ADIPOSITY AND DIABETES IN CHINA: THE CHINA KADOORIE BIOBANK STUDY OF 500,000 MEN AND WOMEN

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A thesis submitted for the degree of Doctor of Philosophy

Trinity Term, 2013

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ABSTRACT

Despite the rapid increase in both adiposity and diabetes in China, substantial uncertainty remains about the relationship between these two conditions in the population. Using data from the China Kadoorie Biobank study of 0.5 million adults recruited during 2004-8 from 10 diverse areas of China, this thesis examines the associations of different adiposity measures (overall adiposity: BMI and percentage body fat; central adiposity: waist circumference, waist-hip ratio, and waist-height ratio) with type 2 diabetes prevalence and incidence. To assess the quality of diagnosis, a separate event-verification study was conducted in ~1,000 reported diabetes cases.

Overall at baseline, the mean age of the analysed participants was 52 years, 41% were men, 32% had a BMI≥25 kg/m^2 (4% ≥30 kg/m^2) and 5.2% had self-reported or screen-detected diabetes. Both cross-sectional and prospective analyses of well-characterised diabetic cases (26,622 prevalent and 2,910 incident cases) showed that adiposity is strongly positively associated with diabetes ($p<0.0001$), throughout all or most of the distribution of each adiposity measure. Per 1 SD higher adiposity measure, measures of central adiposity were associated with ~90% increased risk, compared with ~80-85% increased risk for general adiposity measures. Among measures of central adiposity, waist-hip ratio was the most strongly associated with diabetes prevalence, whereas waist circumference was the most predictive of diabetes incidence. Although measures of central adiposity were the most strongly associated with diabetes risk, there was still a strong positive association with measures of general adiposity after adjusting for central adiposity ($p<0.0001$), and the combination of both types of measure improved risk prediction. Given waist circumference, hip circumference was inversely associated with both diabetes prevalence and incidence ($p<0.0001$). For many of the above associations, there was possible effect modification by age and sex. These findings will provide important and reliable evidence to quantify the level of diabetic risk associated with adiposity, hence to inform clinical interventional strategies and future public health programmes.

To my parents and grandparents

献给我的父母和祖父母们

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Abbreviations

ADA	American Diabetes Association
AUC	Area under the curve
BMI	Body mass index
CDC	Center for Disease Control and Prevention
CKB	China Kadoorie Biobank Study
CVATT	Critical visceral adipose tissue threshold
DM	Diabetes mellitus
DXA	Dual-energy X-ray absorptiometry
FPG	Fasting plasma glucose
HbA1c	Glycated haemoglobin
HC	Hip circumference
HI	Health insurance
ICD-10	The 10th International Classification of Diseases
IDF	International Diabetes Federation
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
LAP	Lipid Accumulation Product Index
MET	Metabolic equivalent of tasks
NEFAs	Non-esterified fatty acids
NIDDM	Noninsulin-dependent diabetes mellitus
OGTT	Oral glucose tolerance test
%BF	Percentage body fat
ROC	Receiver operating characteristic
SD	Standard deviation
WC	Waist circumference
WHO	The World Health Organization
WHR	Waist hip ratio
WHtR	Waist height ratio

1. Introduction

1.1 Diabetes mellitus

Diabetes mellitus (DM) is a group of metabolic diseases characterised by chronic hyperglycaemia, with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both.[1] Diabetes mellitus can be broadly categorised into three subtypes: type 1, type 2 and gestational diabetes. Type 1 diabetes is due primarily to autoimmune-mediated destruction of pancreatic β-cell islets, and usually has earlier onset than type 2 diabetes, and globally accounts for 5-10% of all diabetes cases.[2] Type 2 diabetes generally involves insulin resistance and relative insulin deficiency. It usually has late onset, and accounts for over 90% of cases globally. However, the specific pathogenic mechanisms of type 2 diabetes are still largely unknown.[3] Gestational diabetes occurs specifically in women during pregnancy, and it is beyond the main scope of this thesis.

Insufficient insulin secretion or action produces hyperglycaemia by various mechanisms, including reduced uptake of glucose from the bloodstream by skeletal muscle and the liver. The resulting chronic hyperglycaemia of diabetes may account for much of the long-term organ and tissue damage, including retinopathy, nephropathy, peripheral neuropathy, and autonomic neuropathy.[4] Importantly, diabetes often disturbs lipoprotein metabolism,[5-7] and may raise blood pressure,[8] and is associated with substantially higher risk of atherosclerotic cardiovascular and peripheral arterial disease.[9,10]

Because of its high prevalence and substantial burden of long-term complications, diabetes is now a major global public health challenge in both developed and developing countries.[11,12] The World Health Organization estimated that in 2011 there were 347 million people with diabetes,[13] and that more than 80% of diabetes deaths occur in low- and middle-income countries.[14] Overall, it was estimated that diabetes accounted for 1% of global burden of disease.[15]

1.2 Rising burden of diabetes in China

Having undergone rapid and substantial changes in diet and lifestyle over the last few decades, China is facing a major epidemic of diabetes and related conditions.[16] Despite large geographical variations across different regions of China,[17-22] the overall population prevalence of type 2 diabetes has increased considerably over the past 30 years from < 1%[23] in 1980 to 5.5%[24] in 2002, and was recently reported as 9.7%[25] in 2009. Type 1 diabetes, however, is reported to have an unusually low incidence rate in China: 0.57 per 100,000 at age <18 years compared with, for example, 18-20 per 100,000 in the UK.[26] Despite the relatively low incidence, in absolute terms, there are now over 98 million people in China who suffer from diabetes, which is the largest national total in the world. If the current increasing trend in prevalence of obesity continues, the number of diabetes is projected by the International Diabetes Federation (IDF) to reach 143 million, by the year 2035.[27]

1.3 Adiposity

Type 2 diabetes is associated with a number of known non-modifiable risk factors, such as age[28], family history,[29] and ethnicity;[30] and with several potentially modifiable risk

factors including socioeconomic status,[22,31] physical inactivity,[32] alcohol consumption,[33,34] smoking status,[35-37] and perhaps most importantly, excess adiposity. Excess adiposity is not only a strong independent determinant of diabetes, it may also be a mediator of other modifiable risk factors like socioeconomic status, physical activity and diet. Accurate assessment of human adiposity is therefore important, and a prerequisite to understand the relationship between adiposity and diabetes.

Adipose tissue is a type of loose connective tissue composed mainly of adipocytes,[38] endothelial cells and leukocytes.[39] In adults, adipose tissue consists mostly of white adipocytes, whereas in neonates there are also many heat-generating brown adipocytes.[40] White adipose tissue was traditionally considered as a storage site for fatty acids. But over recent years, it has become increasingly clear that adipose tissue is also an endocrine and secretory organ that regulates lipid and glucose metabolism and produces a large number of hormones and cytokines.[41] Moreover, a number of recent laboratory-based studies have suggested that dysfunction of adipose tissue may play an important role in the pathogenesis of obesity-related insulin resistance and type 2 diabetes.[42-44]

Two main depots of adipose tissue are subcutaneous and visceral adipose tissues, each with somewhat different metabolic features and functions.[41] Visceral adipose tissue, defined here as fat tissue located inside the abdominal cavity and packed between the organs like liver, intestines, and stomach, is generally much more metabolically active than subcutaneous adipose tissue, since it drains directly into the portal vein and therefore may have more immediate and potent effects on liver metabolism.[45] Central adipose tissues, which is a combination of both visceral and abdominal subcutaneous

adipose tissues, are therefore strongly associated with an adverse metabolic risk profile and insulin resistance.[46,47] Accurate measurement of both central adiposity and overall adiposity may provide a more complete understanding of the diabetic risks associated with fat distribution in specific populations.

The most widely used epidemiological and clinical measure of overall adiposity is body mass index (BMI), defined as weight/height^2 (kg/m^2).[48] However, at a given level of BMI, the composition of fat mass and lean mass may vary greatly, which could have different pathogenic consequences.[49] Consequently, there is increasing use of waist circumference, a simple common measure of central adiposity. It is often divided by hip circumference to yield the waist-hip-ratio (WHR), or sometimes by height to yield the waist-height ratio (WHtR).[50] These measures are all confirmed as reasonable measures of central adiposity.[51] Skinfold thickness is sometimes used in epidemiological studies as a measure of subcutaneous adiposity, however, strong intra- and inter-observer variation makes it a less reliable measurement compared to others.[52] More technically advanced methods, including bioelectrical impedance analysis (BIA), imaging methods like CT and MRI, and dual-energy X-ray absorptimetry, are all used for direct or indirect estimation of quantity and distribution of body fat. In epidemiological studies, many of these measures are used for differentiating “overweight” and “obese” population from normal population, and hence for calculating the associated disease risks.

1.4 Prevalence of overweight and obesity in China

During the first three-quarters of the 20th century, China had experienced substantial social upheavals resulting from wars, natural disasters, famine and political turmoil,

which greatly hampered its socioeconomic development. Consequently, overweight and obese population was virtually non-existent in China until the 1980s, when China began its fast economic growth. In 1982, overweight and obesity were rare: 3.5% of adults aged 20-45 were classified as "overweight" by the WHO standard,[53] and only 0.2% as obese.[54] The China National Nutrition (and Health) Surveys conducted in 1992 and 2002 suggested that during that 10 year period, the prevalence of overweight in adult population increased from 15% to 23%, and the prevalence of obesity increased from 2.6% to 6.4%,[55] representing about 8-fold increase over a period of 20 years. Owing to its large population base, the burden and impact of obesity in China is already phenomenal and will worsen further in the future.[56]

1.5 Association of adiposity with diabetes

For decades, excess adiposity has been a known risk factor of many diseases,[57] including diabetes. Several large and well-designed prospective cohort studies,[47,58-61] as well as diabetes prevention trials[62,63] in the Western populations have demonstrated reliably that adiposity, as measured by various anthropometric factors such as BMI, waist circumference, waist-hip-ratio, waist-height-ratio and percentage body fat, is strongly related to risk of diabetes. A few studies further suggested that central adiposity, measured usually by WC or WHR, may be a better measure for risk of diabetes in Western populations compared with overall adiposity (measured usually by BMI),[58,64] but this has not been fully supported by other studies.[65]

It has also been suggested that the same anthropometric measures may have different attributes in Chinese populations compared to other populations. For example, for a

given level of BMI, Chinese have a substantial higher percentage body fat than people of European descent;[66] and at a given level of BMI, WC or WHR, the absolute risk of diabetes is consistently higher in Chinese.[67] Furthermore, a number of studies have shown consistently that, as in Western populations, excess weight in Chinese populations is strongly associated with increased diabetes risks irrespective of how it is measured.[68-70] But meanwhile, there is also some evidence that central obesity is a better predictor for diabetes risk in the Chinese population.[71-73] With a somewhat different body build and body composition,[74] the diabetic risks associated with different anthropometric measures could differ importantly between Chinese and other populations, but the evidence from large-scale prospective studies is very limited.

1.6 Thesis objectives

To characterise in appropriate detail the relationships between adiposity and diabetes in the Chinese population, this thesis analyses the data on 300,000 women and 200,000 men in the China Kadoorie Biobank (CKB) Study, a blood-based prospective cohort study set in 10 diverse areas of China. The specific aims are:

- To examine the associations of diabetes prevalence and incidence with each of several measures of overall and of regional adiposity (termed here as “basic” associations);
- To assess the associations of diabetes prevalence and incidence with different measures of adiposity adjusted simultaneously for other measures of adiposity (termed here as “independent” associations), and jointly with some other measures of adiposity;

- To examine the relevance of hip circumference for diabetes prevalence and incidence with and without adjustment for other adiposity measures; and
- To assess the strength of these associations by levels of potential effect modifiers such as age, sex.

To fulfil these aims, the thesis consists of four main interrelated components: (1) a comprehensive literature review of the relationships between anthropometric measures and diabetes; (2) cross-sectional analyses of baseline diabetes prevalence and its main correlates in the CKB; (3) an independently designed and conducted verification sub-study of diabetes diagnoses in the CKB follow-up dataset; and (4) prospective analyses of diabetes incidence in relation to various baseline measures of adiposity in the CKB, during a maximum of 5.1 years of follow-up until 1 January 2013.

2. Literature review

2.1 Overview

2.1.1 Objectives of literature review

This section provides a comprehensive overview of the scientific evidence about the association between anthropometric risk factors and type 2 diabetes. Its specific objectives are: (i) to identify and systematically review the published epidemiological evidence on the associations of body mass index, waist circumference, hip circumference, waist-hip ratio, waist-height ratio, and body fat percentage, with risk of type 2 diabetes in Chinese populations; (ii) to identify potential confounders of associations between adiposity measures and diabetes, which will help guide the selection of confounders for adjustment in CKB ; (iii) to highlight gaps in scientific knowledge about the foregoing relationships. Although the review focused primarily on the published literatures related to the Chinese population, data from other populations will also be discussed as appropriate.

2.1.2 Methods of literature review

Searches of the published literature were conducted on PUBMED, EMBASE, CHINA ACADEMIC JOURNAL FULL-TEXT DATABASE, GOOGLE SCHOLAR, for the period from 1980 to 2012. In addition, the lists of references from review articles, book chapters, and other relevant articles were also reviewed. Unpublished studies, abstracts, dissertations, theses, and studies published in non-peer-reviewed journals were not included in this review. Terms used in the searches of the English-language databases are summarised in Table 2.1 (for PUBMED, MeSH terms found below the term in the

MeSH tree were included; for EMBASE, related terms were automatically included). Chinese translations of these terms were used in searches of the CHINA ACADEMIC JOURNAL FULL-TEXT DATABASE.

2.1.3 Brief description of the identified studies

Using the searching strategies described above, 18 eligible studies were identified and reviewed, including 7 cross-sectional surveys, 6 cohort studies and 5 meta-analyses. Detailed information about design and other characteristics of these studies is summarised in Table 2.2-2.4. A summary of key results from the reviewed literature is presented in Table 2.5-2.7.

Of the 7 cross-sectional survey that examined the association between anthropometric measures and type 2 diabetes among people with age above 18 years (Table 2.2), 5 were nationally representative surveys conducted in China between 1980 and 2008 (e.g. the China National Diabetes and Metabolic Disorders Study, the China Nutrition and Health Survey) and 2 were the baseline analyses of cohort studies (i.e. the Shanghai Women's Health Study and the Guangzhou Biobank Study). The sample sizes of the cross-sectional studies ranged from 15,000 to 300,000, with 4 involving 200,000 people or more. For anthropometric measures, most studies used BMI, waist and hip circumference, whereas for diagnosis of diabetes it mainly involved fasting plasma glucose (FPG) test or a fasting plasma glucose test plus a subsequent oral glucose tolerance test (OGTT) at the time of survey.

The 6 prospective cohort studies reviewed (Table 2.3) included 4 studies in China, 1 study in Chinese populations in Singapore, and 1 comparative study between Chinese

and U.S. populations which provided a comparison of the strength of association between the Western and Chinese populations. All the studies included adults aged above 20 years who were recruited between 1980s and 2000s from the general population, each with a minimum of 5 years of mean follow-up period. Most Chinese cohorts had a sample size of less than 5,000, except for the Shanghai Women's Health Study (n=72,733). 4 cohorts had complete anthropometric measures of BMI, waist and hip circumference, and 2 cohorts only measured BMI. Diabetes incidence was identified by FPG or OGTT (4 studies), self-report (1 studies), or urine glucose test plus FPG (1 study). Relative risks were estimated by using Cox proportional hazards model in 3 studies, and by using logistic regression in 3 studies.

This review also summarised the results of 5 meta-analyses of the association between various anthropometric measures and diabetes risks, which were published between 2002 and 2012 (Table 2.4). Of these 5 studies, 1 was specifically on Chinese population and 4 involved Chinese populations and a mixed range of other populations. 2 studies involved pooled analyses of individual data and 3 used only published data (number of publications included ranges from 9 to 32). Random effects models (2 studies) and fixed effects models (1 study) were used in the pooled analyses of published data.

2.2 BMI and diabetes

2.2.1 Evidence from cross-sectional studies

The association between BMI and type 2 diabetes was analysed in all cross-sectional studies, most of which involved nationally representative and relatively large sample size ranging from about 15,000 to 300,000 participants. Although different BMI cut-offs

were applied in the analyses of various studies, it was generally consistent with findings in many other populations that obesity, as measured by BMI, was strongly positively associated with type 2 diabetes.

The 1994 National Diabetes Prevention and Control Cooperative Group Study (also known as the 1994 National Diabetes Survey) was, at that time, the largest population-based cross-sectional study of Chinese population (age between 25 and 64), which involved 224,251 participants from 19 provinces of China. In this study, the odds ratio of diabetes for overweight (BMI≥25 kg/m^2) versus normal weight population (BMI<25 kg/m^2) was 2.23 (p for difference=0.0001).[75] In a subsequent analysis of the same study, it was shown that the odds ratio was 1.34 (95%CI: 1.23-1.46) for every 5 kg/m^2 increment in BMI, after adjusting for age, sex, mean blood pressure, fasting plasma triglyceride and fasting plasma insulin.[76] It should be noted that although obesity could affect blood pressure,[77] fasting plasma triglyceride[78-80] and fasting plasma insulin.[81] These factors are either unrelated to diabetes outcome (e.g. blood pressure) or in the causal pathway (e.g. fasting plasma triglyceride, fasting plasma insulin). The adjustment of these factors may, therefore, potentially attenuate the association.

Similar trend of association was observed in the 2001 InterAsia study and the 2008 National Diabetes Survey. The InterAsia study was a collaborative study conducted in China and Thailand. In its Chinese sub-study, 15,236 adult participants were randomly selected from 10 provinces or municipalities of geographically and economically representative regions. In an univariate analysis, the odds ratios for type 2 diabetes were 1.22 (95%CI: 0.93-1.61) for the middle BMI category at 24-27 kg/m^2 compared to reference BMI group (<24 kg/m^2) in males and 1.74 (95%CI: 1.33-2.28) in females. The

odds ratios for high BMI group (≥28 kg/m^2) were 2.49 (95%CI: 1.76-2.53) in males and 2.70 (95%CI: 1.93-3.77) in females.[20] Since they only involved univariate analysis, the strength of association from this study may not be reliable due to potential confounding.

The 2008 National Diabetes Survey recruited 46,239 people aged 20 or older in northeast, north, east, south, central, northwest and southwest China based on degree of urbanization and economic development status. In this study, the mean BMI was 23.6 (95%CI: 23.5-23.7) and the multivariable-adjusted odds ratios for diabetes were 1.43 (95%CI: 1.22-1.67) in overweight group (BMI: 25-29.9 kg/m^2) and 2.17 (95%CI: 1.68-2.81) in obese group (BMI: >30 kg/m^2) in both sexes combined.[25] Again, the inappropriate adjustment for non-confounders like systolic blood pressure and triglycerides may potentially attenuate the associations. In addition, although these cross-sectional studies tended to involve reasonably large sample size and reportedly used multistage, stratified sampling method to ensure the "national representativeness" of study population, the distribution of anthropometric values and the prevalence of diabetes varied greatly across studies. This has raised concerns about potential quality issues as to how the actual sampling was achieved in each study.

This review also included baseline analyses of two relatively large cohort studies in order to understand BMI and its association with diabetes in adult population of specific settings in China. The Shanghai Women's Health Study was a population-based prospective cohort study. 74,942 female permanent residents aged 40-70 years were recruited from 1996 to 2000 from seven urban communities in Shanghai, China. In the cross-sectional analysis of its baseline data, there was an increasing odds ratio for diabetes among overweight (OR=1.71 95%CI: 1.33-2.19) and obese women (OR=2.19,

95%CI: 1.47-3.27), as defined by World Health Organization cut-off points. Meanwhile, women in the highest BMI quartile had a 2.6-fold (OR=2.57, 95%CI: 1.75-3.77) increased risk of diabetes compared to women in the lowest BMI quartile.[82] One major limitation of the study is the potential misclassification of diabetes, for it was diagnosed by urine glucose test and followed, if positive, by a subsequent fasting glucose test. Due to the low sensitivity of the urine glucose test, there could be potential under-report of diabetes (baseline prevalence of diabetes was 2.2%). As obese participants were not properly identified of their diabetic status, the association may be biased towards null.

In the Guangzhou Biobank Cohort Study, 28,946 local residents aged above 50 years in the city of Guangzhou were recruited. The prevalence of diabetes at baseline was 12.5% based on WHO diagnostic criteria. The baseline analysis showed that odds ratios of type 2 diabetes were 1.66 (95%CI: 1.51-1.83) for overweight group (BMI: 23-25 kg/m^2) and 2.19 (95%CI: 2.01-2.39) for obese group (BMI: >25 kg/m^2) as compared to those with BMI <23 kg/m^2.[83] The Guangzhou Biobank Study was based on middle aged and elderly adults, therefore the findings of the study may not be generalisable to other adult age groups of the Chinese population. The use of different cut-offs of BMI also made it difficult to compare with other studies. Moreover, the associations, as in all cross-sectional studies, could be largely affected by reverse causality of the adiposity-diabetes association.

2.2.2 Evidence from prospective cohort studies

There were 6 prospective studies of adiposity and diabetes in Chinese populations, including 4 studies in China, 1 in Chinese populations in Singapore, and 1 comparative study between Chinese and U.S. populations. Nearly all studies reviewed showed

consistently that high BMI is strongly positively associated with increased risk of DM throughout a wide range of BMI distribution.

The Beijing Project 5-year Follow-Up Study was part of the National Diabetes Survey in 1994. Of the original 20,682 participants in the cross-sectional study, 1,566 participants whose 2-h capillary blood glucose test results were ≥ 6.7mmol/L were subsequently administered with OGTT. A 5-year follow-up survey was conducted between 1999 and 2000. Only 902 participants were re-tested with OGTT and 126 participants were diagnosed with type 2 diabetes. In this study, BMI ≥ 25 kg/m^2 was found to be associated with a 2-fold increased risk for developing diabetes (OR=2.00, 95% CI: 1.07-2.37).[84] But no further analysis was performed across BMI categories. Since the study was not originally designed as a cohort study, the follow-up of its participants was rather poor, with only 57.6% participants taking part in the follow-up examination. Almost half of the study participants were lost to follow-up (including 30.9% moved out of Beijing, 11.5% lost due to other logistic reasons).

Conducted in another metropolitan city of Shanghai, the Shanghai Diabetes Study randomly recruited 4,907 people aged between 20 and 90 years old from two middle-income communities during 1998 to 2001. 2,638 (53.8%) participants were re-assessed after 5.5 years for diabetes, in which both overnight fasting glucose and OGTT with a standard glucose load were administered to each participant. The prospective findings revealed that participants with high BMI (≥28 kg/m^2) were associated with an increased risk of type 2 diabetes incidence (RR=2.46, 95%CI: 1.31-4.63), while those in the middle BMI category (24-27.9 kg/m^2) were associated with moderate, yet non-significant increase in the diabetes risk (RR=1.44, 95%CI: 0.86-2.40).[85] Similar to the Beijing Project

5-year Follow-up Study, only 53.4% of initial participants had a second blood glucose test in the follow-up, and the reason for loss to follow-up was unspecified.

The estimated relative risks in both cohort studies could be affected if the missing of participants was not at random, but was related to disease exposure, e.g. socioeconomic characteristics, health behaviours, or disease outcome, e.g. loss to follow up due to death. In a simulated cohort study, such a "relative bias" (defined as the true odds ratio divided by the observed odds ratio) could range from 1.23 for 5% loss to follow up to 25.0 for 40% loss to follow up.[86] Furthermore, a significant loss to follow-up, whether at random or not, could reduce the statistical power of any cohort studies.

The Singapore Chinese Health Study was a population-based prospective cohort study of ethnic Chinese men and women, which involved a relatively large sample size of 63,257 participants aged 45-74 years. During the follow-up period from 1993 to 2004, 1,904 incident diabetes cases were identified through follow-up phone interviews. 49.8% (949 cases) of the self-reported diabetes diagnoses were validated through linkage with hospital records in a nationwide hospital-based discharge summary database. In this study of Singaporean Chinese, those considered as normal weight range (BMI: 18.5-23.0 kg/m^2) had a 2.5-fold increased risk of diabetes (HR=2.47, 95%CI: 1.75-3.48) compared with the reference group (BMI<18.5 kg/m^2). The risks increased with each successively increasing BMI category: the hazard ratios in higher BMI groups (23-27.5 kg/m^2 and >27.5 kg/m^2) were 4.88 (95%CI: 3.48-6.85) and 8.33 (95%CI: 5.88-11.79), respectively.[87] As the study was properly conducted with well-established and reliable follow-up procedures, it provided a better evidence of the BMI-diabetes association than most other studies in China. Nevertheless, since there were significant differences in

socioeconomic development and lifestyles between Singapore and China, the unadjusted confounding factors (e.g. personal income) may limit its generalisability to mainland Chinese at large.

The combined analyses of the People's Republic of China Study and the Atherosclerosis Risk in Communities Study were conducted to compare ethnic differences in the strength of association between BMI and diabetes incidence. Instead of calculating risk ratios, the study compared absolute risk differences between each BMI category and the reference (18.5 kg/m^2 < BMI ≤ 23 kg/m^2) across three ethnic groups (Chinese, American black and American white). At all BMI levels, Chinese and American Blacks had consistently higher risk difference of diabetes than American Whites. With respect to the difference between Chinese and American Blacks, Chinese tended to have higher risk differences for diabetes in those who had a BMI above 25 kg/m^2.[88] One major draw-back of this study was that the results were presented by risk difference, rather than risk ratio. This largely reduced the comparability of its results with other studies. But within the study, it suggested Chinese population might have higher risks for diabetes compared to American populations at any levels of BMI.

2.2.3 Evidence from meta-analyses

4 published meta-analyses have evaluated the risk of diabetes associated with BMI that included all (1 study) or a certain proportion of Chinese (3 studies). The Obesity in Asia Collaboration was initiated in 2002, comprising 21 cross-sectional studies in 10 countries in the Asia-Pacific Region with information on more than 263,000 individuals. Of the total sample size, 145,344 (55%) were Chinese or Chinese origin and 61,776 (23%) were Australian Caucasians. It was one of the few studies to directly compare Asian

population with Caucasian population in a pooled meta-analysis. For per 0.5 SD increment in BMI, the age-adjusted odds ratios for type 2 diabetes were 1.26 (95%CI: 1.20-1.33) and 1.23 (95%CI: 1.19-1.28) in males and females of Asian ethnicity, respectively, whereas for Australian Caucasians the same odds ratios were 1.39 (95%CI: 1.33-1.46) in males and 1.32 (95%CI: 1.28-1.37) in females. One of the important findings from this study was that at any given level of BMI, the absolute risk of diabetes is consistently higher in Asians compared with Caucasians among both men and women.[67]

One comparable study was conducted by Cooperative Meta-analysis Working Group on Obesity in China, by the China Working Group on Obesity. It collected data from 13 cross-sectional studies of about 239,927 individuals aged 20 years or older, with field work carried out between 1990 and 2000 in 21 provinces. Compared to the reference group (BMI<24 kg/m^2), the age-adjusted odds ratios of type 2 diabetes in overweight population (BMI≥24 kg/m^2) were 2.40 for males and 2.14 for females; and the odds ratios in obese population (BMI≥28 kg/m^2) were 2.55 and 2.52 for males and females respectively (no confidence interval was provided).[89]

Due to various study settings and limited data availability for the pooled analysis of all individual data, the associations derived from these two meta-analyses were only adjusted for a limited number of common variables (e.g. age and sex). As a result, the strength of association presented above may be highly confounded by other factors.

Two meta-analyses provided the risks associated with per unit change of BMI. The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Asia Study (DECODA) included 9,095 men and 11,732 women aged 35-74 years from 16

participating cross-sectional cohorts from seven countries in Asia (including 5 studies in China). It showed that the pooled odds ratio for diabetes associated with per standard deviation increase in BMI was 1.52 (95%CI: 1.41-1.64).[90] In another analysis using published data from 32 prospective studies (12 U.S. studies, 9 European studies, 4 Asian studies including 2 in China, and 7 in other regions) in 2004, Vazquez et al. reported that the per standard deviation associated relative risk for incident diabetes was 1.87 (95%CI: 1.67-2.10).[65]

The pooled results of published data should also be interpreted with caution. Apart from possible publication bias, the strong heterogeneity between Asian and Western populations in each meta-analysis could severely affect the generalisability of its results to the Chinese populations.

2.3 Waist circumference and diabetes

2.3.1 Evidence from cross-sectional studies

The earliest available cross-sectional analyses of waist circumference and diabetes in China were conducted in the 1994 National Diabetes Survey. For every 5 centimetre increase in waist circumference, the multivariable-adjusted odds ratio for type 2 diabetes was 1.87 (95% CI: 1.80-1.95) in the survey population.[89] In the 2008 National Diabetes Survey, backward elimination was used in the model building process. Both overall and central obesity were retained in the model, and the estimated odds ratio for central obesity (defined as a waist circumference of 90 cm or more in men and 80 cm or more in women) was 1.39 (95%CI: 1.18-1.63),[25] compared to those with a waist

circumference below the cut-off point. The finding of this study also suggested that central obesity was a significant risk factor independent of BMI.

A different waist circumference cut-off was used in the InterAsia Study. The odds ratios for men with a waist circumference of ≥85 cm and women with a waist circumference of ≥80cm were 1.85 (95%CI: 1.45-2.38) and 2.76 (95%CI: 2.15-3.54), respectively.[24] Although the different cut-offs for men and women were not fully validated, it suggested that central adiposity might have a stronger effect on women compared to men.

Waist circumference was categorized into quartile groups for a more detailed analysis in the Shanghai Women's Health Study baseline analysis. The odds of having diabetes were 3-fold (OR=3.15, 95%CI: 2.07-4.77) and 5-fold (OR=5.15, 95%CI: 3.40-7.79) in the 3rd and 4th quartiles as compared to the 1st quartile.[82]

In the CNNHS 2002, odds ratios were calculated for each 5 cm increment in waist circumference. It revealed that the odds ratios for men with a waist circumference of 85-89, 90-94 and >95 cm were 2.05 (95%CI: 1.65-2.54), 2.92 (95%CI: 2.36-3.60) and 3.62 (95%CI: 2.98-4.40), respectively. For women with a waist circumference of 80-84, 85-89 and >90, the odds ratios were 2.12 (95%CI: 1.74-2.58), 2.75 (95%CI: 2.25-3.37) and 4.10 (95%CI: 3.43-4.88), respectively.[91] Similar to the InterAsia study, this study showed not only a monotonically increasing risk of diabetes with waist circumference, but also somewhat greater effects of central obesity on Chinese women compared to men.

2.3.2 Evidence from prospective cohort studies

Only 2 small prospective cohort studies in China provided information about the association of waist circumference with diabetes. The Beijing Project 5-Year Follow-up Study reported the relative risk for diabetes was 1.46 (95%CI: 0.74-2.87) for centrally obese group (males: ≥90 cm, females: ≥80 cm) compared to normal group (males: <90 cm, females: <80 cm).[84] Nevertheless, the non-significant result was likely to be the consequence of small sample size (n=1,566), limited number of incident cases (n=126) and a significant loss to follow up (42.4%).

The Jiangsu Study recruited 4,582 participants from 1999 to 2004 and followed-up for a mean period of 6.3 years, during which, 160 incident diabetes cases were identified. The study did not apply waist circumference in its analysis directly. Instead, it calculated the Lipid Accumulation Product Index (LAP), a combined indicator of waist circumference and triglyceride concentration, to estimate total body lipid accumulation. Using this transformation of waist circumference, it found that the LAP had a better predicting power for diabetes compared to BMI, as the relative risks were higher across all LAP quartiles than were in BMI quartiles. Meanwhile, the area covered under the Receiver Characteristic Curve of LAP was larger than those of BMI, waist circumference and waist-hip ratio.[92]

There are two potential issues with the Jiangsu Study: firstly, the study used a combined index of both waist circumference and triglyceride concentration to predict diabetes risk. Despite the added value of a metabolic indicator, it did not allow for direct comparison of its results with other studies as few studies used the same approach. Moreover, this study used hospital records for follow-up of diabetes incidence. Despite that it was more

efficient and accurate for diabetes incidence reporting, this method had its inherent disadvantages: the hospital-based follow-up had low detection rate due to the asymptomatic nature of diabetes. Current literature has consistently reported that type 2 diabetes has been under-reported across populations: it was estimated that about 30% of diabetes patients were undiagnosed in the U.S.[93] In China, the under-report of diabetes accounted for up to 60.7% of overall diabetes.[94] As large proportion of diabetic patients would be misclassified as non-diabetes, the hospital follow-up of diabetes in the Jiangsu Study could potentially attenuate the association.

With limited prospective evidence from China, the U.S.-based Nurses' Health Study as well as Health Professionals Follow-Up Study could provide some insights into effects of central obesity. Waist circumference was divided into categories of 2-inch intervals in the Nurses' Health Study, and the age-adjusted relative risks increased progressively from 1.6 (95%CI: 1.0-2.6) in the second category (28-29 inches) to 22.4 (95%CI: 14.8-33.9) in the highest category (≥38 inches) (P_{trend}<0.0001). After adjusting for BMI, relative risks of waist circumference still increased in a monotonic fashion (P_{trend}<0.0001). Apart from one category (28-29 inches), all the hazard ratios for the remaining categories were statistically significant independent of BMI.[58] Similar patterns were observed in the Health Professionals Follow-Up Study, in which the multivariable-adjusted relative risks of waist circumference quintiles increased from 1.9 (95%CI: 1.3-2.9) in the 2nd quintile to 9.7 (95%CI: 6.8-13.8) in the 5th quintile (P_{trend}<0.001). After a further adjustment of BMI, the relative risks were still significant and increased monotonically from 1.7 (95%CI: 1.1-2.5) to 4.5 (95%CI: 3.0-6.7) across quintiles.[95]

2.3.3 Evidence from meta-analyses

The study conducted by the Cooperative Meta-analysis Group of Working Group on Obesity in China concluded that the centrally obese population were 2-fold (for males ≥ 85 cm) and 2.7-fold (for female ≥ 80 cm) more likely to get diabetes than those whose waist circumference were below the cut-offs.[89] This was broadly consistent with the results from the InterAsia study.[24]

In the DECODA study, the pooled age-adjusted odds ratios for diabetes associated with per 1 standard deviation increase in waist circumference was 1.54 (95%CI: 1.43-1.67) for men and 1.70 (95%CI: 1.58-1.82) for women. The sub-analysis of the Chinese population found that the same odds ratios was 1.58 (95%CI: 1.37-1.82) for men, and was 1.55 (95% CI: 1.38-1.74) for women.[90]

The Asia population was compared with Caucasians in the Obesity in Asia Collaboration Study. The results showed that age-adjusted odds ratios for diabetes prevalence associated with 0.5 standard deviation increment in waist circumference were 1.35 (95%CI: 1.28-1.43) and 1.40 (95%CI: 1.32-1.47) for males and females of Asian ethnicity. For Australian Caucasians, the odds ratios were 1.42 (95%CI: 1.36-1.50) for males and 1.50 (95%CI: 1.44-1.58) for females. Similar to BMI levels, for any given level of waist circumference, the absolute risk of diabetes among both men and women was consistently higher in Asians compared with Caucasians.[67]

The meta-analysis of prospective studies by Vazquez et al. found that the overall relative risk for per 1 standard deviation increment in waist circumference was 1.9 (95% CI: 1.6-2.2). Its sub-analysis of the Asian population (2 studies only) reported an overall relative

risk of 2.4 (95%CI: 1.5-4.0), as opposed to the relative risk of 2.1 (95%CI: 1.7-2.6) in the European population (2 studies) and 1.9 (95%CI: 1.4-2.1) in the U.S. population (9 studies).[65] Again, as only a limited number of Chinese studies were conducted and hence included in this meta-analysis, the pooled associations may largely reflect the associations in Western populations.

2.4 Hip circumference and diabetes

There is very limited information available on hip circumference and its risk association with diabetes. The Shanghai Women's Health Study was the only study in China that provided cross-sectional data on hip circumference. It showed that higher quintiles of hip circumference were associated with higher risk for diabetes. Compared to the lowest quintile, the 2nd, 3rd, and 4th quintiles represented about 9% (OR=1.09, 95%CI: 0.75-1.58), 68% (OR=1.68, 95%CI: 1.17-2.40) and 67% (OR=1.67, 95%CI: 1.17-2.39) increased risk, after adjusting for education, income, calorie intake and history of hypertension.[82] No adjustment was made for overall or other central adiposity measures.

One meta-analysis of mostly Western population assessed the association between hip circumference and diabetes. Koning et al. in the EpiDREAM Study found that for per 1 standard deviation increment in hip circumference, the associated odds ratios for diabetes was 1.20 (95%CI: 1.15-1.25), and with a further adjustment of waist circumference, the odds ratios reduced to 0.77 (95%CI: 0.72-0.83).[96] However, since no Chinese populations were included in this meta-analysis, the exact direction and

strength of the hip circumference's independent effect in Chinese populations was largely unknown.

2.5 Waist hip ratio and diabetes

2.5.1 Evidence from cross-sectional studies

In the 1994 National Diabetes Survey, WHR was included into the model to estimate odds ratio for diabetes. It concluded that "WHR instead of BMI gave similar results". However, no further details were provided regarding this result.[75] But in an analysis of a subset of data (n=16,102) from the same study, it showed that the odds ratio for diabetes with each 0.05 increment of WHR was 3.35 (95%CI: 3.17-4.84).[97]

The Shanghai Women's Health Study divided WHR into quartiles and calculated odds ratios for diabetes in each quartile. The risk of diabetes increased steadily with increasing WHR, with the odds ratios in the 2nd, 3rd and 4th quartile being 1.58 (95%CI: 1.00-2.51), 3.36 (95%CI: 2.21-5.09) and 6.05 (95%CI: 4.05-9.04). After a further adjustment of BMI, odds ratios were still statistically significant in the 3rd (OR=3.10, 95%CI: 2.03-4.74) and 4th quartile (OR=5.40, 95%CI: 3.56-8.18), all p for trend < 0.05.[82]

Both the InterAsia Study and the Guangzhou Biobank baseline analysis used WHR tertiles to estimate associated risks for type 2 diabetes. In the InterAsia Study, the univariate odds ratios for 2nd and 3rd WHR tertiles were 1.60 (95%CI: 1.11-2.30) and 2.95 (95%CI: 2.04-4.26) for men, and were 1.76 (95%CI: 1.17-2.64) and 4.42 (95%CI: 2.94-6.65) for women.[24] Without proper controlling for all possible confounding factors, e.g. socio-demographic status, lifestyle factors, it is highly possible that the association was confounded and may not reflect a true strength.

The Guangzhou Biobank Study showed a similar trend that increasing diabetes risk was observed in higher WHR tertiles. The odds ratios for 2nd and 3rd tertiles were 2.24 (95%CI: 2.02-2.50) and 3.99 (95%CI: 3.60-4.42), respectively. A further adjustment of BMI yielded a slightly weaker association, with odds ratios of 2.05 (95%CI: 1.84-2.29) and 3.40 (95%CI: 3.05-3.80) in the 2nd and 3rd tertile.[83]

2.5.2 Evidence from prospective studies

Two prospective cohort studies in this literature review examined WHR and the relative risks for type 2 diabetes. In the Beijing Project 5-Year Follow-Up Study, the relative risk for diabetes in those who had higher WHR (males: ≥0.90; females ≥0.85) was 2.91 (95%CI: 1.46-5.80).[84] In Shanghai Women's Health Study, relative risks for diabetes were analysed in WHR quintiles in the 5.7 years of follow-up. Using 1st quintile as reference group (7 cases), the relative risk for diabetes increased from 0.86 (95%CI: 0.30-2.46) in the 2nd quintile to 2.45 (95%CI: 1.10-5.48) in the last quintile.[98] Because of the small number of incident diabetes cases included in both studies (126 cases and 99 cases, respectively), the observed point estimates were likely to be subject to large random variation.

2.5.3 Evidence from meta-analyses

Both DECODA Study and the EpiDREAM Study provided pooled odds ratios for per 1 standard deviation increment in WHR. In its analysis of cross-sectional studies, the DECODA study reported that the odds ratios for diabetes corresponding to per 1 standard deviation incremental change of WHR were 1.45 (95%CI: 1.39-1.52) in men and 1.28 (95%CI: 1.22-1.34) in women. Specifically, the pooled odds ratios in Chinese men

and women were 1.40 (95%CI: 1.29-1.52) and 1.31 (95%CI: 1.21-1.43) respectively.[90] Similarly, Koning et al. found in the EpiDREAM Study that the pooled odds ratio for per standard deviation increment in waist hip ratio was 1.40 (95%CI: 1.34-1.46) for both sexes combined.[96] Although the EpiDREAM Study did not include Chinese populations, the results appeared similar to that in the Chinese population based studies.

In the Obesity in Asia Collaboration, a 0.5-standard deviation increment of WHR was associated with an age-adjusted odds ratio of 1.47 (95%CI: 1.35-1.60) for men and 1.40 (95%CI: 1.29-1.52) for women of Asian origins. In Caucasians, they were 1.41 (95%CI: 1.33-1.50) and 1.62 (95%CI: 1.52-1.72) for men and women respectively.[99]

Using prospective studies, Vazquez et al. showed that per standard deviation increment of WHR yielded a relative risk for diabetes incidence of 1.88 (95%CI: 1.61-2.19), modestly higher than BMI and waist circumference.[65]

2.6 Waist height ratio and diabetes

Waist-height ratio was less well studied in the Chinese population, and only two pieces of evidence were available for review. One was found from the CNNHS 2002, in which, the adjusted prevalence ratios for glucose tolerance abnormalities (including type 2 diabetes, impaired glucose tolerance and impaired fasting glucose) were reported. For per 1 standard deviation increment in waist height ratio, the prevalence ratios were 1.68 (95%CI: 1.60-1.76) in men and 1.68 (95%CI: 1.61-1.76) in women.[100] Since the disease outcome included a number of related metabolic syndromes rather than diabetes specifically, it was difficult to compare the results with other studies.

In the meta-analysis of the DECODA study, the pooled odds ratios for 1 standard deviation increment of waist height ratio were 1.62 (95%CI: 1.50-1.75) in men and 1.70 (95%CI: 1.59-1.83) in women. For a subset of Chinese within the meta-analysise the pooled odds ratios were 1.62 (95%CI: 1.40-1.87) in men and 1.57 (95%CI: 1.38-1.76) in women.[90]

2.7 Comparison across adiposity measures

2.7.1 Correlation of different anthropometric measures with fasting glucose levels

One study was conducted using 1995-1997 National Diabetes Survey Data to compare the partial correlation coefficients between anthropometric measures and glucose levels. In men, BMI was more strongly correlated with blood glucose levels (r=0.125) than waist circumference (r=0.098), hip circumference (r=0.021) and WHR (r=0.019); while in women, WHR was more strongly correlated with blood glucose levels (r=0.152) than waist circumference (r=0.133), BMI (r=0.065) and hip circumference (r=0.045). However, a slightly different pattern was observed for OGTT 2-h glucose levels. In men, the correlation coefficient of hip circumference changed from 0.021 to -0.006, while other measures remained in the same order. In women, the order of coefficients remained the same, but WHR (r=0.230) and waist circumference (r=0.161) showed stronger correlations with glucose levels.[97]

The InterAsia Study reported age-adjusted partial correlation coefficients between waist circumference/BMI and glucose levels. In its results, waist circumference was shown to

have better correlation with glucose levels over BMI (0.11 versus 0.10 in men, 0.12 versus 0.09 in women), but neither reached statistical significance.[101]

The correlation coefficients are just a primary source of information about the extent to which values of the anthropometric measures and glucose levels are proportional to each other. The differences in absolute values of correlation coefficients in the two reviewed studies may be due to several factors: (1) the different methods for measuring both anthropometric values and glucose levels across studies could substantially affect the coefficients; (2) because of the way in which the regression line is determined (sum of squares of distances of data points from the line), outliers of these studies could have a great influence on the slope of the regression line, and consequently on the value of correlation coefficients; (3) the anthropometric values and plasma glucose levels may have a possible nonlinear relation in cross-sectional studies, as people with lower adiposity may be a direct result of diabetes. The U-shaped relation violates the linear assumption of correlation coefficient, hence produced unreliable results for the two studies.

Although both studies suggested central adiposity measures (e.g. waist circumference and waist hip ratio) were more strongly correlated with fasting plasma glucose levels compared to overall adiposity measure (i.e. BMI), the correlation coefficient on its own couldn't possibly help determine a causal relationship. A set of more robust analyses of the association are therefore needed to further confirm these results.

