data analysis indicated that the age-related increase in IFG also remained after adjustment for insulin resistance and beta cell function, although it decreased substantially. The OR for IGT decreased when both insulin resistance and beta cell function fitted simultaneously into the model, but the risk gradient for IGT still remained across age groups, suggesting an independent effect of age.



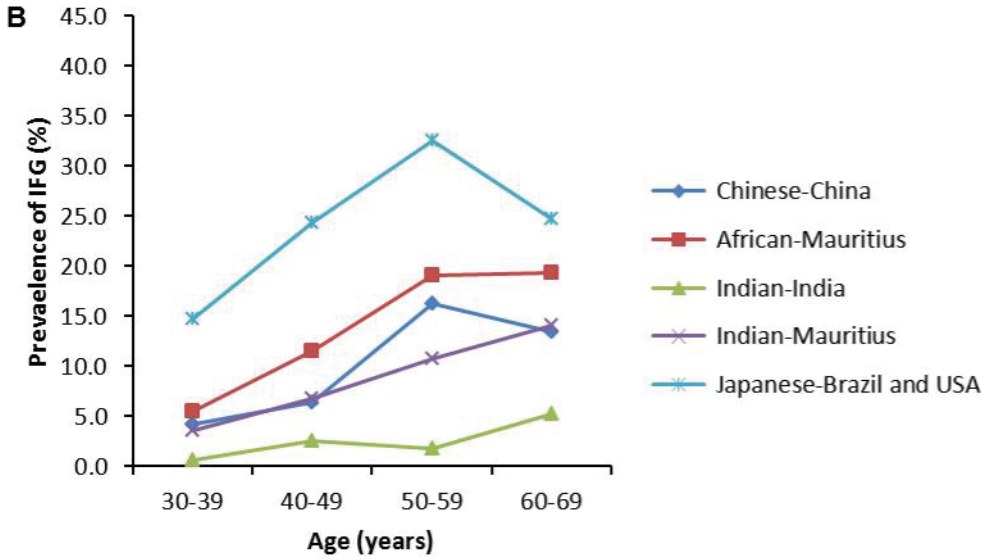




Figure 4 Age- and sex-specific prevalence of impaired fasting glucose (IFG) for men (A) and women (B). $P < 0.05$ for increasing trends for all ethnic groups across age groups, except for Mauritian Indian and Mauritian African men (Study III)

Table 4 Odds ratios and 95% confidence intervals for impaired fasting glucose (IFG) by age among individuals without diabetes (Study III)

| Ethnicity | Age (years) | | | | P for trend |
|---|---|---|---|---|---|
| | 30-39 | 40-49 | 50-59 | 60-69 | |
| Men | | | | | |
| Chinese-China | | | | | |
| Model 1 | 1 | 2.69 (1.70,4.26) | 2.51 (1.49,4.21) | 2.89 (1.68,4.97) | <0.001 |
| Model 2: 1+HOMA-IR | 1 | 2.76 (1.70,4.46) | 2.72 (1.59,4.68) | 3.06 (1.73,5.42) | <0.001 |
| Model 3: 1+HOMA-B | 1 | 2.39 (1.50,3.80) | 2.02 (1.19,3.40) | 2.34 (1.35,4.06) | 0.012 |
| Model 4: 1+HOMA-IR+ HOMA-B | 1 | 2.06 (0.85,5.02) | 1.37 (0.53,3.54) | 1.42 (0.51,3.94) | 0.977 |
| African-Mauritius | | | | | |
| Model 1 | 1 | 1.64 (0.98,2.73) | 2.11 (1.27,3.51) | 1.02 (0.50,2.10) | 0.140 |
| Model 2: 1+HOMA-IR | 1 | 1.58 (0.93,2.70) | 2.28 (1.34,3.87) | 1.01 (0.47,2.15) | 0.117 |
| Model 3: 1+HOMA-B | 1 | 1.59 (0.95,2.67) | 1.99 (1.19,3.33) | 0.98 (0.47,2.01) | 0.212 |
| Model 4: 1+HOMA-IR+ HOMA-B | 1 | 1.01 (0.36,2.85) | 1.51 (0.54,4.18) | 0.27 (0.05,1.43) | 0.497 |
| Indian-India | | | | | |
| Model 1 | 1 | 0.76 (0.23,2.55) | 2.70 (0.99,7.34) | 4.28 (1.40,13.07) | 0.004 |
| Model 2: 1+HOMA-IR | 1 | 0.62 (0.18,2.13) | 2.09 (0.73,5.99) | 4.17 (1.35,12.87) | 0.009 |
| Model 3: 1+HOMA-B | 1 | 0.86 (0.25,2.91) | 2.92 (1.06,8.04) | 4.64 (1.49,14.42) | 0.003 |
| Model 4: 1+HOMA-IR+ HOMA-B | 1 | 0.68 (0.16,2.88) | 1.09 (0.28,4.22) | 4.78 (1.24,18.39) | 0.056 |
| Indian-Mauritius | | | | | |
| Model 1 | 1 | 1.49 (1.03,2.15) | 1.89 (1.27,2.81) | 0.78 (0.41,1.49) | 0.193 |
| Model 2: 1+HOMA-IR | 1 | 1.57 (1.07,2.29) | 2.02 (1.34,3.05) | 0.86 (0.45,1.65) | 0.107 |
| Model 3: 1+HOMA-B | 1 | 1.42 (0.98,2.06) | 1.73 (1.16,2.58) | 0.71 (0.37,1.36) | 0.429 |
| Model 4: 1+HOMA-IR+ HOMA-B | 1 | 1.17 (0.55,2.46) | 1.25 (0.58,2.71) | 0.68 (0.24,1.91) | 0.768 |
| Japanese-Brazil/USA | | | | | |
| Model 1 | 1 | 1.33 (0.71,2.48) | 3.12 (1.67,5.85) | 2.25 (1.22,4.16) | 0.001 |
| Model 2: 1+HOMA-IR | 1 | 1.35 (0.72,2.52) | 3.29 (1.75,6.20) | 2.35 (1.27,4.34) | 0.001 |
| Model 3: 1+HOMA-B | 1 | 1.24 (0.65,2.37) | 2.74 (1.44,5.20) | 1.98 (1.06,3.70) | 0.006 |
| Model 4: 1+HOMA-IR+ HOMA-B | 1 | 1.06 (0.51,2.22) | 2.76 (1.32,5.75) | 1.98 (0.96,4.08) | 0.008 |
| Subtotal | | | | | |
| Model 1 | 1 | 1.66 (1.33,2.07) | 2.26 (1.79,2.86) | 1.74 (1.32,2.28) | <0.001 |
| Model 2: 1+HOMA-IR | 1 | 1.67 (1.33,2.10) | 2.41 (1.90,3.07) | 1.83 (1.38,2.42) | <0.001 |
| Model 3: 1+HOMA-B | 1 | 1.58 (1.26,1.98) | 2.02 (1.59,2.56) | 1.54 (1.17,2.03) | <0.001 |
| Model 4: 1+HOMA-IR+ HOMA-B | 1 | 1.26 (0.94,1.69) | 1.54 (1.14,2.08) | 1.19 (0.84,1.70) | 0.086 |