2.7.2 Comparison of the area under the Receiver-Operating Characteristic Curve

A couple of studies assessed the area under the receiver-operator characteristic curve (AUC) to compare different anthropometric measures in diagnosing diabetes. In the CNNHS 2002, the AUC of ROC curves ranged from 0.70 to 0.75 across different measures. The AUC for BMI was generally lower than the AUCs for waist circumference and WHtR in both sexes. And women had higher AUC than men in waist circumference and WHtR for diagnosing type 2 diabetes.[100]

In the InterAsia Study, the AUCs of BMI, waist circumference and WHR were 0.62 (95%CI: 0.60-0.64), 0.66 (95% CI: 0.64-0.68) and 0.67 (95%CI: 0.65-0.69), respectively.[102] It therefore suggested that WHR and waist circumference were more sensitive and specific in diagnosing type 2 diabetes than was BMI, and the two measurements of central obesity were equal in identifying the risk of diabetes.

In the Jiangsu Prospective Study, it was found that the ROC curve for lipid accumulation product index covered the largest area under the curve (AUC=0.64, 95%CI: 0.57-0.71), followed by WHR (AUC=0.62, 95%CI: 0.54-0.70), waist circumference (AUC=0.61, 95%CI: 0.53-0.69), and BMI (AUC=0.58, 95%CI: 0.50-0.65) in men. Similar pattern with stronger diagnostic power was observed in women: the AUC of LAP was 0.70 (95%CI: 0.65-0.75), followed by WHR (AUC=0.67, 95%CI: 0.62-0.72), WC (AUC=0.64, 95%CI: 0.57-0.69) and BMI (AUC=0.58, 95%CI: 0.53-0.64).[92]

Four anthropometric measurements and their associated ROC curves were analysed in the DECODA Study, adjusting for age and study cohort. It showed that the AUC was the

largest for WHtR (AUC=0.735, 95%CI: 0.72-0.75) and the lowest for BMI (AUC=0.72, 95%CI: 0.71-0.74), with waist circumference (AUC=0.73, 95%CI: 0.71-0.75) and WHR (AUC=0.73, 95%CI: 0.71-0.75) having similar AUC in men. In women, waist circumference (AUC=0.75, 95%CI: 0.73-0.77) and WHtR (AUC=0.75, 95%CI: 0.73-0.76) were both the strongest in diagnosing diabetes, followed by WHR (AUC=0.74, 95%CI: 0.73-0.76) and BMI (AUC=0.74, 95%CI: 0.73-0.76).[90] However, no measurement was significantly better than others as all four confidence intervals were overlapping.

In another meta-analysis of published data, Ashwell et al. analysed results from 31 studies of over 300,000 participants and found that waist height ratio had the highest pooled AUC for both men and women, with AUCs of 0.71 (95%CI: 0.69-0.73) in men and 0.75 (95%CI: 0.73-0.78) in women. This was followed by waist circumference (for men: AUC=0.70, 95%CI: 0.68-0.72; for women: AUC=0.74, 95%CI: 0.72-0.77). BMI was found to have the lowest AUCs in both men (AUC=0.66, 95%CI: 0.64-0.69) and women (AUC=0.70, 95%CI: 0.67-0.73).[103] Both this study and the DECODA study implied WHtR as a superior screening tool for diabetes over waist circumference and BMI.

2.7.3 Comparison of the relative importance of different adiposity measures for diabetes

A number of studies have attempted to assess the relative importance of different anthropometric measures for predicting diabetes, conventionally using 1 (or 0.5) SD of each measure. However, findings from these studies were inconsistent: some showed no material difference between different measures of adiposity, while other studies found WC (or WHtR) to be the best predictor for DM. The findings also tended to differ

somewhat between cross-sectional and prospective studies and between different populations.

In the cross-sectional analysis of Obesity in Asia Collaboration, central obesity was shown to more strongly associated with diabetes than was overall obesity (with exception in Caucasian men). The age-adjusted odds ratios for diabetes prevalence associated with 0.5 standard deviation increment in each anthropometric measure of Asia men were 1.47 (95%CI: 1.35-1.60) for WHR, 1.35 (95%CI: 1.28-1.43) for waist circumference and 1.26 (95%CI: 1.20-1.33) for BMI. In Asian women, they were 1.40 (95%CI: 1.29-1.52) for WHR, 1.40 (95%CI: 1.32-1.47) for waist circumference and 1.23 (95%CI: 1.19-1.28) for BMI. For a cross ethnicity comparison, it also showed that the absolute risk of diabetes was consistently higher in Asians compared with Caucasians among both men and women at any give level of BMI, waist circumference or WHR.[99]

The DECODA Study showed that for 1 standard deviation increase in BMI, WC, WHR and WHtR, the pooled age-adjusted odds ratios for diabetes were 1.52 (95%CI: 1.41-1.64), 1.54 (95%CI: 1.37-1.82), 1.53 (95%CI: 1.41-1.65), and 1.62 (95%CI: 1.50-1.75) respectively in men, and 1.59 (95%CI: 1.48-1.70), 1.70 (95%CI: 1.58-1.82), 1.50 (95%CI: 1.40-1.60), and 1.70 (95%CI: 1.59-1.83) in women. It therefore suggested that WHtR had the strongest association with diabetes compared to BMI, WHR and WC. Although the association between diabetes and anthropometric indicators appeared similar across Asia populations, subgroup analyses revealed that the strengths of association with anthropometric measures in the Chinese men were slightly different: WHtR (1.62) > WC (1.58) > BMI (1.53) > WHR (1.50).[90]

Some other evidence suggested that the different anthropometric measures might have similar effects on diabetes in general. In the meta-analysis conducted by Koning et al., per 1 standard deviation increment of BMI, waist circumference and waist hip ratio was all positively associated with diabetes prevalence, with odds ratios of 1.33 (95%CI: 1.28-1.39), 1.39 (95%CI: 1.34-1.45), 1.40 (95%CI: 1.34-1.46), respectively.[96] Although WHR appeared to have a stronger association, the confidence intervals were overlapping across three anthropometric measures. In the prospective meta-analysis conducted by Vazquez et al. there was no difference in the risks of diabetes for per standard deviation increment across different adiposity measures, with relative risks being 1.87 (95%CI: 1.67-2.10), 1.87 (95%CI: 1.58-2.20), 1.88 (95%CI: 1.61-2.10) for BMI, waist circumference, and waist-hip ratio, respectively.[65]

2.8 Independent and joint associations between adiposity measures and diabetes

The independent effects of different anthropometric measures on diabetes were generally evaluated through adjustment of 2 or more measures of adiposity in the same model. In comparing individual effects of BMI and waist circumference, the InterAsia Study found that waist circumference was significantly related to diabetes independent of BMI, but BMI was not related to diabetes independent of waist circumference.[101]

The cross-sectional analysis of the Shanghai Women's Health Study found similar results, in which the odds ratios for diabetes in the 3rd and 4th WHR quartiles were 3.10 (95%CI: 2.03-4.74) and 5.40 (95%CI: 3.56-8.18) after adjusting for BMI. Again, BMI was no longer independently related to diabetes after adjusting for WHR. Likewise, in the prospective

analysis of the same study, WHR was found to be associated with increased diabetes risk in 4th and 5th quintiles after adjusting for BMI,[98] indicating higher WHR was independently associated with diabetes incidence.

The Shanghai Women's Health study also assessed the joint associations of WHR and BMI with diabetes. By stratifying BMI into three categories, a higher level of WHR was found more strongly associated with diabetes within each BMI category, for example, in the normal BMI group, people in the highest WHR quartile were 7-fold more likely to have diabetes compared to people in the lowest quartile.[82]

Both the InterAsia Study and the Guangzhou Biobank Cohort Study baseline analysis analysed the independent effect of waist circumference by adjusting for BMI. In the InterAsia studies, despite the increasing odds ratios in higher tertiles, only the result in the highest tertile was significant (OR=2.1, 95%CI: 1.3-3.4 for men, OR=2.1, 95%CI: 1.3-3.3 for women). Similar trend was reported in the Guangzhou Biobank Study, with the odds ratios increasing with increasing waist circumference from 1.76 (95%CI: 1.57-1.97) in the 2nd tertile to 2.84 (95%CI: 2.50-3.24) in the 3rd tertile (P_{trend}<0.001). In the Guangzhou Biobank Study, central obesity, as measured by waist circumference and WHR, was positively associated with diabetes risk independent of overall obesity. Moreover, the odds ratios of medium and high WHR tertiles were consistently higher than that of the same tertiles of waist circumference.[83] This indicated that at any levels of BMI, WHR had stronger association with diabetes than did waist circumference.

In comparison, the EpiDREAM Study of cross-sectional studies in 21 countries (except for China) assessed the independent effect of each anthropometric measurement, calculated for per 1 standard deviation incremental change. After adjusting for BMI,

pooled odds ratios of waist circumference were 1.22 (95%CI: 1.13-1.32) in men and 1.39 (95%CI: 1.28-1.50) in women; and the pooled odds ratios of WHR were 1.27 (95%CI: 1.18-1.37) in men and 1.35 (95%: 1.28-1.43) in women. BMI became an non-significant predictor after adjusting for waist circumference (OR=1.11, 95%CI: 0.92-1.35) in men, but remained significant in women (OR=1.23, 95%CI: 1.06-1.42). After adjusting for WHR, BMI remained positively associated with diabetes in both men and women (men: OR= 1.21, 95%CI: 1.13-1.30; women: OR= 1.29, 95%CI: 1.23-1.36).[96]

Little information was available about the independent and joint effects of anthropometric measurements from prospective studies in China. Nevertheless, the U.S.-based Health Professionals Follow-Up Study and Nurses' Health Study conducted relevant analyses to provide some insights into this issue. The Nurses' Health Study assessed the simultaneous effects of overall and central obesity measures, after controlling for all confounders. It concluded all anthropometric indicators were strongly monotonically associated with type 2 diabetes risks, and the tests for trend for all indicators were highly significant. Although the effect of BMI was attenuated, its significance still remained.[58]

Similar results were obtained from the Health Professional's Follow-Up Study. The relative risks across waist circumference (and WHR) quintiles increased monotonically after adjusting for BMI (both p for trend <0.001). Meanwhile, higher BMI quintiles were still significantly associated with increased diabetes risk after adjusting for WHR or waist circumference. In addition, the joint effect of central and overall adiposity was also analysed in this study. It reported that increased waist circumference predicted

increased risk of diabetes within each BMI category, and those who had a high BMI (≥25 kg/m^2) and a high waist circumference (>102 cm) had the highest diabetic risk.[95]

2.9 Summary of findings

2.9.1 Burden and characteristics of obesity and diabetes in China

During the recent decades, the disease burden of both obesity and diabetes has increased rapidly and substantially in the Chinese population. The results from the National Nutrition and Health Surveys showed that the prevalence of adult overweight and obesity (measured by BMI) reached 22.8% and 7.1%, respectively in 2002, representing about 40% and 100% increase in overweight and obesity within just 10 years. Central obesity showed a similar pattern, in which the mean waist circumference of male and female adults increased by 5.8 cm and 3.1 cm respectively in 10 years.[55]

Along with such increases in obesity, there was a significant increase in diabetes prevalence over the same time interval: the age-standardized prevalence of diabetes rose from 2.5% in 1994[70] to 5.5% in 2001,[20] and was estimated to have reached 9.7% in the latest national survey in 2008.[25] The pace of increase was much greater than in Western populations. For example, during the same time period, the overall age-standardized prevalence of diabetes in the U.S. population increased from 8.2% in NHANES 1988-1994 to just 9.3% in NHANES 1999-2002.[104] The fast increase in both obesity and diabetes in China highlights not only the urgency for immediate public health interventions, but also the need for better understanding of the relationship between obesity, diabetes and other common diseases in China.

2.9.2 A leaner population with higher diabetes risks

Despite the rising overweight and obesity in China in recent years, the Chinese population is still relatively lean compared with most Western populations. For example, 68% and 23% of the U.S. adults are overweight and obese respectively,[105] compared to 23% and 7% in Chinese adults. Nevertheless, evidence from this literature review has suggested that the lean body weight in Chinese population may not necessarily protect them against diabetes, and, if anything, they may be at a higher risk for developing diabetes.

In both Chinese and Caucasians, a higher level of BMI, WC, WHR or WHtR is associated with increased risks of diabetes.[58,82,83,95,106] However, evidence has consistently shown that in the Chinese population, the risk of developing type 2 diabetes increased significantly at lower level of BMI, which was still classified as "normal" by the WHO definition.[87,89,107,108] Moreover, a cross-sectional analysis of 21 studies indicated that at any given level of BMI, WC or WHR, the absolute risk of diabetes in men and women was consistently higher in Asians (mainly Chinese) compared with Caucasians.[99] It appears that the lean body build of the Chinese population does not provide strong protection from diabetes, and that the same level of excess adiposity could exert even higher diabetic risks to the Chinese as compared to Caucasians.

2.9.3 An unresolved question of the best simple anthropometric indicator

Although it is well established that obesity is an important risk factor for diabetes, the best simple measure of obesity for predicting obesity, especially in the Chinese population, is yet to be established. In the reviewed literature, several approaches were used to compare anthropometric measurements, but the results were conflicted.

For example, one nationally representative survey found that BMI was more strongly correlated with plasma glucose in men, while WHR and WC were more strongly correlated with plasma glucose in women.[97] But in another national survey, WC had a stronger correlation with glucose levels than BMI in both men and women.[101] By comparing the area under the receiver-operator characteristic, it was relatively consistent that central obesity measurements had both higher sensitivity and specificity in diagnosing diabetes,[85,90,100,102] although only one study found significant difference between central and overall obesity.[90]

The different risks associated with each of different anthropometric measures was widely analysed in meta-analyses, again, with inconsistent findings. Two meta-analyses of cross-sectional data reported that WHR was associated with the highest diabetic risk, followed by WC and BMI.[67,96] However, in the DECODA Study, the relative risks for WHR were only higher than that for BMI, but much lower than those for WHtR and WC.[90] In contrast, a meta-analysis of prospective studies found similar effects for BMI, WC and WHR.[65]

Although there is some evidence that central adiposity measures are better associated with diabetes than the overall adiposity measures from current literature, such findings are still inconclusive. Since evidence of Chinese studies is relatively limited, the best single anthropometric indicator for this specific population remains unrevealed.

2.9.4 The independent effects of central and overall adiposity

The InterASIA Study, Shanghai Women's Health Study and Guangzhou Biobank Study all found that WC or WHR, as central adiposity measures, were strongly associated with

diabetes prevalence at any given level of BMI.[82,83,101] Consistently in all three studies, BMI was no longer associated with diabetes after controlling for central adiposity. It implies that central adiposity may play a major role in developing diabetes in Chinese population, while the effect of overall adiposity may be largely dependent on central adiposity.

This finding differed importantly from those of Western populations. The EpiDREAM Study of cross-sectional studies in 21 countries showed that both central and overall adiposity measures remained positively associated with diabetes after adjusting for each other.[96] Likewise, the prospective evidence from the Health Professionals Follow-Up Study and Nurses' Health Study also found that central and overall adiposity measures were each independently associated with diabetes.[58,95]

Since all the current Chinese evidence is from cross-sectional studies, no conclusive causal relationship could therefore be established. It is important that a prospective analysis using a large sample of Chinese populations to determine: (1) whether the observed disparity between Chinese and the Western populations is consistent in the study of prospective design; and (2) to what extent do central and overall adiposity contribute independently and jointly to the development of diabetes in the Chinese population.

2.9.5 The independent effect of hip circumference

Several prospective studies in the Western populations have previously reported that at any given levels of BMI (or WC), larger hip circumference may protect against diabetes.[109-111] Similar findings were also identified in one meta-analysis included in this

literature review.[96] But to our knowledge, only one prospective study in the Chinese population assessed the association between hip circumference and metabolic syndromes (only indirectly related to diabetes), showing an inverse association between them in women but not in men.[112] The exact direction and strength of the relationship of hip circumference with diabetes risk in the Chinese population remain to be established.

2.9.6 Implication of literature review

It is increasingly evident that diabetes is becoming one of the major health challenges for China. Among the many risk factors for the development of diabetes, obesity is known to be one of the few risk factors that could be modified through lifestyle change. Despite the many studies of adiposity and diabetes in the West, evidence from China-based studies remains very limited, with many important questions unanswered. For a thorough understanding of the relationship between adiposity and diabetes in Chinese populations, large-scale prospective cohort study with robust study design and reliable data is needed to help resolve these uncertainties, hence to provide sound evidence for public health policy and interventions.

Table 2.1 Terms used in literature searches

Types	Terms
Study design:	prospective cohort study, retrospective cohort study, cross-sectional study, nested case-control study, meta-analysis, systematic review, literature review, narrative review
Risk factors:	body mass index, BMI, waist circumference, hip circumference, waist hip ratio, waist height ratio, anthropometry, anthropometric measurement, percentage body fat, body fat distribution, adiposity, overall adiposity, central adiposity, peripheral adiposity, visceral adiposity, subcutaneous adiposity
Outcome of interest:	Type II diabetes mellitus, type 2 diabetes, non-insulin dependent diabetes, noninsulin dependent diabetes, NIDDM, T2DM, adult onset diabetes mellitus
Population:	China, Chinese, Chinese population, Chinese origin, Asian continental ancestry group, Taiwan, Taiwanese, Hong Kong, Macau, Chinese provinces, urban China, rural China

Table 2.2 Description of 7 cross-sectional studies of adiposity and diabetes in China

Research Project (survey year)	Year Published	Sample Size	Population Location	Age (years)	Anthropometric Measurements*	Outcome Measurements*	Methods of Analysis	Adjustment
A. Nationally representative								
China National Diabetes Research Group[23] (1981)	1982	Approximately 300,000	14 Provinces	N/A	N/A	FPG plus OGTT	N/A	N/A
China National Diabetes Prevention and Control Cooperative Group[70] (1994)	1997	224,251	19 Provinces	25-64	Weight, height, BMI, waist and hip circumference	FPG plus OGTT	Age standardization and stepwise multiple logistic regression	Age, sex, hypertension, family history, income, education, occupation
China National Diabetes and Metabolic Disorders Study Group[25] (2009)	2010	46,239	14 Provinces	>25	Weight, height, BMI, waist circumference	OGTT	Age standardization, multinomial logistic regression (backward elimination)	Sex, age, family history, education, BMI/WC, heart rate, SBP, triglycerides, urban/rural
China National Nutrition and Health Survey[113] (2002)	2005	239,972	31 Provinces	>18	Weight, height, BMI, waist circumference	FPG plus OGTT	Not specified	Not specified
The InterAsia Study[24] (2001)	2003	15,236	5 northern provinces and 5 southern provinces	35-74	Weight, height, BMI, Waist and hip circumference	Self-report DM plus FPG	Age standardization and multivariate logistic regression	Sex, age, education level, occupation, marital status, income, region
B. Other regional surveys								
Shanghai Women's Health Studies[82](2000)	2004	57,130	7 urban communities in Shanghai	40-70	Weight, height, BMI, waist and hip circumference	Urine glucose test and subsequent FPG	Age and sex-matched, conditional logistic regression	Education, income, caloric intake, history of hypertension
Guangzhou Biobank Cohort Study[83](2004)	2010	28,946	Guangzhou urban communities	>50	Weight, height, BMI, waist and hip circumference	FPG	Multivariate multinomial logistic regression	Study phase, age, sex, smoking and alcohol use, history of cardiovascular disease, occupation, education, income and total physical activity.

N/A=not available; FPG=fasting plasma glucose; OGTT=oral glucose tolerance test

* Unless otherwise specified, all measured by investigators

Table 2.3 Description of 6 prospective studies of adiposity and diabetes incidence in Chinese populations

Research Project	Study Period	Sample Size	Population Location	Age at Baseline	Mean Years of Follow-up	No. of Cases	Anthropometric Measurements*	Outcome Measurements	Methods of Analysis	Adjustment
The Beijing Project 5-Year Follow-up Study[84]	1994-2000	1,566	Beijing urban/rural communities	>25	5 years	126	BMI, waist circumference	FPG, OGTT and urine test	Univariate ANOVA and logistic regression	Age, sex, education, occupation, smoking, family history of diabetes, and total cholesterol
Shanghai Diabetes Studies[114]	1998-2004	4,907	2 urban communities in Shanghai	20-94	5.5 years	128	BMI, waist and hip circumference	FPG plus OGTT	Logistic regression	N/A
Prevention of Multiple Metabolic Disorders and Metabolic Syndrome in Jiangsu Province[92]	1999-2006	4,582	3 communities in Jiangsu Province	35-74	6.3 years	160	BMI, waist and hip circumference	FPG + Random PG+ Self-reported diabetic drug use	T-test for cross-group comparison; Cox proportional hazard Model	Age, HDL-C, blood pressure, FPG, smoking, alcohol use, family history of diabetes, and physical activities
Shanghai Women's Health Study[98]	2000-date	72,773	7 urban communities in Shanghai	40-70	5.7 years	99	BMI, waist and hip circumference	Urine glucose test and subsequent FPG	Cox proportional hazards model	Age, education, income, caloric intake, history of hypertension
Singapore Chinese Health Study[87]	1993-2004	52,325	Singapore (originated from China)	45-74	6 years	1,904	Self-reported height and weight, BMI	Self-reported diabetes, validated by hospital-based discharge summary database	Cox proportional hazards model	Age, sex, ethnicity, year of interview, hypertension, smoking, education, alcohol use, dietary factors and physical activity
People's Republic of China Study (and Atherosclerosis Risk in Communities Study)[88]	1983-1994	5,980 Chinese (and 10,776 American Whites + 3,582 American Blacks)	Urban and rural populations in Beijing and Guangzhou (and white and black population in four U.S. communities)	45-64	8.2 years (and 8.2 years for whites, 7.9 years for blacks)	292 Chinese (855 whites 435 blacks)	BMI	FPG and self-reported DM	Logistic regression	Age, sex, education, smoking, alcohol use, field centre

N/A=not available; FPG=fasting plasma glucose; OGTT=oral glucose tolerance test

* Unless otherwise specified, all measured by investigators

Table 2.4 Description of 5 meta-analyses of adiposity and diabetes involving Chinese populations

Research Project	Year of Study	Study Design	Study Country	Anthropometric Variables Assessed	Outcome Definition	Statistical Methods
a. Meta-analyses of cross-sectional studies:						
Ashwell et al.[103]	2012	Meta-analysis of published results from 31 cross-sectional studies	Chinese (n=6) Thai (n=3) Japanese (n=2) Korean (n=2) Australian (n=3) Iranian (n=3) Caucasian (n=6) other (n=6)	BMI, waist circumference, waist-height ratio	N/A	Random effects model was used to allow for true effect size to vary in studies of different populations.
Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Asia Study[90]	2008	Pooled analysis of individual cross-sectional data on 20,827 participants from the 16 DECODA Participating cohorts in Asia	Chinese (n=5), Indian (n=6), Mongolian (n=1), Japanese (n=3), Filipino (n=1)	BMI, Waist circumference, waist-hip ratio, waist-stature ratio	FPG or 2-h PG	Analysis was stratified by sex to obtain OR for each individual cohort; ORs were calculated using fixed effects model. Paired homogeneity tests were conducted
Obesity in Asia Collaboration[67]	2007	Pooled analysis of individual cross-sectional data on approximately 263,000 participants (of which, 145,344 were of Chinese origin)	Chinese, Hong Kong, Taiwanese, Indian, Iranian, Japanese, Korean, Philippine, Singaporean, Thai, Australian,	BMI, waist and hip circumference	FPG	Logistic regression stratified by sex and study
Cooperative Meta-analysis Group of Working Group on Obesity in China[89]	2002	Pooled analysis of individual cross-sectional data on 239,972 participants in 21 Provinces in China	Chinese	BMI, Waist circumference	FPG	Not specified
b. Meta-analysis of prospective studies:						
Vazquez et al.[65]	2007	Meta-analysis of published results from 32 Prospective studies	US (n=12), Europe (n=9), Asia (n=4, including 2 studies in China), others (n=7)	BMI, waist circumference, and waist-hip ratio	FPG, or OGTT or Self-reported diabetes	Random effects model was performed and region-specific RRs were generated to enable regional comparison

N/A=not available; FPG=fasting plasma glucose; OGTT=oral glucose tolerance test; 2h-PG=2-hr postprandial plasma glucose

Table 2.5 Key results of the cross-sectional studies in Literature Review

Research project (survey year)	Key results (odds ratio, 95% CI)						Major limitations
	BMI	Waist circumference	Hip circumference	Waist hip ratio	Waist height ratio	% Body fat	
China National Diabetes Prevention and Control Cooperative Group[70] (1994)	For every 5 kg/m^2 increment, OR=1.34 (95%CI: 1.23-1.46); <25: 1.00 (ref) ≥25: 2.23 (p≤0.0001)	For every 5 cm increment, OR=1.87 (95%CI: 1.80-1.95)	-	For every 0.05 increment, OR=3.35 (95%CI: 3.17-4.84)	-	-	Overly adjusting for non-confounders, e.g. blood pressure, fasting plasma triglyceride and insulin may attenuate the association
China National Diabetes and Metabolic Disorders Study Group[25] (2009)	<25 : 1.00 (ref) 25-29.9: 1.43 (1.22-1.67) ≥30: 2.17 (1.68-2.81)	For male >90cm, female > 80cm, OR=1.39 (95% CI: 1.18-1.63)	-	-	-	-	Relatively small sample size; overly adjusting for non-confounders, e.g. blood pressure, triglycerides may attenuate the association
China National Nutrition and Health Survey[113] (2002)	<24 : 1.00 (ref) 24-28: 2.37 (2.22-2.40) >28: 5.22 (4.81-5.66)	Men / Women <85: 1.00 / <80: 1.00 85-89: 2.05 / 80-84: 2.12 90-94: 2.92 / 85-89: 2.75 >95: 3.62 / >90: 4.10 (both p for trend <0.05)	-	-	For every 1-SD increment, the prevalence ratio=1.68 (95%CI: 1.60-1.76)	-	Less than 20% of the study population were tested for plasma glucose; all models were adjusted for age and region only
The InterAsia Study[24] (2001)	Men / Women <24: 1.00 / 1.00 24-27: 1.22 / 1.74 ≥28: 2.49 / 2.70 (both p for trend <0.05)	Men / Women <85: 1 / <80: 1 ≥85: 1.85 / >80: 2.76 (both p for difference < 0.05)	-	Men / Women 1st tertile: 1.00 / 1.00 2nd tertile: 1.60 / 1.76 3rd terrtile: 2.95 / 4.42 (both p for trend <0.05)	-	-	Relatively small sample size; only univariate odds ratios were presented, results may be confounded; WC cut-off was not validated;
Shanghai Women's Health Studies[82](2000)	<18.5: 0.16 (0.02-1.19) 18.5-24.9: 1.00 (ref) 25.0-29.9: 1.71 (1.33-2.19) >30: 2.19 (1.47-3.27)	1st quartile: 1.00 (ref) 2nd quartile: 1.90 (1.22-2.96) 3rd quartile: 3.15 (2.07-4.77) 4th quartile: 5.15 (3.40-7.79)	1st quartile: 1.00 (ref) 2nd quartile: 1.09 (1.22-2.96) 3rd quartile: 1.68 (1.17-2.40) 4th quartile: 1.67 (1.17-2.39)	1st quartile: 1.00 (ref) 2nd quartile:1.58 (1.00-2.51) 3rd quartile: 3.36 (2.21-5.09) 4th quartile: 6.05 (4.05-9.04)	-	-	DM diagnosed by urine glucose test, which may under-report DM prevalent cases
Guangzhou Biobank Cohort Study[83](2004)	<23: 1.00 (ref) 23.0-25.0: 1.66 (1.51-1.83) >25: 2.19 (2.01-2.39)	-	-	1st tertile:1.00 (ref) 2nd tertile: 2.24 (2.02-2.50) 3rd terrtile:3.99 (3.60-4.42)	-	-	Results hardly generalisable to other age groups; results not comparable to other studies as different BMI cut-offs were applied

Table 2.6 Key results of the prospective studies in Literature Review

Research project	Key results (hazard ratio, 95% CI)						Major limitations
	BMI	Waist circumference	Hip circumference	Waist hip ratio	Waist height ratio	% Body fat	
The Beijing Project 5-Year Follow-up Study[84]	<25: 1.00 (ref) ≥25: 2.00 (1.07-2.37)	For men ≥90cm and women ≥ 80cm, HR=1.46 (95% CI: 0.74-2.78)	-	For men ≥0.90 and women ≥ 0.85, HR=2.91 (95% CI: 1.46-5.80)	-	-	Results may not be reliable due to small number of incident diabetes cases (126 cases); 42.4% of the participants were lost to follow-up
Shanghai Diabetes Studies[114]	<24: 1.00 (ref) 24-28: 1.44 (0.86-2.40) ≥28: 2.46 (1.31-4.63)	-	-	-	-	-	Relatively small sample size; 52.6% of the participants were lost to follow-up
Prevention of Multiple Metabolic Disorders and Metabolic Syndrome in Jiangsu Province[92]	Men Women 1st quartile: 1.00 1.00 2nd quartile: 1.01 1.24 3rd quartile: 1.08 1.45 4th quartile: 1.69 1.69 (both p for trend<0.001)	-	-	-	-	-	Follow-up based entirely on hospital record, may result in under-reporting of incident cases; the use of lipid accumulation index is not comparable to other studies
Shanghai Women's Health Study[98]	-	-	-	1st quintile: 1.00 (ref) 2nd quintile: 0.86 (0.30-2.46) 3rd quintile: 1.21 (0.48-3.04) 4th quintile: 1.93 (0.83-4.47) 5th quintile: 2.45 (1.10-5.48)	-	-	Unreliable results based on small number of incident diabetes cases (99 cases)
Singapore Chinese Health Study[87]	<25: 1.00 (ref) 25-27.5: 2.47 (1.75-3.48) 27.5-29.9: 4.88 (3.48-6.85) ≥30: 8.33 (5.88-11.79)	-	-	-	-	-	Findings may not be generalisable to mainland Chinese, due to different socioeconomic development and lifestyles
People's Republic of China Study (and Atherosclerosis Risk in Communities Study)[88]	Risk differences for Chinese Americans <18.5: -1.6 1.9 18.5-23: 0 0 23-25: 4.9 1.7 25-27.5: 9.7 4.6 27.5-30: 14.5 8.8 30-32.5: 18.9 14.1 >32.5: - 21.4	-	-	-	-	-	Results were presented in risk difference, difficult to compare with other studies

Table 2.7 Key results of the meta-analyses in Literature Review

Research project	Key results (relative risk, 95% CI)						Major limitations
	BMI	Waist circumference	Hip circumference	Waist hip ratio	Waist height ratio	% Body fat	
Ashwell et al.[103]	-	-	-	-	-	-	No relative risks were presented, all comparisons were based on AUCs; based on cross-sectional studies only
Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Asia Study[90]	For per 1-SD increment: Men: 1.52 (1.41-1.64) Women: 1.59 (1.48-1.70)	For per 1-SD increment: Men: 1.54 (1.43-1.67) Women: 1.70 (1.58-1.82)	-	For per 1-SD increment: Men: 1.53 (1.41-1.65) Women: 1.50 (1.50-1.75)	For per 1-SD increment: Men: 1.62 (1.50-1.75) Women: 1.70 (1.59-1.83)	-	Included small cross-sectional studies with a relatively small sample size in total; a large heterogeneity across different study populations
Obesity in Asia Collaboration[67]	For per 0.5-SD increment: Asian Men: 1.26 (1.20-1.33) Women: 1.23 (1.19-1.28) Caucasian Men: 1.39 (1.33-1.46) Women: 1.32 (1.28-1.37)	For per 0.5-SD increment: Asian Men: 1.35 (1.26-1.43) Women: 1.40 (1.32-1.47) Caucasian Men: 1.42 (1.36-1.50) Women: 1.50 (1.44-1.58)	-	For per 0.5-SD increment: Asian Men: 1.47 (1.35-1.60) Women: 1.40 (1.20-1.52) Caucasian Men: 1.41 (1.33-1.50) Women: 1.62 (1.52-1.72)	-	-	Large heterogeneity across different study populations in Asia, may not reflect the association in the Chinese population;
Cooperative Meta-analysis Group of Working Group on Obesity in China[89]	Men Women <24: 1.00 1.00 24-28: 2.40 2.14 ≥28: 2.55 2.52 (95%CI not provided)	Men Women <85: 1.00 <80: 1.00 ≥85: 2.05 ≥80: 2.12 (95%CI not provided)	-	-	-	-	Results may be confounded as all models were adjusted for age only; only ½ of participants had information on waist circumference, and ¼ had information on FPG
Vazquez et al.[65]	For per 1-SD increment: Overall: 1.9 (1.7-2.1) Asia: 2.4 (1.7-3.3) US: 1.7 (1.4-2.1) EU: 2.0 (1.6-2.6)	For per 1-SD increment: Overall: 1.9 (1.6-2.2) Asia: 2.4 (1.5-4.0) US: 1.9 (1.4-2.5) EU: 2.1 (1.7-2.6)	-	For per 1-SD increment: Overall: 1.9 (1.6-2.2) Asia: 1.4 (1.1-1.7) US: 1.8 (1.4-2.2) EU: 2.1 (1.7-2.6)	-	-	A limited number of Chinese studies were included in this meta-analysis, the pooled associations may largely reflect the associations in Western populations.

3. Methods

3.1 Study design

The China Kadoorie Biobank Study (CKB) is a large blood-based prospective observational study of 0.5 million men and women, aiming to assess reliably the environmental and genetic risk factors for common chronic diseases in the Chinese population. It involved extensive data collection at baseline by detailed questionnaire survey, physical examination, and with collection and long-term storage of blood samples. The baseline survey took place between June 2004 and July 2008. Every 4-5 years, a re-survey is to be done for a randomly selected 5% of surviving participants, to allow adjustment for "regression dilution bias"[115] of specific risk factors. Cause-specific mortality and morbidity is reported routinely from death and disease registries in each study area. In addition, fatal and non-fatal episodes of any hospitalisation are also identified and reported through linkage with local health insurance claim database. In order to minimise under-reporting of deaths and to detect loss to follow up, active confirmation of vital status is also carried out periodically in all study areas.

3.2 Study population

Those eligible to take part in the study were all non-disabled men and women aged 35-74 years who were permanently residing in 10 geographically defined areas. The areas were selected to cover a wide range of geographic locations and socioeconomic differences (e.g. north-south, east-west). Eligible participants were identified through public registry records. Invitation letters were delivered door-to-door by local community leaders or health workers following extensive publicity campaigns.

Overall, 512,891 participants from 10 study areas were recruited, of whom, 210,222 (41%) were men, 302,669 (56%) were from rural areas. The estimated population response rate (i.e. the percent of all eligible participants agreeing to take part) ranged from 26% to 38% in the rural areas and from 16% to 50% in urban areas.

Prior to start of the CKB Study, approvals from ethics committees of both the University of Oxford and the Chinese Center for Disease Control and Prevention (China CDC) were obtained. In addition, approval was also provided by the ethical committees of the local CDC in each area. Informed consent for allowing access to medical records and long-term storage of blood for anonymised and non-specified future medical research was obtained from each individual participant.

3.3 Baseline data collection

Six directly measured or derived anthropometric measurements, including BMI, waist circumference, hip circumference, waist hip ratio, waist height ratio and percentage body fat, were analysed in this study. All the measures were taken with standard instruments and protocols by trained technicians across the ten study areas. Devices used for measurement were regularly maintained and calibrated to ensure consistency. Participants wore light clothing without shoes and hat during collection of anthropometric data.

Standing height was measured to the nearest 0.1 centimetre (cm) using a stadiometer, and weight was measured to the nearest 0.1 kilogram (kg) using the scale function of a body composition analyser (TBF-300GS Body Composition Analyzer/Scale, TANITA, Tokyo, Japan). Estimated weight of the clothing (typically 0.5 kg in summer, 1.0 kg in

spring/autumn, and 2.0-2.5 kg in winter) was subtracted from the observed weight in order to obtain a person's net weight. BMI was calculated as weight / height^2 (kg/m^2). Waist circumference was measured to the nearest 0.1 cm by positioning the soft nonstretchable tape measure midway between the lowest rib and the iliac crest. When this is not practicable, measure was made at 1 cm above the umbilicus. If the measure was taken on top of undergarments, an estimated 1-2 cm was then subtracted from the reading. Hip circumference was measured around the maximum circumference of the buttocks. Typically, 1 cm was subtracted if measured over a skirt and 2.5 cm if over trousers. Waist-to-hip ratio (WHR) was calculated as waist circumference divided by hip circumference, and waist height ratio (WHtR) was calculated as waist circumference divided by height. Body fat percentages were made from bioelectrical impedance using the in-built proprietary algorithm of the Tanita body composition analyser (TBF-300GS Body Composition Analyzer/Scale, TANITA, Tokyo, Japan).

Random venous blood samples[†] for measuring plasma glucose level were collected from all the participants at baseline before the survey questionnaires were administered. Venous blood draws were administered by trained nurses. A drop of blood was then

[†] By the time this thesis was completed (as of March 2013), an issue was raised with regard to the baseline random glucose test. In the study area of Zhejiang, it was found that the participants were required to undergo overnight fasting before taking the glucose test at baseline for certain additional examination provided locally, despite the standard operating procedures which requires non-fasting tests. Consequently, a certain number of diabetes patients would be misclassified as non-diabetic participants because a more lenient diagnostic criterion was applied (i.e. plasma glucose≥11.1 mmol/L rather than ≥7.0 mmol/L). An immediate investigation was conducted by Dr. Fiona Bragg at CTSU, and a new set of criteria was applied to this particular study area based on glucose level, self-reported symptoms and individual's fasting time. A further number of 1,050 baseline diabetes cases (0.2% of total baseline participants) were subsequently identified. Based on this finding, a sensitivity analysis was performed by the author of this thesis. Shown in Appendix IV, the prospective association between BMI and diabetes did not change materially after excluding data from Zhejiang. Nevertheless, for future publications drawn from this thesis, the 1,050 cases will be re-classified as diabetes cases for the cross-sectional analysis, and will be excluded from all prospective analyses.

taken from the vacuum blood collection tube and was tested using the On Call® Advanced Blood Glucose Monitoring System (ACON Laboratories Inc., USA). All blood glucose tests were administered within 15 minutes of blood collection to avoid potential glycolysis, which could substantially reduce glucose level in the blood sample. Blood collections and tests were conducted under normal room temperature (between 20-25°C). This could largely reduce the effect of temperature on the test consistency across different study sites. The hours since last meal was also collected in the baseline survey, which allowed for further analyses of its influence on random glucose levels. Participants with impaired glucose tolerance (7.8 mmol/L ≤ random plasma glucose < 11.1 mmol/L) were asked to visit the assessment centre the following morning for an overnight fasting plasma glucose test. The baseline questionnaire also collected information about medical history related to the hospital diagnoses and treatment of any subtype of diabetes (and many other conditions). Based on WHO diagnostic criteria for diabetes,[1] screen-detected prevalent diabetes cases were defined as participants having measured random plasma glucose ≥ 11.1 mmol/L in the initial random glucose test or fasting plasma glucose ≥ 7.0 mmol/L in the subsequent overnight fasting plasma glucose test. Self-reported prevalent diabetes were considered as valid diagnoses if supported by any evidence of treatment (i.e. oral hypoglycaemic agents or insulin). Since this study only focused on type 2 diabetes, people with known type 1 diabetes or gestational diabetes were excluded in the subsequent analyses.

Computer-based questionnaires were administered to participants by trained interviewers at 10 assessment centres. It covers a range of information on general demographic and socioeconomic status, dietary pattern, lifestyles (e.g. smoking, alcohol

use, tea drink, and physical activity), and other past medical history (i.e. in addition to diabetes). (See Appendix I: The CKB Baseline Survey Questionnaire)

Major socioeconomic factors include household income, education and occupation. Household income was specified in categories as <2,500, 2,500-4,999, 5,000-9,999, 10,000-19,000, 20,000-34,999 and ≥ 35,000 Yuan per annum (1 Chinese Yuan was approximately equivalent to 0.1 British Pound). Education was classified as "no formal school", "primary school", "middle school", "high school", "technical school/college" and "university", whichever defined the participant's highest education attended. Participant's current occupation was classified as "agriculture", "factory worker", "administrator/manager", "professional/technical", "sales/service worker", "retired", "housewife/husband", and "self-employed". All other professions were categorised into "other or not stated".

Lifestyle factors about which details were sought included smoking status, alcohol use and physical activity. Smoking status was categorised into "never smoker" (never or occasionally smoked in past; and do not smoke now or smoke and have smoked <100 cigarettes in life time), "occasional smoker" (never or occasionally smoked and have smoked 100+ cigarettes in life time. OR smoked daily or on most days in past but only smoke occasionally now), "ex-regular" (smoked daily or on most days in the past and do not smoke now and stopped smoking at least 6 months ago) and "current regular smoker" (smoke daily or on most days now).

Based on a series of survey questions about the types of alcohol consumption and drinking patterns, participants were categorised as "never regular drinker"(never or almost never drinking alcohol in the past 12 months, and no period of drinking at least

once a week in the past), “ex-regular drinker” (never or almost never drinking alcohol in the past 12 months , and having a period lasting at least a year of drinking at least once a week in the past), “occasional or seasonal drinker”(drinking only occasionally or only at certain seasons in the past 12 months and no period of drinking at least once a week in the past), “monthly drinker” (drinking every month but less than weekly in the past 12 months, and no period of drinking at least once a week in the past), “reduced intake” and “weekly drinker”(drinking usually at least once a week in the past 12 months).

To quantify the amount of physical activity, metabolic equivalent of tasks (MET) from the 2011 update of a major compendium of physical activities was used.[116] The MET value for a particular type of physical activity represents the ratio of the energy expended per kilogram of body weight per hour during that activity to that expended when sitting quietly. The number of hours spent per day participating in each activity was multiplied by the MET score for that activity, and the daily amount of physical activity was obtained by summing the MET-hours for activities related to occupation, commuting, housework, and non-sedentary leisure time activities.[117]

3.4 Resurvey

A resurvey was conducted immediately after the completion of the baseline survey in July 2008. The resurvey had two purposes: firstly, a repeat measure of exposures (e.g. anthropometric values, blood pressure or lipids) could help correct for potential “regression dilution” bias, which is normally caused by measurement error, short-term biological variability or long-term fluctuations in risk factor values;[115] and secondly, the repeat interview, measurements and blood assessment in a reasonably representative

sub-sample could help determine the validity of baseline data including prior diagnosis of diabetes and other diseases.

In the resurvey, participants were selected using a cluster random sampling approach (i.e. clinic locations in each of the study areas were used as the basic sampling unit). The survey procedures were identical to that in the baseline survey; and the data collected was almost the same as those collected in the baseline, with only few additional assessments (e.g. lung function, recent hospitalisation). Of the 24,760 participants (5% of baseline) invited for the resurvey, there was a 80% response rate (19,788 participants).

3.5 Follow-up data collection

Non-fatal diabetes incidence is primarily reported through chronic disease registries established in the 10 study areas already available at the start of the CKB or newly established since 2007. In each surveillance site, hospitals within the catchment area were required to report incidence of five major chronic conditions (diabetes, hypertension, cardiovascular disease, stroke, cancer of any site) to local CDC office using a "Chronic Disease Reporting Card" developed for the purpose of national chronic disease reporting. These reporting cards were subsequently linked with the CKB study participants to identify diabetes incidence at regional coordinating centres. With the new development of National Health Insurance Scheme, the health insurance databases are now fully established in all the 10 study areas. Personal information was matched to these databases by participants' unique national ID number, and the coverage of these databases reaches more than 95% of the CKB participants. Through electronic linkage

with health insurance database, diabetes incidences were identified and reported to the International Coordinating Centre in Oxford. However, since the data collected through National Health Insurance Scheme was not complete by the end of February 2013, the prospective analyses of this thesis do not include the insurance data.

Any fatal events occurring among CKB participants were identified at regional centres through regularly checking residential records and matching with official death certificates submitted to the local CDC. For deaths without any proper medical attention, a verbal autopsy was conducted using a validated instrument to identify possible causes. Incident diabetes would be reported if it appeared as an underlying cause of death on the death certificate.

In order to minimise the under-reporting of deaths and to identify loss to follow up (e.g. due to moving home), active confirmation of vital status is also being carried out annually by reviewing residential records at local police bureau and/or visiting local communities. By January 2013, there were a total number of 1,025 participants who were lost to follow up (0.2%).

All incident fatal and non-fatal cases of diabetes (E-11) were coded using the 10th International Classification of Diseases (ICD-10).

3.6 Event verification sub-study

3.6.1 Data retrieval and collection

To assess the quality of the reported incident diabetes (pre-diabetes, type 1 diabetes and type 2 diabetes; gestational diabetes not included in this study) in the CKB cohort,

an event verification study was subsequently conducted for diabetes (as well as three other conditions). Data retrieval and collection procedures were described in detail in Appendix II: Identification and Validation of Stroke, Diabetes, Ischaemic Heart Disease and Cancer Incidence Standard Operating Procedures. The protocol and procedures specified in this SOP were developed after my pilot study in one of the regional centres in China, and I designed and coordinated the diabetes event verification study.

In summary, cases were selected from the 10 areas with a good mixture of hospitals at different tiers. China has a 3-tier medical care system: tier 1 hospitals are normally community-based health centres (equivalent to the UK's primary health care); tier 2 hospitals are township/county hospitals; and tier 3 hospitals are medical centres in metropolitan cities with the highest quality of care. In China, patients normally tend to choose tier 3 hospitals for initial diagnoses and are treated in tier 1 or tier 2 hospitals because of a lower cost. It is very unlikely that a patient would choose an unrecognised hospital or a private practice outside the three-tier public hospital system because of the current reimbursement policy of medical bills. As the chronic disease reporting system and the health insurance cover all the 3 tiers of hospitals, incident diabetes cases are routinely reported from hospitals of 3 different levels. It is therefore important to ascertain cases from all the three tiers of hospitals.

The selection of cases also took into account the availability of medical notes (e.g. events of recent years), sources of reporting (i.e. chronic disease reporting or health insurance data) and feasibility of data collection. An "Essential Event List" was provided to each regional centre, along with a "Backup Event List" in case certain events in the "essential list" could not be successfully retrieved.

Besides the event lists, data abstractors (often field workers from regional centres) were also required to complete a standard "Data Collection Checklist" (see Appendix II: Identification and Validation of Stroke, Diabetes, Ischaemic Heart Disease and Cancer Incidence Standard Operating Procedures, page 15), which specified the key documents to retrieve, photocopy (or photograph) and to collect while in hospital. The key documents for diabetes event adjudication included: (1) the cover page of medical records, admission and discharge notes; (2) the plasma glucose test results (fasting/random/OGTT); (3) the HbA1c level (if performed); (4) prescriptions from medical doctors; and (5) evidence of islet β cell antibodies (if applicable). Any other information which was considered useful for diagnosis adjudication was also abstracted for adjudication.

Special permission was obtained from local health authorities and hospitals for the collection of medical notes. After all relevant notes were abstracted, data collecting staff were required to scan or photo the medical notes. To comply with the local requirement and ensure anonymisation of the collected, medical notes, patients' personal details (name, address, telephone number etc.) were de-identified when copies of key documents were made. The collected key documents and completed Data Collection Checklists were assembled in each regional centre and then sent electronically to National Coordinating Centre in China and International Coordinating Centre in Oxford, UK.

3.6.2 Event adjudication

A team of five medical professionals for event adjudication was established after all the electronic notes were transferred to the International Coordinating Centre in Oxford,

and an event adjudication form for diabetes was subsequently designed by me to guide the review and adjudication process (see Appendix III: CKB Event Adjudication Form for Diabetes).

The event adjudication form consists of nine sections: (1) general information; (2) discharge diagnoses; (3) prior medical history; (4) signs, symptoms and complications; (5) clinical investigations (where several results of the same test were collected, the highest value was recorded.); (6) medications; (7) vital status at discharge; (8) final diagnosis of the reviewer; and (9) the reviewer's remarks. By documenting patients' basic information, clinical investigations and treatment, the survey instrument guided the adjudicators through key information for event ascertainment.

Meanwhile, a set of adjudication rules was established based on the diabetes diagnostic guidelines of the World Health Organization (WHO),[118] the American Diabetes Association (ADA),[119] and the International Diabetes Federation (IDF).[120] In line with the WHO and American Diabetes Association's recent endorsement, glycated haemoglobin (HbA1c) was also used in the diagnosis of diabetes mellitus.[121,122] The clinical diagnostic criteria for diabetes (pre-diabetes, type 1 diabetes and type 2 diabetes) for this event verification study is shown Table 3.1.

Due to the complexity of clinical practice and constrained collection of clinical information, different types of evidence (laboratory, treatment, complication and clinical symptoms) were characterized as strong, medium and weak using the algorithm shown in Table 3.2.

Based on the evidence algorithm, events were defined as “definite”, “probable” or “probably not” by the following rules:

Definite diabetes event: at least one piece of “strong” evidence was identified in the medical notes; or in the absence of “strong” evidence, two pieces of “medium” evidence were identified;

Probable diabetes event: one piece of “medium” evidence was identified in the medical notes with or without “weak” evidence; or

Probably not a diabetes event: absence of “strong” or “medium” evidence, only “weak” evidence was found in the medical notes; or no evidence in support of diabetes at all.

The event adjudicator assessed each event following the above criteria and rules. Complex cases in which a conclusion could not be made by the adjudicator, were forwarded to a second-level review by two senior members of the team, or were forwarded to the adjudicating team meeting for further discussion and conclusion. After an event was adjudicated, data was entered into Microsoft Access database for analysis.

3.7 Statistical methods

3.7.1 Descriptive and cross-sectional analyses

Descriptive statistics were used to summarise sex-specific baseline characteristics. Distributions of demographic, socioeconomic and lifestyle risk factors (including age, area, income, education, occupation, smoking status, alcohol use, and physical activity) were reported by frequency tables.

Mean and standard deviation were reported for continuous variables such as age, height, weight, BMI, waist circumference, hip circumference, waist-hip ratio, waist-height ratio, percentage body fat and random plasma glucose.

Least-square means were used to describe the relations of potential confounders with exposure of interest. Mean values of different adiposity measures (BMI, waist circumference, hip circumference) were computed for categories of each demographic, socioeconomic and lifestyle factor (including age, area, income, education, occupation, smoking status, alcohol use, physical activity, and family history of diabetes) in general linear models. To estimate marginal means over a balanced population, all models for socioeconomic and lifestyle factors were adjusted for covariates of age and area. Tests for trend were performed by entering the categorical variables as continuous parameters in the models. Tests for difference of group means used analysis of variance (ANOVA).

Adjusted prevalences were calculated by using the floating method (by attributing variance to the reference group, the floating method allows for comparing risks in any two groups[123]). Detailed description of the adjusted prevalence is outlined elsewhere.[124] In summary, the adjusted prevalence is based on logistic regression, allowing adjusting for multiple confounders to estimate a potentially less biased prevalence. The adjusted prevalence provides a more straightforward approach to relative risks with real-life public health meanings. It is, therefore, used for the cross-sectional analyses in this study. Since it is essentially equivalent to odds ratios when assessing the risks associated with different categories, the findings in the cross-sectional analyses are also comparable to those in the prospective analyses.

To explore the association between potential confounders and diabetes cases at baseline, the adjusted prevalence of diabetes by demographic, socioeconomic and lifestyle categories was calculated. The age-specific prevalence was adjusted for area, and vice verse. All other models were adjusted for age, area and BMI. For occupation, additional adjustments were made for income and physical activity.

Correlations between different adiposity measures (weight, height, BMI, waist circumference, hip circumference, waist-hip ratio, waist-height ratio and percentage body fat) were calculated using Pearson partial correlation, adjusted for age (as a continuous variable) and area (10 categories). The correlation coefficients between these adiposity measures and baseline random plasma glucose were assessed using the same method, with results presented in both diagram and scatter plots.

In analysing the associations between adiposity measures and baseline random plasma glucose, mean random plasma glucose values were calculated for each quintile of BMI, WC, HC, WHR, WHtR and percentage body fat, adjusted for age, area, income, education, occupation, smoking status, alcohol use, physical activity (MET), and family history of diabetes.

The basic associations between overall and central adiposity measures and diabetes prevalence were assessed using adjusted prevalence. Each adiposity measure was categorised into quintiles, and the prevalence of diabetes was calculated for each quintile after adjustment for all potential confounders, including demographic (age, study area), socioeconomic (household annual income, education, occupation) and lifestyle risk factors (smoking status, alcohol use, physical activity), and family history of diabetes.

Further analyses using the same method were performed to determine the diabetes prevalence associated with each quintile of different adiposity measures after adjustment for one another. In assessing the residual association between BMI and diabetes prevalence, additional adjustments of WC, WC + HC, and WHR were included separately in the multivariable-adjusted model. Similarly, additional adjustment of WC + HC and BMI was made for the association between percentage body fat and diabetes prevalence. For central adiposity measures of waist circumference and waist height ratio, BMI and BMI + HC were added separately to the original models for basic associations, whereas for WHR, additional adjustment for BMI was made. The association between hip circumference and diabetes was also analysed both in the basic model and in the advanced model that adjusted separately for BMI and BMI + WC.

The joint associations of diabetes prevalence with waist and hip circumference were analysed. Hip circumference was stratified into tertiles and the association with diabetes prevalence for waist circumference was analysed in each hip circumference tertile after fully adjusting for BMI and all other confounders. Similarly, waist circumference was stratified into tertiles to analyse the joint association with hip circumference after adjustment of BMI and other confounders.

The joint associations of central adiposity and BMI were analysed using the same approach. BMI was stratified into tertiles, and the adjusted prevalence for quintiles of central adiposity measures were computed in each BMI tertile. Adjustment for adiposity covariate (i.e. hip circumference) and confounders were made in the regression models.

Participants with missing data at baseline (e.g. values of different adiposity measures or random glucose test, n=304) were excluded from main analyses. In addition, outliers

with extreme anthropometric values (<0.01 percentile or >99.99 percentile) were also excluded to minimise any potential measurement errors. These included a total of 961 participants, including standing height <125cm (n=40) or >190cm (n=36), waist circumference <50cm (n=31) or >125cm (n=74), hip circumference <60cm (n=78) or >130cm (n=46), BMI <15kg/m^2 (n=400) or >40kg/m^2 (n=117), and waist-hip ratio >1.25 (n=139). Consequently, 38 prevalent diabetes cases were excluded from baseline analyses.

3.7.2 Event verification sub-study

The analysis of data was primarily focused on descriptive statistics to summarize basic characteristics (e.g. types of initial diagnosis, department of admission, number of clinical tests performed, numbers of complications, and types of medication) of the diabetes cases for event adjudication and the true positive rates between reported disease incidence and adjudication results. Stratified analysis of true-positive rates for diabetes diagnoses by area, tier of hospital, and reporting method were calculated. The true-positive rates reflected the probability of a reported hospitalization diabetes diagnosis being confirmed by independent adjudication of clinical records. Using the binomial distribution, 95% Wilson score confidence intervals[125] were also calculated for each true-positive rate to allow for comparison between strata. For quality control purposes, data related to retrieval and matching was also analysed.

3.7.3 Prospective analyses

The prospective analyses were based on follow-up from the baseline to 1 January 2013, with a mean follow-up period of 5.1 years. All participants who had self-reported or

screen-detected diabetes at baseline, or had missing components of adiposity measures, or who were lost to follow-up were excluded.

The age-specific crude incidence rate of type 2 diabetes was calculated by dividing the number of cases by total person-years in that age group. The crude incidence rate was also calculated separately by area (urban/rural), and for each quintile of BMI, waist circumference, hip circumference, waist hip ratio, waist height ratio and percentage body fat.

In analysing prospective associations of diabetes incidence (fatal or non-fatal), the Cox proportional hazard model was used. All models used in the analyses were stratified on study area and age at risk (5-year age band). This approach allowed for non-proportional hazards assumption between age groups or among study areas, while proportional hazard assumption remained unviolated within each 5-year age band or within each study area. As in the cross-sectional analyses, 95% confidence intervals of the hazard ratios were calculated using the floating absolute risk method,[124] which allows for comparing risks between any two groups by assigning variance to the reference group.

Unless otherwise indicated, common demographic, socioeconomic and lifestyle confounders (i.e. income, education, smoking status, alcohol use, and physical activity), and family history of diabetes were also routinely adjusted in the Cox regression models. Tests for log-linear trend were performed by entering the adiposity categories as continuous parameters in the Cox regression model.

Adiposity measures were divided into several categories using conventional or specific cut points that tended to yield adequate numbers of people in each group for analysis.

The cut-off points for BMI were 18.5, 20, 22, 24, 26, 28 and 30 kg/m^2; for waist circumference, they were 70, 75, 80, 85, 90 and 95 cm; for hip circumference, they were 85, 90, 95 and 100 cm; for WHR, 0.85, 0.90, 0.95 and 1.00; and for WHtR, 0.45, 0.50, 0.55 and 0.60. For percentage body fat, sex-specific cut-off points were used: for men, the cut-offs were at 15%, 20%, 25%, 30% and 35%; for women, they were 25%, 30%, 35%, 40% and 45%. Adjustments were made for common demographic, socioeconomic, lifestyle confounders and family history of diabetes, as described previously.

To facilitate comparison of the strength of the association across different adiposity measures, all measures were also divided into quintiles, and the multivariable-adjusted relative risks were also estimated for each quintile of different measures. Adjustment of age and area was performed initially, and additional socioeconomic and lifestyle confounders were added into the Cox models subsequently.

In addition, baseline BMI, WC, HC, WHR, WHtR and percentage body fat were divided by their sex-specific standard deviations, and each was subsequently fitted into the Cox regression model as a continuous variable, adjusted for all potential confounders. In this way, hazard ratios for diabetes incidence corresponding to a 1-SD increment in each indicator were estimated to allow for comparison of the relative importance across indicators. All results were reported for both sexes separately and combined.

Besides the basic model with adjustment of socio-demographic and lifestyle confounders, the association between BMI quintiles and diabetes incidence was further examined in four different models: additional adjustment for HC only; additional adjustment for WC only; additional adjustment for WC and HC; and additional

adjustment for WHR. For percentage body fat, additional adjustment was made for BMI, WC and WHR, respectively.

Further additional adjustments were also made when assessing the effects of waist circumference, waist hip ratio and waist height ratio, in order to fully understand the effects of central adiposity measures for diabetes incidence. Specifically, the association between waist circumference and diabetes was analysed in three additional models: additional adjustment of BMI only; additional adjustment of HC only; and additional adjustment of BMI + HC. Similarly, waist height ratio was analysed in two additional models: additional adjustment of BMI and additional adjustment of BMI + HC. The waist hip ratio was additionally adjusted for BMI only.

Similarly, for the multivariable-adjusted hazard ratios corresponding to a 1-SD increment in each adiposity measure, additional adjustments were made to the models to examine the associations of one measure independent of other measures. For BMI, additional adjustment was made for waist circumference and hip circumference. For percentage body fat, additional adjustment was made for waist circumference, hip circumference and BMI. For both WC and WHtR, the fitted Cox models were additionally adjusted for hip circumference and BMI. The hazard ratios for WHR were additionally adjusted for BMI only. And the hazard ratios for hip circumference, on the other hand, were adjusted for waist circumference and BMI. All results were reported for both sexes separately and combined.

To examine the joint association of waist and hip circumference with diabetes incidence, participants were categorised into 6 groups by both waist tertile (males: <76.7 cm, 76.7-85.9 cm, ≥85.9cm; females: <74.0 cm, 74.0-82.3 cm, ≥82.3cm) and the median value of

hip circumference (males: 90.1 cm; females: 90.5 cm). The hazard ratio associated with each group was analysed in a Cox model adjusted for potential confounders and BMI simultaneously.

Similarly, to analyse the joint associations of BMI and central adiposity measures with diabetes, combined variables with properties of both adiposity measures were created. For this purpose, median value of BMI was used as a cut-off for low and high BMI levels (males: 23.1 kg/m^2; females: 23.5kg/m^2). Meanwhile, tertiles were created for WC (males: <76.7 cm, 76.7-85.9 cm, ≥85.9cm; females: <74.0 cm, 74.0-82.3 cm, ≥82.3cm), WHR (males: <0.87, 0.87-0.92, ≥0.92; females: <0.84, 0.84-0.89, ≥0.89), and WHtR (males: <0.47, 0.47-0.52, ≥0.52; females: <0.48, 0.48-0.53, ≥0.53). Consequently, the new variable comprised of 6 categories was used for analysing each of the joint effects of BMI and WC, BMI and WHR, and BMI and WHtR. With Cox regression, all the models were adjusted for common demographic, socioeconomic and lifestyle confounders. For the joint associations of BMI-WC and BMI-WHtR, additional adjustments for hip circumference were made in respective models.

Effect modification by sex and age for the exposure-outcome associations was examined prospectively for BMI, waist circumference, hip circumference, waist hip ratio and waist height ratio. Multiplicative interaction terms of age and adiposity, and sex and adiposity were included and tested in the Cox regression models (significant at $p<0.05$). After identifying potential effect modification, the age-specific (<50 years, 50-64 years, and ≥65 years) and sex-specific hazard ratios for per standard deviation increment in BMI, waist circumference, hip circumference, waist hip ratio, and waist height ratio were

calculated. Tests for difference were conducted between different age groups and between sexes. An additional test for trend was conducted across age groups.

All analyses were performed separately for men and women. All tests were two-sided, and p values <0.05 were considered statistically significant. All analyses were conducted using SAS 9.2 software (SAS Institute, Cary, North Carolina). The macros used for Cox regression model and for calculating adjusted prevalence were developed by the CKB statistical group in Oxford. All graphs were produced using R software (version 2.10.1). All actual analyses and preparation of graphs were done by the author of this thesis.

Table 3.1 Clinical criteria for diagnosis of diabetes

Type	Criteria	
Type 1 diabetes	Islet β cell antibodies (+)	
Pre-diabetes (IGT/IFG)	Fasting plasma glucose (if measured) <7.0 mmol/L and 7.8 mmol/L ≤ Oral glucose tolerance test <11.1 mmol/L	6.1 mmol/L≤ Fasting plasma glucose <7.0 mmol/L and (if measured) Oral glucose tolerance test <7.8 mmol/L or 5.7%≤ HbA1c <6.5%
Type 2 diabetes	Fasting plasma glucose ≥7.0 mmol/L or 2-hr post prandial plasma glucose ≥11.1 mmol/L or 75g oral glucose tolerance test ≥11.1 mmol/L or Random plasma glucose ≥11.1 mmol/L plus typical symptoms or HbA1C ≥6.5%	

Table 3.2 Level of evidence for event adjudication

Type	Evidence	Strong	Medium	Weak
Laboratory evidence	Plasma glucose test	×		
	HbA1c test	×		
	Islet β cell antibodies	×		
	Urine glucose test			×
Treatment	Insulin	×		
	Oral hypoglycemic agent		×	
	Traditional Chinese medicine			×
Complication	Any diabetes-induced	×		
Clinical	Diabetes history		×	
	Doctor's impression/symptom			×

4. Results

4.1 Results: cross-sectional analyses

4.1.1 Baseline characteristics

After excluding participants with missing data (n=304) or with extreme values (n=961) from the baseline dataset, there were 511,835 participants (209,875 male, 301,960 female), henceforth termed the "study population", of whom 26,622 had diabetes (10,410 males, 16,212 females). About 40% (10,460 cases) of diabetes prevalent cases were detected through baseline screening. The overall prevalence of diabetes was 5.2%, but was slightly higher in females (5.4%) than males (5.0%), and twice as high in urban as in rural areas (urban 7.2%, rural 3.6%). Mean age at baseline was 51.2 years, and people with diabetes were on average 5 (male) to 8 (female) years older than people without. In the study population, about 20% of the prevalent diabetes cases were found in just one of the 10 study areas: the city of Harbin. Among different socioeconomic factors, a disproportionally lower number of diabetes cases were found in people working in agricultural and related sectors, while almost 40% of all diabetes cases were found in people who were retired.

The baseline socioeconomic characteristics of the study population are shown in Table 4.1.1, and baseline lifestyle characteristics are shown in Table 4.1.2. In sum, a higher proportion of diabetes cases were observed in men who were current smokers (49.7%), occasional or weekly alcohol drinkers (56.0%), and in women who were non-smokers (92.5%) and non-drinkers (71.0%). For both sexes, nearly a third of diabetes cases (male 30.0%, female 32.5%) were in the lowest quintile of physical activity.

Table 4.1.3 summarises the anthropometric characteristics of the study population by diabetes status. Across all overall and central adiposity measures, people in diabetic groups consistently had higher mean anthropometric values than did people in non-diabetic groups. For example, the mean BMI of male participants was 24.8 kg/m^2 (SD=3.4) in the diabetic group and 23.4 kg/m^2 (SD=3.2) in the non-diabetic group; and the mean BMI of female participants were 25.2 kg/m^2 (SD=3.7) and 23.7 kg/m^2 (SD=3.4) respectively. In both diabetic and non-diabetic groups, women tended to have higher mean values of overall adiposity (i.e. BMI and percentage body fat) than did men, while men tended to have higher mean values of central adiposity (i.e. waist circumference and waist-hip ratio) than did women.

The mean random plasma glucose at baseline was much higher in the diabetic group than in the non-diabetic group for both men (12.8 versus 5.6 mmol/L) and women (12.7 versus 5.8 mmol/L).

4.1.2 Demographic, socioeconomic and lifestyle factors as potential confounders

The associations of adiposity measures with diabetes prevalence (or incidence) may well be confounded by other variables that are associated independently both with adiposity measures and with diabetes prevalence (or incidence). These may include several major demographic, socioeconomic and lifestyle factors and their potential effects are described below.

4.1.2.1 Associations with adiposity measures

Age

Table 4.1.4(a) shows the cross-sectional associations of BMI with age in both sexes. In men, mean BMI increased slightly from 23.69 kg/m^2 (95%CI: 23.65-23.72) at age 30-39 years to 23.78 kg/m^2 (95%CI: 23.75-23.80) at age 40-49 years, then declining steadily to 22.69 kg/m^2 (95%CI: 22.65-22.74) at age 70-79 years. In women, mean BMI increased from 23.07 kg/m^2 (95%CI: 23.04-23.10) at age 30-39 years to 24.20 kg/m^2 (95%CI: 24.18-24.23) at age 50-59 years, then declining gradually to 23.55 kg/m^2 (95%CI: 23.50-23.60) at age 70-79 years.

A broadly similar pattern was also seen for waist circumference (Table 4.1.5(a)) and other adiposity measures. For men, the mean waist circumference increased up to 82.98 cm (95%CI: 82.91-83.06) at age 40-49 years, and gradually declined to 81.37 cm (95%CI: 81.23-81.51) at age 70-79 years. For women, the mean waist circumference increased up to age 60-69 years (81.48 cm, 95%CI: 81.40-81.55), then declined to 81.23 cm (95%CI: 81.11-81.39) at age 70-79 years.

Sex

As previously discussed in 4.1.1, women tended to have higher mean values of overall adiposity (i.e. BMI and percentage body fat) than did men, irrespective of their diabetes status. On average, mean BMI was about 0.39 kg/m^2 (95%CI: 0.36-0.43) higher and mean percentage body fat was about 10.0% (95%CI: 9.8-11.0) higher in women than in men. In contrast, men tended to have higher mean values of central adiposity (i.e. waist circumference, waist hip ratio and waist height ratio) than did women. For waist circumference, there was about 3.10 cm (95%CI: 2.51-3.27) difference between men and women; for waist hip ratio and waist height ratio, the differences were both about 0.2.

Study area

There were substantial regional variations in mean anthropometric values. The mean BMI, waist circumference and hip circumference of urban men and women were significantly higher than those of their rural counterparts, as shown in Table 4.1.6. On average, urban males had 1.62 kg/m^2 (95%CI: 1.59-1.64) higher BMI, 5.27 cm (95%CI: 5.19-5.35) greater waist circumference and 4.97 cm (95%CI: 4.92-5.03) greater hip circumference than rural males. Urban females had 0.74 kg/m^2 (95%CI: 0.72-0.76) higher BMI 1.22 cm (95%CI: 1.15-1.28) greater waist circumference, and 3.78 cm (95%CI: 3.73-3.83) greater hip circumference than rural females.

The highest mean BMI and waist circumference were observed in Qingdao, a northern city of China, while the lowest mean values were observed in various rural areas. In most urban areas, men had higher mean BMI and hip circumference than women, while the opposite was true in rural areas (Tables 4.1.4(a) and 4.1.5(a)).

Household income

Tables 4.1.4 (a) and 4.1.5 (a) show the baseline mean anthropometric values by household income. The mean BMI in men increased from 22.58 kg/m^2 (95%CI: 22.50-22.66) in the lowest annual income category (<2,500 Yuan) to 24.10 kg/m^2 (95%CI: 24.07-24.13) in the highest annual income category (≥35,000 Yuan) and in women it increased from 23.17 kg/m^2 (95%CI: 23.10-23.24) to 23.88 kg/m^2 (95%CI: 23.85-23.91). Similarly, the mean waist circumference in men increased from 79.20 cm (95%CI: 78.96-79.43) to 84.89 cm (95%CI: 84.79-84.98) across income categories and in women it increased from 77.01 cm (95%CI: 76.82-77.21) to 79.92 cm (95%CI: 79.83-80.01) (all p

for trend < 0.0001). There was a similar increasing trend of waist-hip ratio and percentage body fat with increasing household income in both sexes.

Education

The associations of adiposity measures with levels of education differed markedly between males and females. In women, the mean anthropometric values were typically the highest in those with primary school education, then decreased steadily with increasing level of education (i.e. middle school, high school, college and university). In men, however, the mean anthropometric values consistently increased monotonically with educational level (Tables 4.1.4(a) and 4.1.5(a)).

Occupation

Men with self-reported occupation as administrator/manager had the highest mean BMI (24.48 kg/m^2, 95%CI: 24.41-24.56) and those who were self-employed had the highest waist circumference (85.82 cm, 95%CI: 85.60-86.04). In contrast, men in agriculture-related jobs had the lowest mean BMI (22.73 kg/m^2, 95%CI: 22.70-22.76) and waist circumference (79.56 cm, 95%CI: 79.47-79.65).

In women, those who were retired had the highest mean BMI (24.67 kg/m^2, 95%CI: 24.63-24.71) and waist circumference (81.47 cm, 95%CI: 81.37-81.57). Women who were administrator/manager had the lowest BMI (22.98 kg/m^2, 95%CI: 22.88-23.09) and waist circumference (76.95 cm, 95%CI: 76.66-77.23). Results for other occupational categories are shown in Tables 4.1.4 (a) and 4.1.5 (a).

Physical activity

There was a declining trend of mean BMI and waist circumference with increasing level of physical activity as measured by MET in both men and women (Tables 4.1.4 (b) and 4.1.5 (b)). Mean BMI decreased from 23.55 kg/m^2 in the 1st MET quintile (lowest activity) to 23.17 kg/m^2 in the 5th MET quintile (highest activity) in males, and from 23.89 kg/m^2 to 23.38 kg/m^2 in females (p for trend<0.0001 in both sexes). Similarly, mean waist circumference decreased from 82.86 cm in the 1st MET quintile to 80.84 cm in the 5th quintile in males, and from 79.57 cm to 78.76 cm in females (both p for trend<0.0001).

Alcohol consumption

The associations of alcohol consumption with adiposity measures are shown in Tables 4.1.4 (b) and 4.1.5 (b). In both sexes, reduced alcohol drinkers had the highest BMI (males 24.07 kg/m^2, 95%CI: 24.01-24.13; females 23.98 kg/m^2, 95%CI: 23.81-24.16) and waist circumference (males 84.22 cm, 95%CI: 84.04-84.40; females 80.24 cm, 95%CI: 79.75-80.72). Among males, never drinkers had the lowest mean BMI (23.28 kg/m^2, 95%CI: 23.25-23.31) and waist circumference (81.42 cm, 95%CI: 81.33-81.52), while among women, monthly drinkers had the lowest mean BMI (23.47 kg/m^2, 95%CI: 23.37-23.57) and waist circumference (78.79 cm, 95%CI: 78.52-79.07) (All p for difference<0.0001).

Smoking status

In both sexes, ex-regular smokers had the highest mean BMI (males 24.17 kg/m^2, 95%CI: 24.13-24.21; females 24.23 kg/m^2, 95%CI:24.10-24.36) and waist circumference (males 84.32 cm, 95%CI: 84.21-84.44; females 81.07 cm, 95%CI: 80.72-81.42); while current regular smokers had the lowest mean BMI (males 23.10 kg/m^2, 95%CI: 23.08-23.12;

females 23.03 kg/m^2, 95%CI: 22.96-23.11) and waist circumference (males 81.48 cm, 95%CI: 81.42-81.54; females 78.11 cm, 95%CI:77.90-78.33) (Tables 4.1.4 (b) and 4.1.5 (b)).

Family history of diabetes

On average, males with family history of diabetes had a 0.58 kg/m^2 (95%CI: 0.53-0.63) higher BMI, and a 1.99 cm (95%CI: 1.82-2.15) higher waist circumference, than those without. Likewise, females with family history of diabetes had a 0.37 kg/m^2 (95%CI: 0.33-0.42) higher BMI, and a 1.14 cm (95%CI: 1.01-1.27) greater waist circumference, compared to those with no reported family history of diabetes (both p for difference<0.0001) (Tables 4.1.4 (b) and 4.1.5 (b)).

4.1.2.2 Associations with diabetes prevalence

Figures 4.1.1-4.1.6 present the adjusted prevalence of diabetes by age, area, annual household income, highest education attended, occupation, and selected lifestyle factors.

As shown in Figure 4.1.1, the prevalence of diabetes in males increased monotonically with age, from 1.16% (95%CI: 0.86-1.58) at age 30-34 years to 8.34% (95%CI: 7.92-8.77) at age 70-79 years; in females, the prevalence increased from 0.95% (95%CI: 0.67-1.31) in the lowest age group to 10.71% (95%CI: 10.32-11.11) at age 65-69 years, then decreased slightly at age 70-79 years to 9.83% (95%CI: 9.40-10.28).

The prevalence of diabetes was generally higher in urban than in rural areas (Figure 4.1.2). After adjusting for age and BMI, the prevalence of diabetes in urban areas ranged from <5% (males 4.99%, 95%CI: 4.70-5.29; females 4.16%, 95%CI: 3.94-4.38) in Suzhou

to around 9.5% (males 9.44%, 95%CI: 9.03-9.87; females 9.56%, 95%CI: 9.20-9.94) in Harbin; while the prevalence in most rural areas were under 4% in both sexes, with only two exceptions in females from Henan (5.07%, 95%CI: 4.85-5.30) and Hunan (4.23%, 95%CI: 4.02-4.47).

After allowing for age, area and BMI, there appeared to be a higher prevalence of diabetes among people with higher income (Figure 4.1.3 (a)). In males, it increased from 4.17% (95%CI: 3.67-4.72) in the lowest income category to 5.48% (95%CI: 5.22-5.75) in the highest income category (p for trend <0.0001). A similar, but non-significant pattern was also observed in females.

After the same adjustment, the prevalence of diabetes was slightly higher in men with middle school (5.25%, 95%CI: 5.07-5.43) or college (5.36%, 95%CI: 4.96-5.79) education than those with no formal education (4.12%, 95%CI: 3.80-4.48). In women, the prevalence was higher in those with primary school (5.48%, 95%CI: 5.31-5.66) or middle school (5.68%, 95%CI: 5.50-5.87) education than those with college education (5.01%, 95%CI: 4.37-5.79) or with no formal education (5.07%, 95%CI: 4.86-5.29) (Figure 4.1.3 (b)).

As observed in Figure 4.1.4, the adjusted diabetes prevalence varied substantially across different occupation groups. People in the retired group had the highest diabetes prevalence (males 7.99%, 95%CI: 7.59-8.41; females 8.00%, 95%CI: 7.71-8.32), followed by self-employed males (6.92%, 95%CI: 6.22-7.69) and unemployed females (7.48%, 95%CI: 6.71-8.33). Both males and females working in agricultural sectors had the lowest prevalence (males 3.19%, 95%CI: 3.00-3.39; females 3.87%, 95%CI: 3.68-4.08). A further adjustment of income and physical activity did not materially change the

strength and the relative order of associations between diabetes prevalence and various occupation groups.

Independently of BMI, the prevalence of diabetes declined modestly as physical activity increased (Figure 4.1.5). In males, the adjusted prevalence decreased from 5.96 (95%CI: 5.75-6.18) in the lowest quintile of MET (hours per day) to 3.86% (95%CI: 3.62-4.11) in the highest quintile of MET. In females, it decreased from 6.61% (95%CI: 6.40-6.82) to 4.32% (95%CI: 4.11-4.54) across quintiles of MET (p for trend<0.001).

The BMI-independent associations with alcohol consumption are shown in Figure 4.1.6 (a). Ex-regular drinkers of both sexes had the highest prevalence of diabetes (males 8.54%, 95%CI: 7.94-9.19; females 8.25%, 95%CI: 6.96-9.86) (potentially reflecting a tendency for people with diabetes to quit drinking: i.e. a “reverse” causation); while the lowest prevalence among males was observed in monthly drinkers (3.90%, 95%CI: 3.55-4.27), and among females in weekly drinkers (2.59%, 95%CI: 2.25-2.99).

The BMI-independent associations with smoking behaviour are shown in Figure 4.1.6 (b). Ex-regular smokers of both sexes had the highest diabetes prevalence (males 6.05%, 95%CI: 5.80-6.31; females 6.49%, 95%CI: 5.80-7.26), perhaps again reflecting reverse causation, and current regular smokers of both sexes had the lowest diabetes prevalence (males 4.65%, 95%CI: 4.53-4.79; females 5.25%, 95%CI: 4.82-5.71).

Even after allowing for age, study area, BMI, and physical activity, those with family history of diabetes had a much higher prevalence of diabetes compared to those without. The adjusted prevalence was about three-fold higher in people with a self-

reported family history in both males (12.79% versus 4.43%) and females (13.44% versus 4.77%).

4.1.2.3 Summary of potential confounders

Based on the above analysis, we consider age, study area, household income, education, occupation, physical activity, alcohol use, smoking status, and family history of diabetes had strong or medium independent associations with both adiposity and diabetes prevalence, and hence are potential confounders of associations between diabetes and measures of adiposity.

As none of these variables would be regarded as being importantly on the causal pathway linking adiposity with diabetes (i.e. intermediate factors) or as common effects of adiposity and diabetes (i.e. colliders), it is appropriate to adjust for them as potential confounders while assessing the associations of adiposity with diabetes.

4.1.3 Baseline associations of adiposity with random plasma glucose

4.1.3.1 Correlation coefficients

After adjustment for age and area, WHR had a stronger correlation with random plasma glucose (0.15), than did WHtR (0.13), WC (0.11), BMI (0.08) and percent body fat (0.06) (all $p<0.0001$) in males. These results were qualitatively identical in females, with stronger correlation with WHR (0.17), than with WHtR (0.15), WC (0.14), BMI (0.09) or percent body fat (0.08) (all $p<0.0001$). These results are showed in Table 4.1.7.

4.1.3.2 Mean random plasma glucose by adiposity measures

Figures 4.1.7-4.1.9 show the adjusted mean random plasma glucose by sex-specific anthropometric quintile. Broadly similar trends were observed for all adiposity measures,

with the mean glucose level increasing with each measure (all p for trend<0.0001). In males, the strongest association was observed for WHR, with mean glucose increasing from 5.97 mmol/L (95%CI: 5.94-6.01) in the lowest quintile to 6.86 mmol/L (95%CI: 6.82-6.90) in the highest quintile. For both waist circumference and waist height ratio, the associations were less as strong, with the mean glucose levels increasing from 6.06 (95%CI: 6.02-6.10) to 6.75 mmol/L (95%CI: 6.71-6.78) and from 6.05 (95%CI: 6.02-6.09) to 6.76 mmol/L (95%CI: 6.72-6.79), respectively. For BMI, the trend appeared to be flatter, with mean values increasing from 6.19 (95%CI: 6.15-6.23) to 6.64 mmol/L (95%CI: 6.60-6.67), as was percent body fat (from 6.26 to 6.60 mmol/L).

Similarly, for females, WHR showed the strongest association with mean random glucose, increasing from 5.96 mmol/L (95%CI: 5.91-6.01) in the lowest quintile to 7.06 mmol/L (95%CI: 7.01-7.12) in the highest quintile. Weaker positive associations were observed for WC, WHtR, BMI and percentage body fat.

The very weak positive association for hip circumference (Figure 4.1.8 (b)) became very strongly negative after further adjustment for waist circumference (Figure 4.1.10 (b)).

4.1.4 Baseline associations of adiposity with diabetes prevalence

4.1.4.1 Basic associations

Figures 4.1.11-4.1.13 show the prevalence of diabetes in quintiles of each adiposity measure, after basic adjustment for demographic, socioeconomic, lifestyle factors and family history of diabetes, but not for other adiposity measures (associations with these basic adjustments being termed henceforth “basic associations”). In general, the prevalence of diabetes increased with increasing level of each of the adiposity measures.

In both sexes, the strongest association was observed for WHR (Figure 4.1.13 (a)), with the prevalence increasing from 2.13% (95% CI: 1.97-2.28) in the lowest quintile to 9.01% (95% CI: 8.74-9.30) in the highest quintile in males and from 1.70% (95% CI: 1.58-1.82) to 11.00% (95% CI: 10.72-11.28) in females.

For both WC (Figure 4.1.12 (a)) and WHtR (Figure 4.1.13 (b)), the associations with diabetes prevalence were less strong. The adjusted prevalence of diabetes increased from 2.59% (95% CI: 2.42-2.78) in the lowest WC quintile to 8.20% (95% CI: 7.93-8.49) in the highest WC quintile in males, and from 2.34% (95% CI: 2.20-2.48) to 9.23% (95% CI: 9.00-9.46) in females. Similarly, across WHtR quintiles it increased from 2.49% (95% CI: 2.32-2.67) to 8.05% (95% CI: 7.79-8.32) in males, and from 2.33% (95% CI: 2.19-2.49) to 9.26% (95% CI: 9.03-9.50) in females.

For BMI (Figure 4.1.11 (a)), a measurement of overall obesity, the association appeared to be flatter, with the prevalence of diabetes increasing from 3.00% (95% CI: 2.81-3.19) in the 1st quintile to 7.33% (95% CI: 7.07-7.59) in the 5th quintile in males, and from 3.25% (95% CI: 3.10-3.41) to 7.48% (95% CI: 7.27-7.69) in females. A weaker strength of association was observed for percent body fat (Figure 4.1.11 (b)), with the prevalence increasing from 3.34% (95% CI: 3.15-3.54) to 7.15% (95% CI: 6.89-7.43) in males, and from 3.36% (95% CI: 3.21-3.52) to 7.19% (95% CI: 6.98-7.40) in females.

4.1.4.2 Associations adjusted for other adiposity measures

4.1.4.2.1 Overall adiposity

Figure 4.1.14 shows the prevalence of diabetes by BMI quintile before and after adjusting for waist circumference in each sex. After adjusting for waist circumference,

the positive association of BMI with diabetes attenuated significantly, becoming a slightly inverse association in males (Figure 4.1.14 (a)), with the WC-adjusted prevalence ranging across the BMI quintiles from 5.33% (95%CI: 4.89-5.82) to 4.78% (95%CI: 4.51-5.08). In females, the association became more strongly inverse (Figure 4.1.14 (b)), with the WC-adjusted prevalence ranging across BMI quintiles from 6.90% (95%CI: 6.47-7.35) down to 4.17% (95%CI: 3.99-4.36).

As illustrated in Figures 4.1.15, these inverse associations were obliterated after additionally adjusting for hip circumference (i.e. in addition to waist circumference). After adjusting for WHR, the association between BMI and diabetes disappeared in men (Figure 4.1.16 (a)), and became slightly inverse in women (Figure 4.1.16(b)).

Similar effects were observed for percentage body fat, as another measure of overall adiposity. After additional adjustment of waist and hip circumference, the association was flattened in males (Figure 4.1.17(a)), with prevalence ranging from 5.51% (95%CI: 5.12-5.93) to 5.13% (95%CI: 4.88-5.39) across percentage body fat quintiles. In females, there appeared to be an inverse association after adjusting for waist and hip circumference, with prevalence decreasing from 6.57% (95%CI: 6.19-6.97) to 4.40% (95%CI: 4.23-4.58) across percentage body fat quintiles (Figure 4.1.17(b)).

4.1.4.2.2 Central adiposity

Adjustment for BMI tended to make the association between waist circumference and diabetes prevalence somewhat stronger, especially in women (Figure 4.1.18). In women (Figure 4.1.18(b)), the BMI-adjusted prevalence increased by 6-fold from 1.67% (95%CI: 1.54-1.80) to 10.68% (95%CI: 10.23-11.15) across waist circumference quintiles, while in men (Figure 4.1.18(a)), it increased by about 4-fold from 2.24% (95%CI: 2.04-2.46) to

8.71% (95%CI: 8.21-9.24). A further additional adjustment of hip circumference strengthened the association between waist circumference and diabetes prevalence for both sexes (Figure 4.1.18), with the BMI + HC-adjusted prevalence increasing from 1.60% (95%CI: 1.45-1.77) in the lowest WC quintile to 10.14% (95%CI: 9.51-10.81) in highest quintile in males, and from 1.19% (95%CI: 1.10-1.29) to 11.15% (95%CI: 11.62-12.70) in females.

Additional adjustment for BMI and HC yielded similar, but mostly smaller effects on the association between WHtR and diabetes. Adjusting for BMI alone slightly increased the strength of association in males (Figure 4.1.19 (a)), with the BMI-adjusted prevalence increasing from 2.21% (95%CI: 2.01-2.44) to 8.39% (95%CI: 7.91-8.91) across WHtR quintiles. In females (Figure 4.1.19(b)), adjusting for BMI greatly increased the association, with the prevalence increasing from 1.75% (95%CI: 1.61-1.89) to 10.58% (95%CI: 10.12-11.05). After a further adjustment for hip circumference, the association became stronger, with the prevalence increasing from 2.06% (95%CI: 1.87-2.27) in the lowest WHtR quintile to 8.73% (95%CI: 8.22-9.27) in highest quintile in males, and from 1.64% (95%CI: 1.52-1.78) to 10.91% (95%CI: 10.44-11.40) in females.

The association between WHR and diabetes prevalence, on the other hand, was largely unaffected by the additional adjustment for BMI in both males and females (Figure 4.1.20). Across WHR quintiles, the BMI-adjusted prevalence of diabetes increased from 2.15% (95%CI: 1.98-2.33) to 8.94% (95%CI: 8.60-9.30) in males, and from 1.64% (95%CI: 1.52-1.77) to 11.10% (95%CI: 10.77-11.44) in females.

4.1.4.2.3 Hip circumference

With basic adjustment, the prevalence of diabetes increased monotonically across quintiles of hip circumference, from 4.27% to 6.31% for men and from 4.27% to 6.46% for women (Figure 4.1.21). However, after adjusting for BMI, the association reversed to a strongly negative trend in both sexes, with the prevalence decreasing from 6.25% (95%CI: 5.80-6.73) in the lowest quintile to 3.70% (95%CI: 3.48-3.93) in the highest quintile for males, and from 7.74% (95%CI: 7.35-8.16) to 3.53% (95%CI: 3.40-3.70) for females. Even stronger inverse associations were observed after additionally adjusting for waist circumference (also shown in Figure 4.1.21). The BMI- and WC-adjusted prevalence in the lowest hip quintile was about three times higher than that in the highest quintile for men (8.32% versus 2.48%) and about four times higher for women (10.14% versus 2.28%).

4.1.4.3 Joint associations of adiposity measures

4.1.4.3.1 Waist and hip circumference

Figure 4.1.22 shows the associations between waist circumference and diabetes prevalence in each hip circumference tertile. In general, waist circumference was strongly associated with diabetes prevalence across all hip circumference tertiles. Within low and medium hip circumference tertiles, there were curvilinear trends between waist and diabetes prevalence in both sexes: that is, there was a relatively steady increase in prevalence across lower waist quintiles, and a sharper increase across higher waist quintiles. The associations in the highest hip circumference tertile, on the other hand, appeared to be nearly linear, though less steep, across waist quintiles in both men and women.

In another stratified analysis, the association of hip circumference with diabetes prevalence was assessed for each waist circumference tertile after adjusting for BMI and other confounders (Figure 4.1.23). In both sexes, there were strong inverse associations between hip circumference and diabetes prevalence across all waist strata. In males (Figure 4.1.23(a)), the association appeared to be linear in the low and medium waist strata, but curvilinear in the high waist stratum; while in females (Figure 4.1.23(b)), it appeared to be linear in the low waist stratum, but curvilinear in both the medium and high waist strata. The inverse association between hip circumference and diabetes tended to be somewhat stronger in the higher waist circumference tertiles in both sexes.