| | | | | | |
|---|---|---|---|---|---|
| Women | | | | | |
| Chinese-China | | | | | |
| Model 1 | 1 | 1.20 (0.78,1.86) | 2.58 (1.68,3.98) | 2.61 (1.55,4.39) | <0.001 |
| Model 2: 1+HOMA-IR | 1 | 1.29 (0.82,2.02) | 2.45 (1.57,3.84) | 2.69 (1.58,4.60) | <0.001 |
| Model 3: 1+HOMA-B | 1 | 1.03 (0.66,1.60) | 2.06 (1.33,3.21) | 2.04 (1.20,3.48) | <0.001 |
| Model 4: 1+HOMA-IR+ HOMA-B | 1 | 1.24 (0.55,2.81) | 1.77 (0.79,3.99) | 1.88 (0.72,4.96) | 0.107 |
| African-Mauritius | | | | | |
| Model 1 | 1 | 2.04 (1.10,3.79) | 3.32 (1.87,5.90) | 3.60 (1.95,6.62) | <0.001 |
| Model 2: 1+HOMA-IR | 1 | 2.36 (1.25,4.46) | 3.63 (2.01,6.55) | 4.17 (2.22,7.85) | <0.001 |
| Model 3: 1+HOMA-B | 1 | 1.76 (0.94,3.28) | 2.83 (1.57,5.07) | 2.94 (1.58,5.49) | <0.001 |
| Model 4: 1+HOMA-IR+ HOMA-B | 1 | 1.71 (0.36,8.18) | 2.48 (0.57,10.75) | 4.01 (0.81.19.94) | 0.076 |
| Indian-India | | | | | |
| Model 1 | 1 | 4.26 (1.14,15.94) | 3.11 (0.61,15.81) | 11.04 (2.49,45.98) | 0.003 |
| Model 2: 1+HOMA-IR | 1 | 4.59 (1.18,17.87) | 3.33 (0.64,17.49) | 12.45 (2.66,58.32) | 0.003 |
| Model 3: 1+HOMA-B | 1 | 3.88 (1.03,14.57) | 2.96 (0.58,15.09) | 9.96 (2.25,44.08) | 0.005 |
| Model 4: 1+HOMA-IR+ HOMA-B | 1 | 3.21 (0.69,14.99) | 3.14 (0.51,19.23) | 11.77 (2.18,63.52) | 0.006 |
| Indian-Mauritius | | | | | |
| Model 1 | 1 | 1.65 (1.01,2.69) | 2.77 (1.71,4.50) | 4.21 (2.49,7.10) | <0.001 |
| Model 2: 1+HOMA-IR | 1 | 1.90 (1.15,3.16) | 3.11 (1.88,5.14) | 4.97 (2.89,8.56) | <0.001 |
| Model 3: 1+HOMA-B | 1 | 1.45 (0.88,2.38) | 2.29 (1.40,3.76) | 3.37 (1.98,5.74) | <0.001 |
| Model 4: 1+HOMA-IR+ HOMA-B | 1 | 0.86 (0.20,3.71) | 2.34 (0.66,8.26) | 1.29 (0.32,5.21) | 0.396 |
| Japanese-Brazil/USA | | | | | |
| Model 1 | 1 | 1.90 (0.97,3.73) | 2.43 (1.27,4.68) | 2.42 (1.23,4.77) | 0.013 |
| Model 2: 1+HOMA-IR | 1 | 1.87 (0.95,3.69) | 2.56 (1.32,4.93) | 2.37 (1.20,4.67) | 0.014 |
| Model 3: 1+HOMA-B | 1 | 1.92 (0.97,3.81) | 2.32 (1.20,4.49) | 2.46 (1.24,4.89) | 0.015 |
| Model 4: 1+HOMA-IR+ HOMA-B | 1 | 1.72 (0.71,4.15) | 2.47 (1.05,5.80) | 2.42 (1.01,5.83) | 0.040 |
| Subtotal | | | | | |
| Model 1 | 1 | 1.66 (1.28,2.14) | 2.86 (2.22,3.68) | 3.30 (2.49,4.36) | <0.001 |
| Model 2: 1+HOMA-IR | 1 | 1.82 (1.40,2.37) | 3.03 (2.34,3.92) | 3.57 (2.68,4.76) | <0.001 |
| Model 3: 1+HOMA-B | 1 | 1.49 (1.15,1.93) | 2.42 (1.87,3.13) | 2.80 (2.11,3.72) | <0.001 |
| Model 4: 1+HOMA-IR+ HOMA-B | 1 | 1.35 (0.96,1.90) | 1.73 (1.24,2.41) | 2.04 (1.41,2.93) | <0.001 |

Model 1 adjusted for body mass index and studies. HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-B, homeostasis model assessment of beta cell function

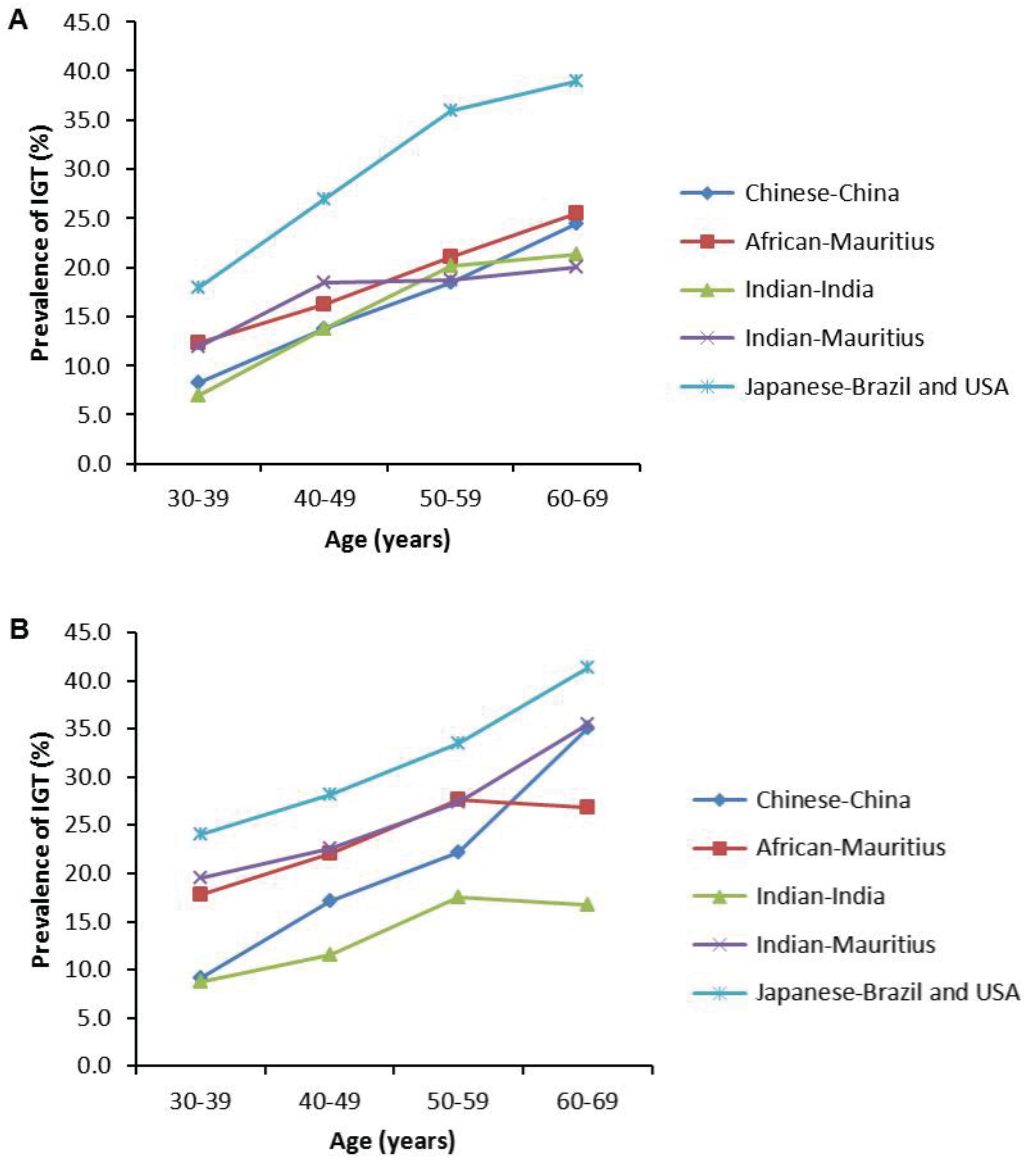



Figure 5 Age- and sex-specific prevalence of impaired glucose tolerance (IGT) for men (A) and women (B). $P < 0.05$ for increasing trends for all ethnic groups across age groups. (Study III)