4.1.4.3.2 BMI and central adiposity measures

Interactions between central and overall adiposity measures were tested in logistic regression models. It showed that BMI was an effect modifier for the association of waist circumference (p for interaction<0.0001), WHtR (p for interaction <0.0001) and WHR (p for interaction<0.0001) with diabetes prevalence in females; while in males, BMI was found to interact with waist circumference (p for interaction=0.01) and WHtR (p for interaction=0.006), but not with WHR (p for interaction=0.37).

The associations between central adiposity measures and diabetes prevalence were analysed in each BMI stratum. In both men and women, an increasing waist circumference was associated with a significantly higher prevalence of diabetes within each BMI tertile (Figures 4.1.24(a) and 4.1.24(b)).

However, within each waist circumference tertile, a higher BMI was no longer associated with higher diabetes prevalence. Similarly, no strong modifying effect of BMI was

observed for the association between WHR and diabetes. WHR showed consistent and similar strength of associations with diabetes prevalence at all the BMI levels (data not shown).

4.1.5 Main findings from the resurvey

Of the 512,891 participants at the CKB baseline, around 4% (19,788 participants) participated in the resurvey, which was conducted on average 2.6 years after baseline survey. As shown in Table 4.1.8, there was good agreement on the diabetes case report between baseline and resurvey (Kappa statistics=0.65, 95%: 0.58-0.73). Of the 993 diabetes cases from the baseline, 831 cases were confirmed in the resurvey; and among 18,795 non-diabetes participants, 583 were identified as diabetes cases in the resurvey.

All anthropometric indicators investigated in this study were highly correlated between baseline and resurvey (Table 4.1.9). The Pearson partial correlation coefficients for BMI (r=0.935, 95%CI: 0.933-0.937) and percentage body fat (r=0.899, 95%CI: 0.896-0.901) were among the highest across all the measures. A relatively low correlation was observed for waist hip ratio (correlation coefficient: 0.678, 95%CI: 0.671-0.686). This is probably due to the compound nature of the parameter, which reflects random measurement errors in both waist and hip circumference. With a high agreement of anthropometric values between baseline and resurvey, the “regression dilution bias” is, therefore, not considered as a major factor to impact the findings of the present study.

Table 4.1.1 Baseline demographic and socioeconomic characteristics†, by baseline diabetes status

	Male		Female	
	Non-Diabetes	**Diabetes**	**Non-Diabetes**	**Diabetes**
Number of participants	199,465	10,410	285,748	16,212
Age, years (%)				
30-39	14.6	4.2	16.7	2.4
40-49	28.7	18.9	31.8	14.9
50-59	30.2	33.4	30.7	36.6
60-69	19.1	29.5	15.6	34.3
70-79	7.4	14.1	5.1	11.9
Mean (SD)	52.1 (10.9)	57.5 (10.1)	50.5 (10.4)	58.3 (9.1)
Area (%)				
Qingdao (urban)	7.2	11.1	6.4	10.5
Harbin (urban)	10.5	22.7	11.0	18.3
Haikou (urban)	5.0	7.4	6.2	6.7
Suzhou (urban)	10.7	10.4	10.3	8.6
Liuzhou (urban)	8.9	14.1	10.0	13.8
Sichuan (rural)	10.3	7.6	11.6	8.1
Gansu (rural)	9.4	5.3	10.3	6.3
Henan (rural)	13.5	8.9	11.8	11.7
Zhejiang (rural)	11.7	6.0	11.3	7.6
Hunan (rural)	12.9	6.6	11.2	8.4
Annual household income, Yuan (%)				
<2,500	3.0	2.5	3.0	4.1
2,500-4,999	6.4	4.9	7.1	6.9
5,000-9,999	17.0	12.6	19.7	17.9
10,000-19,999	28.3	29.7	29.4	32.0
20,000-34,999	25.3	27.2	24.3	23.4
≥35,000	20.1	23.2	16.5	15.6
Education (%)				
No formal school	9.0	6.9	25.1	29.3
Primary school	33.5	28.8	31.3	34.5
Middle school	32.5	31.7	25.6	21.7
High school	17.4	19.7	13.6	10.9
Technical school/college	4.4	6.6	3.0	2.4
University	3.3	5.4	1.5	1.3
Occupation (%)				
Agriculture & related	44.6	21.6	41.5	24.2
Factory worker	19.3	15.4	11.0	3.8
Administrator/manager	3.3	4.2	1.4	0.6
Professional/technical	3.7	3.6	2.7	1.1
Sales/service workers	4.9	5.4	5.1	2.5
Retired	13.5	37.2	16.7	39.1
Housewife/husband	2.7	3.8	15.2	24.2
Self-employed	3.5	3.2	2.2	1.2
Unemployed	2.7	4.0	2.6	2.0
Other or not stated	1.7	1.6	1.6	1.3

† Unadjusted

Table 4.1.2 Baseline lifestyle characteristics†, by baseline diabetes status

	Male		Female	
	Non-Diabetes	**Diabetes**	**Non-Diabetes**	**Diabetes**
Number of participants	199,465	10,410	285,748	16,212
Smoking (%)				
Never	14.2	18.1	95.1	92.5
Occasional	11.3	10.4	1.8	2.1
Ex- regular	12.8	21.8	0.8	2.0
Current regular	61.7	49.7	2.3	3.4
Alcohol use (%)				
Never regular	20.2	23.7	63.2	71.0
Ex-regular	3.6	7.0	0.4	0.8
Occasional or seasonal	31.7	27.4	32.5	25.6
Monthly	6.4	4.4	1.4	0.9
Reduced intake	4.7	8.8	0.4	0.5
Weekly	33.5	28.6	2.1	1.2
Physical activity in MET, hrs/day (%)				
1st quintile (<17)	19.5	30.0	19.3	32.5
2nd quintile (17-22.4)	19.8	24.2	19.8	23.5
3rd quintile (22.4-27.7)	20.0	19.7	20.1	19.5
4th quintile (27.7-34.4)	20.2	15.3	20.3	14.5
5th quintile (>34.4)	20.5	10.7	20.6	10.0

† Unadjusted

Table 4.1.3 Baseline mean (SD)† of anthropometric characteristics and random glucose levels

	Male		Female	
	Non-Diabetes	**Diabetes**	**Non-Diabetes**	**Diabetes**
Weight, kg	64.0 (10.8)	68.3 (11.5)	56.5 (9.4)	59.6 (10.1)
Height, m	1.65 (0.07)	1.66 (0.09)	1.54 (0.06)	1.54 (0.06)
BMI, kg/m²	23.4 (3.2)	24.8 (3.4)	23.7 (3.4)	25.2 (3.7)
Waist circumference, cm	81.8 (9.7)	87.6 (9.9)	78.7 (9.4)	85.1 (9.7)
Hip circumference, cm	90.5 (6.8)	93.2 (7.2)	91.0 (6.8)	92.9 (7.7)
Waist-hip ratio	0.90 (0.06)	0.94 (0.06)	0.86 (0.07)	0.92 (0.07)
Waist-height ratio	0.49 (0.06)	0.53 (0.06)	0.51 (0.06)	0.55 (0.06)
Percentage body fat, %	21.9 (6.2)	24.0 (6.3)	31.9 (7.1)	34.6 (7.3)
Random plasma glucose, mmol/L	5.6 (1.2)	12.8 (5.7)	5.8 (1.1)	12.7(5.7)

† Means unadjusted

Table 4.1.4(a) Mean adiposity values by demographic and socioeconomic factors: BMI

	Male		Female	
	BMI (kg/m^2)	95% CI	BMI (kg/m^2)	95%CI
Age years†				
30-39	23.69	(23.65, 23.72)	23.07	(23.04, 23.10)
40-49	23.78	(23.75, 23.80)	23.92	(23.90, 23.94)
50-59	23.56	(23.54, 23.58)	24.20	(24.18, 24.23)
60-69	23.17	(23.14, 23.20)	24.01	(23.98, 24.04)
70-79	22.69	(22.65, 22.74)	23.55	(23.50, 23.60)
p for trend		**<0.0001**		**<0.0001**
Area‡				
Qingdao (urban)	25.29	(25.24, 25.34)	25.69	(25.64, 25.73)
Harbin (urban)	24.79	(24.75, 24.83)	24.26	(24.23, 24.30)
Haikou (urban)	23.43	(23.37, 23.49)	23.18	(23.13, 23.23)
Suzhou (urban)	23.90	(23.86, 23.95)	23.92	(23.88, 23.95)
Liuzhou (urban)	23.82	(23.78, 23.87)	23.63	(23.59, 23.67)
Sichuan (rural)	22.79	(22.75, 22.83)	23.46	(23.43, 23.50)
Gansu (rural)	21.95	(21.91, 22.00)	23.18	(23.14, 23.22)
Henan (rural)	23.61	(23.58, 23.65)	24.64	(24.61, 24.68)
Zhejiang (rural)	22.68	(22.64, 22.72)	22.91	(22.87, 22.94)
Hunan (rural)	22.09	(22.05, 22.13)	22.52	(22.48, 22.55)
p for heterogeneity		**<0.0001**		**<0.0001**
Annual household income (Yuan)*				
<2,500	22.58	(22.50, 22.66)	23.17	(23.10, 23.24)
2,500-4,999	22.71	(22.65, 22.76)	23.51	(23.46, 23.55)
5,000-9,999	22.94	(22.90, 22.97)	23.68	(23.65, 23.71)
10,000-19,999	23.35	(23.32, 23.38)	23.82	(23.80, 23.85)
20,000-34,999	23.62	(23.59, 23.65)	23.75	(23.73, 23.78)
≥35,000	24.10	(24.07, 24.13)	23.88	(23.85, 23.91)
p for trend		**<0.0001**		**<0.0001**
Education*				
No formal school	22.86	(22.81, 22.91)	23.81	(23.78, 23.84)
Primary school	23.23	(23.20, 23.25)	23.98	(23.96, 24.01)
Middle school	23.48	(23.46, 23.51)	23.77	(23.74, 23.80)
High school	23.67	(23.64, 23.71)	23.29	(23.26, 23.33)
Technical	24.06	(24.00, 24.13)	22.88	(22.81, 22.95)
University	24.08	(24.01, 24.16)	22.81	(22.71, 22.91)
p for difference		**<0.0001**		**<0.0001**
Occupation**				
Agriculture & related	22.73	(22.70, 22.76)	23.29	(23.26, 23.31)
Factory worker	23.37	(23.33, 23.41)	23.21	(23.16, 23.25)
Administrator/manage	24.48	(24.41, 24.56)	22.98	(22.88, 23.09)
Professional/technical	24.01	(23.94, 24.08)	22.98	(22.90, 23.05)
Sales/service workers	23.99	(23.93, 24.05)	23.58	(23.53, 23.64)
Retired	24.31	(24.26, 24.35)	24.67	(24.63, 24.71)
House wife/husband	23.13	(23.05, 23.21)	23.99	(23.95, 24.02)
Self-employed	24.42	(24.35, 24.49)	24.14	(24.06, 24.22)
Unemployed	23.50	(23.42, 23.59)	23.81	(23.73, 23.88)
Other or not stated	23.74	(23.64, 23.85)	23.97	(23.87, 24.07)
p for difference		**<0.0001**		**<0.0001**

†Adjusted for area

‡ Adjusted for age

* Adjusted for age and area

**Adjusted for age, area and physical activity

Table 4.1.4(b) Mean adiposity values by lifestyle factors and family history of diabetes: BMI*

	Male		Female	
	BMI (kg/m^2)	**95% CI**	**BMI (kg/m^2)**	**95%CI**
Physical activity-MET**				
1st quintile	23.56	(23.53, 23.59)	23.89	(23.86, 23.93)
2nd quintile	23.59	(23.56, 23.62)	23.88	(23.85, 23.91)
3rd quintile	23.44	(23.41, 23.47)	23.71	(23.69, 23.74)
4th quintile	23.34	(23.31, 23.37)	23.55	(23.52, 23.58)
5th quintile	23.17	(23.14, 23.20)	23.40	(23.37, 23.42)
p for trend		**<0.0001**		**<0.0001**
Smoking status				
Never	23.79	(23.76, 23.83)	23.75	(23.73, 23.76)
Occasional	23.79	(23.75, 23.83)	23.86	(23.77, 23.95)
Ex- regular	24.17	(24.13, 24.21)	24.23	(24.10, 24.36)
Current regular	23.10	(23.08, 23.12)	23.03	(22.96, 23.11)
p for difference		**<0.0001**		**=0.001**
Alcohol consumption				
Never regular	23.28	(23.25, 23.31)	23.80	(23.78, 23.82)
Ex-regular	23.68	(23.61, 23.75)	23.91	(23.73, 24.09)
Occasional or seasonal	23.41	(23.38, 23.43)	23.63	(23.60, 23.65)
Monthly	23.52	(23.46, 23.57)	23.47	(23.37, 23.57)
Reduced intake	24.07	(24.01, 24.13)	23.98	(23.81, 24.16)
Weekly	23.43	(23.41, 23.46)	23.50	(23.38, 23.55)
p for difference		**<0.0001**		**<0.0001**
Family history of diabetes				
Yes	23.98	(23.93, 23.98)	24.09	(24.04, 24.13)
No	23.40	(23.38, 23.42)	23.71	(23.70, 23.73)
p for difference		**<0.0001**		**<0.0001**

* Adjusted for age and area

** MET quintile: <17.0 hours/day, 17.0-22.4 hours/day, 22.4-27.7 hours/day, 27.7-34.4 hours/day, and >34.4 hours/day

Table 4.1.5(a) Mean adiposity values by demographic and socioeconomic factors: WC

	Male		Female	
	WC (cm)	**95% CI**	**WC (cm)**	**95%CI**
Age years†				
30-39	82.37	(82.26, 82.47)	75.31	(75.23, 75.39)
40-49	82.98	(82.91, 83.06)	78.22	(78.16, 78.28)
50-59	82.31	(82.23, 82.38)	80.64	(80.58, 80.70)
60-69	81.87	(81.78, 81.96)	81.48	(81.40, 81.55)
70-79	81.37	(81.23, 81.51)	81.25	(81.11, 81.39)
p for trend		**<0.0001**		**<0.0001**
Area‡				
Qingdao (urban)	87.53	(87.38, 87.68)	83.85	(83.73, 83.98)
Harbin (urban)	87.41	(87.29, 87.53)	79.65	(79.56, 79.75)
Haikou (urban)	83.53	(83.35, 83.70)	78.12	(77.99, 78.25)
Suzhou (urban)	81.50	(81.38, 81.63)	78.82	(78.72, 78.93)
Liuzhou (urban)	84.30	(84.16, 84.43)	78.40	(78.30, 78.51)
Sichuan (rural)	78.74	(78.61, 78.86)	77.47	(77.37, 77.56)
Gansu (rural)	79.98	(79.85, 80.11)	80.26	(80.15, 80.36)
Henan (rural)	82.42	(82.31, 82.54)	81.42	(81.33, 81.52)
Zhejiang (rural)	77.89	(77.77, 78.02)	75.43	(75.33, 75.53)
Hunan (rural)	78.52	(78.40, 78.64)	77.39	(77.29, 77.49)
p for heterogeneity		**<0.0001**		**<0.0001**
Annual household income (Yuan)*				
<2,500	79.20	(78.96, 79.43)	77.01	(76.82, 77.21)
2,500-4,999	79.45	(79.28, 79.61)	77.89	(77.76, 78.02)
5,000-9,999	80.08	(79.98, 80.19)	78.55	(78.47, 78.63)
10,000-19,999	81.72	(81.64, 81.81)	79.26	(79.20, 79.33)
20,000-34,999	82.97	(82.88, 83.05)	79.42	(79.35, 79.50)
≥35,000	84.89	(84.79, 84.98)	79.92	(79.83, 80.01)
p for trend		**<0.0001**		**<0.0001**
Education*				
No formal school	79.82	(79.67, 79.97)	79.25	(79.17, 79.32)
Primary school	81.41	(81.33, 81.49)	79.97	(79.90, 80.03)
Middle school	82.51	(82.43, 82.59)	79.07	(79.00, 79.14)
High school	83.13	(83.02, 83.23)	77.63	(77.53, 77.73)
Technical school/college	84.17	(83.98, 84.36)	76.62	(76.42, 76.82)
University	83.98	(83.76, 84.20)	76.32	(76.05, 76.59)
p for difference		**<0.0001**		**<0.0001**
Occupation**				
Agriculture & related	79.56	(79.47, 79.65)	77.68	(77.60, 77.76)
Factory worker	82.23	(82.11, 82.34)	77.84	(77.73, 77.96)
Administrator/manager	85.59	(85.37, 85.81)	76.95	(76.66, 77.23)
Professional/technical	83.82	(83.61, 84.03)	77.02	(76.81, 77.22)
Sales/service workers	84.31	(84.13, 84.49)	78.94	(78.79, 79.10)
Retired	85.04	(84.90, 85.17)	81.47	(81.37, 81.57)
House wife/husband	81.10	(80.85, 81.35)	80.05	(79.96, 80.14)
Self-employed	86.01	(85.79, 86.22)	80.42	(80.20, 80.65)
Unemployed	82.86	(82.62, 83.11)	79.23	(79.02, 79.44)
Other or not stated	83.42	(83.11, 83.72)	79.56	(79.29, 79.82)
p for difference		**<0.0001**		**<0.0001**

†Adjusted for area

‡ Adjusted for age

* Adjusted for age and area

**Adjusted for age, area and physical activity

Table 4.1.5(b) Mean adiposity values by lifestyle factors and family history of diabetes: WC*

	Male		Female	
	WC (cm)	**95% CI**	**WC (cm)**	**95%CI**
Physical activity-MET (%)**				
1st quintile	82.86	(82.77, 82.94)	79.57	(79.48, 79.65)
2nd quintile	82.82	(82.72, 82.91)	79.31	(79.24, 79.39)
3rd quintile	82.19	(82.09, 82.28)	78.98	(78.91, 79.06)
4th quintile	81.75	(81.65, 81.84)	78.73	(78.66, 78.81)
5th quintile	80.84	(80.73, 80.94)	78.76	(78.68, 78.84)
p for trend		**<0.0001**		**<0.0001**
Smoking status				
Never	82.53	(82.42, 82.63)	79.08	(79.03, 79.12)
Occasional	82.75	(82.62, 82.87)	79.61	(79.37, 79.85)
Ex- regular	84.32	(84.21, 84.44)	81.07	(80.72, 81.42)
Current regular	81.48	(81.42, 81.54)	78.11	(77.90, 78.33)
p for difference		**<0.0001**		**<0.0001**
Alcohol consumption				
Never regular	81.42	(81.33, 81.52)	79.21	(79.16, 79.26)
Ex-regular	82.93	(82.73, 83.14)	79.59	(79.10, 80.07)
Occasional or seasonal	81.83	(81.75, 81.91)	78.81	(78.74, 78.88)
Monthly	82.42	(82.26, 82.58)	78.79	(78.52, 79.07)
Reduced intake	84.22	(84.04, 84.40)	80.24	(79.75, 80.72)
Weekly	82.62	(82.54, 82.69)	78.81	(78.59, 79.04)
p for difference		**<0.0001**		**<0.0001**
Family history of diabetes				
With family history	84.04	(83.88, 84.20)	80.15	(80.02, 80.28)
Without family	82.06	(82.01, 82.11)	79.01	(78.97, 79.05)
p for difference		**<0.0001**		**<0.0001**

* Adjusted for age and area

** MET quintile: <17.0 hours/day, 17.0-22.4 hours/day, 22.4-27.7 hours/day, 27.7-34.4 hours/day, and >34.4 hours/day

Table 4.1.6 Difference in mean anthropometric values* between urban and rural areas

		Male			Female		
		Mean	**95% CI**	**p value**	**Mean**	**95% CI**	**p value**
BMI, kg/m^2	Urban	24.30	(24.27, 24.31)		24.09	(24.07, 24.11)	
	Rural	22.67	(22.65, 22.69)		23.35	(23.33, 23.37)	
	Difference	1.62	(1.59, 1.64)	<0.0001	0.74	(0.72,0.76)	<0.0001
Waist circumference, cm	Urban	84.95	(84.88, 85.02)		79.64	(79.58, 79.69)	
	Rural	79.68	(79.61, 79.74)		78.42	(78.37, 78.47)	
	Difference	5.27	(5.19, 5.35)	<0.0001	1.22	(1.15, 1.28)	<0.0001
Hip circumference, cm	Urban	93.49	(93.44, 93.53)		93.04	(93.00, 93.08)	
	Rural	88.51	(88.47, 88.55)		89.26	(89.23, 89.30)	
	Difference	4.97	(4.92, 5.03)	<0.0001	3.78	(3.73, 3.83)	<0.0001
Waist-hip ratio	Urban	0.91	(0.91, 0.91)		0.86	(0.85, 0.86)	
	Rural	0.90	(0.90, 0.90)		0.88	(0.88, 0.88)	
	Difference	0.0085	(0.0079, 0.0090)	<0.0001	-0.022	(-0.022, -0.021)	<0.0001

* Adjusted for age

Table 4.1.7 Pearson partial correlation coefficients* among anthropometric measurements and random glucose, by sex

	Height	Weight	BMI	Waist circumference	Hip circumference	Waist hip ratio	Waist height ratio	Percent body fat	Random glucose
					Male				
Height	1								
Weight	0.525	1							
BMI	0.071	0.883	1						
Waist circumference	0.271	0.856	0.857	1					
Hip circumference	0.422	0.845	0.762	0.803	1				
Waist hip ratio	0.026	0.552	0.635	0.821	0.332	1			
Waist height ratio	-0.053	0.709	0.865	0.945	0.700	0.841	1		
Percent body fat	0.042	0.697	0.798	0.729	0.621	0.588	0.753	1	
Random glucose	-0.016	0.061	0.080	0.109	0.039	0.146	0.125	0.063	1
					Female				
Height	1								
Weight	0.477	1							
BMI	0.036	0.893	1						
Waist circumference	0.201	0.828	0.842	1					
Hip circumference	0.366	0.853	0.786	0.774	1				
Waist hip ratio	-0.034	0.467	0.550	0.802	0.246	1			
Waist height ratio	-0.112	0.687	0.842	0.950	0.669	0.824	1		
Percent body fat	0.002	0.780	0.890	0.781	0.702	0.539	0.792	1	
Random glucose	-0.015	0.075	0.093	0.140	0.043	0.173	0.147	0.075	1

*Adjusted for area and age, all $p<0.0001$

Table 4.1.8 Consistency of diabetes cases between baseline and re-survey

Baseline (n)	Resurvey (n)		
	Diabetes	Non-diabetes	Total
Diabetes	831	162	993
Non-diabetes	583	18,212	18,795
Total	1,414	18,374	19,788

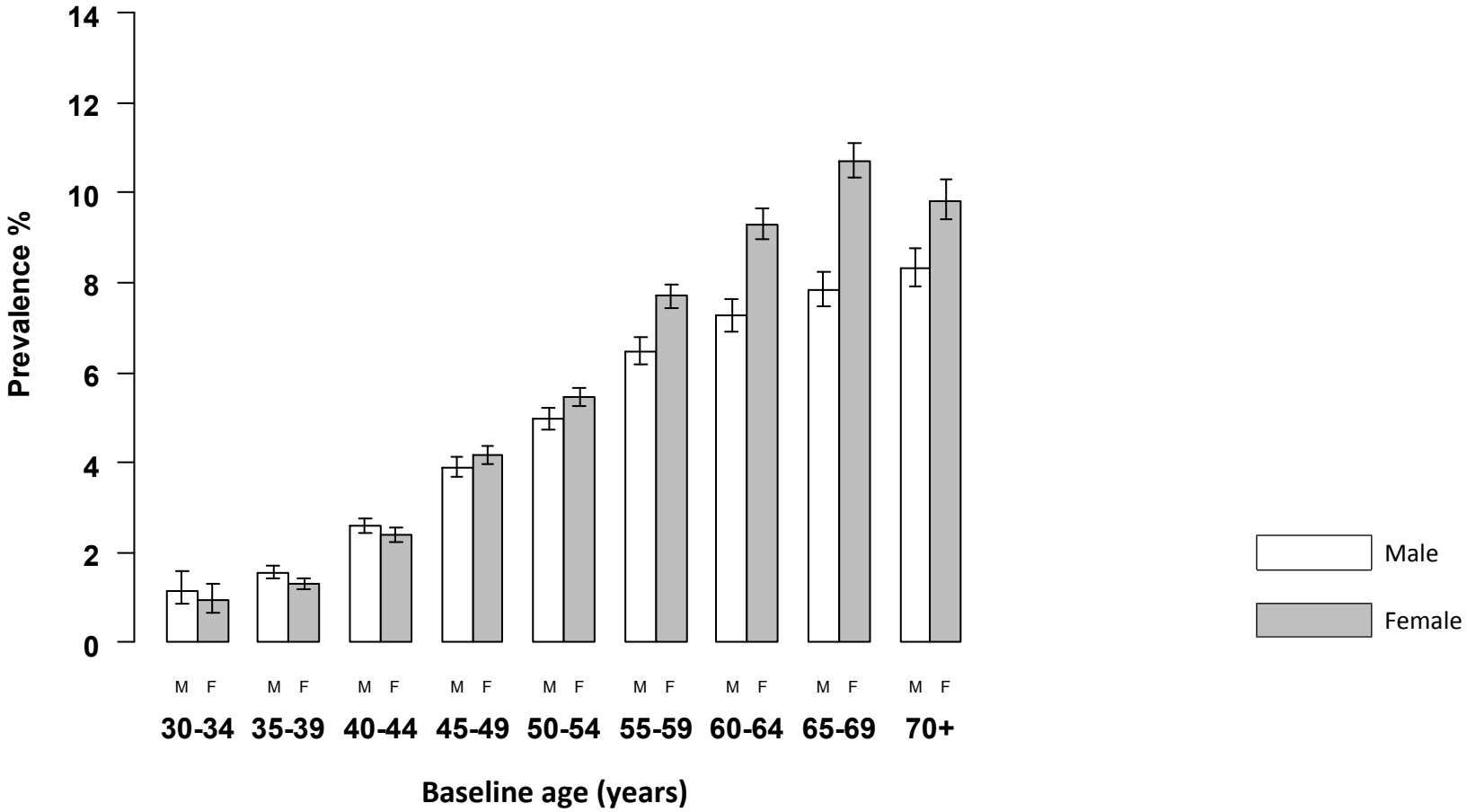
Kappa statistics=0.65 (95%CI: 0.58-0.73)

Table 4.1.9 Pearson partial correlation coefficients of anthropometric measurements between baseline and re-survey†

Variable	Correlation coefficient	95% CI
Height	0.992	(0.991, 0.992)
Weight	0.960	(0.959, 0.961)
BMI	0.935	(0.933, 0.937)
Waist circumference	0.842	(0.838, 0.846)
Hip circumference	0.816	(0.811, 0.820)
Waist hip ratio	0.678	(0.671, 0.686)
Waist height ratio	0.839	(0.835, 0.843)
Percent body fat	0.899	(0.896, 0.901)

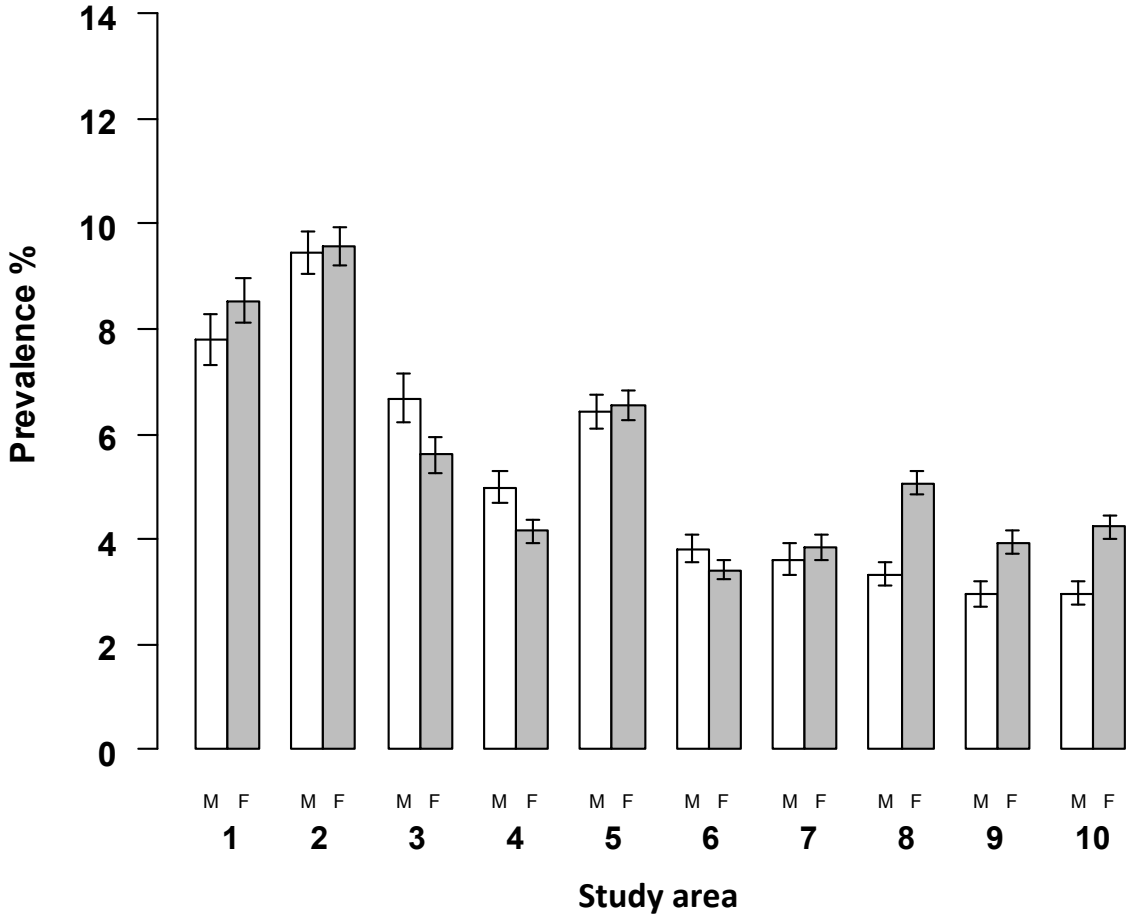
†Adjusted for area and age, all $p<0.0001$

Figure 4.1.1 Prevalence* of diabetes by age group



*Adjusted for area

Figure 4.1.2 Prevalence* of diabetes by area



Urban:

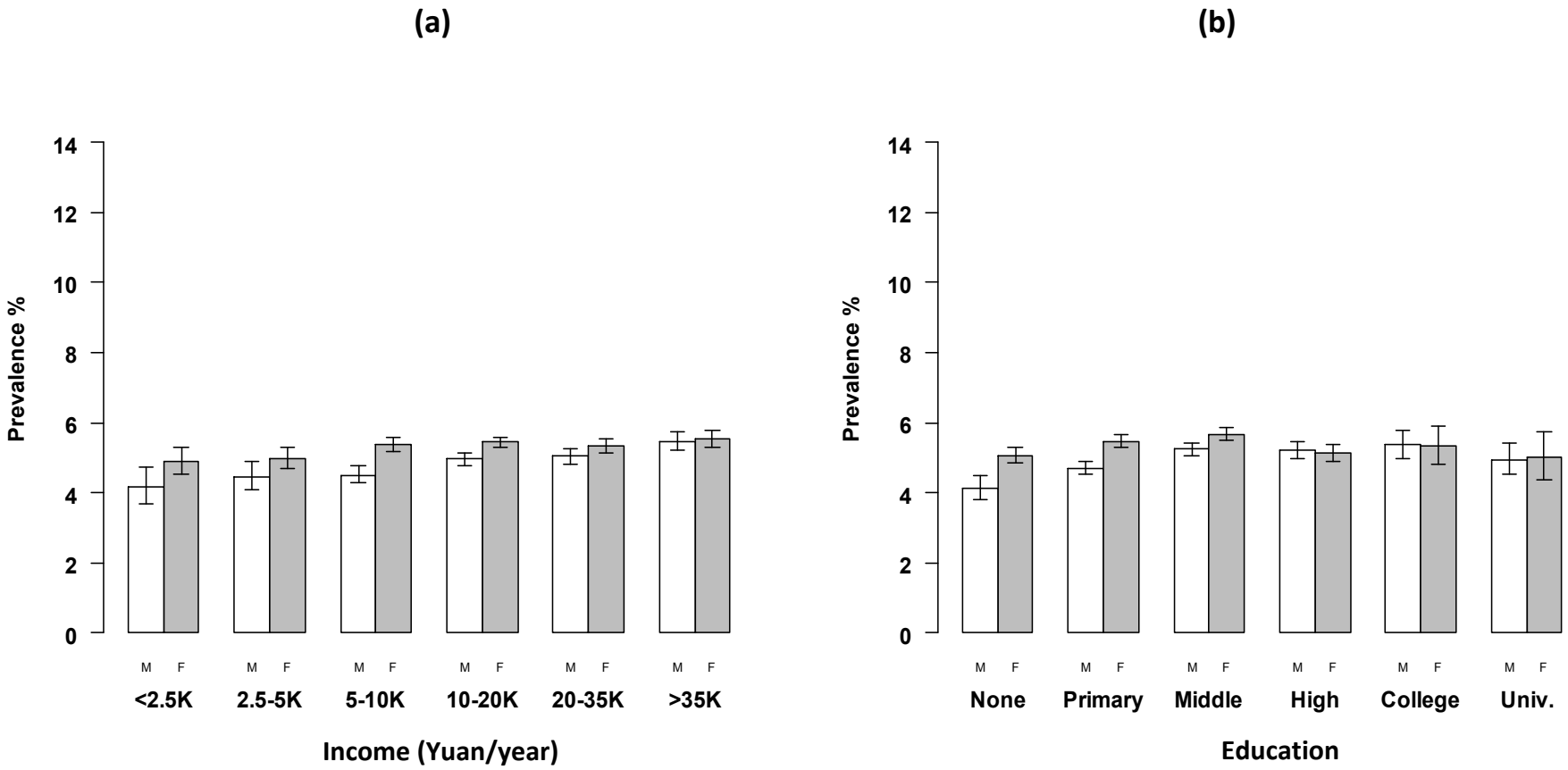
1 Qingdao
2 Harbin
3 Haikou
4 Suzhou
5 Liuzhou

Rural:

6 Sichuan
7 Gansu
8 Henan
9 Zhejiang
10 Hunan

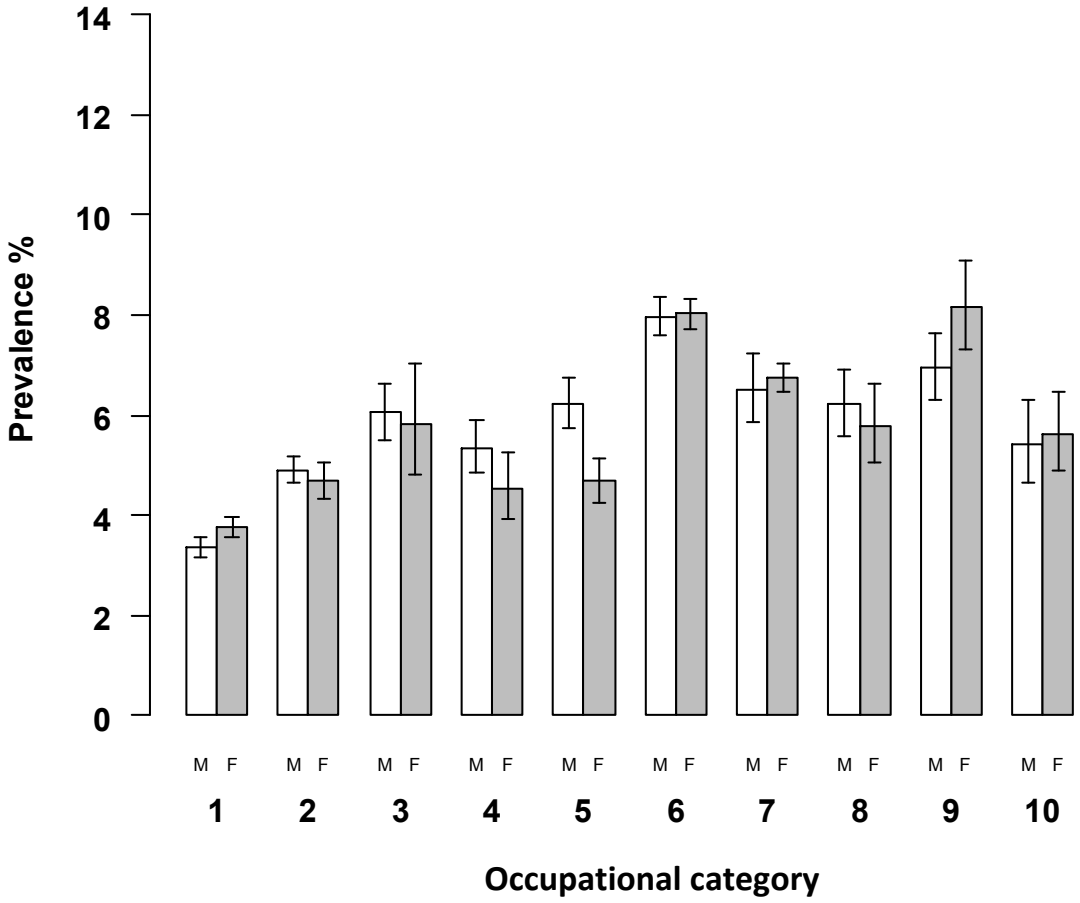
*Adjusted for age

Figure 4.1.3 Prevalence* of diabetes by (a) annual household income and (b) highest education



*Adjusted for age, area and BMI

Figure 4.1.4 Prevalence* of diabetes by occupation



Occupation:

1 Agriculture

2 Factory worker

3 Administrator / manager

4 Professional / technical

5 Sales & service workers

6 Retired

7 House wife / husband

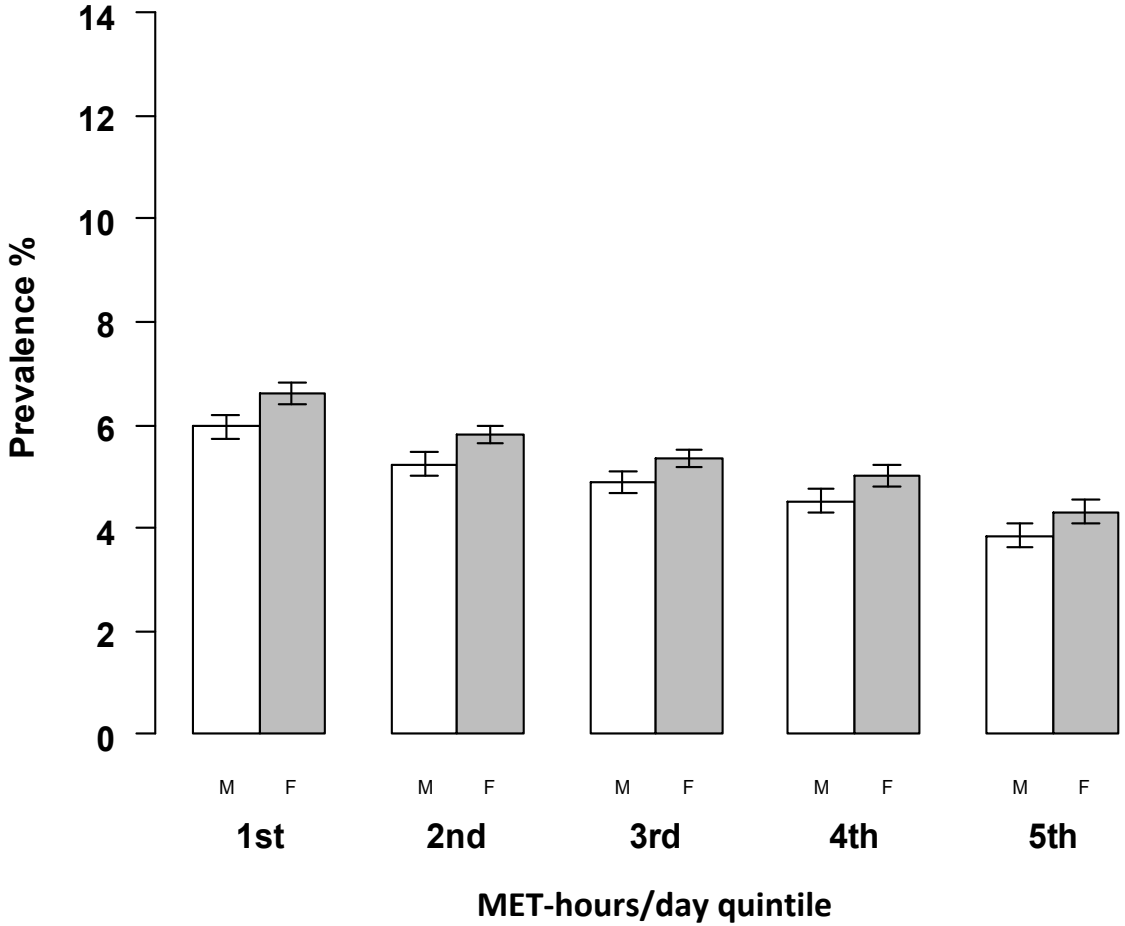
8 Self-employed

9 Unemployed

10 Other or not stated

*Adjusted for age, area, BMI and physical activity (MET, hours/day)

Figure 4.1.5 Prevalence* of diabetes by physical activity (MET quintile)

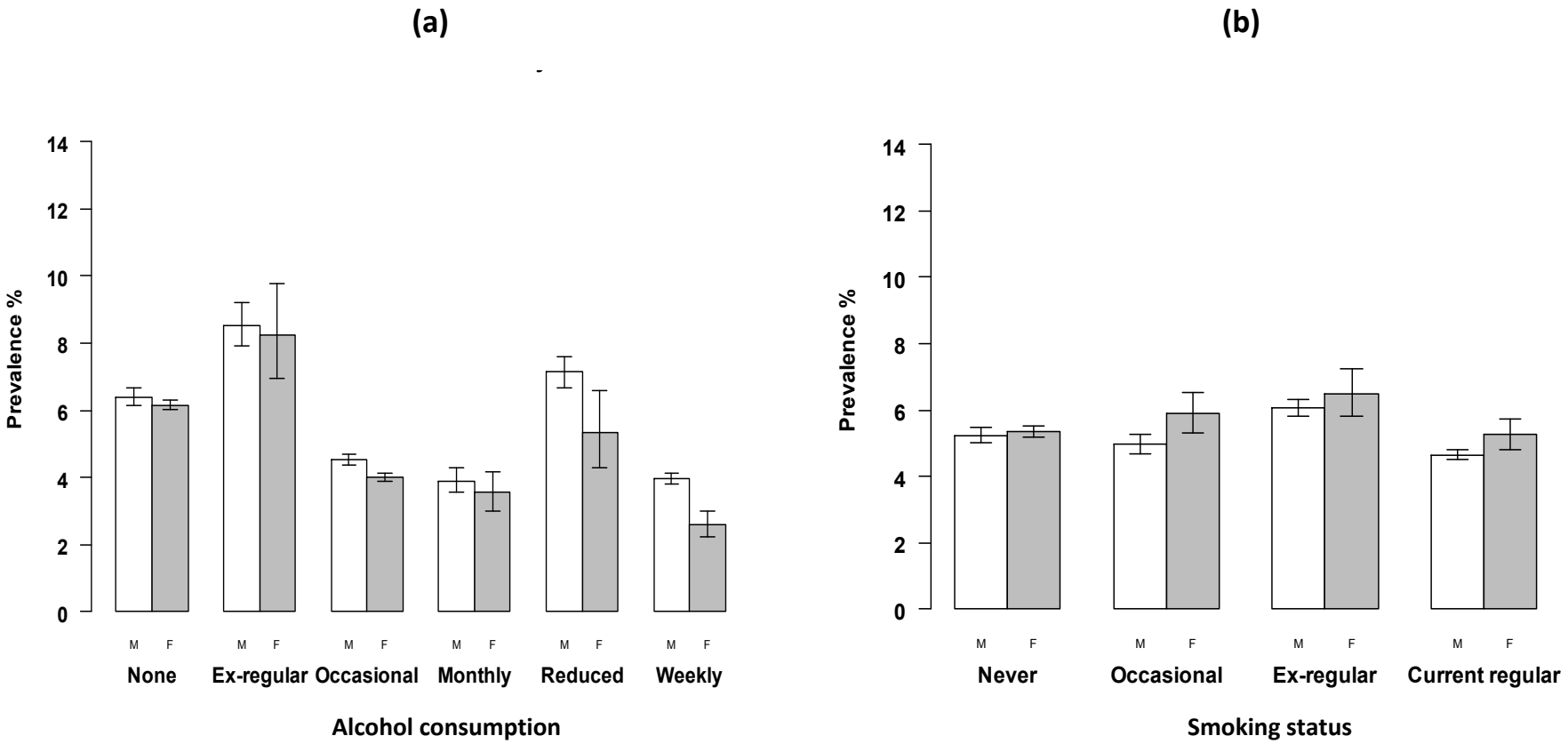


Cut-offs points for each MET quintile, MET hours/day

1st	<17.0
2nd	17.0-22.4
3rd	22.4-27.7
4th	27.7-34.4
5th	>34.4

*Adjusted for age, area and BMI

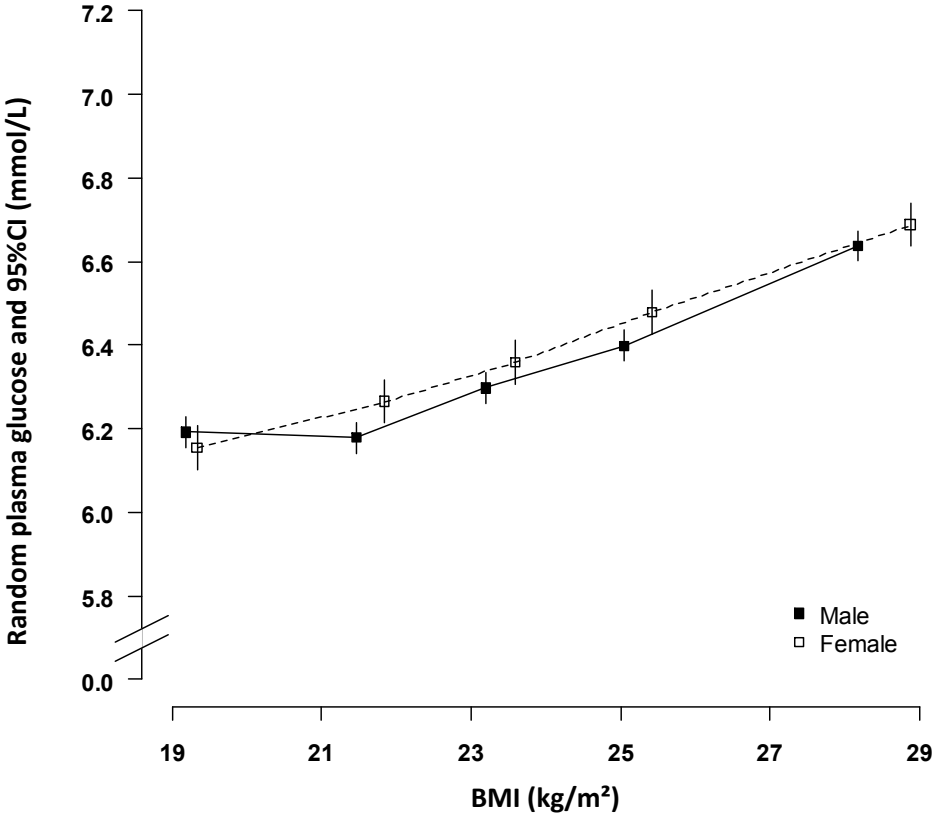
Figure 4.1.6 Prevalence* of diabetes by (a) alcohol use and (b) smoking status



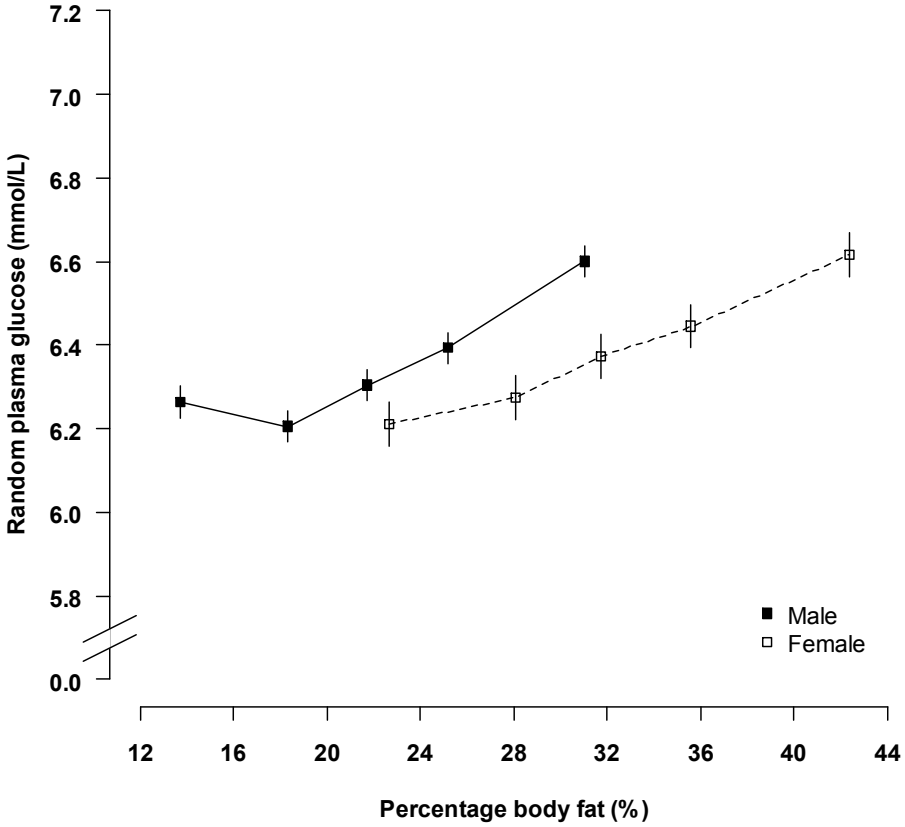
*Adjusted for age, area and BMI

Figure 4.1.7 Baseline mean* random plasma glucose by quintile of (a) BMI† and (b) percentage body fat†

(a) **(b)**



Random plasma glucose and 95%CI (mmol/L)

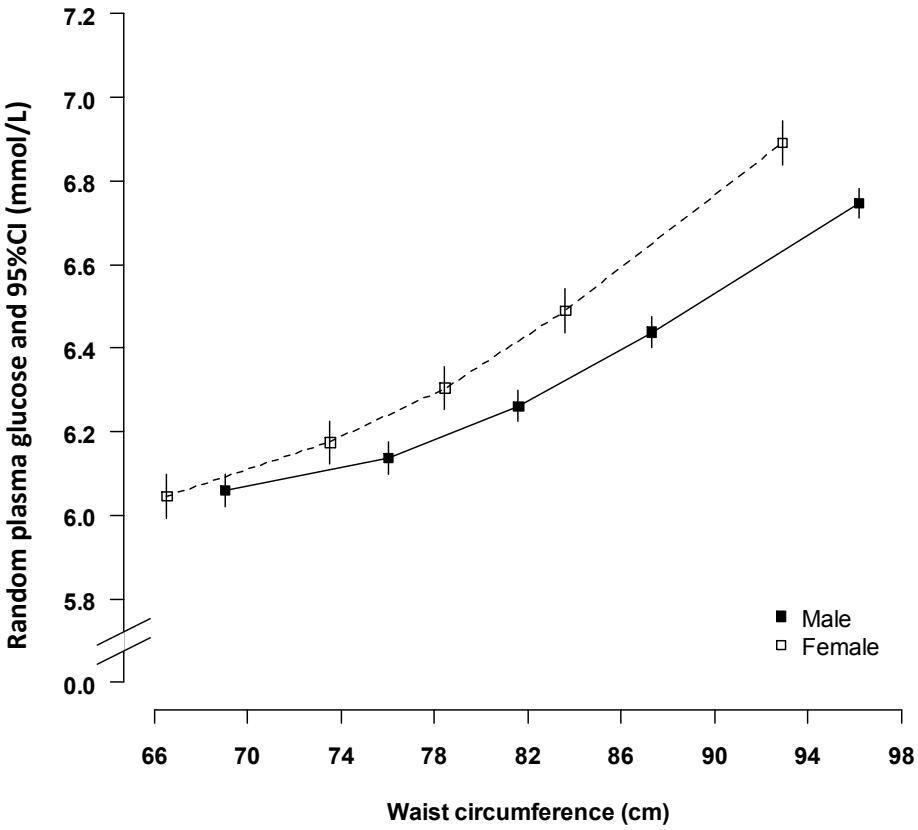


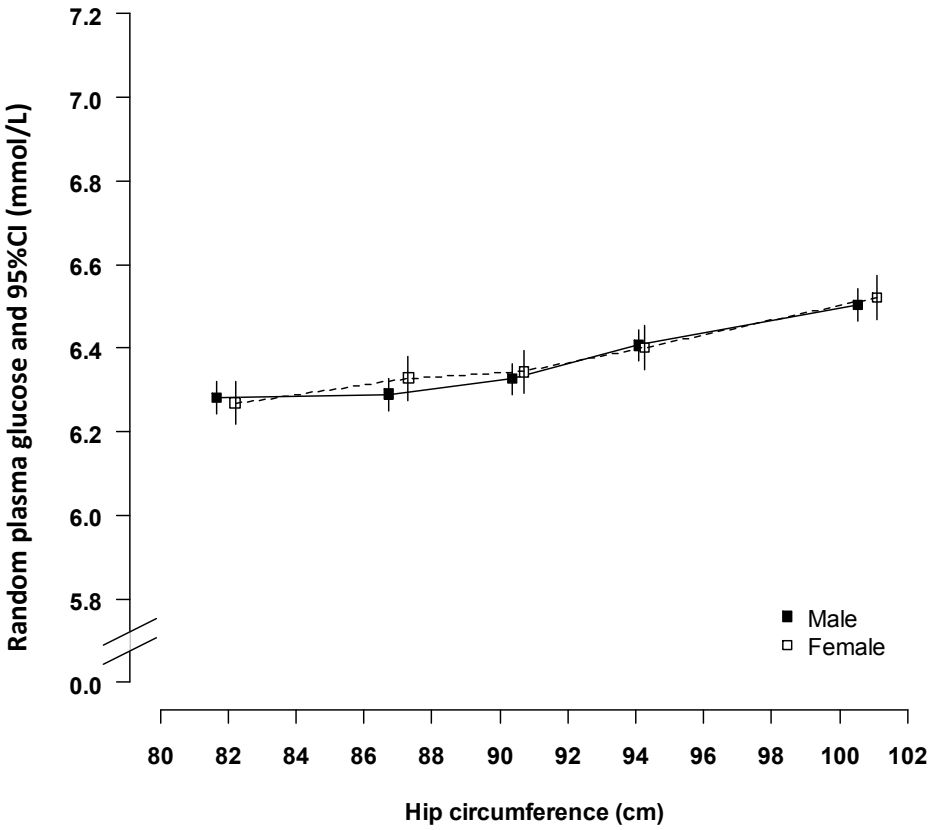
*Adjusted for age, area, income, education, occupation, smoking status, alcohol use, physical activity (MET-hours/day), and family history of diabetes

† Sex-specific quintiles

Figure 4.1.8 Baseline mean* random plasma glucose by quintile of (a) waist circumference† and (b) hip circumference†

(a) **(b)**



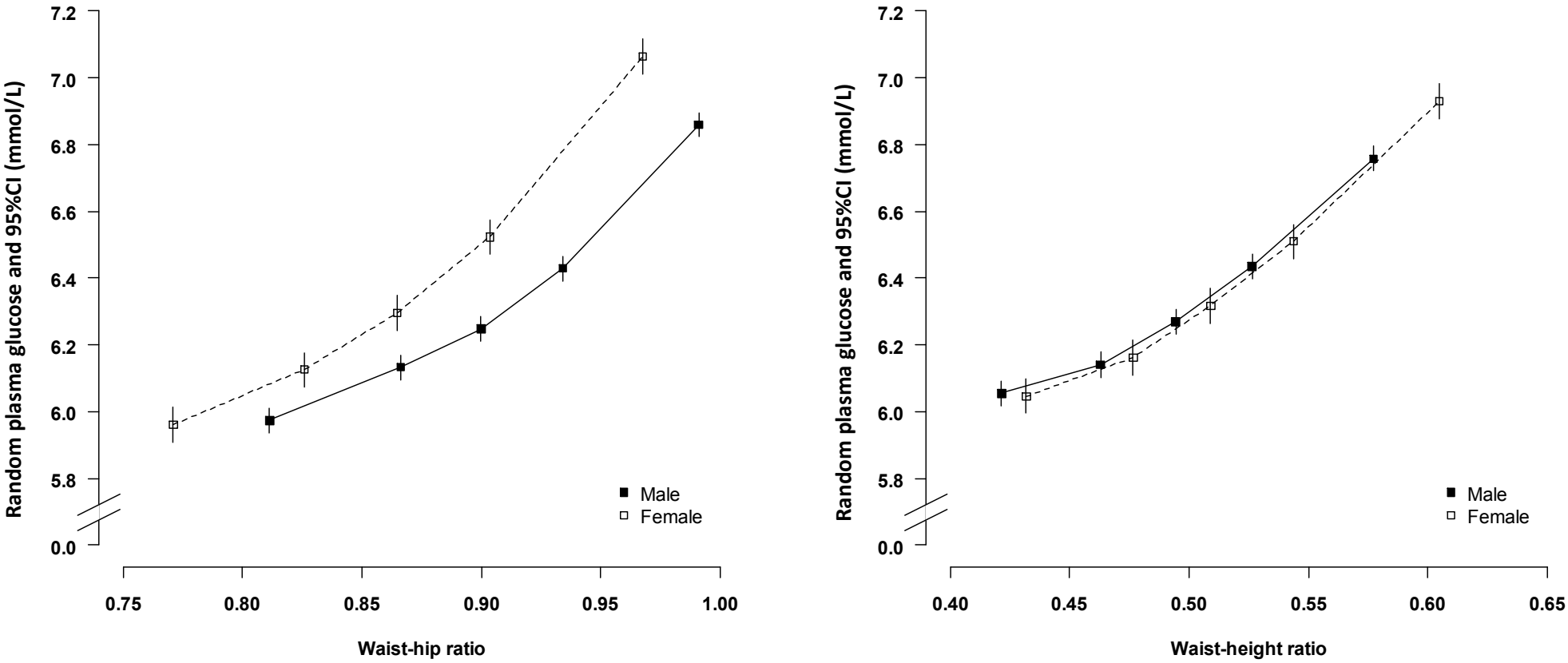


*Adjusted for age, area, income, education, occupation, smoking status, alcohol use, physical activity (MET-hours/day), and family history of diabetes

† Sex-specific quintiles

Figure 4.1.9 Baseline mean* random plasma glucose by quintile of (a) waist hip ratio† and (b) waist height ratio†

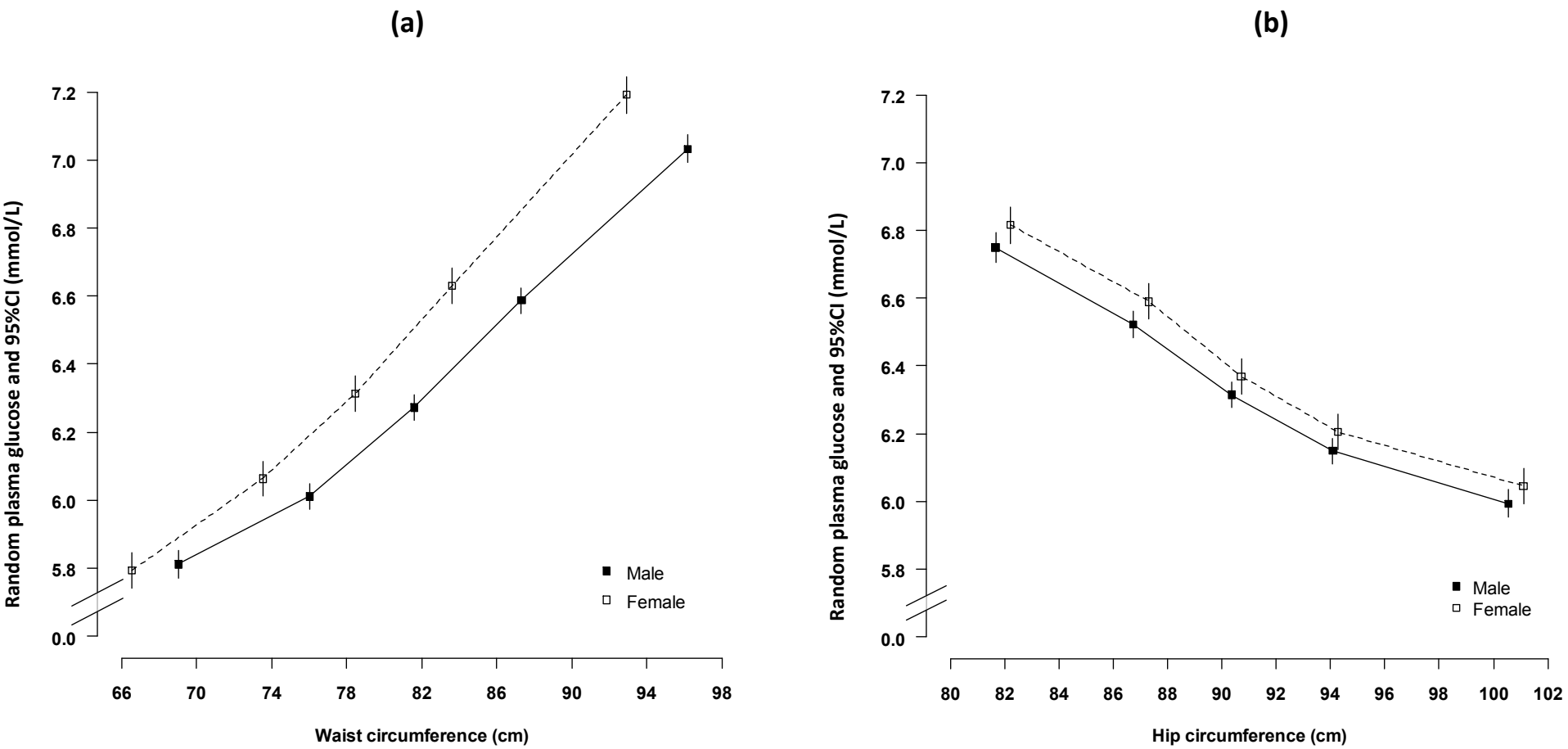
(a) **(b)**



*Adjusted for age, area, income, education, occupation, smoking status, alcohol use, physical activity (MET-hours/day), and family history of diabetes

† Sex-specific quintiles

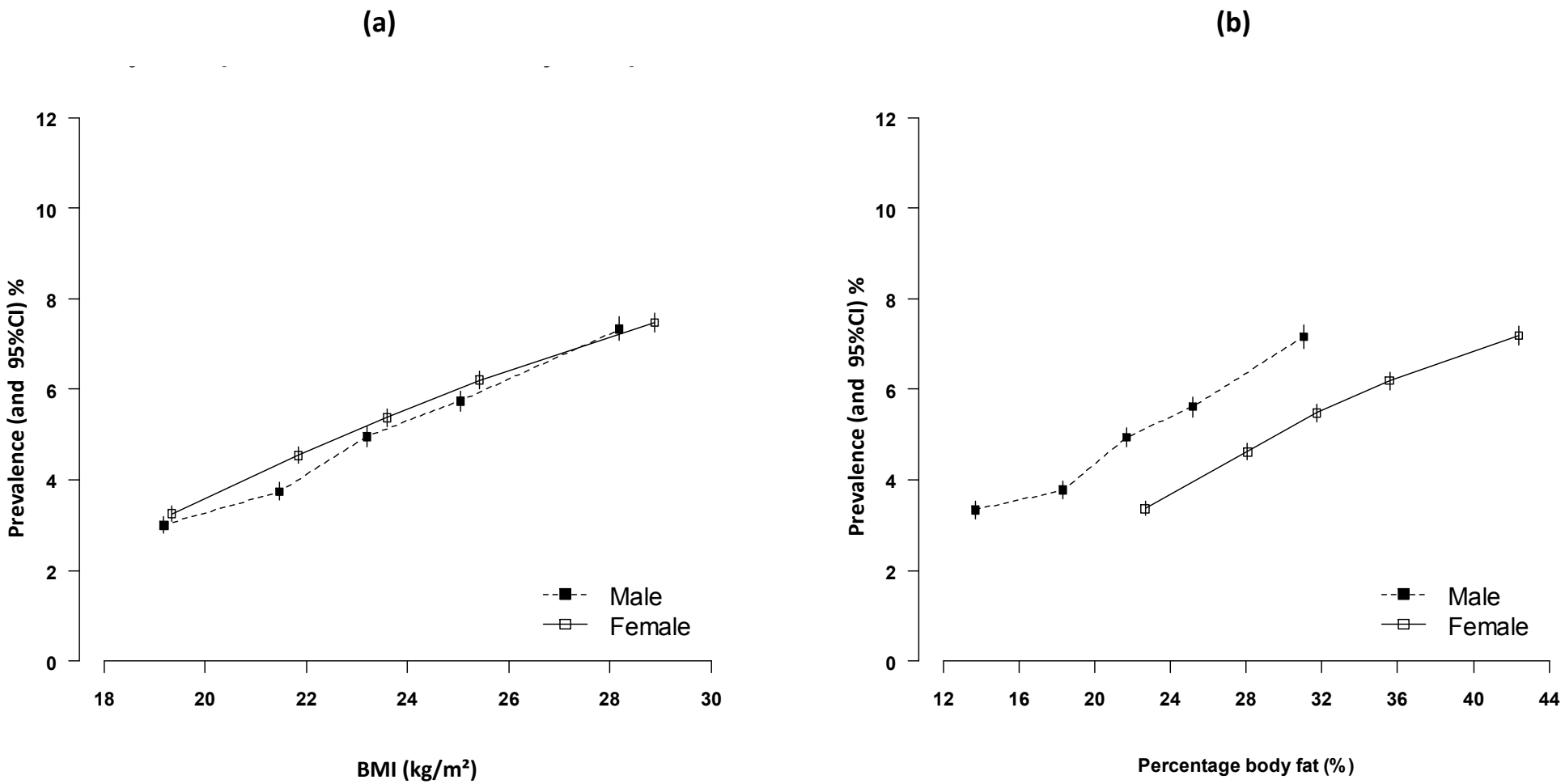
Figure 4.1.10 Baseline mean* random plasma glucose by quintile of (a) waist circumference† and (b) hip circumference†, after additional adjustment



*Adjusted for age, area, income, education, occupation, smoking status, alcohol use, physical activity (MET-hours/day), and family history of diabetes; waist circumference was additionally adjusted for hip circumference; hip circumference was additionally adjusted for waist circumference;

† Sex-specific quintiles

Figure 4.1.11 Basic associations* of diabetes prevalence with (a) BMI† and (b) percentage body fat†

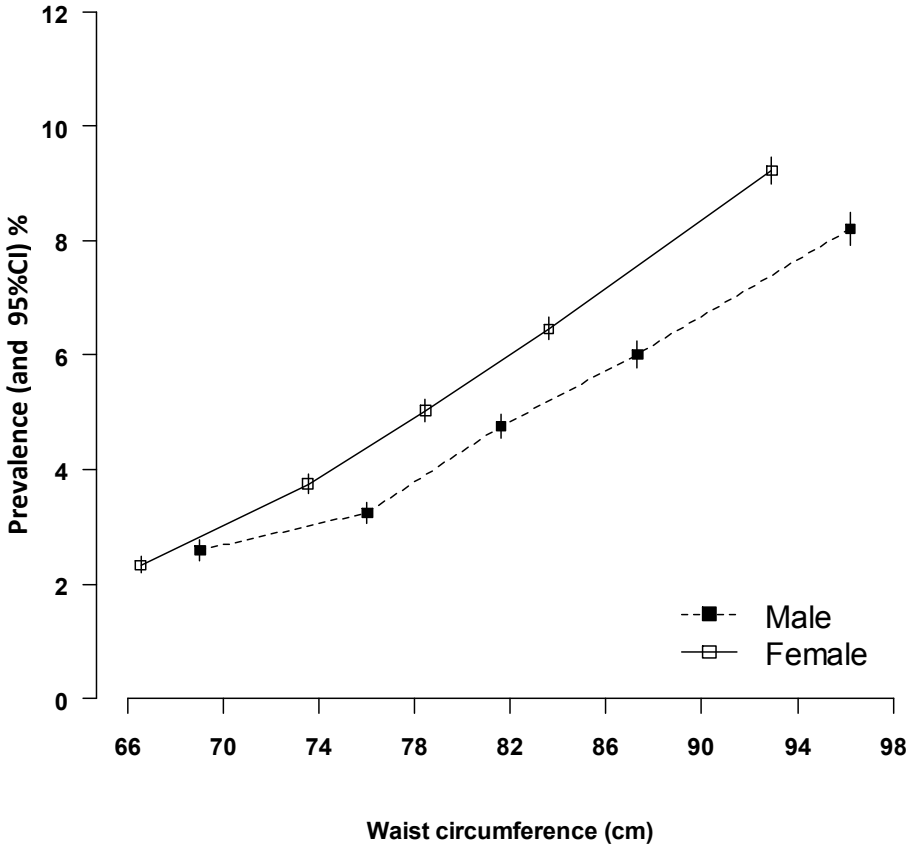


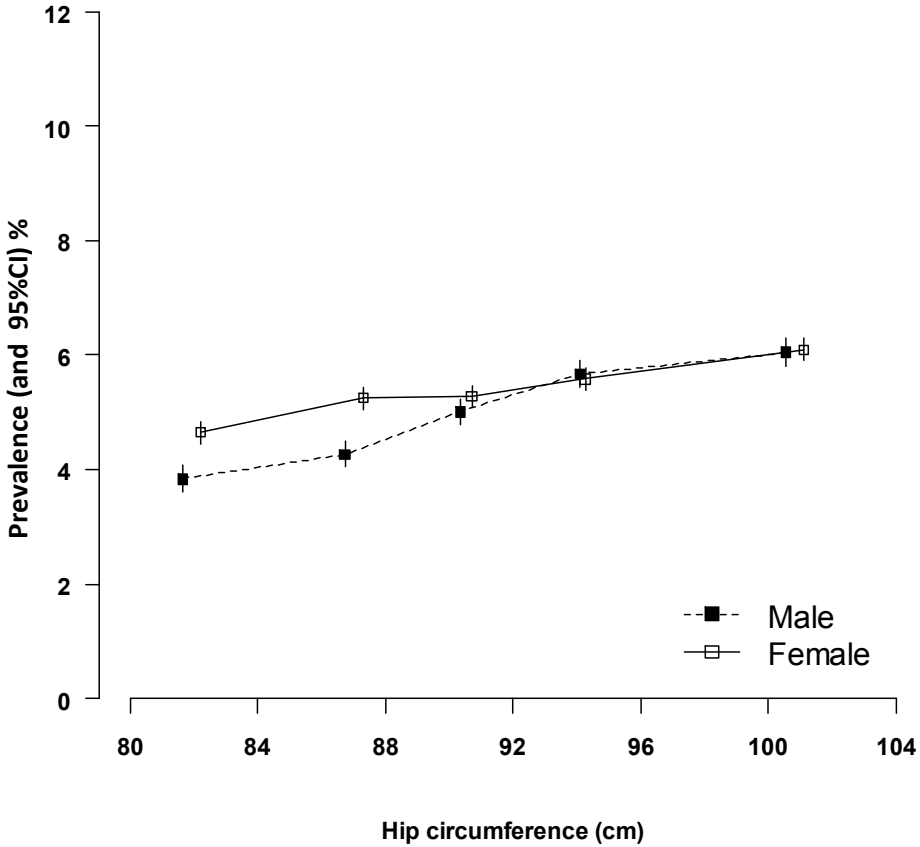
* Adjusted for age, area, income, education, occupation, smoking status, alcohol use, physical activity (MET-hours/day), and family history of diabetes (but not for other adiposity measures)

† Sex-specific quintiles

Figure 4.1.12 Basic associations* of diabetes prevalence with (a) waist circumference† and (b) hip circumference†

(a) (b)



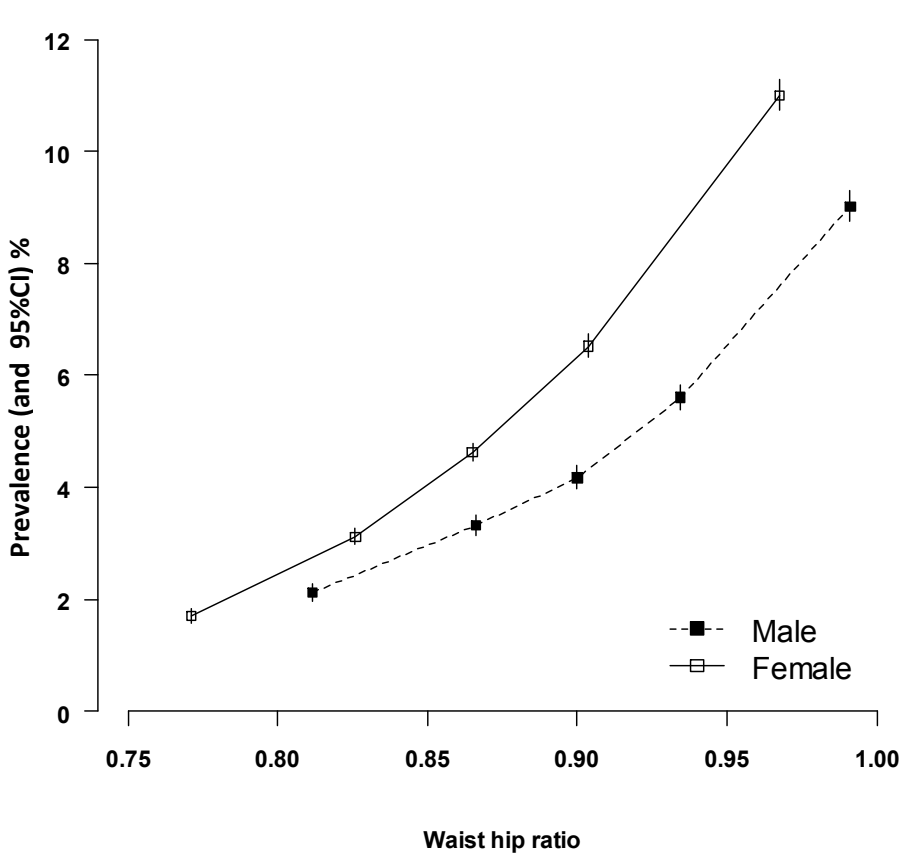


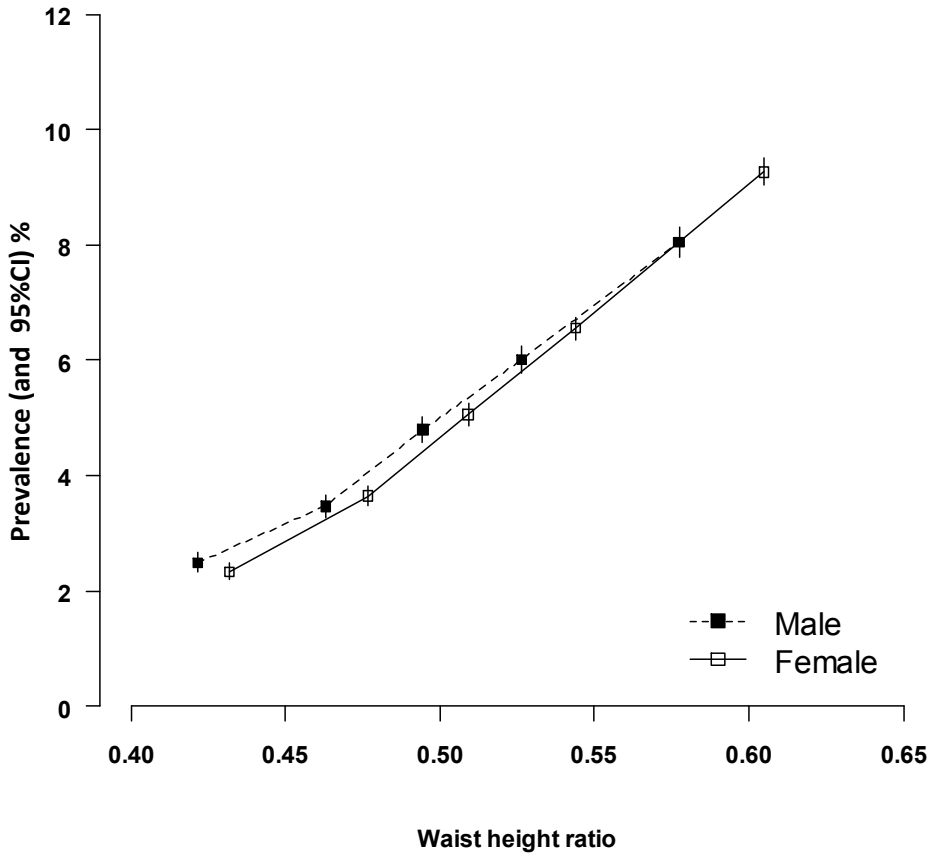
* Adjusted for age, area, income, education, occupation, smoking status, alcohol use, physical activity (MET-hours/day), and family history of diabetes (but not for other adiposity measures)

† Sex-specific quintiles

Figure 4.1.13 Basic associations* of diabetes prevalence with (a) waist hip ratio† and (b) waist height ratio†

(a) **(b)**

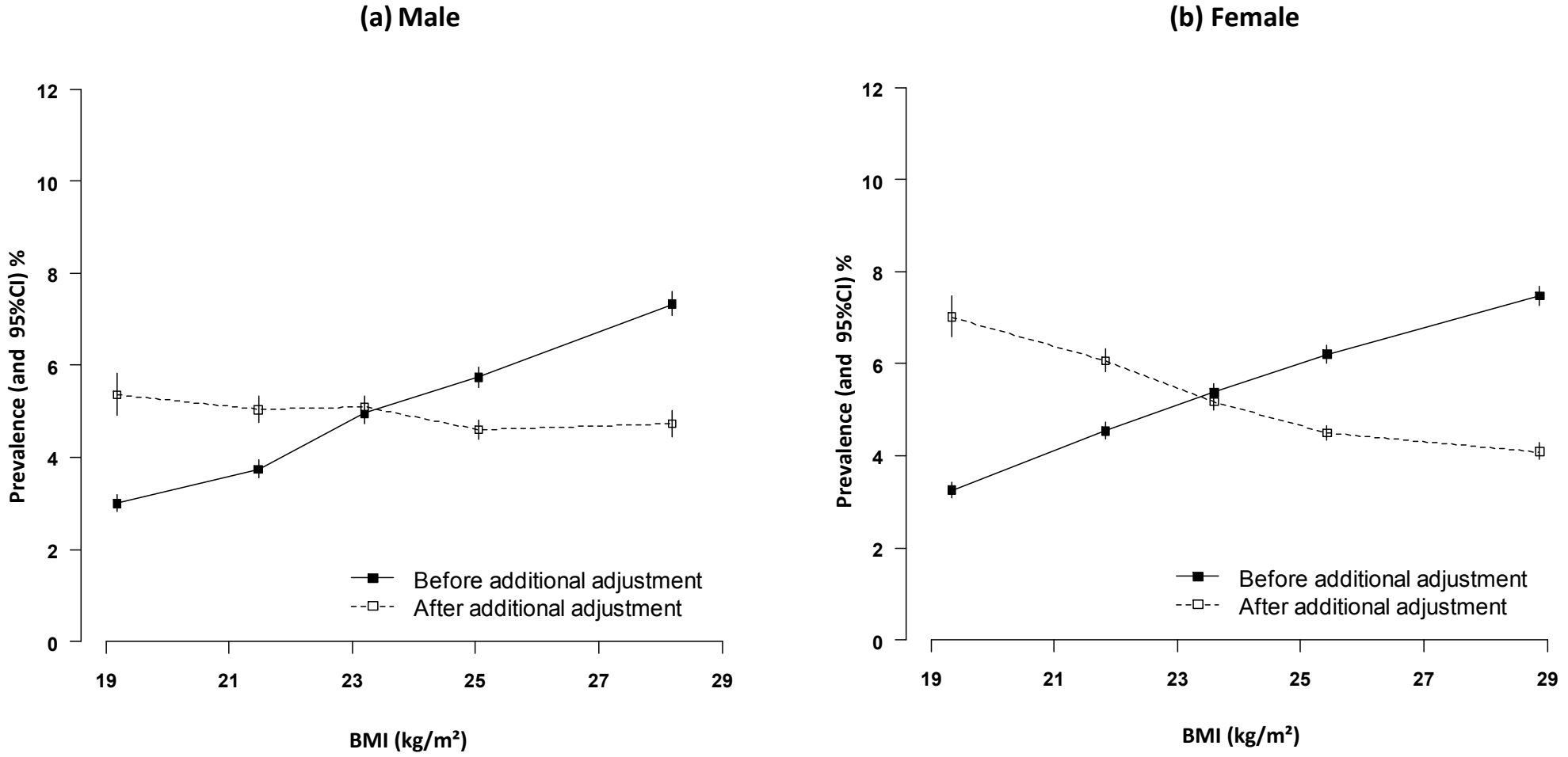




* Adjusted for age, area, income, education, occupation, smoking status, alcohol use, physical activity (MET-hours/day), and family history of diabetes (but not for other adiposity measures)

† Sex-specific quintiles

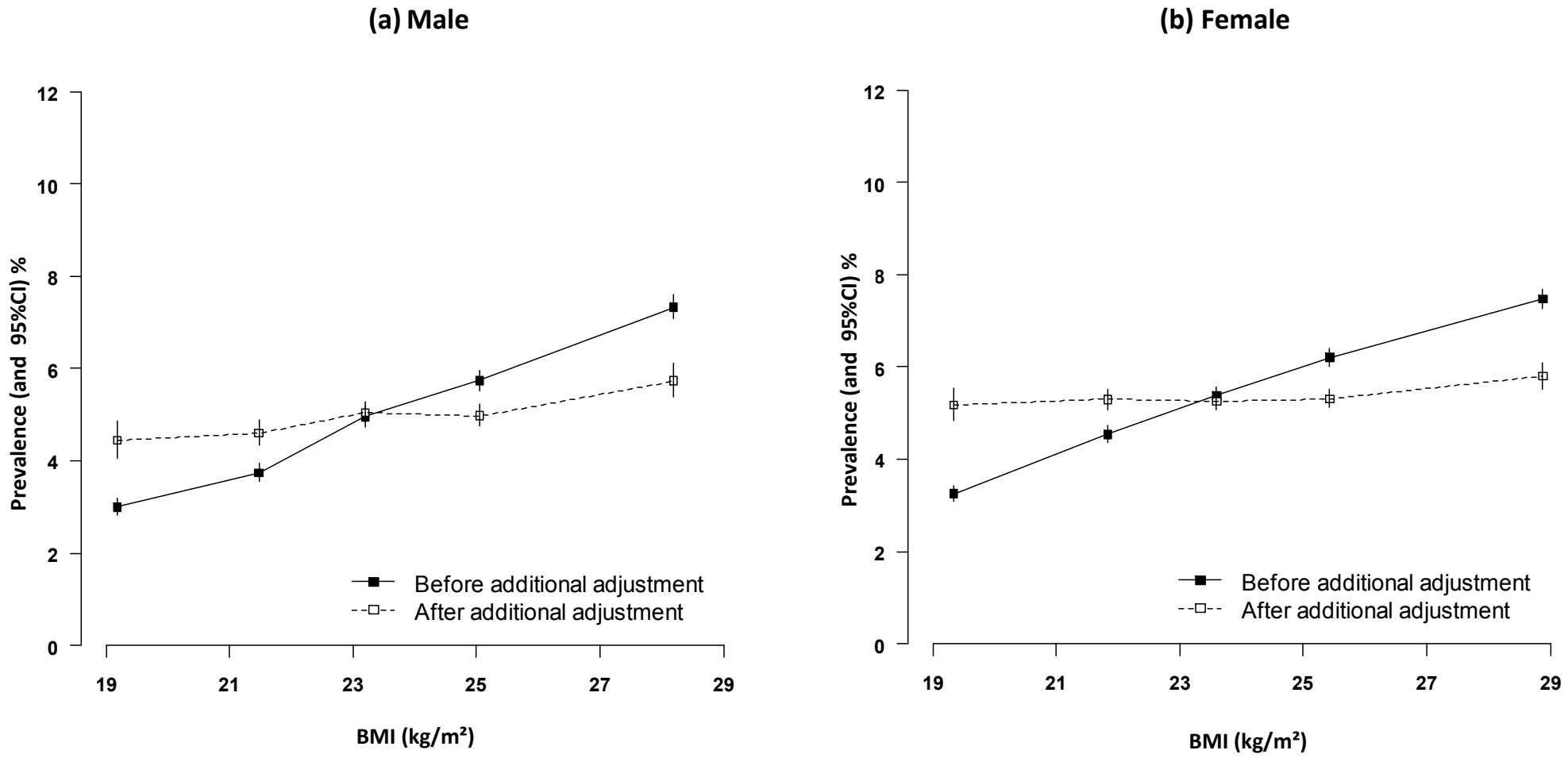
Figure 4.1.14 Prevalence of diabetes by BMI quintile before† and after‡ additional adjustment for waist circumference, by sex



†"Before"= basic association (i.e. adjusted for age, area, income, education, occupation, smoking status, alcohol use, physical activity (MET-hours/day), and family history of diabetes)

‡"After"=additionally adjusted for waist circumference

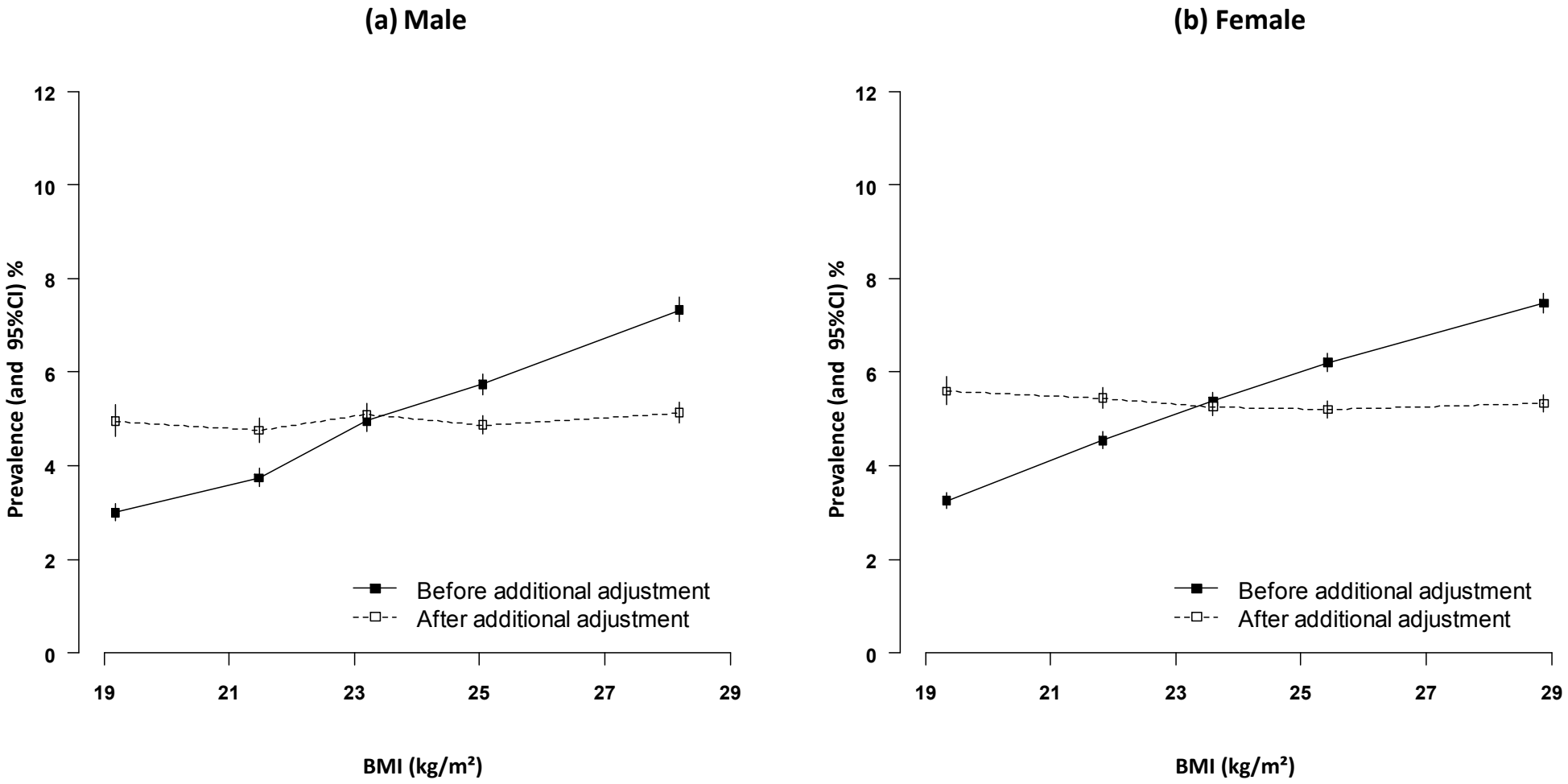
Figure 4.1.15 Prevalence of diabetes by BMI quintile before† and after‡ additional adjustment for WC and HC, by sex