Table 5 Odds ratios and 95% confidence intervals for impaired glucose tolerance (IGT) by age among individuals without diabetes (Study III)

| Ethnicity | Age (years) | | | | P for trend |
|---|---|---|---|---|---|
| | 30-39 | 40-49 | 50-59 | 60-69 | |
| Men | | | | | |
| Chinese-China | | | | | |
| Model 1 | 1 | 1.73 (1.25,2.38) | 2.54 (1.78,3.63) | 3.57 (2.46,5.19) | <0.001 |
| Model 2: 1+HOMA-IR | 1 | 1.72 (1.25,2.38) | 2.61 (1.82,3.74) | 3.58 (2.45,5.22) | <0.001 |
| Model 3:1+HOMA-B | 1 | 1.67 (1.21,2.30) | 2.40 (1.67,3.44) | 3.39 (2.32,4.93) | <0.001 |
| Model 4: 1+HOMA-IR+ HOMA-B | 1 | 1.53 (1.10,2.12) | 2.15 (1.49,3.10) | 2.97 (2.02,4.35) | <0.001 |
| African-Mauritius | | | | | |
| Model 1 | 1 | 1.31 (0.78,2.18) | 1.83 (1.10,3.04) | 2.59 (1.45,4.62) | 0.001 |
| Model 2: 1+HOMA-IR | 1 | 1.25 (0.74,2.11) | 1.88 (1.12,3.16) | 2.64 (1.46,4.74) | <0.001 |
| Model 3: 1+HOMA-B | 1 | 1.30 (0.78,2.18) | 1.82 (1.09,3.03) | 2.58 (1.44,4.61) | 0.001 |
| Model 4: 1+HOMA-IR+ HOMA-B | 1 | 1.04 (0.61,1.79) | 1.58 (0.93,2.69) | 2.29 (1.26,4.18) | 0.004 |
| Indian-India | | | | | |
| Model 1 | 1 | 2.22 (1.30,3.81) | 3.56 (2.01,6.29) | 4.78 (2.40,9.54) | <0.001 |
| Model 2: 1+HOMA-IR | 1 | 2.06 (1.20,3.56) | 3.27 (1.83,5.84) | 4.58 (2.28,9.20) | <0.001 |
| Model 3: 1+HOMA-B | 1 | 2.27 (1.33,3.90) | 3.61 (2.04,6.39) | 4.84 (2.42,9.66) | <0.001 |
| Model 4: 1+HOMA-IR+ HOMA-B | 1 | 2.07 (1.19,3.61) | 3.15 (1.74,5.70) | 4.50 (2.22,9.12) | <0.001 |
| Indian-Mauritius | | | | | |
| Model 1 | 1 | 1.54 (1.12,2.12) | 1.75 (1.22,2.49) | 2.07 (1.35,3.20) | <0.001 |
| Model 2: 1+HOMA-IR | 1 | 1.57 (1.14,2.17) | 1.80 (1.25,2.59) | 2.20 (1.42,3.40) | <0.001 |
| Model 3: 1+HOMA-B | 1 | 1.56 (1.14,2.15) | 1.79 (1.25,2.56) | 2.13 (1.38,3.29) | <0.001 |
| Model 4: 1+HOMA-IR+ HOMA-B | 1 | 1.50 (1.08,2.08) | 1.63 (1.12,2.35) | 2.00 (1.29,3.11) | <0.001 |
| Japanese-Brazil/USA | | | | | |
| Model 1 | 1 | 2.13 (1.17,3.90) | 3.62 (2.00,6.56) | 4.05 (2.29,7.17) | <0.001 |
| Model 2: 1+HOMA-IR | 1 | 2.19 (1.19,4.04) | 3.93 (2.15,7.18) | 4.37 (2.45,7.82) | <0.001 |
| Model 3: 1+HOMA-B | 1 | 2.14 (1.17,3.90) | 3.65 (2.00,6.63) | 4.07 (2.29,7.24) | <0.001 |
| Model 4: 1+HOMA-IR+ HOMA-B | 1 | 2.17 (1.15,4.07) | 3.46 (1.86,6.43) | 3.95 (2.17,7.19) | <0.001 |
| Subtotal | | | | | |
| Model 1 | 1 | 1.65 (1.38,1.98) | 2.33 (1.92,2.83) | 3.04 (2.46,3.76) | <0.001 |
| Model 2: 1+HOMA-IR | 1 | 1.64 (1.36,1.97) | 2.39 (1.97,2.91) | 3.11 (2.51,3.85) | <0.001 |
| Model 3: 1+HOMA-B | 1 | 1.64 (1.37,1.97) | 2.30 (1.90,2.80) | 3.01 (2.43,3.72) | <0.001 |
| Model 4: 1+HOMA-IR+ HOMA-B | 1 | 1.52 (1.26,1.83) | 2.07 (1.70,2.53) | 2.73 (2.20,3.39) | <0.001 |

| | | | | | |
|---|---|---|---|---|---|
| Women | | | | | |
| Chinese-China | | | | | |
| Model 1 | 1 | 1.72 (1.29,2.31) | 1.92 (1.39,2.66) | 3.84 (2.68,5.47) | <0.001 |
| Model 2: 1+HOMA-IR | 1 | 1.80 (1.34,2.42) | 1.84 (1.32,2.56) | 3.93 (2.74,5.64) | <0.001 |
| Model 3: 1+HOMA-B | 1 | 1.71 (1.27,2.29) | 1.89 (1.36,2.63) | 3.77 (2.63,5.41) | <0.001 |
| Model 4: 1+HOMA-IR+ HOMA-B | 1 | 1.61 (1.19,2.17) | 1.51 (1.07,2.11) | 3.22 (2.23,4.65) | <0.001 |
| African-Mauritius | | | | | |
| Model 1 | 1 | 1.19 (0.78,1.82) | 1.45 (0.96,2.20) | 1.51 (0.95,2.39) | 0.039 |
| Model 2: 1+HOMA-IR | 1 | 1.29 (0.84,2.00) | 1.49 (0.98,2.28) | 1.62 (1.01,2.60) | 0.023 |
| Model 3: 1+HOMA-B | 1 | 1.23 (0.80,1.89) | 1.51 (0.99,2.30) | 1.57 (0.99,2.51) | 0.027 |
| Model 4: 1+HOMA-IR+ HOMA-B | 1 | 1.19 (0.77,1.84) | 1.24 (0.80,1.92) | 1.37 (0.85,2.22) | 0.178 |
| Indian-India | | | | | |
| Model 1 | 1 | 1.57 (0.99,2.49) | 3.03 (1.79,5.11) | 3.31 (1.72,6.38) | <0.001 |
| Model 2: 1+HOMA-IR | 1 | 1.50 (0.94,2.40) | 2.89 (1.70,4.90) | 3.16 (1.63,6.12) | <0.001 |
| Model 3: 1+HOMA-B | 1 | 1.54 (0.97,2.45) | 3.00 (1.77,5.06) | 3.24 (1.68,6.26) | <0.001 |
| Model 4: 1+HOMA-IR+ HOMA-B | 1 | 1.38 (0.86,2.22) | 2.74 (1.61,4.66) | 2.87 (1.48,5.58) | <0.001 |
| Indian-Mauritius | | | | | |
| Model 1 | 1 | 1.03 (0.79,1.34) | 1.37 (1.03,1.82) | 2.19 (1.57,3.04) | <0.001 |
| Model 2: 1+HOMA-IR | 1 | 1.12 (0.85,1.47) | 1.46 (1.08,1.95) | 2.40 (1.71,3.37) | <0.001 |
| Model 3: 1+HOMA-B | 1 | 1.05 (0.80,1.37) | 1.41 (1.05,1.88) | 2.28 (1.63,3.19) | <0.001 |
| Model 4: 1+HOMA-IR+ HOMA-B | 1 | 1.04 (0.79,1.37) | 1.27 (0.94,1.71) | 1.98 (1.40,2.80) | <0.001 |
| Japanese-Brazil/USA | | | | | |
| Model 1 | 1 | 1.49 (0.87,2.55) | 2.01 (1.18,3.42) | 2.82 (1.67,4.78) | <0.001 |
| Model 2: 1+HOMA-IR | 1 | 1.50 (0.87,2.58) | 2.05 (1.20,3.50) | 2.79 (1.64,4.75) | <0.001 |
| Model 3: 1+HOMA-B | 1 | 1.49 (0.87,2.56) | 2.01 (1.18,3.43) | 2.83 (1.67,4.80) | <0.001 |
| Model 4: 1+HOMA-IR+ HOMA-B | 1 | 1.42 (0.82,2.47) | 1.92 (1.12,3.31) | 2.60 (1.52,4.46) | <0.001 |
| Subtotal | | | | | |
| Model 1 | 1 | 1.31 (1.13,1.53) | 1.66 (1.41,1.96) | 2.48 (2.07,2.98) | <0.001 |
| Model 2: 1+HOMA-IR | 1 | 1.38 (1.18,1.61) | 1.67 (1.41,1.97) | 2.56 (2.13,3.08) | <0.001 |
| Model 3: 1+HOMA-B | 1 | 1.32 (1.13,1.55) | 1.68 (1.42,1.98) | 2.51 (2.09,3.02) | <0.001 |
| Model 4: 1+HOMA-IR+ HOMA-B | 1 | 1.27 (1.08,1.48) | 1.45 (1.22,1.71) | 2.20 (1.83,2.66) | <0.001 |

Model 1 adjusted for body mass index and studies. HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-B, homeostasis model assessment of beta cell function

## 5.4 Normoglycemia and cardiovascular mortality in Europeans without a prior history of diabetes (Study IV)

During a median follow-up of 9.0 years, a total of 827 CVD deaths in men and 246 in women was accumulated to estimate the relationship between elevated 2hPG and CVD outcomes within the normoglycemic range (Table 6). In comparison with individuals whose 2hPG returned to FPG levels (Group I), mortality from CVD was significantly higher in both men and women whose 2hPG did not (Group II) (7.4 versus 5.4; 2.3 versus 1.4 per 1,000 person-years, respectively, $P < 0.05$ for all). Individuals in Group II were older and had greater levels of BMI, blood pressure, fasting insulin concentrations than those in Group I in both sexes ($P < 0.001$ for all comparisons).

HR for CVD mortality was 1.22 (1.05-1.41) in men and 1.40 (1.03-1.89) in women whose 2hPG did not return to FPG level as compared with those in whom it did, adjusting for age, study cohort, BMI, FPG, total serum cholesterol, smoking and hypertension status. Further analysis in the two FPG subgroups did not alter the results either. HRs (95% CIs) for the CVD mortality were 1.27 (1.08-1.48) in individuals with a FPG $\leq$ 5.6 mmol/L and 1.26 (1.00-1.59) in those with a FPG 5.6-6.1 mmol/L, for Group II versus Group I. The trends did not alter after adjustment for fasting insulin concentrations in a subgroup including 9978 men and 7350 women. The corresponding figures were 1.25 (1.05-1.50) and 1.60 (1.03-2.48) for CVD mortality in men and in women respectively.

The trends did not change after the categorical glucose variables were replaced by the continuous variables. HRs (95% CIs) corresponding to one unit (mmol/L) increase in the difference between the 2hPG and the FPG concentrations (2hPG-FPG) were 1.09 (1.03-1.16) and 1.09 (0.97-1.23) for the CVD deaths in men and in women respectively.

Table 6 Baseline characteristics of study cohorts, and number of deaths from cardiovascular diseases (CVD) in individuals with fasting plasma glucose (FPG) < 6.1 mmol/L and 2h plasma glucose (2hPG) < 7.8 mmol/L (Study IV)

| Countries and Studies | No. (men/women) | Age, year Mean (range) | FPG (mmol/L)* | 2hPG (mmol/L)* | Fasting insulin (ρmol/L)*† | total cholesterol (mmol/L)* | No. of CVD deaths (men/women) | Median of follow-up years ($25^{th}$,$75^{th}$ percentiles) |
|---|---|---|---|---|---|---|---|---|
| Denmark | | | | | | | | |
| Glostrup | 461/544 | 54 (39,70) | 5.4 (5.4,5.5) | 5.9 (5.8,5.9) | NA | 6.90 (6.83,6.97) | 98/61 | 17.1 (15.6,19.1) |
| Finland | | | | | | | | |
| East-West | 187/- | 76 (70,90) | 5.2 (5.1,5.3) | 5.6 (5.5,5.8) | -0.14(-0.30,0.01) | 5.13 (4.96,5.30) | 69/- | 8.8 (4.6,14.8) |
| FINRISK 1987 | 985/1100 | 53 (44,64) | 5.1 (5.1,5.1) | 5.6 (5.5,5.6) | NA | 6.39 (6.34,6.44) | 125/58 | 19.8 (19.8,19.9) |
| FINRISK 1992 | 566/814 | 54 (44,64) | 5.3 (5.2,5.3) | 5.5 (5.4,5.5) | 0 (-0.05,0.06) | 5.92 (5.86,5.98) | 28/11 | 14.9 (14.8,14.9) |
| FINRISK 2002 | 842/1323 | 57 (45,74) | 5.5 (5.5,5.5) | 5.5 (5.5,5.6) | -0.02 (0.06,0.02) | 5.69 (5.64,5.74) | 5/3 | 4.8 (4.8,4.9) |
| Helsinki Policemen | 687/- | 45 (31,69) | 5.6 (5.5,5.6) | 5.4 (5.3,5.5) | 0.06 (-0.02,0.14) | 6.50 (6.42,6.59) | 199/- | 32.9 (21.8,36.2) |
| Oulu | 93/172 | 55 (55,55) | 5.4 (5.4,5.5) | 6.1 (5.9,6.2) | NA | 5.72 (5.58,5.85) | 1/2 | 10.0 (10.0,10.1) |
| Vantaa | 147/188 | 65 (64,66) | 5.3 (5.2,5.3) | 6.2 (6.1,6.3) | -0.07 (-0.19,0.04) | 5.63 (5.51,5.76) | 16/6 | 13.3 (13.1,13.6) |
| Italy | | | | | | | | |
| Cremona Study | 618/794 | 57 (40,88) | 5.0 (5.0,5.0) | 4.9 (4.9,5.0) | -0.02 (-0.07,0.04) | 6.03 (5.97,6.09) | 54/47 | 15.1 (14.6,15.6) |
| Poland | | | | | | | | |
| MONICA | 98/116 | 57 (44,73) | 5.3 (5.2,5.3) | 5.7 (5.5,5.8) | -0.02 (-0.16,0.12) | 5.52 (5.37,5.68) | 9/1 | 6.5 (6.4,6.5) |
| Sweden | | | | | | | | |
| Malmö | -/834 | 54 (48,57) | 5.6 (5.6,5.7) | 6.6 (6.5,6.7) | NA | 5.97 (5.89,6.05) | -/11 | 14.6 (13.7,17.8) |
| MONICA | 1315/1365 | 46 (25,74) | 5.1 (5.1,5.1) | 5.2 (5.2,5.3) | 0.05 (0,0.11) | 6.25 (6.20,6.29) | 31/11 | 12.6 (2.6,16.6) |
| ULSAM | 651/- | 71 (70,74) | 5.1 (5.1,5.1) | 5.8 (5.7,5.9) | -0.11 (-0.20,-0.03) | 5.25 (5.16,5.34) | 62/- | 10.2 (9.1,11.1) |
| The Netherlands | | | | | | | | |
| Hoorn Study | 798/975 | 61 (49,77) | 5.3 (5.2,5.3) | 5.0 (4.9,5.0) | -0.05 (-0.09,0) | 6.38 (6.33,6.44) | 41/19 | 8.9 (8.3,9.3) |
| Zutphen Study | 289/- | 76 (70,90) | 5.3 (5.2,5.3) | 5.1 (5.0,5.7) | -0.14 (-0.27,-0.02) | 5.31 (5.19,5.44) | 29/- | 4.7 (4.6,4.8) |
| UK | | | | | | | | |
| ELY | 262/411 | 53 (40,67) | 5.5 (5.5,5.5) | 5.6 (5.5,5.7) | 0.01 (-0.07,0.08) | 6.42 (6.33,6.50) | 11/3 | 14.6 (13.9,15.4) |
| Goodinge Study | 214/346 | 52 (39,76) | 5.7 (5.6,5.7) | 5.5 (5.4,5.6) | 0.01 (-0.07,0.10) | 6.36 (6.26,6.45) | 10/7 | 8.7 (8.4,9.0) |
| Newcastle Heart Project | 224/254 | 53 (30,76) | 5.5 (5.5,5.5) | 5.5 (5.4,5.6) | 0.01 (-0.08,0.10) | 5.75 (5.64,5.85) | 13/2 | 8.9 (8.5,9.3) |
| Whitehall II study | 4129/1638 | 49 (39,62) | 5.1 (5.1,5.2) | 5.2 (5.2,5.3) | 0.03 (0,0.06 ) | 6.61 (6.58,6.64) | 26/4 | 5.9 (5.6,6.1) |
| Total | 12566/10874 | 54 (25,90) | 5.3 (5.2,5.3) | 5.4 (5.4,5.4) | 0 (-0.01,0.01) | 6.23 (6.21,6.24) | 827/246 | 9.0 (5.8,14.9) |

*Age-adjusted mean (95% confidence interval). †9978 men and 7350 women with z score transformation. MONICA, Monitoring of trends and determinants in cardiovascular disease; NA, not available; ULSAM, the Uppsala Longitudinal Study of Adult Men study.