†"Before"= basic association (i.e. adjusted for age, area, income, education, occupation, smoking status, alcohol use, physical activity (MET-hours/day), and family history of diabetes)

‡"After"=additionally adjusted for waist circumference and hip circumference

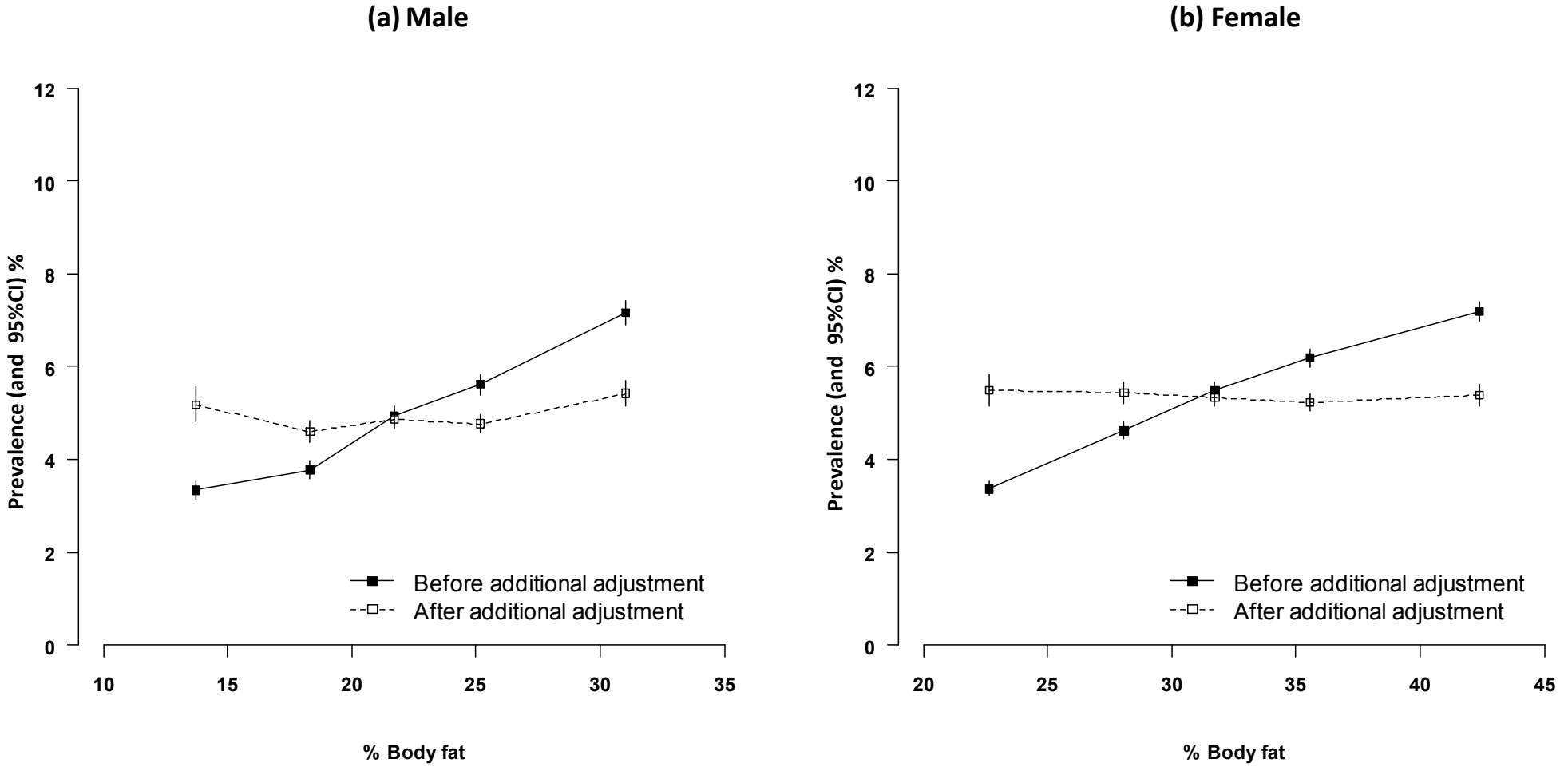
Figure 4.1.16 Prevalence of diabetes by BMI quintile before† and after‡ additional adjustment for waist hip ratio, by sex



†"Before"= basic association (i.e. adjusted for age, area, income, education, occupation, smoking status, alcohol use, physical activity (MET-hours/day), and family history of diabetes)

‡"After"=additionally adjusted for waist hip ratio

Figure 4.1.17 Prevalence of diabetes by percentage body fat quintile before† and after‡ additional adjustment for WC + HC, by sex

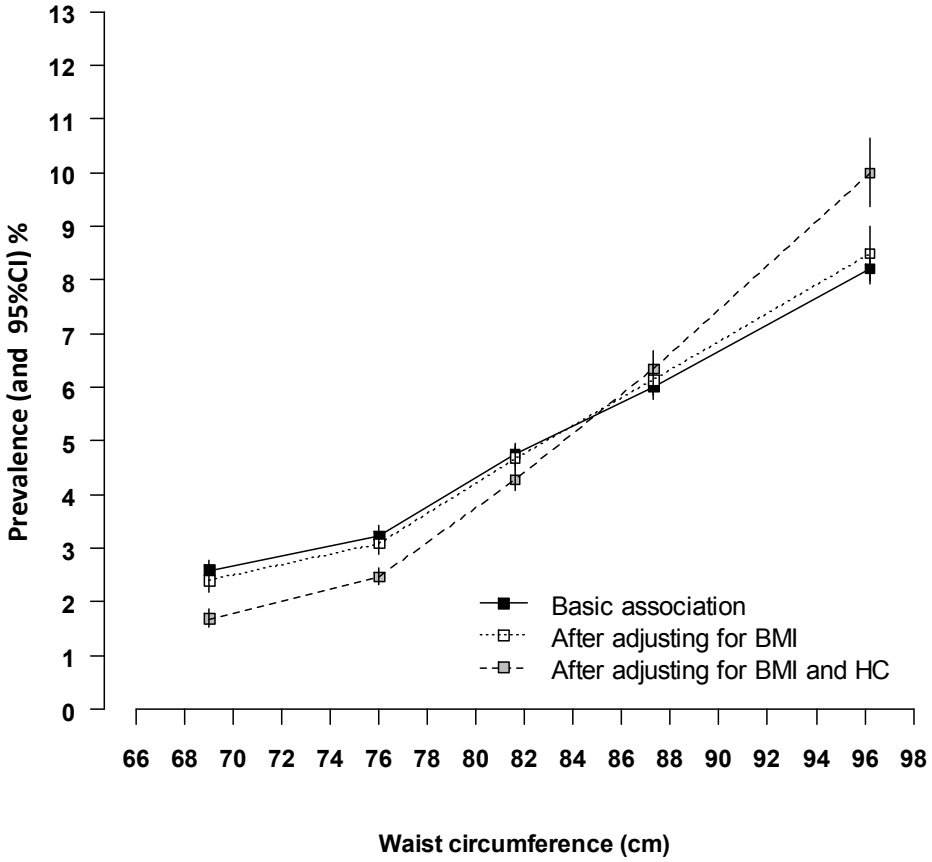


†"Before"= basic association (i.e. adjusted for age, area, income, education, occupation, smoking status, alcohol use, physical activity (MET-hours/day), and family history of diabetes)

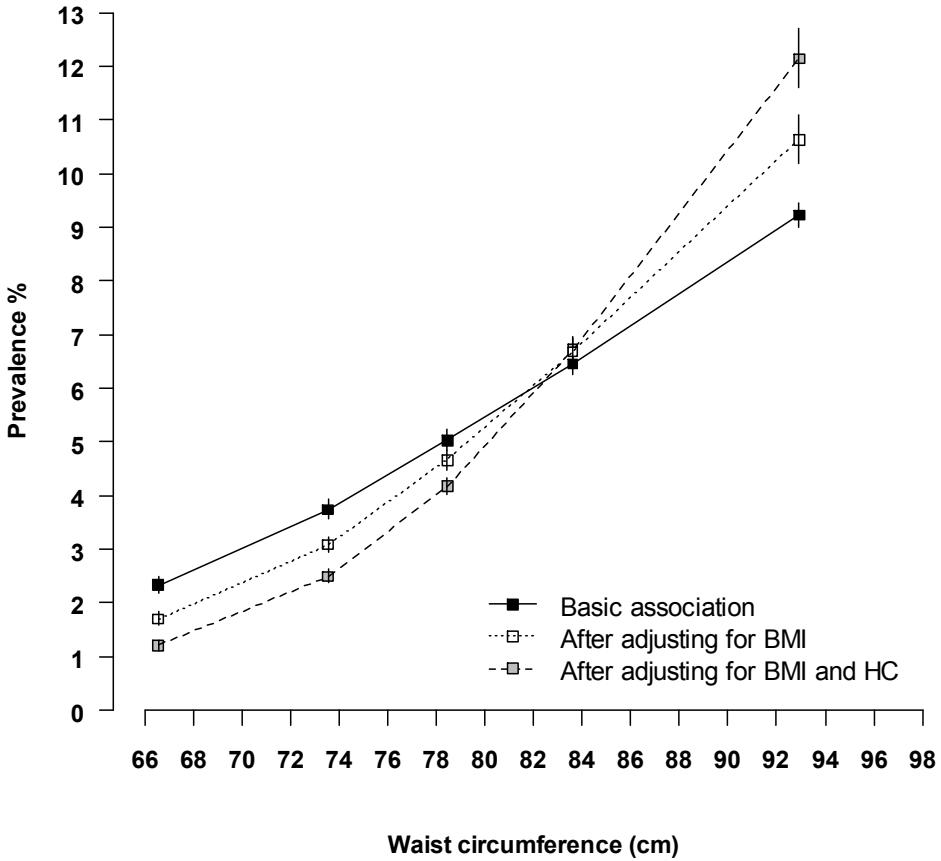
‡"After"=additionally adjusted for waist circumference and hip circumference

Figure 4.1.18 Prevalence of diabetes by waist circumference quintile before† and after‡ additional adjustment for BMI + HC, by sex

(a) Male **(b) Female**



Prevalence (and 95%CI) %

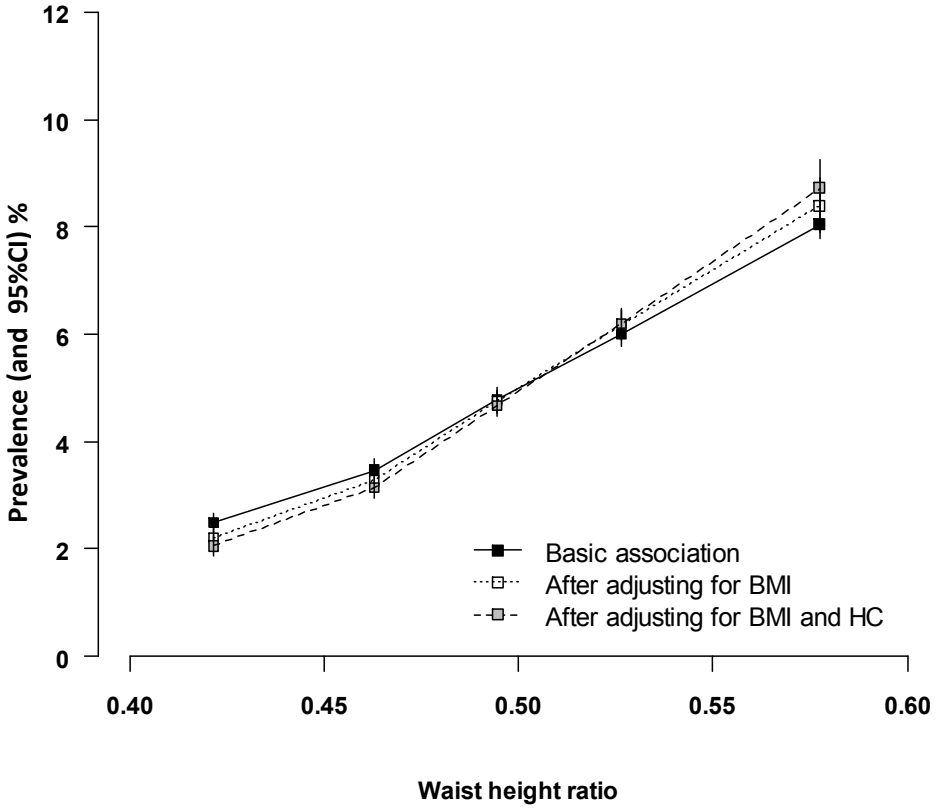


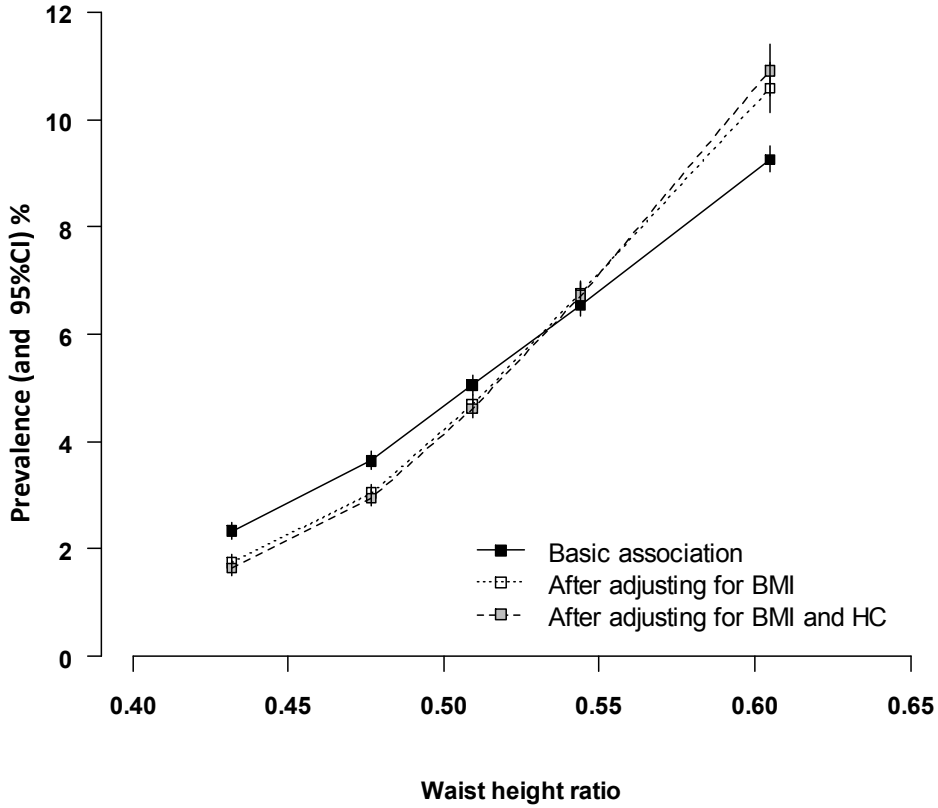
†"Before"= basic association (i.e. adjusted for age, area, income, education, occupation, smoking status, alcohol use, physical activity (MET-hours/day), and family history of diabetes)

‡"After"=additionally adjusted for BMI, or adjusted for BMI and hip circumference simultaneously

Figure 4.1.19 Prevalence of diabetes by WHtR quintile before† and after‡ additional adjustment for BMI + HC, by sex

(a) Male **(b) Female**



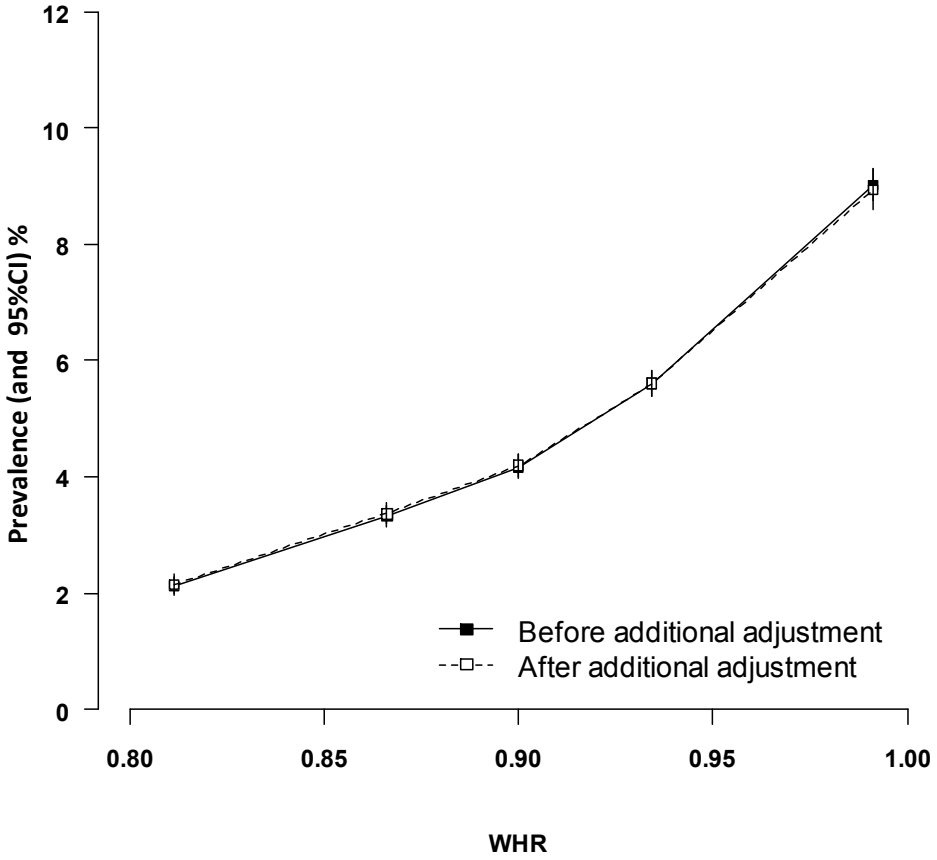


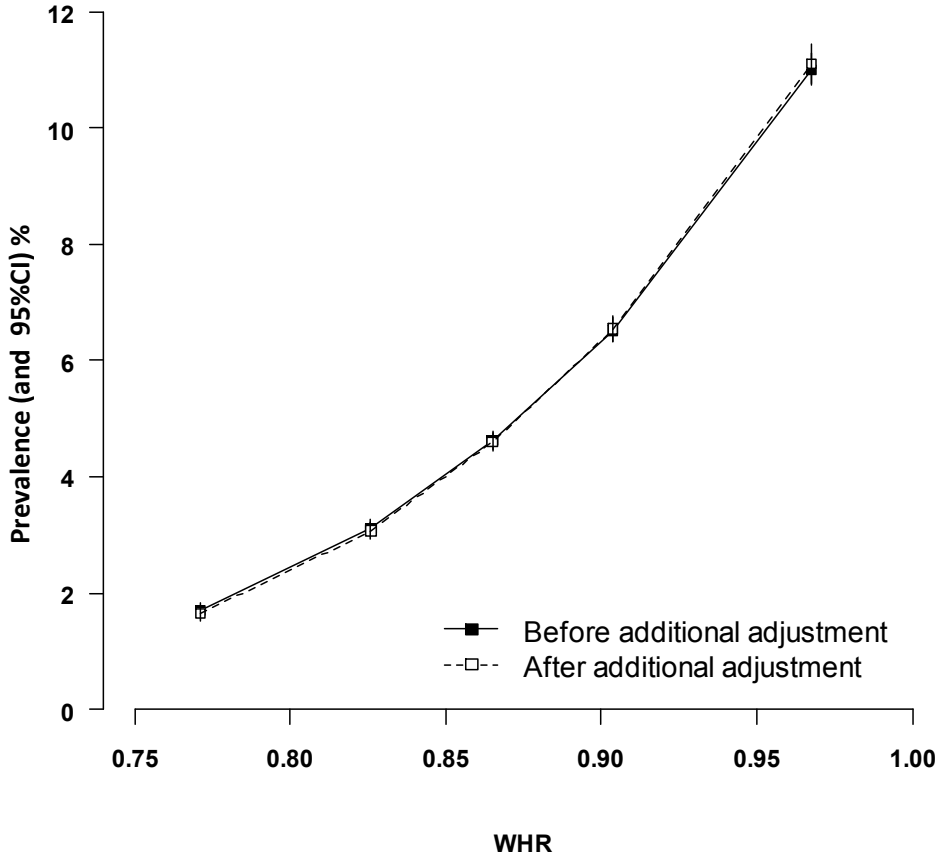
†"Before"= basic association (i.e. adjusted for age, area, income, education, occupation, smoking status, alcohol use, physical activity (MET-hours/day), and family history of diabetes)

‡"After"=additionally adjusted for BMI, or adjusted for BMI and hip circumference simultaneously

Figure 4.1.20 Prevalence of diabetes by WHR quintile before† and after‡ additional adjustment for BMI, by sex

(a) Male **(b) Female**



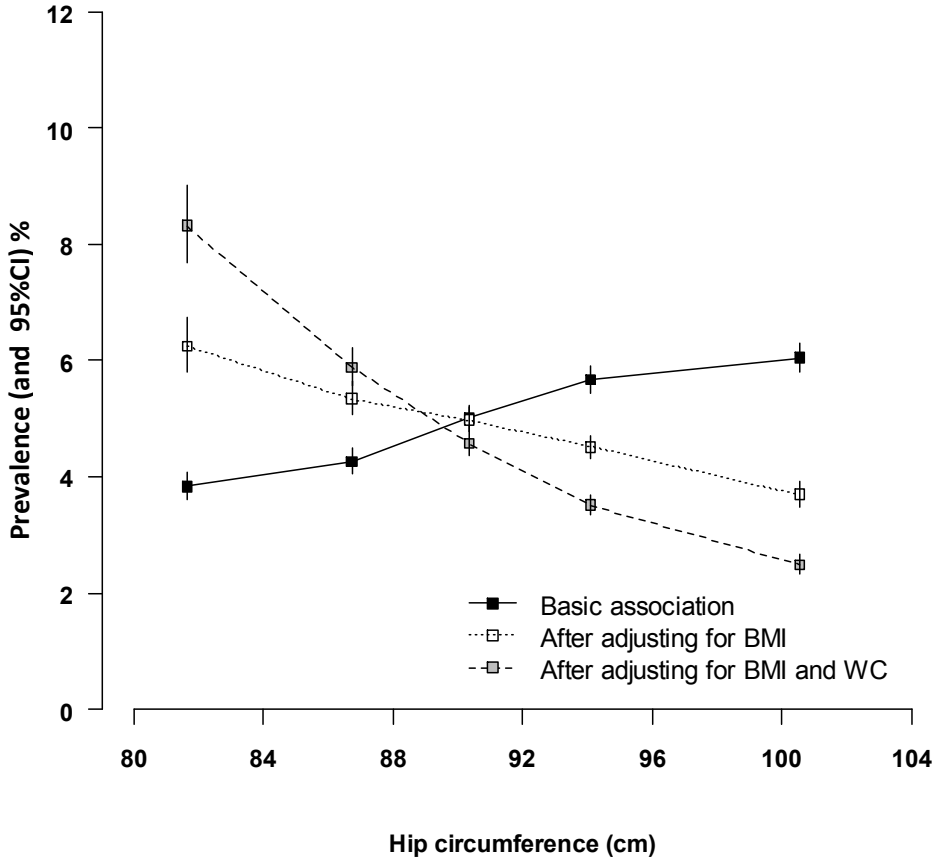


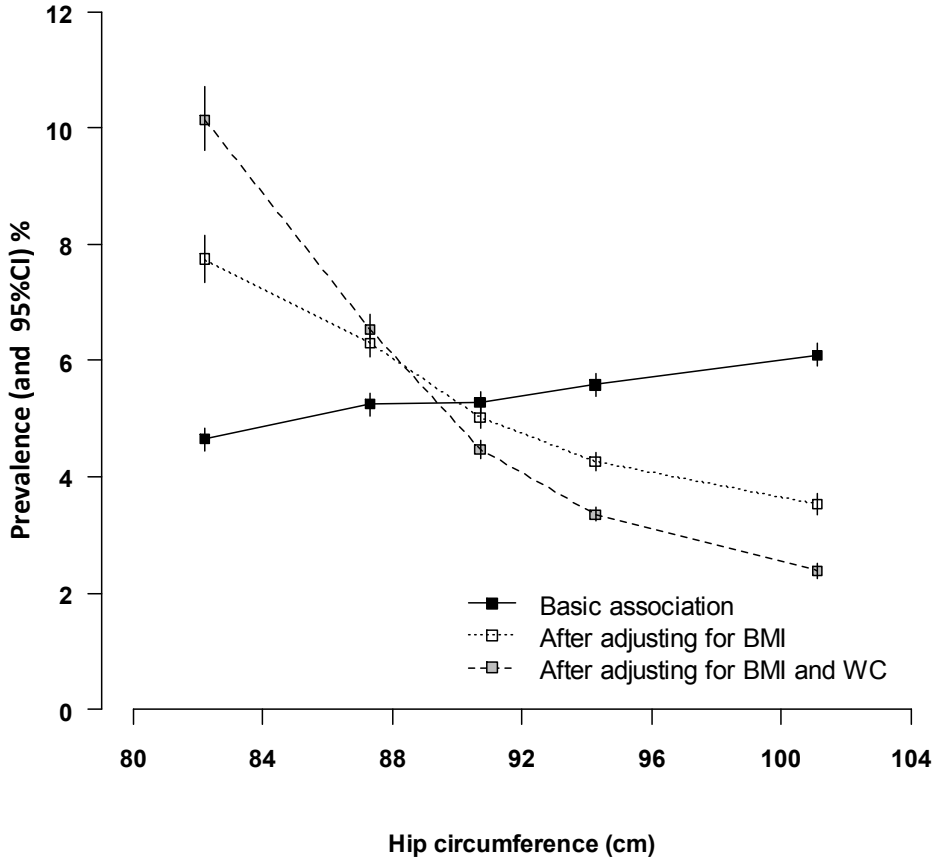
†"Before"= basic association (i.e. adjusted for age, area, income, education, occupation, smoking status, alcohol use, physical activity (MET-hours/day), and family history of diabetes)

‡"After"=additionally adjusted for BMI

Figure 4.1.21 Prevalence of diabetes by hip circumference quintile before† and after‡ additional adjustment for BMI +WC, by sex

(a) Male **(b) Female**

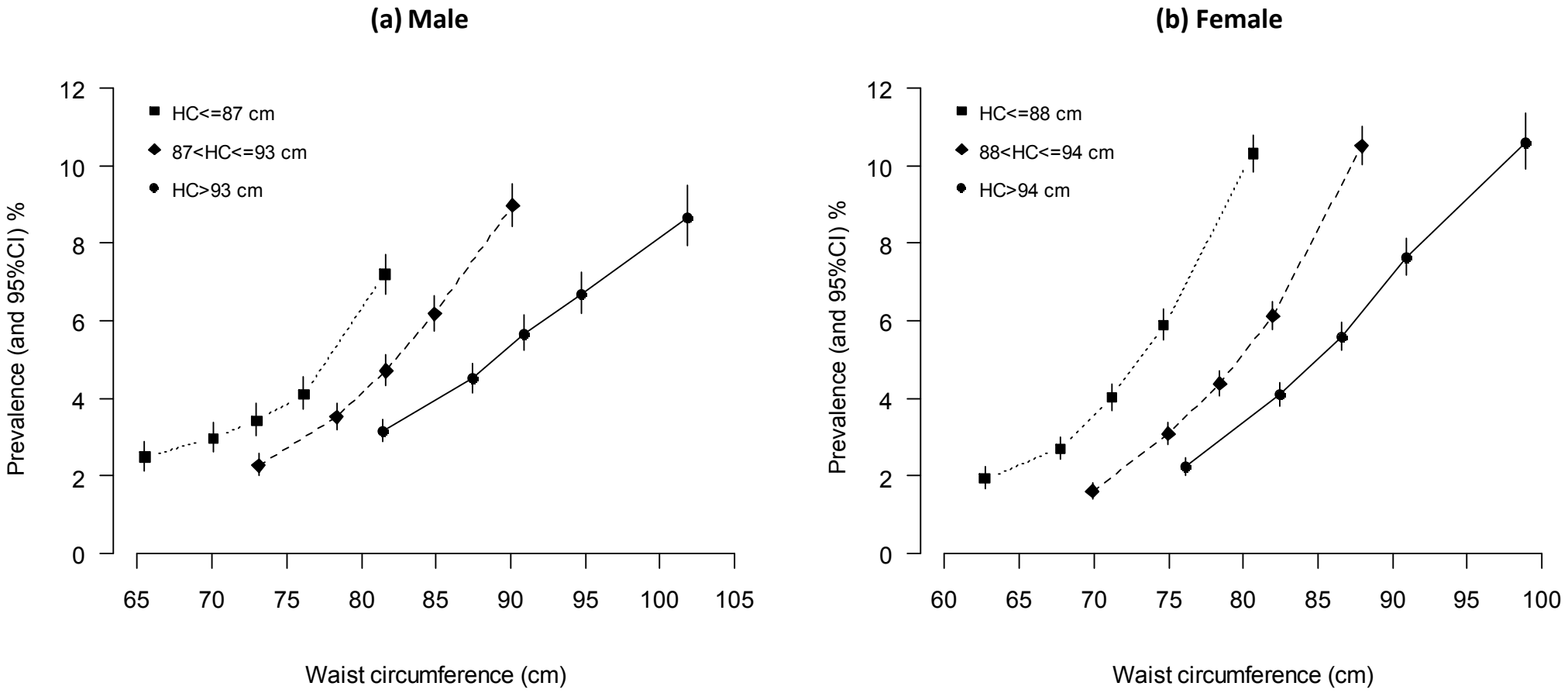




†"Before"= basic association (i.e. adjusted for age, area, income, education, occupation, smoking status, alcohol use, physical activity (MET-hours/day), and family history of diabetes)

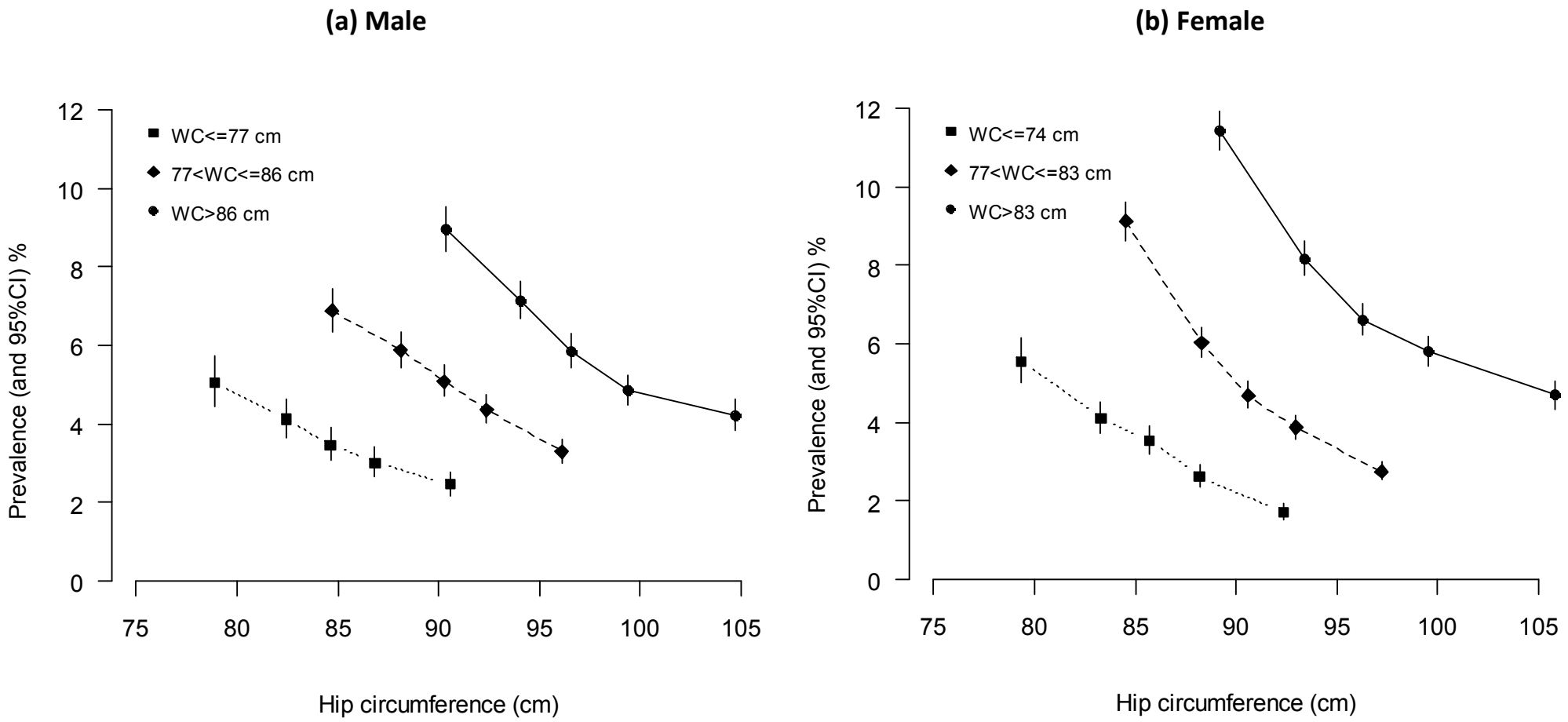
‡"After"=additionally adjusted for BMI, or adjusted for BMI and waist circumference simultaneously

Figure 4.1.22 Prevalence† of diabetes by waist quintile in each hip circumference tertile, by sex



† Adjusted for age, area, household income, education, occupation, physical activity (MET-hours/day), alcohol consumption, smoking status, family history of diabetes and BMI, stratified by hip circumference tertile

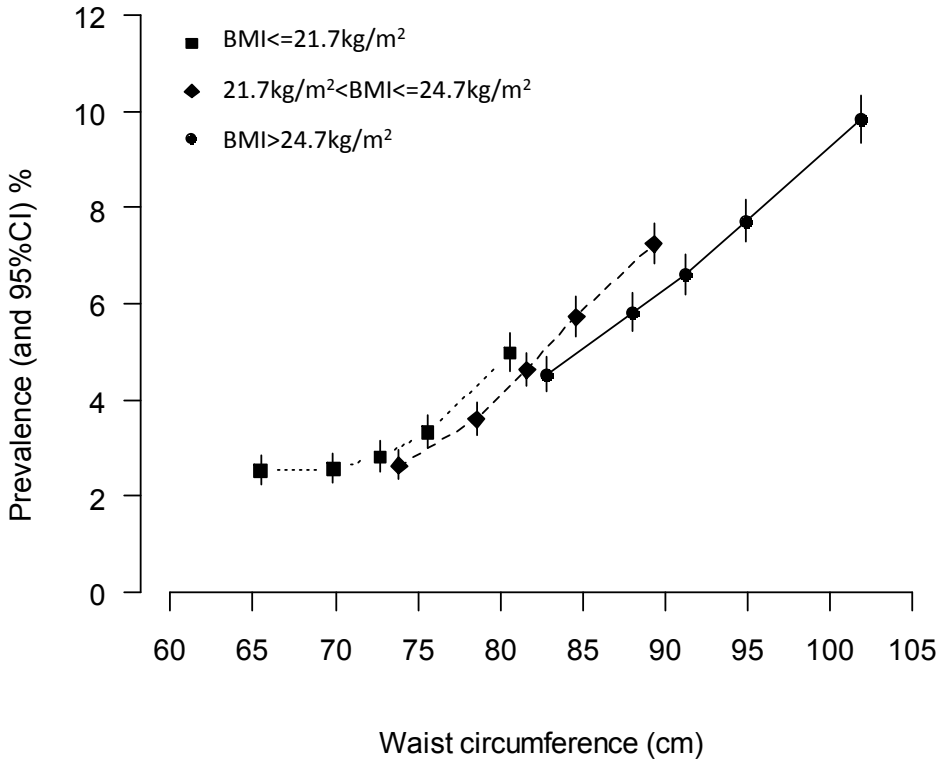
Figure 4.1.23 Prevalence† of diabetes by hip quintile in each waist circumference tertile, by sex

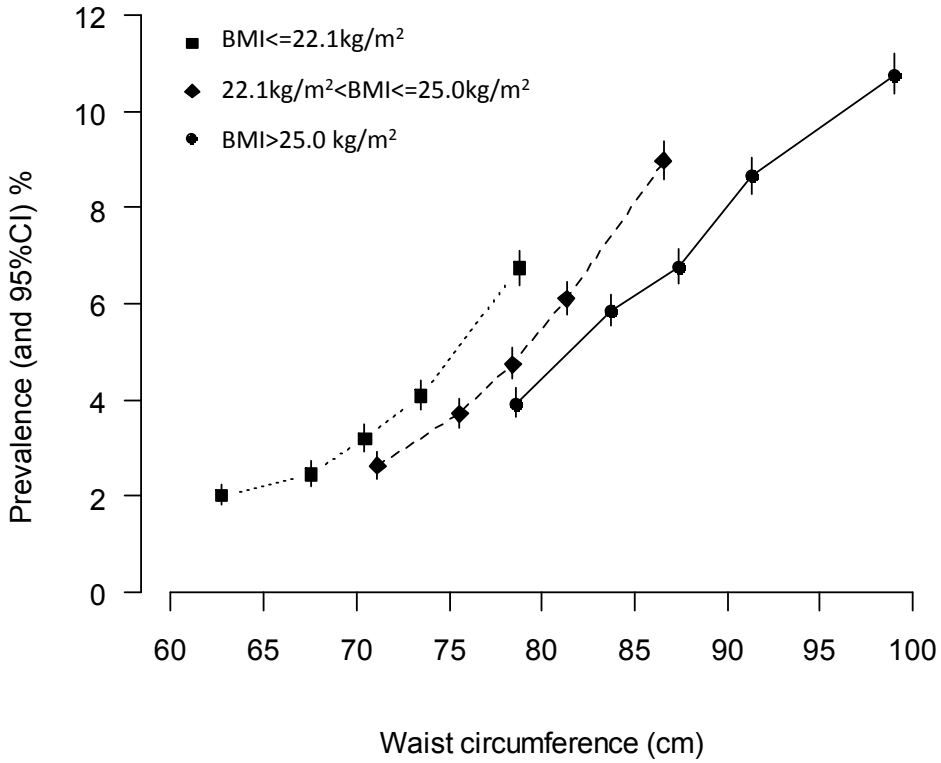


† Adjusted for age, area, household income, education, occupation, physical activity (MET-hours/day), alcohol consumption, smoking status, family history of diabetes and BMI, stratified by waist circumference tertile

Figure 4.1.24 Prevalence† of diabetes by waist circumference quintile in each BMI tertile, by sex

(a) Male **(b) Female**





† Adjusted for age, area, household income, education, occupation, physical activity (MET-hours/day), alcohol consumption, smoking status, and family history of diabetes, stratified by BMI tertile

4.2 Results: event verification sub-study

4.2.1 Basic characteristics of the sample population

Overall, a total of 1,170 cases of incident diabetes cases were selected in the "essential list" for data retrieval and collection from the 10 regional centres. The number selected in each area was roughly proportional to the total number of events reported in each area in the follow up period (detailed in Section 3.6). In case medical records were unavailable for collection or missing, backup lists with a total of 1,129 events were provided to the regional centres at the same time to ensure that required quantity of medical notes could be met.

Table 4.2.1 presents the clinical characteristics of the incident diabetes cases retrieved for event adjudication. Overall, 22.1%, 41.8% and 36.1% of the events for adjudication were retrieved from tier 1 (lowest level), tier 2 (medium level) and tier 3 (highest level) hospitals, respectively. More than 90% of the diabetic patients were from endocrinology or internal medicine department, and 48.9% with a discharge summary having diabetes as main diagnosis. Of those reviewed, 79.7% didn't have known diabetes history at hospital admission, and 68.4% had no known diabetes-related complications. With respect to diagnostic criteria, 87.7% of the patients were tested for fasting plasma glucose; 41.8% and 38.4% undertook random plasma glucose test and HbA1c test, respectively; 12.9% of the patients were tested for OGTT, and 19.4% were tested for urine glucose. Moreover, about 2.5% of the selected cases were tested for islet β cell antibodies as part of procedures for diagnosing type 1 diabetes. All the patients were on at least one type of medication, among which, 56.8% were using oral hypoglycaemic

agent, 47.4% were using insulin, and about 6.7% using traditional Chinese medicine. It should be noted that these categories were not mutually exclusive, for example: 21.7% of the patients were using both insulin and oral hypoglycaemic agent, and 4.5% of the patients were using both oral hypoglycaemic agent and traditional Chinese medicine.

4.2.2 Evaluation of medical notes retrieval process

Complete medical notes for 831 cases in the follow-up period between October 2005 and September 2011 were collected for adjudication, among which, 638 cases were from chronic disease reporting system and 193 cases were from health insurance databases. As shown in Table 4.2.2, overall, 76.3% of the medical notes were retrieved from the essential list, with the proportion being higher in urban than in rural areas (80.6% versus 71.3%). More medical notes in essential lists were retrieved from higher tiers of hospitals compared to lower tiers of hospitals. And the proportion of notes retrieved from essential list was much higher for reporting through health insurance system (97.9%) than for reporting through chronic disease surveillance system (69.7%).

The proportion of successful matching (shown in Table 4.2.3 and 4.2.4) is defined as the date and diagnosis shown on the medical notes match exactly to the event reported in the CKB follow-up database. The proportion varied across areas, from the lowest of 41.1% in Sichuan to 100% in Qingdao, with an average of 79.1%. The type of reporting source and geographic locations significantly affected the matching rate (chronic disease reporting 74.8% versus health insurance 93.3%; urban 89.2% versus rural 67.4%). Moreover, the top-ranking (tier 3) hospitals had much higher matching rate compared with low ranking (tier 1) hospital (95.3% versus 58.2%).

Of the 831 diabetes cases collected, 14 (1.7%) were pre-diabetes in the hospital discharge diagnosis, 4 (0.5%) were type 1 diabetes, 797 (95.9%) were type 2 diabetes, 1 case (0.1%) was latent autoimmune diabetes of adults, and 3 (0.4%) were other type of diabetes (e.g. drug or acute injury induced). (Shown in Table 4.2.5)

4.2.3 Main findings from the event adjudication

For the diabetes events reported originally to the CKB database, 89.2% were classified as type 2 diabetes, 10.3% were unspecified diabetes, and 0.5% were type 1 diabetes. By checking the clinical evidence presented in medical records against diagnostic criteria for subtypes of diabetes, events were adjudicated and re-classified by the adjudicator. As a result, 14 cases (1.7%) were classified as pre-diabetes (IFG/IGT), 4 (0.5%) were type 1 diabetes, 802 (96.5%) were type 2 diabetes, 1 was classified as latent autoimmune diabetes of adulthood (LADA), 3 were re-classified as other diabetes (e.g. drug or acute injury induced), and 7 reported cases s were non-diabetes. A total of 12 reported diabetes events were refuted for its originally reported diagnosis. (Table 4.2.4)

Based on the evidence algorithm and adjudication rules, the detailed adjudication results were shown in Table 4.2.6. Overall, 774 of 831 reported events met the criteria for “definite diabetes”, with a true positive rate of 93.1% (95% CI: 91.2-94.6), 45 events (5.4%, 95%CI: 4.1-7.2) were classified as “probable diabetes” and 12 events were refuted with a false positive rate of 1.4% (95%CI: 0.8-2.5). The highest true positive rates were observed in two study areas (Gansu: 100%, 95%CI: 91.4-100; and Hunan: 100%, 95%CI: 96.5-100), while the lowest was observed in Henan (84.0%, 95%CI: 74.5-90.4). Nevertheless, Harbin and Haikou were found to have the highest false positive rates, with a proportion of 3.0% (95%CI: 1.1-7.4) and 4.7% (95%CI: 1.3-15.5) respectively.