## 5.5 Normoglycemia, coronary heart disease and ischemic stroke incidence in Europeans without a prior history of diabetes (Study V)

A total of 3743 men and 3916 women from 9 Finnish and Swedish study groups, who were free of CVD at enrolment, was included to study the relationship between elevated 2hPG and the incidence of CHD and ischemic stroke within the normoglycemic range (Table 7). The incidences of ischemic stroke, and combined CHD and ischemic stroke were higher in Group II than in Group I in men (4.5 versus 2.8; 11.3 versus 8.7 per 1,000 person-years, $P < 0.05$ for all comparisons), but not in women. In addition, mean values of age, BMI, 2hPG, blood pressure and fasting insulin were significantly greater in Group II than in those in Group I in both sexes ($P < 0.05$ for all comparisons), except BMI and systolic blood pressure in women.

Hazard ratios for ischemic stroke and composite CVD events were significantly higher in Group II than in Group I in men, but not in women, adjusting for age, study cohort, BMI, FPG, total serum cholesterol, smoking status and hypertension status. The corresponding figures were 1.40 (1.06-1.85) and 1.20 (1.01-1.42) for men, 0.94 (0.59-1.50) and 1.10 (0.79-1.54) for women respectively. HRs corresponding to one unit (mmol/L) increase in the difference between the 2hPG and the FPG (2hPG-FPG) was significantly increased for the CHD events in women [1.24 (1.03-1.50)] and composite CVD events in all individuals [1.08 (1.01-1.15)].

In the sensitivity analysis, multivariate-adjusted HRs (95% CIs) for the composite CVD events for Group II versus Group I were 1.09 (0.91-1.30) and 1.41 (1.06-1.86) in the FPG categories of $\leq$ 5.6 mmol/L and 5.6-6.1 mmol/L; and 1.16 (0.96-1.40) and 1.27 (0.99-1.64) in the age groups of < 60 years and $\geq$ 60 years, respetively. In addition, the same data analysis was also conducted in a subgroup of 4082 individuals with fasting insulin concentrations, producing a HR (95% CI) of 1.10 (0.90-1.34) in a multivariate model with unadjusted fasting insulin, to 1.09 (0.89-1.33) and 1.10 (0.90-1.34) when the model fit to fasting insulin and HOMA-IR seperately. Neither the fasting insulin levels nor the HOMA-IR changed the trends substantially.

Table 7 Baseline characteristics of the study cohorts and the number of first events of coronary heart disease and ischemic stroke during the follow-up in individuals with both normal fasting (FPG < 6.1 mmol/L) and 2-h plasma glucose (2hPG < 7.8 mmol/L) levels (Study V)

| Countries and Studies | No. (men/women) | Age years Mean (range) | FPG* (mmol/L) | 2hPG* (mmol/L) | Fasting insulin*† (ρmol/L) | Total cholesterol* (mmol/L) | No.of events (men/women) CHD | Ischemic stroke | Median of follow-up years |
|---|---|---|---|---|---|---|---|---|---|
| Finland | | | | | | | | | |
| East-West Study | 125/- | 76 (70-90) | 5.2 (0.04) | 5.4 (0.10) | -0.22 (0.10) | 4.94 (0.11) | 27/- | 24/- | 10.4 |
| FINRISK 1987 | 859/1006 | 53 (44-64) | 5.1 (0.01) | 5.5 (0.03) | NA | 6.36 (0.03) | 142/59 | 57/46 | 20.8 |
| FINRISK 1992 | 496/747 | 53 (44-64) | 5.2 (0.01) | 5.5 (0.03) | 0 (0.03) | 5.90 (0.03) | 32/18 | 8/11 | 15.9 |
| Helsinki Policemen Study | 578/- | 45 (31-69) | 5.7 (0.02) | 5.3 (0.05) | 0.09 (0.05) | 6.44 (0.05) | 141/- | 77/- | 34.5 |
| Oulu Study | 93/172 | 55 (55-55) | 5.4 (0.03) | 6.1 (0.07) | -0.02 (0.18) | 5.68 (0.07) | 4/4 | 5/5 | 16.8 |
| Vantaa Study | 120/168 | 65 (64-66) | 5.2 (0.03) | 6.2 (0.07) | -0.12 (0.06) | 5.51 (0.07) | 16/15 | 14/9 | 17.3 |
| Sweden | | | | | | | | | |
| Malmö Prevention Project | -/821 | 54 (48-57) | 5.5 (0.02) | 6.7 (0.04) | -0.02 (0.33) | 5.94 (0.04) | -/2 | -/16 | 14.6 |
| MONICA | 923/1002 | 45 (25-74) | 5.1 (0.01) | 5.3 (0.03) | 0.07 (0.03) | 6.37 (0.03) | 50/17 | 12/19 | 16.4 |
| ULSAM | 549/- | 71 (70-73) | 5.1 (0.02) | 5.5 (0.06) | -0.17 (0.05) | 5.10 (0.06) | 54/- | 38/- | 10.2 |
| Total | 3743/3916 | 53 (25-90) | 5.2 (0.01) | 5.6 (0.01) | 0 (0.02) | 5.99 (0.02) | 466/115 | 235/106 | 16.4 |

*Age-adjusted means (standard error). †Z score for 2443 men and 1639 women who had fasting insulin measurements. FPG, fasting plasma glucose; 2hPG, two-hour plasma glucose; CHD, coronary heart disease; MONICA, Monitoring of trends and determinants in cardiovascular disease; NA, not available; ULSAM, the Uppsala Longitudinal Study of Adult Men study.

# 6 DISCUSSION

## 6.1 Risk factors associated with the increased prevalence of type 2 diabetes in the Chinese population

With the development of urbanization and aging, the prevalence of type 2 diabetes has increased at an alarming rate around the world. Two population-based cross-sectional surveys carried out 5 years apart demonstrated that the prevalence of type 2 diabetes increased remarkably in Chinese adults. The increased prevalence of diabetes was more prominent in rural areas than in urban areas. Age, a positive FHD and obesity were significantly associated with the increase in type 2 diabetes after adjustments for other conventional risk factors.

Urbanization is associated with unhealthy lifestyles such as physical inactivity, high-fat diets, and obesity, which are involved in the etiology of diabetes (Muntner et al., 2005; Reynolds et al., 2007; Yang et al., 2010). It is well documented that the prevalence of type 2 diabetes was substantially higher in urban areas than in rural areas either in high-income or in low- and middle-income countries (International Diabetes Federation, 2009). In the past three decades, rapid urbanization and economic development have been implicated in the increased prevalence of diabetes in China. The prevalence of diabetes increased substantially from less than 1.0% in 1980 (National Diabetes Co-operative Study Group, 1981) to 9.7% in 2008 (Yang et al., 2010). The effect of socioeconomic status, i.e. income and education, on the risk of diabetes may be partly mediated by obesity. Our study showed a significant inverse association between educational or income levels and risk of diabetes in women, but opposite results were observed in rural men. As shown in study I, the prevalence of type 2 diabetes rose together with an increase in obesity. The mean BMI and WC increased dramatically in rural areas during a 5-year period, whereas the corresponding figures remained stable in urban areas. This may explain the greater increase in the prevalence of diabetes in rural areas than in urban areas. Meanwhile, the prevalence of intermediate hyperglycemia has also increased dramatically over the past five years. Based on the current trends of obesity and intermediate hyperglycemia, it can be expected that diabetes will continue to increase, particularly in rural areas in the near future if there is no intervention.

The randomized controlled clinical trials have confirmed that weight reduction and lifestyle modification could prevent or delay the onset of diabetes among individuals with IFG/IGT (Knowler et al., 2002; Kosaka et al., 2005; Pan et al., 1997a; Ramachandran et al., 2006; Tuomilehto et al., 2001). However, the increased use of vehicles has replaced physical

activity over the last 20 years in China. Outcomes from Chinese National Health and Nutrition Surveys demonstrated that average weekly physical activity levels among Chinese adults declined by 32% between 1991 and 2006 (Ng et al., 2009). Similarly, a sedentary lifestyle increased dramatically over the study period in our findings. Only about 15% of the study population attended moderate or vigorous leisure time physical activity due to the decrease in space for public activities and the increase in private vehicles and home entertaiment such as television and Internet games. Additionally, a relatively low proportion of weight-bearing activities may partly explain why physical activity did not have an effect on the prevalence of diabetes in this study. Our recent data showed that the awareness rates of individuals recognizing the risk factors of diabetes were still low in the survey of 2006, with figures of 36%, 34% and 18% for obesity, FHD and physical inactivity respectively (Zhang et al., 2012). This is alarming and calls for immediate action to promote healthy lifestyle in parallel with the economic development.

## 6.2 Ethnic differences in the joint effect of a family history of diabetes and obesity on type 2 diabetes

Type 2 diabetes is a complex disorder, and both genetic and environmental factors play vital roles in the disease's development. Both a positive FHD and obesity have been well recognized as independent risk factors for diabetes (Hu et al., 2009; Mykkänen et al., 1990; Ning et al., 2009). The synergistic effect of a positive FHD with obesity on diabetes was statistically significant in some studies (Chen et al., 2010; Hilding et al., 2006; Knowler et al., 1981; Morris et al., 1989; Sargeant et al., 2000), but not in others (Boer et al.,1996; Fujimoto et al.,1991). Our current study showed that the joint effect of a positive FHD with obesity on the risk of diabetes was only observed in Finnish men, but not in Finnish women or the Chinese. However, the study question needs to be further investigated due to several limitations in the current data analysis. Firstly, the study was made only among a narrow age range so the findings may not be able to be extrapolated to the general population; secondly, the diabetes awareness in the Chinese study was low at the time of the survey (Zhang et al., 2012), which might lead to an underestimation of the FHD, and weaken its relative effect.

The strong synergistic effect observed in Finnish men may be a chance finding certain lifestyle factors, which warrants further investigation. A study in the Netherlands has observered the synergistic effect of BMI with a positive FHD in women only, whereas WC and a positive FHD work synergistically in both sexes (van Dam et al., 2001). Although the synergistic effect of a

positive FHD with obesity is absent, a strong association of obesity with diabetes in individuals without FHD was observed in both sexes for both the Finns and the Chinese. The effects of the two factors were stronger in the Chinese than in the Finns since the former had a higher prevalence of diabetes in the same BMI (WC) and FHD categories. Similarly, our previous reports based on the DECODA and DECODE studies showed that, the prevalence of newly diagnosed diabetes was higher in the Chinese than in Europeans in the same BMI or WC categories across BMI or WC distributions (Nyamdorj et al., 2010). Previous studies have shown that body fat levels, i.e. visceral fat mass and subcutaneous adipose tissue, were substantially higher in the Chinese for a given BMI level than in Europeans (Lear et al., 2007). Obviously, the traditional cardiovascular risk factors such as age, blood pressure and lifestyle factors cannot fully explain the diabetes difference in the current study. The low level of leisure time physical activity (38.6% in China and 81.1% in Finland) might contribute to the high prevalence of diabetes in the Chinese.

Family history of diabetes represents valuable information on genetic and environmental exposure. Individuals with a positive FHD have displayed early features of metabolic syndrome, such as obesity, elevated blood glucose and dyslipidemia consistent with findings in this study (Groop et al., 1996; Li et al., 2000). Familial factors play a vital role on the relationship between insulin sensitivity and glucose effectiveness (the ability of glucose to promote its own disposal), which may modulate the risk of the development of intermediate hyperglycemia and diabetes (Arslanian et al., 2005; Lopez et al., 2009). The lifestyle and behavioral factors, such as physical inactivity and an unhealthy diet, as well as obesity, are commonly shared by family members (Kosti et al., 2008). Individuals with a positive FHD may benefit from both early identification of an increased risk of diabetes and aggressive primary diabetes prevention (Uusitupa et al., 2011). Considering the strong association between two risk factors and type 2 diabetes, obesity and FHD can be useful screening tools to identify people at a high risk of diabetes (American Diabetes Association, 2004; Annis et al., 2005; Gao et al., 2010; Griffin et al., 2000; Harrison et al., 2003; Lindstrom & Tuomilehto, 2003) and to fight against the growing epidemic of diabetes.

## 6.3 Insulin resistance, insulin secretion and intermediate hyperglycemia in relation to aging

The prevalence of IFG and IGT increased with age in people of Asian origin. The age-related increase in IFG leveled off when both insulin resistance and beta cell function were fitted into

the model in most of the ethnic groups studied, but the age-related increase in IGT could not be fully explained by the age-related decline in insulin sensitivity and beta cell function. Aging per se or unmeasured age-related factors have played an important role in the decline in glucose tolerance, whereas disorders in insulin metabolism largely explained the age-related increase in IFG. The results of this study lent support to our earlier study among Europeans (Qiao et al., 2005).

Insulin resistance and reduced beta cell function are the hallmarks of intermediate hyperglycemia. The isolated IFG is associated with reduced hepatic insulin sensitivity and beta cell dysfunction (DeFronzo, 2004), while the isolated IGT is associated with peripheral insulin resistance and defective insulin secretion (Bogardus et al., 1984). It should also be noted that the homeostasis model assessment of insulin resitance is calculated based on fasting values and may reflect hepatic insulin resistance better than peripheral insulin resistance. Although the homeostasis model assessment of insulin resistance and beta cell function correlated reasonably well with the clamp tests when used to assess the risk of type 2 diabetes in cross-sectional or prospective studies (Bonora et al., 2000; Haffner et al., 1996; Haffner et al., 1997), as a surrogate measure it has limitations on assessing beta cell function as compared with a direct measure of insulin secretion (Festa et al., 2008).

Aging is associated with increased body fat and decreased physical activity, which may contribute to the decline in insulin sensitivity in the elderly and consequently to the deterioration in glucose metabolism. On the other hand, body fat loss after exercise improves glucose metabolism and is associated with the reversal of insulin resistance in the elderly (Misra et al., 2008; O'Leary et al., 2006). Experimental studies have also shown that the age-related decline in insulin sensitivity is most likely attributed to body composition and physical fitness, rather than age per se (Basu et al., 2003; Chiu et al., 2000; Chiu et al., 2005). Whether the reduced insulin sensitivity and impaired glucose metabolism result from chronological age or lifestyle-related factors such as adiposity and physical inactivity remains debatable (Karakelides et al., 2010; Lanza & Nair, 2009). However, hyperglycemia has been shown to be able to accelerate the loss of beta cell mass because beta cells from older individuals appear to be more sensitive to the adverse effects of glucose induced apotosis (Maedler et al., 2006). More studies on the issue are required to understand the underlying mechanism of the age-related deteriroration in glucose tolerance.

## 6.4 Normoglycemia and cardiovascular mortality and morbidity

The relationship between glucose levels and CVD has been extensively investigated. A J-shaped relationship between FPG and CVD was observed among Europeans without a prior history of diabetes (Barr et al., 2009; DECODE Study Group, 2003b). Different from the FPG-CVD relationship, a linear or graded, rather than a J-shaped relationship between post-challenge glucose levels and CVD risk, has been reported in many studies (Barr et al., 2009; Coutinho et al., 1999; DECODE Study Group, 2003b; Levitan et al., 2004). Irrespective of influence on the prior history of diabetes and CVD, an elevated 2hPG is also a better predictor than FPG for the incidence of CHD (Qiao et al., 2002; Smith et al., 2002) and ischemic stroke (Hyvarinen et al., 2009) among general populations with hyperglycemia, as compared with those with normoglycemia. Thus far, none of the studies have restricted the comparison between glucose and CVD outcomes to the individuals with normoglycemia, a category considered as having a relatively low risk for either diabetes (Abdul-Ghani et al., 2006; Ferrannini et al., 2005; Reynolds et al., 2006) or CVD profiles (Succurro et al., 2009). It confirmed that individuals whose 2hPG did not return to the FPG levels had a higher risk of CVD mortality (study IV) and morbidity (study V) than those whose 2hPG did even in normoglycemic range. Moreover, the conventional risk factors adjusted in the current study did not explain the differences in CVD risk between the two glucose groups.

The higher CVD risk associated with the elevated 2hPG was consistently observed in the stratified analysis in the two FPG categories (FPG $\leq$ 5.6mmol/L, 5.6 < FPG $\leq$ 6.1mmol/L), suggesting the effect was independent of the FPG levels. Moreover, the difference between the 2hPG and the FPG, as a continuous variable, also increased risk of CVD in a multivariate-adjusted model. Our study, therefore, confirmed that the association of glucose with a risk of CVD may extend to 2hPG levels below the current definition for IGT. The time that is required for the 2hPG concentration return to, or drop below, the FPG level depends on the insulin response during the OGTT and peripheral/hepatic insulin sensitivity. Elevated fasting insulin levels have been shown to contribute to the progress of diabetes and CVD among individuals with normoglycemia (Abdul-Ghani et al., 2006; Succurro et al., 2009). Insulin resistance and its clustering with other metabolic disorders such as obesity and hypertension might be associated with increased CVD mortality and morbidity observed in Group II. It indicated that the 2hPG concentration was higher in Group II than in Group I, regardless of the elevated fasting insulin levels, suggesting that insulin resistance already occurred among individuals with normoglycemia by the current definition. Independent of the conventional risk

factors, the progressive deterioration of insulin sensitivity and beta cell function occurred during the normoglycemic stage (Kahn, 2001; O'Malley et al., 2010; Piche et al., 2005). Since the insulin levels during the OGTT were not available in this study, further exploration of the issue is warranted.