Table 4.2.7 showed the adjudication results by tier of hospital, area and reporting source. Both true positive rates and false positive rates were higher in urban areas (93.7% and 2.0%) compared to rural areas (92.5% and 0.8%). In both urban and rural areas, higher levels of hospitals generally had better validity of diabetes report. The true positive rates increased from 89.7% (95%CI: 84.5-93.3) in the lowest tier of hospital (i.e. tier 1 level) to 96.0% (95%CI: 93.1-97.7) in the highest tier of hospital (i.e. tier 3 level). Meanwhile, the proportion of "probable diabetes" decreased from 9.8% (95%CI: 6.3-15.0) in tier 1 hospitals to 1.7% (95%CI: 0.7-3.9) in tier 3 hospitals. The highest false positive rate was also observed in tier 3 hospitals (2.3%, 95%CI: 1.1-4.7), compared to tier 1 hospitals (0.5%, 95%CI: 0.1-2.9). In addition, despite that both reporting sources showed high validity, the events reported by health insurance data had a significantly higher true positive rates (97.4%, 95%CI: 94.1-98.9) compared to chronic disease reporting (91.8%, 95%CI: 89.4-93.7).

Table 4.2.1 Basic clinical characteristics of diabetes cases for event adjudication

	N	%
Total	831	100%
Tier of hospital†		
Tier 1	184	22.1%
Tier 2	347	41.8%
Tier 3	300	36.1%
Department of admission		
Endocrinology	167	20.1%
Internal medicine	608	73.2%
Traditional Chinese medicine	92	11.1%
Other	53	6.4%
Discharge diagnosis		
Diabetes as main diagnosis	406	48.9%
Diabetes not as main diagnosis	412	50.7%
Duration of diabetes		
No diabetes history	662	79.7%
≤ 1 year	42	5.1%
1-5 years	56	6.7%
> 5 years	22	2.6%
Unknown	49	5.9%
Number of diabetes complications		
None/unknown	568	68.4%
1	163	19.6%
2	83	10.0%
≥3	17	2.0%
Type of clinical tests performed		
Fasting plasma glucose	729	87.7%
OGTT	107	12.9%
Random plasma glucose	347	41.8%
HbA1c	319	38.4%
Urine	161	19.4%
Islet β cell antibodies	21	2.5%
None/unknown	16	1.9%
Treatment given		
Oral hypoglycemic agent	472	56.8%
Insulin	394	47.4%
Traditional Chinese medicine	56	6.7%

†Tier 3 represents the highest level of hospital, and tier 1 represents the lowest level

Table 4.2.2 Summary of data retrieval for event adjudication, by tier of hospital†, area and reporting source

	No. of retrieved medical notes			% of notes retrieved from essential list	No. of events in essential and backup lists			% of essential list retrieved
	No. from essential list	No. from backup list	Total		No. in essential list	No. in backup list	Total	
Hospital level								
Tier 1	133	51	184	72.3%	427	494	921	31.1%
Tier 2	232	115	347	66.9%	404	459	863	57.4%
Tier 3	269	31	300	89.7%	339	176	515	79.4%
Area								
Urban	358	86	444	80.6%	557	379	936	64.3%
Rural	276	111	387	71.3%	613	750	1363	45.0%
Reporting source								
Chronic disease report	445	193	638	69.7%	960	1122	2082	46.4%
Health insurance	189	4	193	97.9%	210	7	217	90.0%
Total	**634**	**197**	**831**	**76.3%**	**1170**	**1129**	**2299**	**54.2%**

†Tier 3 represents the highest level of hospital, and tier 1 represents the lowest level

Table 4.2.3 Proportion of retrieved medical records which were successfully matched to the long-term follow-up data, by area and reporting source

	Chronic disease reporting (%)	Health insurance (%)	Total (%)
Area			
Qingdao (urban)	-	100.0%	100.0%
Harbin (urban)	100.0%	96.4%	98.5%
Haikou (urban)	95.3%	-	95.3%
Suzhou (urban)	62.7%	66.7%	62.9%
Liuzhou (urban)	95.3%	-	95.3%
Sichuan (rural)	41.1%	-	41.1%
Gansu (rural)	0.0%	85.0%	82.9%
Henan (rural)	62.9%	81.8%	65.4%
Zhejiang (rural)	70.5%	87.5%	71.8%
Hunan (rural)	67.8%	94.7%	72.6%
Total	**74.8%**	**93.3%**	**79.1%**

Table 4.2.4 Proportion of retrieved medical records which were successfully matched to the long-term follow-up data, by area and tier of hospital†

	Urban (%)	Rural (%)	Total (%)
Tier 1	44.0%	63.4%	58.2%
Tier 2	91.5%	68.3%	76.1%
Tier 3	96.4%	82.6%	95.3%
Total	**89.2%**	**67.4%**	**79.1%**

†Tier 3 represents the highest level of hospital, and tier 1 represents the lowest level.

Table 4.2.5 Consistency between reported discharge diagnosis and independently adjudicated diagnosis

	Adjudicated							
Reported	Pre-diabetes	Type 1 DM	LADA	Type 2 DM	Gestational	Other diabetes	Non-diabetes	Reported total
Type 1 DM	-	3	-	1	-	-	-	4
Type 2 DM	14	-	1	726	-	-	-	741
Not specified	-	1	-	75	-	3	7	86
Adjudicated total	14	4	1	802	-	3	7	831

Table 4.2.6 No.(%) of cases adjudicated as definite diabetes, probable diabetes and non-diabetes, by area and reporting source

		Definite diabetes			Probable diabetes			Non- diabetes		
	No. of cases	Disease reporting	Health insurance	Total (%)	Disease reporting	Health insurance	Total (%)	Disease reporting	Health insurance	Total (%)
Area										
Qingdao	56	-	54	96.4% (87.8-99.0)	-	2	3.6% (1.0-12.1)	-	-	0.0% (0-6.4)
Harbin	134	69	55	92.5% (86.8-95.9)	6	-	4.5% (2.1-9.5)	3	1	3.0% (1.1-7.4)
Haikou	43	40	-	93.0% (81.4-97.6)	1	-	2.3% (0.4-12.0)	2	-	4.7% (1.3-15.5)
Suzhou	105	93	3	91.4% (84.5-95.4)	7	-	6.7% (3.3-13.2)	2	-	1.9% (0.5-6.7)
Liuzhou	106	102	-	96.2% (90.7-98.5)	3	-	2.8% (1.0-7.9)	1	-	0.9% (0.2-5.1)
Sichuan	56	54	-	96.4% (87.8-99.0)	2	-	3.6% (1.0-12.2)	-	-	0.0% (0-6.4)
Gansu	41	1	40	100.0% (91.4-100)	-	-	0.0% (0-8.6)	-	-	0.0% (0-8.6)
Henan	81	58	10	84.0% (74.5-90.4)	11	1	14.8% (8.7-24.1)	1	-	1.2% (0.2-6.6)
Zhejiang	103	82	7	86.4% (78.4-91.7)	12	-	11.7% (6.8-19.3)	1	1	1.9% (0.5-6.7)
Hunan	106	87	19	100.0% (96.5-100)	-	-	0.0% (0-3.5)	-	-	0.0% (0-3.5)
Total	**831**	**586**	**188**	**93.1% (91.2-94.6)**	**42**	**3**	**5.4% (4.1-7.2)**	**10**	**2**	**1.4% (0.8-2.5)**

Table 4.2.7 No. (%) of cases adjudicated as definite diabetes, probable diabetes and non-diabetes by area, tier of hospital† and reporting source

	No. cases	Definite diabetes (n)	% (95% CI)	Probable diabetes (n)	% (95% CI)	Non-diabetes (n)	% (95% CI)
Hospital level							
Tier 1	184	165	89.7% (84.5-93.3)	18	9.8% (6.3-15.0)	1	0.5% (0.1-2.9)
Tier 2	347	321	92.5% (89.2-94.8)	22	6.3% (4.2-9.4)	4	1.2% (0.4-3.0)
Tier 3	300	288	96.0% (93.1-97.7)	5	1.7% (0.7-3.9)	7	2.3% (1.1-4.7)
Area							
Urban	444	416	93.7% (91.0-95.6)	19	4.3% (2.8-6.6)	9	2.0% (1.1-3.8)
Rural	387	358	92.5% (89.4-94.7)	26	6.7% (4.6-9.6)	3	0.8% (0.2-2.3)
Reporting source							
Chronic disease	638	586	91.8% (89.4-93.7)	42	6.6% (4.9-8.8)	10	1.6% (0.8-2.9)
Health insurance	193	188	97.4% (94.1-98.9)	3	1.6% (0.6-4.5)	2	1.0% (0.3-3.6)
Total	**831**	**774**	**93.1% (91.2-94.6)**	**45**	**5.4% (4.1-7.2)**	**12**	**1.4% (0.8-2.5)**

†Tier 3 represents the highest level of hospital, and tier 1 represents the lowest level.

4.3 Results: prospective analyses

4.3.1 Incident diabetes cases in the follow-up of the CKB Study

During a mean 5.1 years of follow-up, a total number of 2,912 (1,070 men and 1,842 women) incident cases of diabetes were identified among participants who were free of diabetes at recruitment. Of them, 53 cases (2%) were reported by the death registry and 2,859 (98%) were reported by the chronic disease reporting system. No data was available from the health insurance database for the present prospective analysis.

The crude incidence rates were 106 per 100,000 person-years and 126 per 100,000 person-years for men and women respectively. In males, the incidence rates increased from 34 per 100,000 person-years in the youngest age group (30-39 years) to 174 per 100,000 person-years in the highest age group (70-79 years), and in females, it increased from 32 per 100,000 person-years to 247 per 100,000 person-years. The diabetes incidence rate was higher in rural areas (males: 125 per 100,000 person-years; females: 150 per 100,000 person-years) than in urban areas (males: 79 per 100,000 person-years; females: 94 per 100,000 person-years) (Table 4.3.1).

It should be noted that the diabetes incidence rate of the urban city of Qingdao was unusually low (2 cases only, incidence rate=1.2 per 100,000 person-years). This is due to (1) late entry of the study area into the cohort; (2) unavailability of the disease surveillance system in the initial years of follow-up. Consequently, it was decided that all the data from Qingdao was excluded from the prospective analyses in this thesis, after which the difference between urban and rural was attenuated significantly (urban males: 97.5 per 100,000 person-years; urban females: 109.6 per 100,000 person-years).

Additional analyses using the latest health insurance data also confirmed the same pattern that the diabetes incidence rate was higher in rural areas and among female participants (data not shown).

Other baseline demographic, socioeconomic, lifestyle and anthropometric characteristics of the non-diabetic study population used in prospective analyses are shown in Tables 4.1.1-4.1.6, and were described previously in Section 4.1.

4.3.2 Basic, independent and joint associations of adiposity with diabetes incidence

4.3.2.1 Basic associations

The crude incidence rates of diabetes by quintile of BMI, percentage body fat, waist circumference, hip circumference, waist hip ratio and waist height ratio are shown in Tables 4.3.2-4.3.7, respectively. In general, the incidence rates increased across all categories of BMI, waist circumference, hip circumference, waist hip ratio and waist height ratio, and the incident rates within each quintile were generally higher in women than in men.

After adjusting for age, area, education, occupation, household income, alcohol consumption, smoking status, physical activity and family history of diabetes, each of the adiposity measures was strongly and positively associated with the risk of diabetes in both males and females. However, the strength of association appeared somewhat stronger in males than in females.

4.3.2.1.1 BMI

To examine the association between BMI values and the risk of diabetes, BMI was divided into 8 categories using cut-off points of 18.5, 20, 22, 24, 26, 28 and 30 kg/m^2. Figure 4.3.1 shows that the risk of diabetes increased progressively with increasing BMI in both sexes (except for those with a BMI less than 18.5 kg/m^2). The multivariable-adjusted hazard ratios associated with the 8 categories (<18.5 kg/m^2, 18.5-20 kg/m^2 [reference group], 20-22 kg/m^2, 22-24 kg/m^2, 24-26 kg/m^2, 26-28 kg/m^2, 28-30 kg/m^2 and >30 kg/m^2) were 1.22 (95%CI: 0.83-1.80), 1.00 (95%CI: 0.74-1.34), 1.38 (95%CI: 1.15-1.65), 2.16 (95%CI: 1.87-2.49), 3.61 (95%CI: 3.18-4.09), 5.78 (95%CI: 5.07-6.60), 8.34 (95%CI: 6.99-9.96) and 14.73 (95%CI: 11.93-18.18) in males. The association in females appeared less strong, with multivariable-adjusted hazard ratios of 1.07 (95%CI: 0.78-1.44), 1.00 (95%CI: 0.78-1.29), 1.51 (95%CI: 1.31-1.73), 1.95 (95%CI: 1.74-2.19), 3.31 (95%CI: 3.02-3.64), 4.91 (95%CI: 4.44-5.43), 6.11 (95%CI: 5.38-6.96) and 8.54 (95%CI: 7.41-9.85) from the lowest to the highest BMI category (p for trend < 0.0001 in both sexes).

BMI was also divided into quintiles and as shown in Table 4.3.2, the age- and area-adjusted hazard ratios of BMI increased from 1.00 (95%CI: 0.82-1.22) in the lowest quintile to 6.40 (95%CI: 5.81-7.06) in the highest quintile in males, and increased from 1.00 (95%CI: 0.85-1.17) to 5.84 (95%CI: 5.42-6.30) in females (both p for trend < 0.0001). After further adjustment for education, occupation, household income, alcohol consumption, smoking status, physical activity and family history of diabetes, the associations remained unchanged.

Using the WHO cut-offs for obesity,[126] the multivariable-adjusted hazard ratios for diabetes in normal (BMI<25 kg/m^2), overweight (25 kg/m^2 ≤ BMI <30 kg/m^2) and obese (BMI ≥ 30 kg/m^2) men were 1.00 (95%CI: 0.91-1.10), 3.38 (95%CI: 2.95-3.87) and 7.79 (95%CI: 6.31-9.62). The same hazard ratios for women were 1.00 (95%CI: 0.93-1.07), 2.92 (95%CI: 2.65-3.23) and 4.75 (95%CI: 4.12-5.48), respectively. When applying the Chinese cut-offs for obesity,[91] the multivariable-adjusted hazard ratios for diabetes in normal (BMI<24 kg/m^2), overweight (24 kg/m^2 ≤ BMI <28 kg/m^2) and obese (BMI ≥ 28 kg/m^2) groups were 1.00 (95%CI: 0.90-1.11), 2.72 (95%CI: 2.50-2.98) and 6.22(95%CI: 5.42-7.14) in men, and were 1.00 (95%CI: 0.92-1.09), 2.49 (95%CI: 2.33-2.66) and 4.45 (95%CI: 4.04-4.90) in women.

The multivariable-adjusted hazard ratios for per 1 standard deviation (3.21 kg/m^2 in men and 3.41 kg/m^2 in women) increment in BMI were 1.99 (95%CI: 1.88-2.11) in males and 1.78 (95%CI: 1.71-1.86) in females (Figure 4.3.8). The hazard ratio for both sexes combined was 1.85 (95%CI: 1.79-1.91).

4.3.2.1.2 Percentage body fat

There was a log-linear association between percentage body fat and diabetes risk in both sexes, as shown in Figure 4.3.2. In males, those in the highest percentage body fat group (>35%) had a fourteen times (95%CI: 11.45-17.66) as high risk of diabetes as those in the lowest group (<15%); in women, there was an 8-fold (95%CI: 6.98-9.26) difference in risk between the highest body fat percentage group (>45%) and the lowest group (<25%).

The multivariable-adjusted hazard ratios across percentage body fat quintiles increased from 1.00 (95%CI: 0.81-1.23) to 6.34 (95%CI: 5.72-7.01) in males, and from 1.00 (95%CI:

0.85-1.17) to 5.67 (95%CI: 5.26-6.10) in females (Table 4.3.3, both p for trend < 0.0001). It was estimated that 1-standard deviation increment in percentage body fat (6.18 in men and 7.04 in women) was associated with an 85% (95%CI: 75%-95%) increase in diabetes risks in men, and a 77% (95%CI: 70%-85%) increased risk in women (Figure 4.3.8).

4.3.2.1.3 Waist circumference

Waist circumference was also associated with diabetes incidence in both sexes, and the association also appeared stronger in men than in women. The multivariable-adjusted hazard ratios in 7 waist categories (<70 cm, 70-75 cm, 75-80 cm, 80-85 cm, 85-90 cm, 90-95 cm, >95 cm) increased monotonically from 1.00 (95%CI: 0.77-1.30) to 11.17 (95%CI: 9.66-12.90) in males, and from 1.00 (95%CI: 0.84-1.18) to 8.75 (95%CI: 7.61-10.05) in females (Figures 4.3.3).

After controlling for all potential confounders, the hazard ratios across waist quintiles were 1.00 (95%CI: 0.83-1.21), 1.44 (95%CI: 1.21-1.72), 2.42 (95%CI: 2.08-2.80), 4.20 (95%CI: 3.74-4.70) and 7.48 (95%CI: 6.71-8.35) in males, and were 1.00 (95%CI: 0.86-1.16), 1.53 (95%CI: 1.34-1.74), 2.20 (95%CI: 1.97-2.47), 3.42 (95%CI:3.12-3.75) and 6.16 (95%CI: 5.71-6.66) in females (Table 4.3.4, both p for trend < 0.0001). Compared to BMI, waist circumference showed a stronger association with diabetes incidence when comparing the highest vs. lowest quintiles, in both men and women.

Based on Figure 4.3.8, it was estimated that per 1 standard deviation increment (9.66 in men and 9.35 cm in women) in waist circumference was associated with 2.03 (95%CI: 1.91-2.16) increased risk of diabetes in males and 1.86 (95%CI: 1.78-1.94) increased risk

in females. For males and females combined, it was 1.91 (95%CI: 1.85-1.98), which was somewhat stronger than that for BMI.

4.3.2.1.4 Hip circumference

The baseline hip circumference also predicted diabetes in both sexes (Figure 4.3.4). However, the association of diabetes with hip circumference was weaker than with all other adiposity measures. After adjusting for confounders, males with a hip circumference of 90-95 cm had a roughly tripled risk (HR=2.73, 95%CI: 2.46-3.03) for diabetes compared to males with a hip circumference of less than 85 cm (reference group). For those with a hip circumference of greater than 100 cm, the hazard ratio increased to 6.26 (95%CI: 5.13-7.65). Similarly, women with a hip circumference of 90-95cm had a doubled risk (HR=2.23, 95%CI: 2.05-2.42) for diabetes, compared to those with a hip circumference of less than 85 cm; and the hazard ratio increased to 3.94 (95%CI: 3.42-4.54) for those with a hip circumference greater than 100 cm.

After the same adjustment for confounders, the hazard ratios from the lowest to the highest quintile increased from 1.00 (95%CI: 0.85-1.18) to 4.53 (95%CI: 3.92-5.23) in males, and from 1.00 (95%CI: 0.89-1.12) to 3.31 (95%CI: 2.98-3.68) in females (Table 4.3.5, both p for trend < 0.0001).

For per 1-standard deviation (6.73 in men and 6.76 cm in women) increment in hip circumference, the hazard ratios for diabetes were 1.76 (95%CI: 1.64-1.88) in males and 1.53 (95%CI: 1.46-1.60) in females, with the combined hazard ratio for both sexes being 1.60 (95%CI: 1.54-1.66).

4.3.2.1.5 Waist hip ratio

The risk of diabetes was strongly and positively associated with waist hip ratio. Males with a waist hip ratio between 0.90 and 0.95 had a tripled risk for diabetes (HR=2.96, 95%CI: 2.63-3.33) compared to those with a waist hip ratio of < 0.85 (reference group). Comparing to the same reference group in females, the risk was about 3.5 times as great (HR=3.52, 95%CI: 3.24-3.84) in those with a waist hip ratio between 0.85 and 0.90. For males with a WHR > 0.95, the risk of diabetes was about 8.6 times as great (HR=8.61, 95%CI: 7.50-9.88) as those in the reference group; and for females with a WHR > 0.95, the risk was more than 7 times as great (HR=7.35, 95%CI: 6.38-8.47) (Figure 4.3.6).

Nevertheless, unlike the cross-sectional associations shown in previous analyses, the strength of association between waist hip ratio and diabetes incidence appeared slightly weaker than several other adiposity measures (e.g. BMI, waist circumference or waist height ratio). The multivariable-adjusted hazard ratios increase from 1.00 (95%CI: 0.81-1.23) in the lowest WHR quintile to 6.76 (95%CI: 6.17-7.42) in the highest WHR quintile in men, and increased from 1.00 (95%CI: 0.82-1.22) to 5.96 (95%CI: 5.56-6.40) in women (Table 4.3.6, both p for trend < 0.0001).

As is shown in Figure 4.3.8, the hazard ratios for per 1 standard deviation (Men: 0.06; women: 0.07) increment in WHR were 1.83 (95%CI: 1.73-1.93) in males and 1.80 (95%CI: 1.72-1.88) in females. Again, unlike the cross-sectional data, the hazard ratio for WHR appeared smaller than that for BMI, waist circumference and waist height ratio in males. In females, the hazard ratio was also smaller than that for waist circumference and waist height ratio, but somewhat greater than that for BMI.

4.3.2.1.6 Waist height ratio

As with other adiposity measures, the risk of diabetes was also strongly and positively associated with waist height ratio (Figure 4.3.7). In males, the hazard ratios increased monotonically from 1.00 (95%CI: 0.83-1.20) in the reference group of WHtR < 0.45 to 11.98 (95%C: 9.82-14.61) in the group of WHtR > 0.60. In females, it increased from 1.00 (95%CI: 0.83-1.20) to 9.01 (95%CI: 8.10-10.03).

The association between waist height ratio and diabetes incidence was analysed based on WHtR quintiles using multivariable-adjusted model (shown in Table 4.3.7). The relative risks increased from 1.00 (95%CI: 0.83-1.21) in the lowest quintile to 7.06 (95%CI: 6.38-7.82) in the highest quintile in males, and from 1.00 (95%CI: 0.85-1.18) to 6.81 (95%CI: 6.31-7.35) in females (both p for trend < 0.0001).

For per 1-standard deviation (0.06 in both sexes) increment in waist height ratio, the hazard ratios for diabetes were 1.98 (95%CI: 1.87-2.10) in males, and 1.89 (95%CI: 1.81-1.97) in females. The combined hazard ratio for both sexes was 1.92 (95%CI: 1.86-1.99) (Figure 4.3.8), which was the strongest among all different anthropometric measures.

4.3.2.2 Independent associations

4.3.2.2.1 Overall adiposity

In addition to the basic models (i.e. adjusting for socio-demographic and lifestyle confounders), the associations between overall adiposity and diabetes incidence were further examined in four different models: additional adjustment of hip circumference only; additional adjustment of waist circumference only; additional adjustment of waist

circumference and hip circumference together; and additional adjustment of waist hip ratio. Results of different models are shown in Tables 4.3.2 and 4.3.3.

BMI

After additionally adjusting for hip circumference, the positive association between BMI and diabetes incidence became stronger (shown in Table 4.3.2). The hazard ratios for the highest BMI quintile increased from 6.43 (95%CI: 5.81-7.10) to 6.98 (95%CI: 6.04-8.06) in males, and from 5.84 (95%CI: 5.42-6.30) to 7.34 (95%CI: 6.59-8.20) in females. In contrast, after controlling for waist circumference, the strength of the association of BMI with diabetes, though remained positive, was greatly attenuated: the hazard ratios for the highest BMI quintile decreased from 6.43 (95%CI: 5.81-7.10) to 2.10 (95%CI: 1.80-2.46) in males and from 5.84 (95%CI: 5.42-6.30) to 2.17 (95%CI 1.94-2.43) in females.

As with waist hip ratio, additionally adjusting for waist and hip circumference had similar attenuating effect on the association of BMI with diabetes. The WC-, HC- and multivariable-adjusted hazard ratios across BMI quintiles were 1.00 (95%CI: 0.73-1.37), 1.02 (95%CI: 0.81-1.28), 1.27 (95%CI: 1.08-1.49), 1.58 (95%CI: 1.38-1.80) and 2.68 (95%CI: 2.26-3.16) in males, and were 1.00 (95%CI: 0.79-1.26), 1.36 (95%CI: 1.16-1.59), 1.50 (95%CI: 1.33-1.69), 2.07 (95%CI: 1.88-2.27) and 3.09 (95%CI: 2.73-3.50) in women (both p for trend < 0.0001, Table 4.3.2).

The WC- and multivariable-adjusted hazard ratios for per 1 standard deviation increment in BMI were also calculated to allow for comparison across different adiposity measures. As shown in Figure 4.3.9, the hazard ratios were 1.52 (95%CI: 1.38-1.68) in

males (SD=3.21kg/m^2) and 1.35 (95%CI: 1.26-1.45) in females (SD=3.41 kg/m^2). The hazard ratio for both sexes combined was 1.40 (95%CI: 1.32-1.48).

Percentage body fat

Similar to BMI, additional adjustment for waist circumference or waist hip ratio also greatly attenuated the association of percentage body fat with diabetes incidence (shown in Table 4.3.3). The association between percentage body fat and diabetes incidence was also attenuated by adjustment for BMI. At any given level of waist circumference, the hazard ratios per 1 standard deviation (men: 6.18%; women: 7.04%) increment in percentage body fat were 1.41 (95%CI: 1.30-1.52) for men and 1.39 (95%CI: 1.31-1.48) in women (Figure 4.3.9). Both BMI and percentage body fat showed similar strength of association with diabetes after adjusting for central adiposity measures.

4.3.2.2.2 Central adiposity

Associations of diabetes with measures of central adiposity (waist circumference, waist hip ratio and waist height ratio) were also assessed after additional adjustment as described previously in Section 3.7.3. Results of respective models are shown in Tables 4.3.4, 4.3.6, 4.3.7, and Figure 4.3.9.

Waist circumference

After additional adjustment for hip circumference, the strength of the association between waist circumference and diabetes incidence was greatly increased (Table 4.3.4). The hazard ratios for the highest waist quintile increased by about 30%, from 7.48 (95%CI: 6.71-8.35) to 9.68 (95%CI: 8.29-11.31) in males, and from 6.16 (95%CI: 5.71-6.66) to 7.88 (95%CI: 7.08-8.77) in females. As expected, an opposite effect was observed

after additional adjustment for BMI, with the hazard ratios for the highest waist quintile decreasing from 7.48 (95%CI: 6.71-8.35) to 3.89 (95%CI: 3.32-4.57) in males and from 6.16 (95%CI: 5.71-6.66) to 3.25 (95%CI 2.90-3.65) in females.

The multivariable and BMI-adjusted hazard ratios for diabetes across waist quintiles were 1.00 (95%CI: 0.74-1.35), 1.35 (95%CI: 1.08-1.68), 1.98 (95%CI: 1.69-2.31), 2.82 (95%CI: 2.50-3.18) and 3.89 (95%CI: 3.31-4.57) in males, and were 1.00 (95%CI: 0.80-1.24), 1.29 (95%CI: 1.11-1.51), 1.63 (95%CI: 1.45-1.84), 2.18 (95%CI: 1.99-2.39) and 3.25 (95%CI: 2.90-3.65) in females (both p for trend < 0.0001, Table 4.3.4).

After adjusting for BMI, the hazard ratios for diabetes associated with 1 standard deviation increment in waist circumference were 1.64 (95%CI: 1.48-1.82) in males and 1.57 (95%CI: 1.46-1.68) in females (Figure 4.3.9). The BMI-adjusted hazard ratios for waist circumference were slightly higher than the BMI-adjusted hazard ratios for waist hip ratio in both sexes; and were about the same level as that for waist height ratio, although these differences were not statistically significant.

Waist hip ratio

Like other central adiposity measures, the association between waist hip ratio and diabetes incidence was greatly attenuated after additionally adjusting for BMI. The attenuation appeared greater than that for waist circumference and waist height ratio. Across WHR quintiles the BMI-adjusted hazard ratios increased from 1.00 (95%CI: 0.78-1.28) to 3.48 (95%CI: 3.10-3.90) in males, and from 1.00 (95%CI: 0.80-1.25) to 3.22 (95%CI: 2.96-3.49) in females (Table 4.3.6, both p for trend < 0.0001). At a given level of BMI, the hazard ratios associated with 1 standard deviation increment in WHR were

1.49 (95%CI: 1.39-1.60) and 1.51 (95%CI: 1.43-1.59) in males and females, respectively (Figure 4.3.9). It appeared that the BMI-adjusted association was less strong than that for other central adiposity measures.

Waist height ratio

After adjusting for BMI, waist height ratio remained a significant predictor for diabetes. The hazard ratios increased from 1.00 (95%CI: 0.74-1.35) in the lowest WHtR quintile to 3.76 (95%CI: 3.21-4.42) in the highest quintiles in males, and from 1.00 (95%CI: 0.80-1.25) to 3.79 (95%CI: 3.38-4.25) in females (Table 4.3.7, both p for trend < 0.0001). The strength of association was similar to that for WC after the same adjustment. The BMI-adjusted hazard ratios for 1 standard deviation increment of WHtR were 1.63 (95%CI: 1.47-1.80) in males and 1.62 (95%CI: 1.50-1.74) in females, which were quantitatively consistent with that for WC (Figure 4.3.9).

4.3.2.2.3 Hip circumference

As described previously, with basic multivariable-adjustment for socio-demographic and lifestyle confounders, hip circumference was positively associated with diabetes incidence. The association was further examined with additional adjustment for BMI and WC.

As shown in Table 4.3.5, the additional adjustment for BMI greatly attenuated the association toward null in males, and turned to an inverse association in females. Additionally adjusting for waist circumference had a similar effect in both sexes, which reversed the originally positive HC-diabetes association to a strongly inverse association. Simultaneously adjusting for BMI and waist circumference in the same model yielded a

more strongly inverse association between hip circumference and diabetes. The BMI- and WC-adjusted hazard ratios decreased from 1.00 (95%CI: 0.79-1.27) in the lowest hip quintile to 0.49 (95%CI: 0.41-0.59) in the highest quintile in males, and from 1.00 (95%CI: 0.85-1.17) to 0.46 (95%CI: 0.40-0.52) in females (both p for trend < 0.0001).

Using hip circumference < 85 cm as the reference group in both sexes, men with a hip circumference between 90 and 95 cm had the hazard ratio for diabetes reduced by about 30% (HR=0.70, 95%CI: 0.63-0.77) after simultaneous adjustment for BMI and waist circumference (Figure 4.3.5), while for those with a hip circumference between 95 and 100 cm, the risk was reduced by about 50% (HR=0.51, 95%CI: 0.43-0.60). For females, a hip circumference between 90 and 95 cm was associated with about 40% reduced risk for diabetes (HR=0.62, 95%CI: 0.57-0.67), and a hip circumference above 95 cm was found to have more than 50% reduced risk (HR=0.47, 95%CI: 0.42-0.54).

After adjusting for BMI and waist circumference, the hazard ratios for per 1 standard deviation (men: 6.73 cm; women: 6.76 cm) increment in hip circumference were 0.83 (95%CI: 0.74-0.93) in men, and 0.77 (95%CI: 0.71-0.83) in women. The hazard ratio for men and women combined was 0.79 (95%CI: 0.74-0.84) (Figure 4.3.9).

4.3.2.3 Joint associations

4.3.2.3.1 Waist and hip circumference

The joint effect of waist and hip circumference is shown in Table 4.3.8. In each stratum of hip circumference, an increased waist circumference was associated with a greater risk of diabetes. However, such increase was less strong in people with higher hip circumference. In males, the BMI-adjusted hazard ratios across waist circumference

tertiles increased from 1.00 (95%CI: 0.79-1.27) to 2.88 (95%CI: 2.32-3.57) in the low hip circumference group (≤90.1 cm), and from 1.13 (95%CI: 0.64-2.01) to 2.27 (95%CI: 1.95-2.65) in the high hip circumference group (>90.1 cm). In females, the corresponding increases were from 1.00 (95%CI: 0.84-1.19) to 2.71 (95%CI: 2.31-3.01) in the low hip circumference group (≤90.5 cm), and from 0.69 (95%CI: 0.43-1.10) to 2.18 (95%CI: 1.94-2.44) in the high group (>90.5 cm).

At each level of waist circumference, a higher hip circumference appeared to be associated with a lower risk of diabetes in both sexes. For example, at the highest waist circumference tertile, the risk for those with a low hip circumference was about 25% greater than those with a high hip circumference; and similar finding was observed for people in the medium or the lowest waist circumference tertiles, except for the lowest waist circumference tertile in men.

4.3.2.3.2 BMI and central adiposity measures

To analyse the joint associations of BMI and central adiposity measures, participants were categorised into 6 groups by tertile of each central adiposity measure and the median value of BMI (males: 23.1 kg/m^2; females 23.5 kg/m^2). The joint associations between BMI and central adiposity (i.e. WC, WHR, WHtR) are presented in Table 4.3.9.

For both male and female, hazard ratios were consistently higher in the high BMI stratum across tertiles of each central adiposity measure, compared to those in the low BMI stratum. Within the same BMI stratum, higher central adiposity was consistently associated with higher risk of diabetes. For example, in males, the hazard ratios across waist tertiles were 1.00 (95%CI: 0.81-1.23), 1.88 (95%CI: 1.26-2.93), and 4.77 (95%CI: 3.04-7.50) in the low BMI stratum; and were 1.92 (95%CI: 1.26-2.93), 3.25 (95%CI: 2.86-

3.70) and 6.53 (95%CI: 5.70-7.48) in the high BMI stratum. Similarly, the corresponding hazard ratios for women were 1.00 (95%CI: 0.86-1.16), 2.12 (95%CI: 1.85-2.42) and 3.24 (95%CI: 2.46-4.27) in the low BMI stratum, and were 1.71 (95%CI: 1.22-2.41), 2.94 (95%CI: 2.64-3.28) and 6.46 (95%CI: 5.85-7.13) in the high BMI stratum.

Like waist circumference, increased WHR (or WHtR) was also associated with a greater risk of diabetes within the each BMI stratum. For WHR, the hazard ratios increased from 1.00 (95%CI: 0.84-1.19) to 2.74 in males with a BMI ≤ 23.1 kg/m^2, and from 2.14 (95%CI: 1.59-2.87) to 5.93 (95%CI: 5.45-6.45) in those with a BMI > 23.1 kg/m^2. In females, the corresponding increases in hazard ratios were from 1.00 (95%CI: 0.87-1.15) to 3.04 in those with a BMI ≤ 23.5 kg/m^2, and from 1.89 (95%CI: 1.54-2.31) to 5.89 (95%CI: 5.51-6.30) in those with a BMI > 23.5 kg/m^2. Similar results were also found for WHtR.

However, the strength of relationship between measures of central adiposity and diabetes did not appear to differ by level of BMI. For example, in both sexes, those in the 3rd tertile of WC, WHR or WHtR were generally associated with a 3-fold increased risk for diabetes compared to those in the 1st tertile irrespective of BMI levels.

4.3.3 Effect modification of other factors on the associations between adiposity and diabetes

4.3.3.1 Sex

As shown in Figure 4.3.8, the risks for diabetes associated with 1 standard deviation increment in different adiposity measures were generally higher in males than in females. For example, the multivariable-adjusted hazard ratios for 1-SD increment in BMI were 1.99 (95%CI: 1.88-2.11) in males and 1.78 (95%CI: 1.71-1.86) in females (p for

heterogeneity=0.002). Similarly, the hazard ratios for 1-SD increment in waist circumference, as an indicator of central adiposity, were 2.03 (95%CI: 1.91-2.16) in males and 1.86 (95%CI: 1.78-1.94) in females (p for heterogeneity=0.02). Without additionally adjusting for other adiposity measures, the positive association between hip circumference and diabetes was also stronger in males (HR=1.76, 95%CI: 1.64-1.88) than in females (HR=1.53, 95%CI: 1.46-1.60). The point estimates for body fat percentage, WHR and WHtR, though not statistically significant, were also higher in males compared to in females. These results suggest that sex may be an effect modifier for the association between adiposity and incident diabetes.

4.3.3.2 Age

A significant interaction between age and different adiposity measures was found (all p for interaction<0.05). It also appeared that with the same increment (i.e. 1 standard deviation) in overall and central adiposity measures, people in younger age groups tended to have higher risk of diabetes. For example, with 1 standard deviation increment in BMI, people in age group 35-49, 50-64, and 65-79 had 97% (95%CI: 85%-111%), 85% (95%CI: 77%-94%) and 71% (95%CI: 59%-84%) increased diabetes risks, respectively (p for trend=0.004). Similarly, for 1 standard deviation increase in waist circumference, the corresponding excess risks in these three age groups were 115% (95%CI: 100%-131%), 90% (95%CI: 80%-99%) and 75% (95%CI: 62%-89%) (p for trend < 0.001;Table 4.3.10). Similar modifying effect of age for WHR and WHtR was also found (both p for trend < 0.01).

Table 4.3.1 Distribution of incident diabetes by baseline age and study area

	Male			Female		
	No. cases	Person-years	Incidence rate†	No. cases	Person-years	Incidence rate†
Age group, years						
30-39	51	148,877	34	78	245,391	32
40-49	231	293,390	79	365	469,344	78
50-59	347	304,426	114	718	449,174	160
60-69	318	188,565	169	505	224,625	225
70-79	121	69,379	174	176	71,193	247
Area						
Qingdao*	2	76,512	3	-	91,281	-
Harbin	55	99,767	55	98	158,541	62
Haikou	10	47,288	21	23	83,698	27
Suzhou	159	103,877	153	326	150,413	217
Liuzhou	103	86,508	119	136	139,101	98
Subtotal (urban)	**329**	**413,952**	**79**	**583**	**623,034**	**94**
Sichuan	127	104,765	121	246	169,118	145
Gansu	9	94,442	10	15	151,486	10
Henan	45	138,819	32	74	173,934	43
Zhejiang	527	121,108	435	862	174,823	493
Hunan	33	131,552	25	62	167,332	37
Subtotal (rural)	**741**	**590,686**	**125**	**1,259**	**836,693**	**150**
Total	**1,070**	**1,004,637**	**106**	**1,842**	**1,459,727**	**126**

†Crude incidence rate=No. cases per 100,000 person-year

* The urban city of Qingdao was excluded from all subsequent prospective analyses, because of the late entry of the study area also that the disease surveillance system was not fully established by the time of this thesis

Table 4.3.2 Baseline BMI and diabetes incidence, by sex

	BMI quintile (kg/m²), male					
	1 (<20.5)	2 (20.5-22.3)	3 (22.3-24.0)	4 (24.0-26.1)	5 (≥26.1)	P for trend
No. of cases	92	102	162	262	450	
No. of person-years	177,893	183,179	187,499	192,583	186,937	
Crude incident rate (per 100,000 person-years)	52	56	86	136	240	
Age- and area-adjusted RR (95%CI)	1.0 (0.8-1.2)	1.2 (1.0-1.4)	1.9 (1.6-2.2)	3.1 (2.7-3.5)	6.4 (5.8-7.1)	<.0001
Model 1: Multivariable†-adjusted HR (95%CI)	1.0 (0.8-1.2)	1.2 (1.0-1.4)	1.9 (1.6-2.2)	3.1 (2.7-3.5)	6.4 (5.8-7.1)	<.0001
Model 2: Model 1 + HC-adjusted HR (95%CI)	1.0 (0.8-1.3)	1.2 (1.0-1.5)	2.0 (1.7-2.3)	3.2 (2.9-3.7)	7.0 (6.0-8.1)	<.0001
Model 3: Model 1 + WC-adjusted HR (95%CI)	**1.0 (0.7-1.4)**	**1.0 (0.8-1.2)**	**1.2 (1.0-1.4)**	**1.3 (1.2-1.5)**	**2.1 (1.8-2.5)**	**<.0001**
Model 4: Model 1 + WC + HC-adjusted HR (95%CI)	1.0 (0.7-1.4)	1.0 (0.8-1.3)	1.3 (1.1-1.5)	1.6 (1.4-1.8)	2.7 (2.3-3.2)	<.0001
Model 5: Model 1 + WHR-adjusted HR (95%CI)	1.0 (0.8-1.3)	1.0 (0.8-1.2)	1.3 (1.1-1.5)	1.7 (1.5-1.9)	2.9 (2.6-3.3)	<.0001

	BMI quintile (kg/m²), female					
	1 (<20.8)	2 (20.8-22.6)	3 (22.6-24.3)	4 (24.3-26.5)	5 (≥26.5)	P for trend
No. of cases	158	209	283	440	752	
No. of person-years	272,135	262,430	278,722	275,720	279,420	
Crude incident rate (per 100,000 person-years)	58	79	102	160	269	
Age- and area-adjusted HR (95%CI)	1.0 (0.9-1.2)	1.6 (1.4-1.8)	2.0 (1.8-2.3)	3.3 (3.0-3.6)	5.8 (5.4-6.3)	<.0001
Model 1: Multivariable†-adjusted HR (95%CI)	1.0 (0.9-1.2)	1.6 (1.4-1.8)	2.0 (1.8-2.3)	3.3 (3.0-3.6)	5.8 (5.3-6.2)	<.0001
Model 2: Model 1 + HC-adjusted HR (95%CI)	1.0 (0.8-1.2)	1.7 (1.4-1.9)	2.2 (2.0-2.5)	3.8 (3.5-4.2)	7.3 (6.6-8.2)	<.0001
Model 3: Model 1 + WC-adjusted HR (95%CI)	**1.0 (0.8-1.3)**	**1.3 (1.1-1.5)**	**1.3 (1.2-1.5)**	**1.7 (1.5-1.8)**	**2.2 (1.9-2.4)**	**<.0001**
Model 4: Model 1 + WC + HC-adjusted HR (95%CI)	1.0 (0.8-1.3)	1.4 (1.2-1.6)	1.5 (1.3-1.7)	2.1 (1.9-2.3)	3.1 (2.7-3.5)	<.0001
Model 5: Model 1 + WHR-adjusted HR (95%CI)	1.0 (0.8-1.2)	1.2 (1.1-1.4)	1.3 (1.2-1.5)	1.8 (1.7-2.0)	2.8 (2.6-3.0)	<.0001

†Multivariable adjustment: age, area, education, household income, alcohol consumption, smoking status, physical activity, and family history of diabetes

Table 4.3.3 Baseline percentage body fat and diabetes incidence, by sex

	Percentage body fat quintile (%), male					
	1 (<16.4)	2 (16.4-19.9)	3 (19.9-23.2)	4 (23.2-27.1)	5 (≥27.1)	P for trend
No. of cases	95	118	158	258	439	
No. of person-years	181,321	183,194	188,157	183,289	192,129	
Crude incident rate (per 100,000 person-years)	52	64	83	140	228	
Age- and area-adjusted HR (95%CI)	1.0 (0.8-1.2)	1.5 (1.2-1.7)	2.1 (1.8-2.5)	3.7 (3.2-4.1)	6.4 (5.8-7.1)	<.0001
Model 1: Multivariable†-adjusted HR (95%CI)	1.0 (0.8-1.2)	1.5 (1.2-1.8)	2.2 (1.9-2.5)	3.7 (3.2-4.1)	6.3 (5.7-7.0)	<.0001
Model 2: Model 1 + BMI-adjusted HR (95%CI)	1.0 (0.8-1.3)	1.3 (1.1-1.6)	1.6 (1.3-1.8)	2.1 (1.9-2.4)	2.8 (2.4-3.2)	<.0001
Model 3: Model 1 + WC-adjusted HR (95%CI)	**1.0 (0.8-1.3)**	**1.2 (1.0-1.5)**	**1.4 (1.2-1.6)**	**1.8 (1.6-2.0)**	**2.4 (2.2-2.8)**	**<.0001**
Model 4: Model 1 + WHR-adjusted HR (95%CI)	1.0 (0.8-1.3)	1.2 (1.0-1.4)	1.4 (1.2-1.7)	2.0 (1.8-2.3)	3.0 (2.6-3.3)	<.0001