Insulin resistance promotes arteriosclerosis through the mechanism of dyslipidemia, but also as a proinflammatory state. Both insulin resistance and endothelial dysfunction, commonly occurring with hyperglycemia, have been considered as the underlying mechanism contributing to the development of arteriosclerosis (Bakker et al., 2009; Balletshofer et al., 2000; Boger et al., 1998; Dignat-George & Sampol, 2000; Goldfine et al., 2003). Additionally, excess proinsulin has exhibited moderate but significant associations with blood pressure and total cholesterol, triglycerides and low density lipoprotein cholesterol regardless of diabetic status (Haffner et al., 1993; Hanley et al., 2001; Yudkin et al., 1997). Hyperglycemia promotes the production of reactive oxygen species and also increases the production of advanced glycation end-products (AGEs), and these molecules are crucial in the pathogenesis of endothelial damage that precedes arteriosclerotic changes of the vascular wall (Goh & Cooper, 2008; Yamagishi et al., 2005). One possibility is that hyperglycemia-induced early arteriogenesis leads to an increased probability of CVD in later life. Despite accumulated evidence linking hyperglycemia to an increased risk of macro-vascular diseases (Klein, 1995), the molecular mechanisms underlying vascular damage are not clear. Additionally, markers of inflammation and endothelial dysfunction, both of which have been shown to relate more strongly to post-load than to fasting plasma glucose concentrations, and might represent unmeasured confounders which underlie the observed relationships (Yudkin, 2002; Yudkin et al., 1999). To what extent these factors contribute to the increased risk of CVD in people with a high normal 2hPG is not known, and needs to be further investigated.

## 6.5 Methodological considerations

***Strength***

Firstly, the study consisted of Europeans and populations of Asian origin, and all the studies were population-based with a random sampling approach, except the Helsinki Policemen Study and the Hong Kong Workforce Survey on Cardiovascular Risk Factors (occupational studies). Secondly, a standard 2-h OGTT was performed in all the studies to classify individuals with type 2 diabetes, intermediate hyperglycemia and normoglycemia. Populations of the same ethnicity were pooled to increase statistical power and study cohort was also considered as a

covariate in the data analysis. The CVD mortality and incident CHD or ischemic stroke events in both Finnish and Swedish cohorts has been obtained through their national registers which have been approved to be valid, complete and uniformly classified according to the ICD coding.

***Limitations***

There are limitations in the current study. Cross-sectional study design (studies I, II and III) was not able to determine the direction of associations, or a causal relationship. Fasting insulin assays were different between the study cohorts. In order to reduce the discrepancies caused by differences in laboratory methods among these studies (studies III-V), we have calculated a cohort-specific *Z*-score for fasting insulin concentrations, which was used in the data analyses. Both HOMA-IR and HOMA-B, as surrogate indicators of insulin sensitivity and insulin action, do not directly reflect the capacity of beta cells to confront the glucose challenge. Due to the low number of incidents of CHD or ischemic stroke cases in Finnish and Swedish women, the findings require further investigation. Other conventional risk factors, such as HbA1c levels and WC were not available for all groups included in studies IV and V. In addition, some lifestyle-related factors such as diet and physical activity, which may have a potential contribution to the CVD, were not available either. To what extent these missing variables influence the normoglycemia-CVD relationship need to be further investigated.

# 7 SUMMARY AND CONCLUSIONS

The key findings related to the specific aims are summarized below:

1) Established risk factors have greatly contributed to the secular increase in the prevalence of diabetes in the Chinese population, and changes in these factors could explain the recent dramatic increase in the prevalence of diabetes, particularly in rural areas. Considering the increasing prevalence of obesity and physical inactivity, massive health promotions and lifestyle interventions are urgently required in China.

2) Both a positive FHD and obesity played key roles on the presence of diabetes both in the Chinese and Finnish populations, but a joint effect of both factors on the risk of diabetes was significant only in Finnish men.

3) The deterioration of the glucose metabolism among non-diabetic populations of people of Asian origin with age could not be fully explained by the age-related decline in insulin sensitivity and insulin secretion, estimated by the homeostasis model assessment.

4) The elevated 2hPG was positively and significantly associated with CVD outcomes independent of FPG even in individuals whose fasting and postload glucose concentrations were within a normal range. The deterioration in insulin resistance and CVD risk factor profiles also extended to the normoglycemic range.

The results from this research are in line with other recent studies showing that type 2 diabetes has dramatically increased in China, and that obesity is the major modifiable risk factor contributing to the fast increase in the prevalence of diabetes, also in China, where people have traditionally been relatively lean. The socioeconomic status is closely and inversely associated with the presence of diabetes. Obesity is strongly associated with intermediate hyperglycemia and insulin resistance. Massive health promotions and lifestyle interventions, particularly at the general population level will be required to tackle the increasing trend in diabetes prevalence in China.

Obesity and a positive FHD are major risk factors for developing diabetes. Excess food consumption and a sedentary lifestyle lead to obesity, characteristically with central distribution due to visceral fat accumulation, insulin resistance and rising blood glucose levels. Individuals with a positive FHD and obesity may benefit from both early identification of the increased risk of diabetes and aggressive primary diabetes prevention. Evidence from epidemiological study has also confirmed that FHD and obesity can be useful screening tools to identify people at a

high risk of diabetes. Improvement of diabetes awareness and obesity intervention are needed to strengthen the prevention of diabetes. The deterioration of intermediate hyperglycemia, particularly IGT, with age cannot be fully explained by the age-related decline in the homeostasis model assessment of insulin sensitivity and insulin secretion in populations of Asian orgin. This indicates age per se or certain unmeasured factors might have contributed to the deterioration in glucose tolerance when getting old, and may provide an insight into research on the pathophysiology of glucose metabolism.

Accumulated evidence indicates that 2hPG is superior to FPG in relation to the assessment of the risk of future CVD events in subjects without a prior history of diabetes at baseline. Several studies have demonstrated that people whose 2hPG did not return to the FPG levels during OGTT had a significantly higher risk of developing type 2 diabetes and a worse cardiovascular risk factor profile than individuals whose 2hPG did even within a normoglycemic range. Our study lent further support to previous studies by showing that people who failed to return their post-load glucose concentration to their fasting levels, even within a normal glucose range, were insulin resistant and had a higher CVD mortality and morbidity compared with those who were able to return their FPG levels. The findings further supported the view that the CVD risk extends well below the diabetes diagnostic value based on the post-challenge glucose levels, and may have certain clinical implications regarding diabetes diagnosis and glycemic management target.

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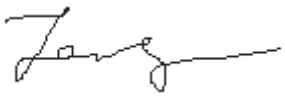

Helsinki, June 2013

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## APPENDIX Methodologies used in each study cohort.

| Countries and studies | Blood sample | Fasting and 2-hour glucose | Total cholesterol | Fasting insulin |
|---|---|---|---|---|
| **China** | | | | |
| Hong Kong Cardiovascular Risk Factor Prevalence Study | Plasma | Hexokinase method (Hitachi 747 analyser with Boehringer Mannheim, Germany) | Cholesterol oxidase (CHOD) method; Hitachi 717 analyser (Hitachi Instruments, California, USA). | Microparticle enzyme immunoassay |
| Hong Kong Workforce survey on CVD Risk Factors | Venous Plasma | Glucose oxidase method (Diagnostic Chemicals reagent kit, Canada) | Enzymatic method, with reagents (Baker Instruments Corporation, Allentown, PA 18103, USA) with Cobas Mira analyzer (Hoffman-La Roche and Co., Basle Switzerland). | Radioimmunoassay (Pharmacia Insulin RIA 100, Pharmacia Diagnostics AB, Uppsala, Sweden) |
| Qingdao Diabetes Survey 2001–2002 | Plasma | Glucose oxidase method (AMS Analyser Medical System, SABA-18, Italy) | Enzymatic method (AMS Analyzer Medical System, SABA-18, Rome, Italy) | Radioimmunoassay (Beijing North Institute of Biological Technology) |
| Qindao Diabetes Survey 2006 | Serum | Glucose oxidase method (OLYMPUS-AU640 Automatic analyzers) | Enzymatic method (Olympus reagent) With OLYMPUS-AU640 Automatic Analyzers (Olympus Optical. Tokyo, Japan) | Immunoassay, Chemiluminescence; CIA ABBOTT, AXSYM, USA |
| **Denmark** | | | | |
| Glostrup | Venous whole blood | Glucose-oxidase | Enzymatic colorimetric methods (GPO-PAP and CHOD-PAP; Roche Molecular Biochemicals, Mannheim, Germany) | Fluoroimmunoassay technique (AutoDELFIA; Perkin Elmer-Wallac, Turku, Finland). |
| **Finland** | | | | |
| East-West men Study | Venous Plasma | Glucose dehydrogenase | Enzymatic techniques (Monotest, Boehringer Mannheim GmbH, FRG) Olli C3000 photometer (Kone Oy, Finland) | Radioimmunoassay (non-spcific) Pharmacia Diagnostics, Uppsala, Sweden |
| The National FINRISK Study 1987 | Venous whole blood | Glucose dehydrogenase | Enzymatic techniques (Cholesterol oxidase-peroxidase-amidopyrine, CHOD-PAP, Boehringer-Mannheim, Mannheim, Germany) | Radioimmunoassay (non-spcific) |
| The National FINRISK Study 1992 | Venous Plasma | Glucose dehydrogenase | Enzymatic techniques (Cholesterol oxidase-peroxidase-amidopyrine, CHOD-PAP, Boehringer-Mannheim, Mannheim, Germany) | Radioimmunoassay (non-spcific) |
| The National FINRISK Study 2002 | Plasma | Hexokinase assay (Thermo Electron Oy) | Enzymatic method (CHOD-PAP; Thermo Elektron Oy, Finland) | Mikroparticle Entzyme immunoassay. Abbott Laboratories AxSYM® |

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|---|---|---|---|---|
| Helsinki Policemen Study | Venous whole blood | o-toluidine | Estimation method of Abell et al. | Radioimmunoassay (non-spcific) |
| Oulu Study | Capillary whole blood | glucose dehydrogenase (Merck Diagnostica, Darmstadt, FRC). | Enzymatic method (CHOD-PAP, Boehringer Mannheim, Mannheim, Germany). | Radioimmunoassay ( the Phadeseph Insulin RIA100 kit, Pharmacia Diagnostics AB, Uppsala, Sweden) |
| Vantaa Study | Venous whole blood | Glucose oxidase (Beckman Instruments, Fullerton, California) | Enzymatic techniques (Boehringer-Mannheim) | Radioimmunoassay (Phasedeph, Pharmacia Diagnostics, Uppsala, Sweden) |
| **India** | | | | |
| Chennai Urban Population Study (CUPS) 1997 | Plasma | GOD-POD method, with kit (Boehringer Mannheim, Germany ) and Ciba Corning Express Plus Autoanalyser (Corning, Medfield, MA, USA) | CHOD-PAP method (Boehringer Mannheim, Germany) Corning Express Plus Auto Analyser (Corning, medfied, MA, USA) | Enzyme-linked Immunosorbent Assay (ELISA) Dako kit (Dako Diagnostics, Denmark) |
| Chennai Urban Rural Epidemiological Study (CURES) 2004 | Plasma | Glucose oxidase-peroxidase method (Hitachi 912 Autoanalyser (Hitachi, Mannheim, Germany) | CHOD-PAP method with Hitachi-912 Autoanalyser (Hitachi, Mannheim, Germany) using kits supplied by Roche Diagnostics (Mannheim, Germany). | Enzyme-linked Immunosorbent Assay (ELISA) |
| **Italy** | | | | |
| Cremona Study | Plasma | GOD-PAP glucose oxidase (Boehringer Mannheim, Milan, Italy) | Enzymatic techniques (Boehringer-Mannheim, Mannheim, Germany) with CIBA Corning 550 Express Auto-analyser | Radioimmunoassay |
| **Janpanese/Brazil and USA** | | | | |
| São Paulo 92-93 Study | Plasma | Glucose oxidase method | Enzymatic method, automatic analyzer, monoclonal antibody-based immunofluorimetric assay (AutoDelfia, PerkinElmer Life Sciences Inc, Norton, OH, USA) | Radioimmunoassay |
| São Paulo 99-00 Study | Plasma | Glucose oxidase method | Enzymatic method, automatic analyzer, monoclonal antibody-based immunofluorimetric assay (AutoDelfia, PerkinElmer Life Sciences Inc, Norton, OH, USA) | Monoclonal antibody-based immunofluorimetric assay |
| Seattle Study | Serum | Automated glucose oxidase method | Enzymatic method, Abbott ABA 200 bichromatic analyzer | Immunoprecipitation radioimmunoassay (double antibody) |

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|---|---|---|---|---|
| **Mauritius** | | | | |
| Mauritius 87 | Plasma | Yellow Springs Instruments (YSI) glucose analyzer, OH, USA | Manual enzymatic colorimetric method (Coulter Minikem Spectrophotometer), (Boeringer Cat no 701912) | A modified radioimmunoasay ( processed by Soeldner and Slone,1965) |
| Mauritius 92 | Plasma | Yellow Springs Instruments (YSI) glucose analyzer, OH, USA | Automated enzymatic method with Chemistry Profile Analyser Model LS (Coulter- France) | A modified radioimmunoasay ( processed by Soeldner and Slone,1965) |
| Mauritius 98 | Plasma | Yellow Springs Instruments (YSI) glucose analyzer, OH, USA | Automated enzymatic methods; Cobas Mira analyzer (Roche Diagnostics, France) | Enzyme-linked Immunosorbent Assay (ELISA).DAKO, Novo, UK |
| **Poland** | | | | |
| MONICA Study | Serum | Glucose oxidase | Direct Liebermann-Burchard method (Boehringer-Mannheim) | Immunoradiometric assay method (Polatom, Swierk, Poland). |
| **Sweden** | | | | |
| Malmö Study | Plasma | Glucose oxidase (Beckman analyzer) | Routine methods at the Department of Clinical Chemistry at Malmö University Hospital | Radioimmunoassay (non-spcific) |
| MONICA Study | Plasma | Glucose oxidase (Beckman analyzer) | Enzymatic techniques (Boehringer-Mannheim GmbH, Germany) | Double antibody radioimmunoassay (non-spcific) Phadeseph Insulin RIA, Pharmacia Diagnostics, Uppsala, Sweden |
| ULSAM Study | Plasma | Glucose oxidase (Beckman analyzer) | Enzymatic techniques using IL Test Cholesterol Trinders's Method and IL Test Enzymatic-colorimetric Method for use in a Monarch apparatus (Instrumentation Laboratories, Lexington,USA).http://www.pubcare.uu.se/ULSAM/ invest/70yrs/meth70.htm#09) | Enzymatic immunological assay (Enzymmun, Boehringer Mannheim, Mannheim, Germany) |
| **The Netherlands** | | | | |
| Hoorn Study | Plasma | Glucose dehydrogenase | Enzymatic techniques (Boehringer- Mannheim, Mannheim, Germany); | Double-antibody radioimmunoassay (specific) Antibody: linco SP21 |
| Zutphen Study | Venous Plasma | Hexokinase (Abbott Epx) | Enzymatic techniques (CHOD-PAP Enzymatic method after Enzymatic techniques (CHOD88 mono-test kit, Boehringer-Mannheim) | Radioimmunoassay (non-spcific)( Pharmacia Diagnostics, Uppsala, Sweden) |
| **United Kingdom** | | | | |
| Ely Study | Plasma | Hexokinase assay | Enzymatic techniques, RA 1000 (Bayer | Enzyme-linked Immunosorbent |

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|---|---|---|---|---|
| | | | Diagnostics, Basingstoke, Hants, UK) | Assay ELISA (specific) |
| Goodinge Study | Plasma | Glucose-oxidase (Beckman, Brea, California) | Cholesterol esterase method (Boehringer Mannheim, Lewes, Sussex, U.K.) | Immunoradiometricassay (specific) |
| Newcastle Study | Plasma | Glucose oxidase (Hitachi 717 analyser) | Cholesterol oxidase/peroxidase method with Cobas Bio centrifugal analyzer (Roche Products Ltd, Welwyn Garden City, UK) | Enzyme-linked Immunosorbent Assay ELISA (specific).DAKO Diagnostics Ltd, UK |
| Whitehall II study | Plasma | Electrochemical glucose oxidase. | Cobas Fara centrifugal analyzer (Roche Diagnostics System, Nutley, NJ). | Radioimmunoassay |