	Percentage body fat quintile (%), female					
	1 (<26.0)	2 (26.0-29.8)	3 (29.8-33.4)	4 (33.4-37.7)	5 (≥37.7)	P for trend
No. of cases	156	187	304	435	760	
No. of person-years	270,432	269,763	275,923	275,219	277,082	
Crude incident rate (per 100,000 person-years)	58	69	110	158	276	
Age- and area-adjusted HR (95%CI)	1.0 (0.8-1.2)	1.5 (1.3-1.7)	2.2 (1.9-2.4)	3.4 (3.1-3.7)	5.8 (5.4-6.2)	<.0001
Model 1: Multivariable†-adjusted HR (95%CI)	1.0 (0.9-1.2)	1.5 (1.3-1.7)	2.2 (1.9-2.4)	3.3 (3.1-3.7)	5.7 (5.3-6.1)	<.0001
Model 2: Model 1 + BMI-adjusted HR (95%CI)	1.0 (0.8-1.3)	1.3 (1.1-1.5)	1.6 (1.4-1.8)	2.1 (1.9-2.3)	2.8 (2.5-3.1)	<.0001
Model 3: Model 1 + WC-adjusted HR (95%CI)	**1.0 (0.8-1.2)**	**1.3 (1.1-1.5)**	**1.5 (1.3-1.6)**	**1.8 (1.7-2.0)**	**2.5 (2.2-2.7)**	**<.0001**
Model 4: Model 1 + WHR-adjusted HR (95%CI)	1.0 (0.8-1.2)	1.2 (1.0-1.3)	1.4 (1.3-1.6)	2.0 (1.7-2.1)	2.9 (2.6-3.1)	<.0001

†Multivariable adjustment: age, area, education, household income, alcohol consumption, smoking status, physical activity and family history of diabetes

Table 4.3.4 Baseline waist circumference and diabetes incidence, by sex

	Waist circumference quintile (cm), male					
	1 (<73.0)	2 (73.0-78.5)	3 (78.5-84.0)	4 (84.0-90.1)	5 (≥90.1)	P for trend
No. of cases	112	109	178	283	386	
No. of person-years	188,093	181,115	194,972	184,608	179,310	
Crude incident rate (per 100,000 person-years)	60	60	91	152	215	
Age- and area-adjusted HR	1.0 (0.8-1.2)	1.4 (1.2-1.7)	2.3 (2.0-2.7)	4.1 (3.6-4.6)	7.2 (6.5-8.1)	<.0001
Model 1: Multivariable†-adjusted HR (95%CI)	1.0 (0.8-1.2)	1.4 (1.2-1.7)	2.4 (2.1-2.8)	4.2 (3.7-4.7)	7.5 (6.7-8.3)	<.0001
Model 2: Model 1 + HC-adjusted HR (95%CI)	1.0 (0.8-1.3)	1.5 (1.2-1.9)	2.7 (2.3-3.2)	5.1 (4.5-5.7)	9.7 (8.3-11.3)	<.0001
Model 3: Model 1 + HC + BMI-adjusted HR (95%CI)	1.0 (0.7-1.4)	1.4 (1.1-1.8)	2.2 (1.9-2.6)	3.4 (3.0-3.9)	5.2 (4.4-6.3)	<.0001
Model 4: Model 1 + BMI-adjusted HR (95%CI)	**1.0 (0.7-1.3)**	**1.3 (1.1-1.7)**	**2.0 (1.7-2.3)**	**2.8 (2.5-3.2)**	**3.9 (3.3-4.6)**	**<.0001**

	Waist circumference quintile (cm), female					
	1 (<70.5)	2 (70.5-75.6)	3 (75.6-80.5)	4 (80.5-86.4)	5 (≥86.4)	P for trend
No. of cases	166	207	294	427	748	
No. of person-years	279,539	279,768	273,543	365,504	270,055	
Crude incident rate (per 100,000 person-years)	59	74	107	161	276	
Age- and area-adjusted HR	1.0 (0.9-1.2)	1.5 (1.3-1.7)	2.2 (2.0-2.5)	3.4 (3.1-3.7)	6.2 (5.7-6.7)	<.0001
Model 1: Multivariable†-adjusted HR (95%CI)	1.0 (0.9-1.2)	1.5 (1.3-1.7)	2.2 (2.0-2.5)	3.4 (3.1-3.7)	6.2 (5.7-6.7)	<.0001
Model 2: Model 1 + HC-adjusted HR (95%CI)	1.0 (0.8-1.2)	1.6 (1.4-1.9)	2.5 (2.2-2.8)	4.0 (3.7-4.4)	7.9 (7.1-8.8)	<.0001
Model 3: Model 1 + HC + BMI-adjusted HR (95%CI)	1.0 (0.8-1.3)	1.4 (1.2-1.6)	1.8 (1.6-2.0)	2.6 (2.3-2.8)	4.2 (3.7-4.8)	<.0001
Model 4: Model 1 + BMI-adjusted HR (95%CI)	**1.0 (0.8-1.2)**	**1.3 (1.1-1.5)**	**1.6 (1.5-1.8)**	**2.2 (2.0-2.4)**	**3.3 (2.9-3.6)**	**<.0001**

†Multivariable adjustment: age, area, education, household income, alcohol consumption, smoking status, physical activity, and family history of diabetes

Table 4.3.5 Baseline hip circumference and diabetes incidence, by sex

	Hip circumference quintile (cm), male					
	1 (<84.6)	2 (84.6-88.5)	3 (88.5-92.0)	4 (92.0-96.1)	5 (≥96.1)	P for trend
No. of cases	156	144	256	264	248	
No. of person-years	191,805	179,659	192,554	184,429	179,652	
Crude incident rate (per 100,000 person-years)	81	80	133	142	138	
Age- and area-adjusted HR (95%CI)	1.0 (0.9-1.2)	1.4 (1.3-1.7)	2.3 (2.0-2.6)	2.9 (2.6-3.3)	4.6 (4.0-5.3)	<.0001
Model 1: Multivariable†-adjusted HR (95%CI)	1.0 (0.8-1.2)	1.5 (1.3-1.7)	2.3 (2.0-2.6)	2.9 (2.6-3.3)	4.5 (3.9-5.2)	<.0001
Model 2: Model 1 + BMI-adjusted HR (95%CI)	1.0 (0.8-1.3)	1.0 (0.8-1.1)	1.0 (0.9-1.1)	0.8 (0.7-1.0)	0.9 (0.7-1.0)	<.0001
Model 3, Model 1 + WC + BMI-adjusted HR (95%CI)	**1.0 (0.8-1.3)**	**0.8 (0.7-1.0)**	**0.8 (0.7-0.9)**	**0.5 (0.5-0.6)**	**0.5 (0.4-0.6)**	**<.0001**
Model 4, Model 1 + WC-adjusted HR (95%CI)	1.0 (0.8-1.3)	0.9 (0.8-1.0)	0.9 (0.8-1.0)	0.7 (0.6-0.8)	0.7 (0.6-0.8)	<.0001

	Hip circumference quintile (cm), female					
	1 (<85.3)	2 (85.3-89.0)	3 (89.0-92.2)	4 (92.2-96.4)	5 (≥96.4)	P for trend
No. of cases	275	343	370	416	438	
No. of person-years	267,774	290,802	275,644	269,001	265,189	
Crude incident rate (per 100,000 person-years)	103	118	134	155	165	
Age- and area-adjusted HR	1.0 (0.9-1.2)	1.4 (1.3-1.6)	2.0 (1.8-2.2)	2.4 (2.2-2.7)	3.3 (3.0-3.7)	<.0001
Model 1: Multivariable†-adjusted HR (95%CI)	1.0 (0.9-1.2)	1.4 (1.3-1.6)	2.0 (1.8-2.2)	2.4 (2.2-2.7)	3.3 (3.0-3.7)	<.0001
Model 2: Model 1 + BMI-adjusted HR (95%CI)	1.0 (0.9-1.2)	0.9 (0.8-1.0)	0.9 (0.8-1.0)	0.8 (0.7-0.8)	0.7 (0.6-0.8)	<.0001
Model 3, Model 1 + WC + BMI-adjusted HR (95%CI)	**1.0 (0.9-1.2)**	**0.8 (0.7-0.9)**	**0.7 (0.6-0.8)**	**0.5 (0.5-0.6)**	**0.5 (0.4-0.5)**	**<.0001**
Model 4, Model 1 + WC-adjusted HR (95%CI)	1.0 (0.9-1.2)	0.9 (0.8-1.0)	0.9 (0.8-1.0)	0.7 (0.7-0.8)	0.7 (0.6-0.8)	<.0001

†Multivariable adjustment: age, area, education, household income, alcohol consumption, smoking status, physical activity, and family history of diabetes

Table 4.3.6 Baseline waist hip ratio and diabetes incidence, by sex

	Waist-hip-ratio quintile, male					
	1 (<0.85)	2 (0.85-0.89)	3 (0.89-0.92)	4 (0.92-0.96)	5 (≥0.96)	P for trend
No. of cases	92	84	184	233	475	
No. of person-years	179,484	139,241	224,104	196,177	189,094	
Crude incident rate (per 100,000 person-years)	51	60	82	118	251	
Age- and area-adjusted HR (95% CI)	1.0 (0.8-1.2)	1.6 (1.4-1.9)	2.4 (2.0-2.8)	3.4 (3.0-3.8)	6.8 (6.2-7.5)	<.0001
Model 1, Multivariable†-adjusted HR (95% CI)	1.0 (0.8-1.2)	1.6 (1.4-1.9)	2.4 (2.0-2.8)	3.4 (3.0-3.8)	6.8 (6.2-7.4)	<.0001
Model 2, Model 1 + BMI-adjusted HR (95% CI)	**1.0 (0.8-1.3)**	**1.4 (1.2-1.7)**	**1.8 (1.5-2.1)**	**2.1 (1.9-2.4)**	**3.5 (3.1-3.9)**	**<.0001**
	Waist-hip-ratio quintile, female					
	1 (<0.80)	2 (0.80-0.84)	3 (0.84-0.88)	4 (0.88-0.92)	5 (≥0.92)	P for trend
No. of cases	121	174	241	433	873	
No. of person-years	273,479	279,899	233,430	278,370	303,231	
Crude incident rate (per 100,000 person-years)	44	62	103	155	288	
Age- and area-adjusted HR (95% CI)	1.0 (0.8-1.2)	1.3 (1.1-1.5)	2.2 (2.0-2.5)	3.6 (3.3-3.9)	6.1 (5.7-6.5)	<.0001
Model 1, Multivariable†-adjusted HR (95% CI)	1.0 (0.8-1.2)	1.3 (1.1-1.5)	2.2 (2.0-2.4)	3.5 (3.2-3.9)	6.0 (5.6-6.4)	<.0001
Model 2, Model 1 + BMI-adjusted HR (95% CI)	**1.0 (0.8-1.2)**	**1.1 (0.9-1.3)**	**1.6 (1.5-1.8)**	**2.3 (2.1-2.5)**	**3.2 (3.0-3.5)**	**<.0001**

†Multivariable adjustment: age, area, education, household income, alcohol consumption, smoking status, physical activity, and family history of diabetes

Table 4.3.7 Baseline waist height ratio and diabetes incidence, by sex

	Waist-height-ratio quintile, male					
	1 (<0.45)	2 (0.45-0.48)	3 (0.48-0.51)	4 (0.51-0.54)	5 (≥0.54)	P for trend
No. of cases	107	115	168	256	422	
No. of person-years	189,761	188,317	187,001	183,647	179,373	
Crude incident rate (per 100,000 person-years)	56	61	90	139	234	
Age- and area-adjusted HR (95%CI)	1.0 (0.8-1.2)	1.4 (1.2-1.7)	2.3 (2.0-2.6)	3.8 (3.4-4.3)	7.0 (6.3-7.7)	<.0001
Model 1: Multivariable†-adjusted HR (95%CI)	1.0 (0.8-1.2)	1.5 (1.2-1.8)	2.3 (2.0-2.7)	3.9 (3.4-4.4)	7.1 (6.4-7.8)	<.0001
Model 2: Model 1 + HC-adjusted HR (95%CI)	1.0 (0.8-1.2)	1.4 (1.2-1.7)	2.2 (1.9-2.6)	3.7 (3.3-4.2)	6.6 (5.8-7.5)	<.0001
Model 3: Model 1 + BMI-adjusted HR (95%CI)	**1.0 (0.7-1.4)**	**1.4 (1.1-1.7)**	**1.9 (1.6-2.2)**	**2.6 (2.3-3.0)**	**3.8 (2.3-4.4)**	**<.0001**
Model 4: Model 1 + HC + BMI-adjusted HR (95%CI)	1.0 (0.7-1.3)	1.4 (1.1-1.7)	1.9 (1.6-2.2)	2.7 (2.3-3.0)	3.8 (3.2-4.5)	<.0001

	Waist-height-ratio quintile, female					
	1 (<0.46)	2 (0.46-0.49)	3 (0.49-0.52)	4 (0.52-0.56)	5 (≥0.56)	P for trend
No. of cases	149	190	305	425	773	
No. of person-years	282,415	277,265	274,115	270,272	264,335	
Crude incident rate (per 100,000 person-years)	52	69	111	157	292	
Age- and area-adjusted HR (95%CI)	1.0 (0.9-1.2)	1.5 (1.3-1.8)	2.4 (2.2-2.7)	3.5 (3.2-3.8)	6.9 (6.4-7.4)	<.0001
Model 1: Multivariable†-adjusted HR (95%CI)	1.0 (0.9-1.2)	1.5 (1.3-1.8)	2.4 (2.2-2.7)	3.5 (3.2-3.8)	6.8 (6.3-7.3)	<.0001
Model 2: Model 1 + HC-adjusted HR (95%CI)	1.0 (0.8-1.2)	1.5 (1.3-1.8)	2.5 (2.2-2.8)	3.5 (3.2-3.9)	7.1 (6.4-7.8)	<.0001
Model 3: Model 1 + BMI-adjusted HR (95%CI)	**1.0 (0.8-1.3)**	**1.3 (1.1-1.6)**	**1.9 (1.7-2.2)**	**2.4 (2.2-2.6)**	**3.8 (3.4-4.3)**	**<.0001**
Model 3: Model 1 + HC + BMI-adjusted HR (95%CI)	1.0 (0.8-1.3)	1.4 (1.2-1.6)	2.0 (1.7-2.2)	2.5 (2.2-2.7)	4.2 (3.7-4.7)	<.0001

†Multivariable adjustment: age, area, education, household income, alcohol consumption, smoking status, physical activity, and family history of diabetes

Table 4.3.8 Joint effect of WC and HC in predicting the risk of diabetes

	Male		Female	
	HC≤90.1 cm	**HC>90.1 cm**	**HC≤90.5 cm**	**HC>90.5 cm**
WC*				
1st tertile	1.00 (0.79-1.27)	1.13 (0.64-2.01)	1.00 (0.84-1.19)	0.69 (0.43-1.10)
2nd tertile	1.82 (1.56-2.11)	1.41 (1.56-2.11)	1.80 (1.61-2.01)	1.10 (0.94-1.29)
3rd tertile	2.88 (2.32-3.57)	2.27 (1.95-2.65)	2.71 (2.37-3.01)	2.18 (1.94-2.44)

*Hazard ratios adjusted for age, area, education, household income, alcohol use, smoking status, physical activity, family history of diabetes and BMI

Table 4.3.9 Joint effect of BMI and central adiposity measures in predicting the risk of diabetes*

	Male		Female	
	BMI≤23.1 kg/m²	BMI>23.1 kg/m²	BMI≤23.5 kg/m²	BMI>23.5 kg/m²
WC†				
1st tertile	1.00 (0.81-1.23)	1.92 (1.26-2.93)	1.00 (0.86-1.16)	1.71 (1.22-2.41)
2nd tertile	1.88 (1.53-2.30)	3.25 (2.86-3.70)	2.12 (1.85-2.42)	2.94 (2.64-3.28)
3rd tertile	4.77 (3.04-7.50)	6.53 (5.70-7.48)	3.24 (2.46-4.27)	6.46 (5.85-7.13)
WHR				
1st tertile	1.00 (0.84-1.19)	2.14 (1.59-2.87)	1.00 (0.87-1.15)	1.89 (1.54-2.31)
2nd tertile	1.62 (1.31-2.00)	3.01 (2.57-3.54)	1.85 (1.59-2.16)	3.27 (3.00-3.79)
3rd tertile	2.74 (2.17-3.46)	5.93 (5.45-6.45)	3.04 (2.61-3.53)	5.89 (5.51-6.30)
WHtR†				
1st tertile	1.00 (0.83-1.21)	1.76 (1.16-2.68)	1.00 (0.86-1.16)	1.23 (0.80-1.87)
2nd tertile	1.79 (1.46-2.20)	2.78 (2.44-3.18)	1.75 (1.52-2.01)	2.62 (2.32-2.95)
3rd tertile	2.68 (1.61-4.46)	5.07 (4.49-5.71)	2.67 (2.13-3.34)	4.86 (4.44-5.32)

*Hazard ratios adjusted for age, area, education, household income, alcohol use, smoking status, physical activity and family history of diabetes

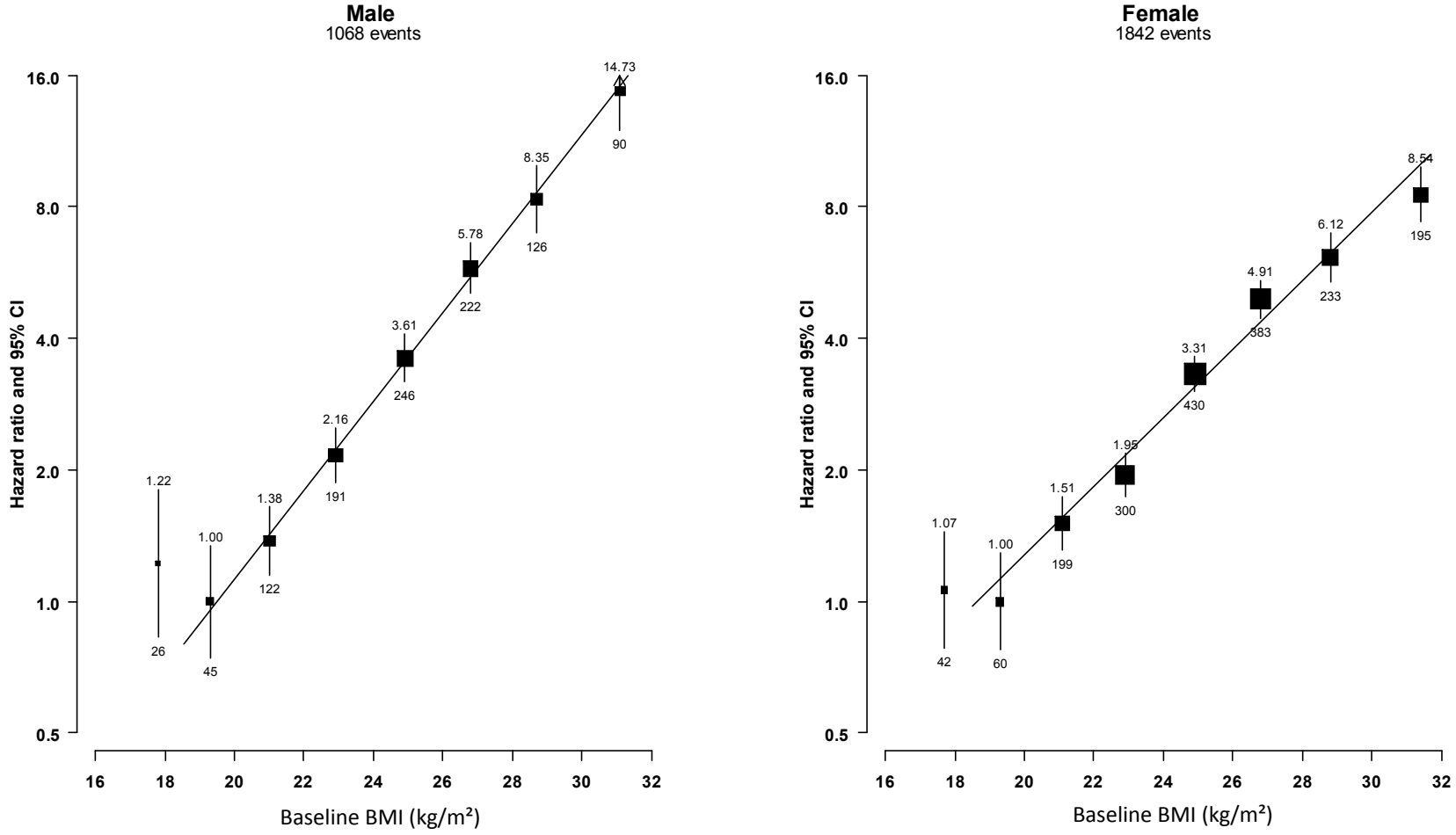
†Additional adjustment: hip circumference

Table 4.3.10 Age-specific hazard ratios for diabetes associated with 1 SD increase in BMI and waist circumference

		BMI		Waist circumference	
	No. cases	**Hazard ratio***	**95% Confidence interval**	**Hazard ratio***	**95% Confidence interval**
Age group, years					
35-49	813	1.97	(1.85, 2.11)	2.15	(2.00, 2.31)
50-64	1496	1.85	(1.77, 1.94)	1.90	(1.80, 1.99)
65-79	601	1.71	(1.59, 1.84)	1.75	(1.62, 1.89)
Trend test		**χ^2=8.2, p= 0.004**		**χ^2=15.7, p<0.001**	

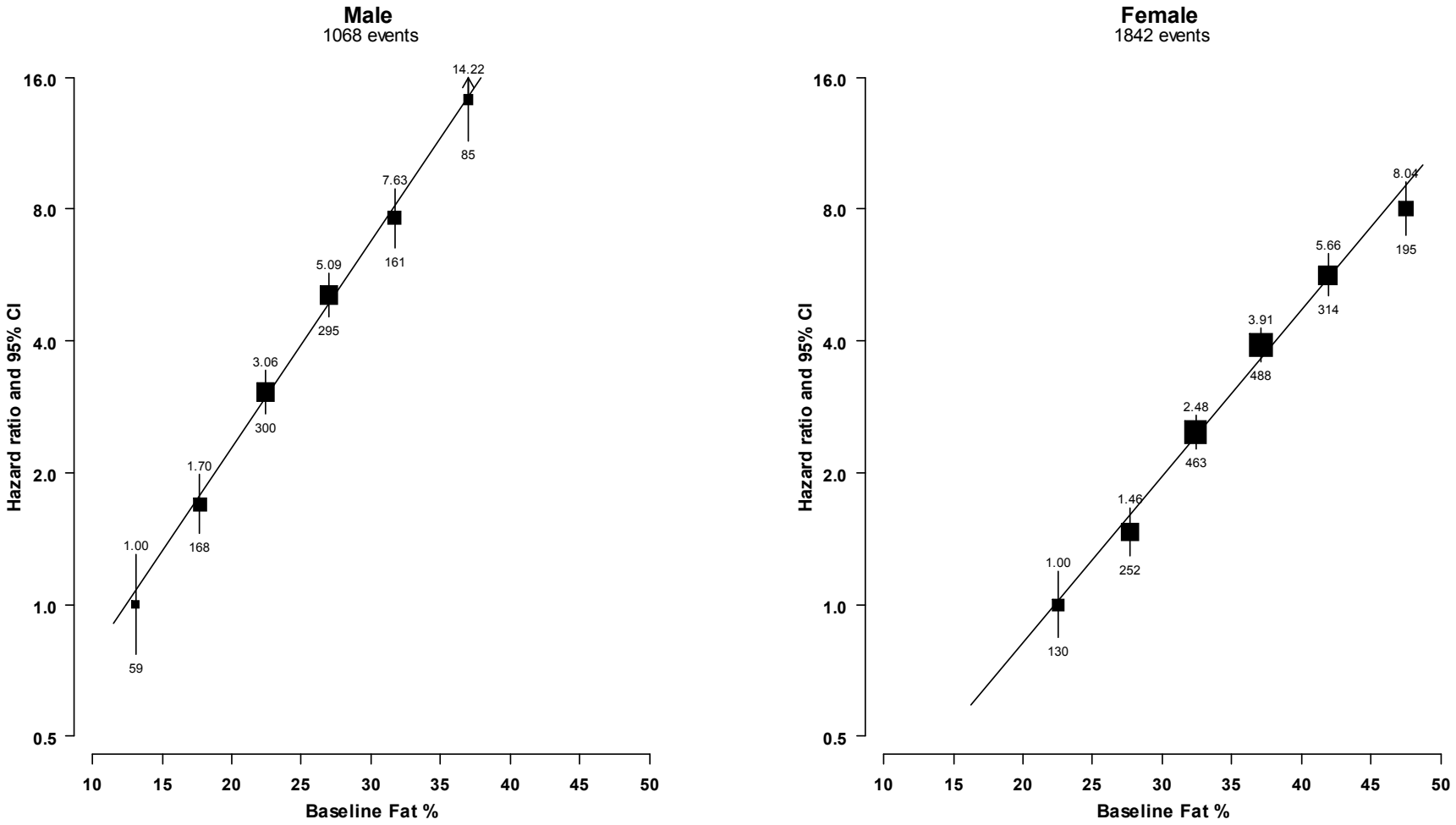
* Hazard ratios for 1 standard deviation increment in BMI or waist circumference, adjusted for age, area, education, household income, alcohol use, smoking status, physical activity and family history of diabetes

Figure 4.3.1 Hazard ratios* for incident diabetes by baseline BMI, by sex



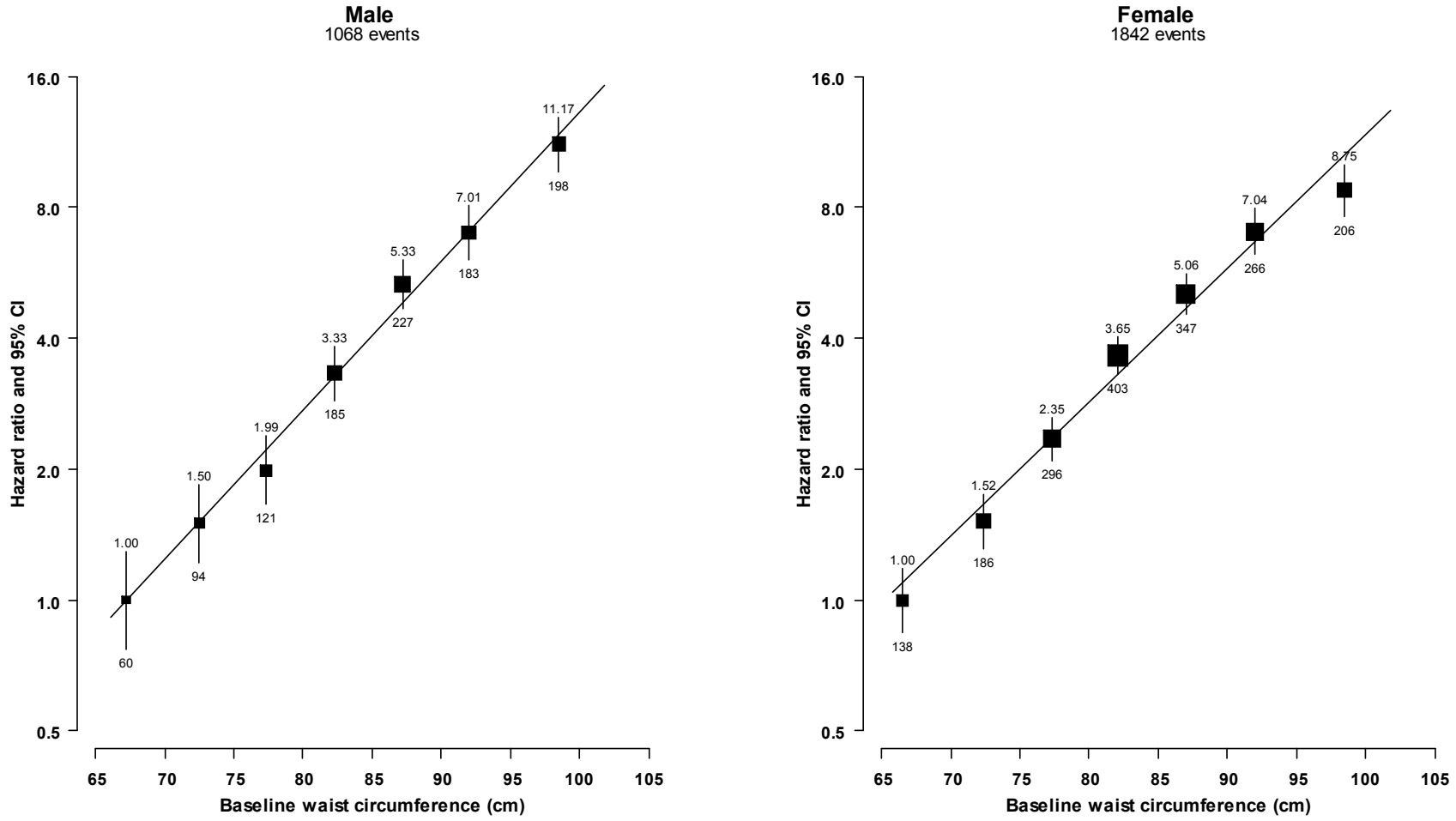
*Adjusted for age, area, education, household income, alcohol use, smoking status, physical activity and family history of diabetes

Figure 4.3.2 Hazard ratios* for incident diabetes by baseline percentage body fat, by sex



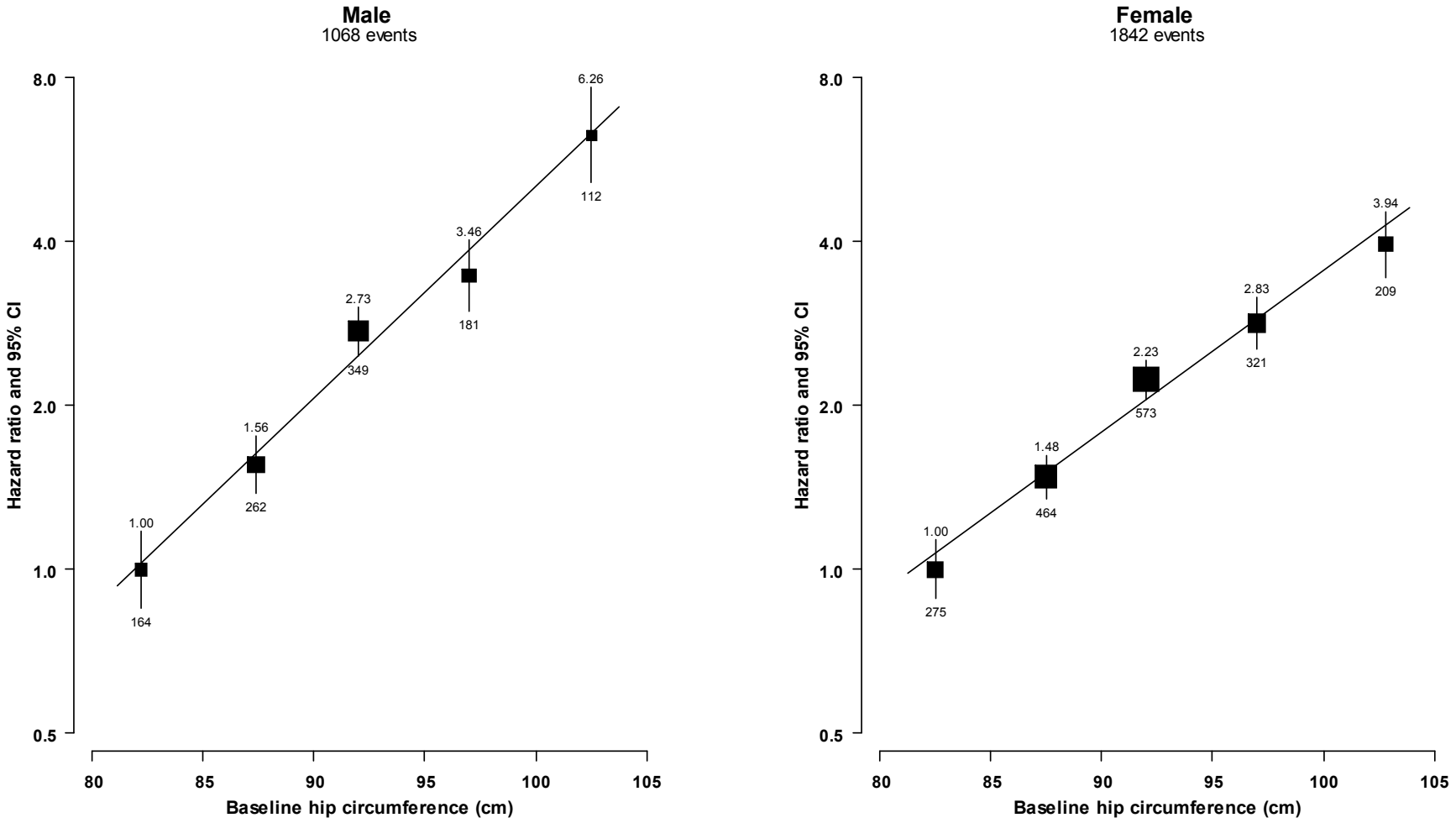
*Adjusted for age, area, education, household income, alcohol use, smoking status, physical activity and family history of diabetes

Figure 4.3.3 Hazard ratios* for incident diabetes by baseline waist circumference, by sex



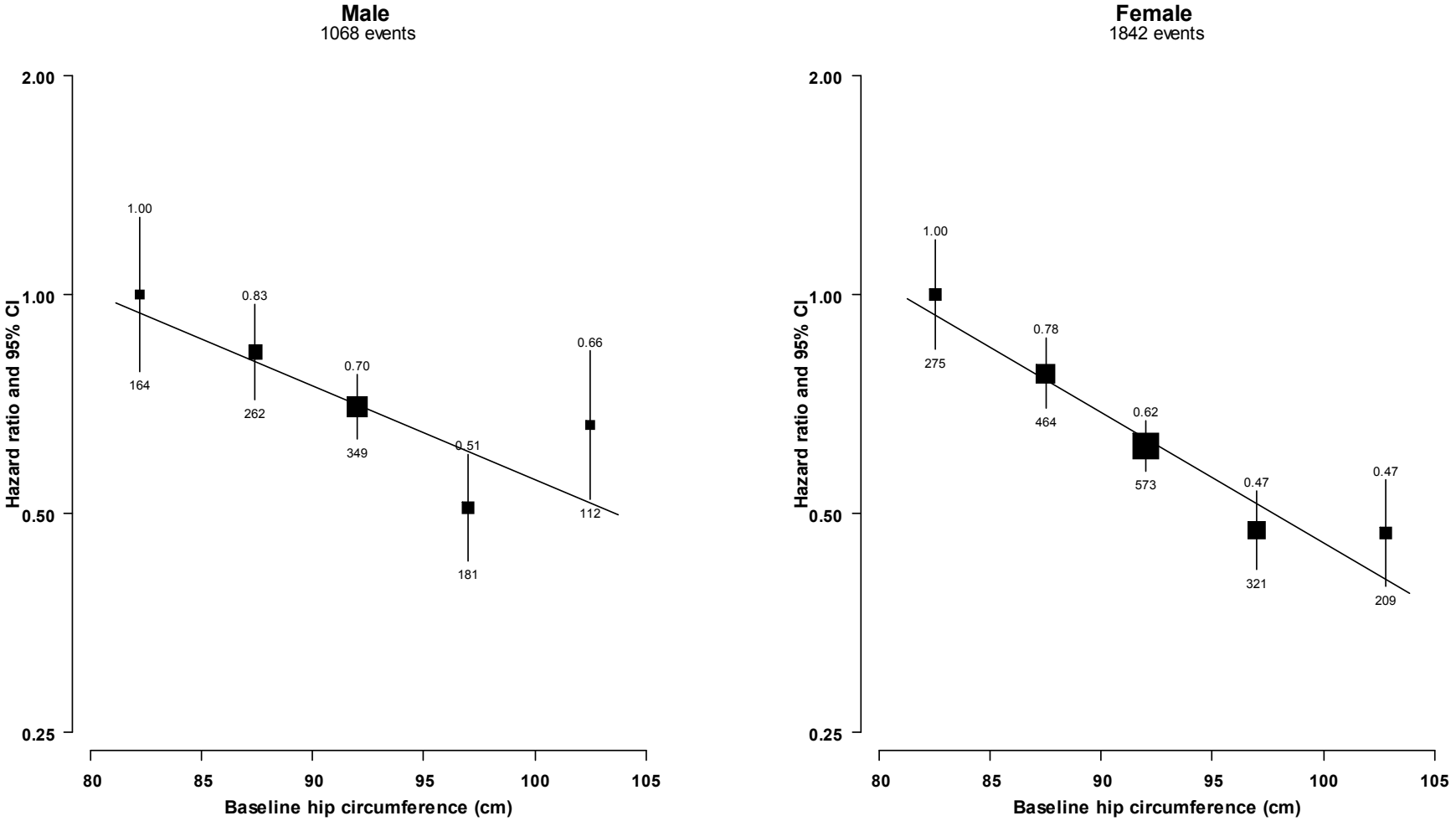
*Adjusted for age, area, education, household income, alcohol use, smoking status, physical activity and family history of diabetes

Figure 4.3.4 Hazard ratios* for incident diabetes by baseline hip circumference, by sex



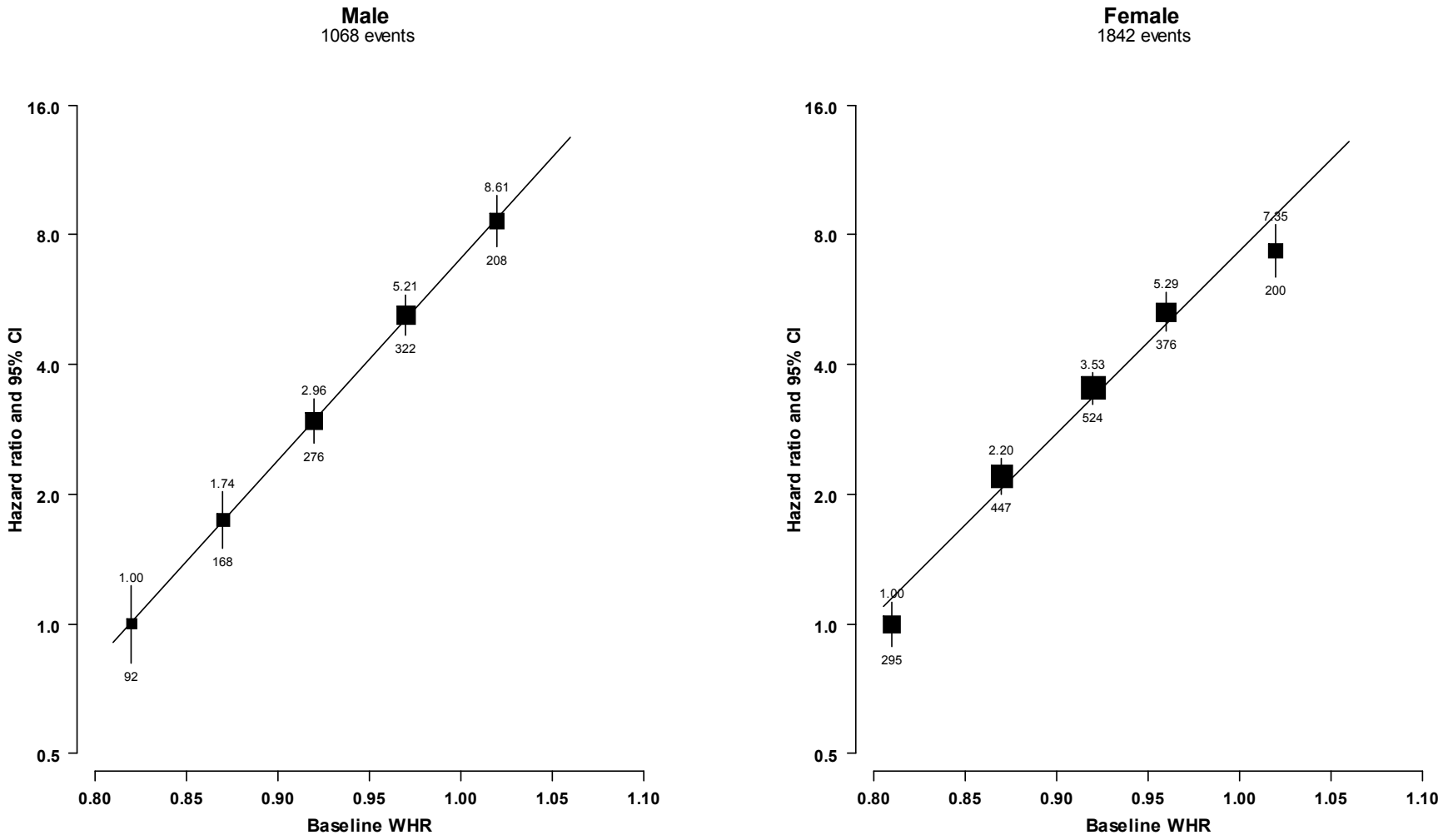
*Adjusted for age, area, education, household income, alcohol use, smoking status, physical activity and family history of diabetes

Figure 4.3.5 Hazard ratios* for incident diabetes by baseline hip circumference, with additional adjustment for BMI and waist circumference, by sex



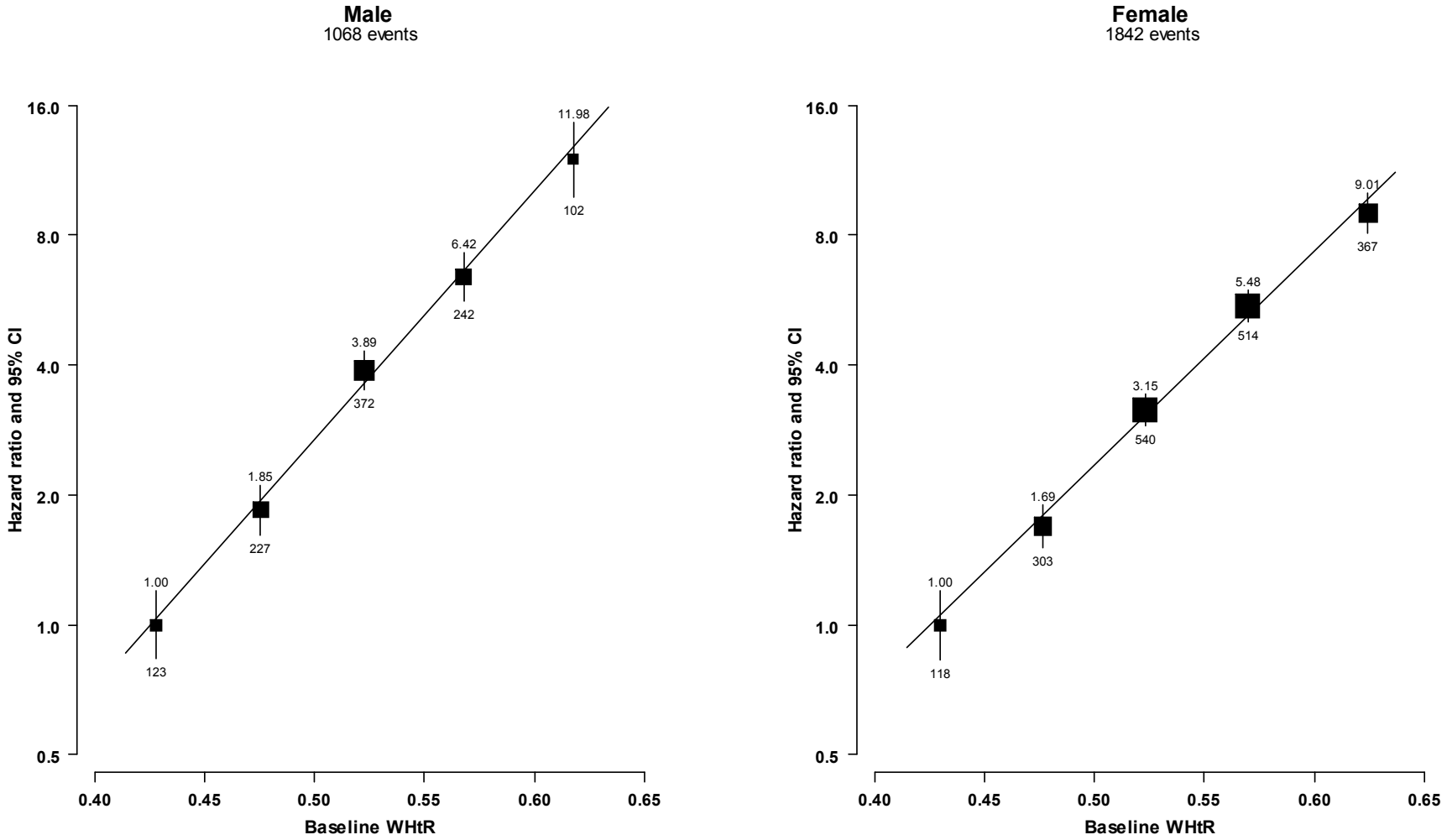
*Adjusted for age, area, education, occupation, household income, alcohol use, smoking status, physical activity, family history of diabetes, WC and BMI

Figure 4.3.6 Hazard ratios* for incident diabetes by baseline waist hip ratio, by sex



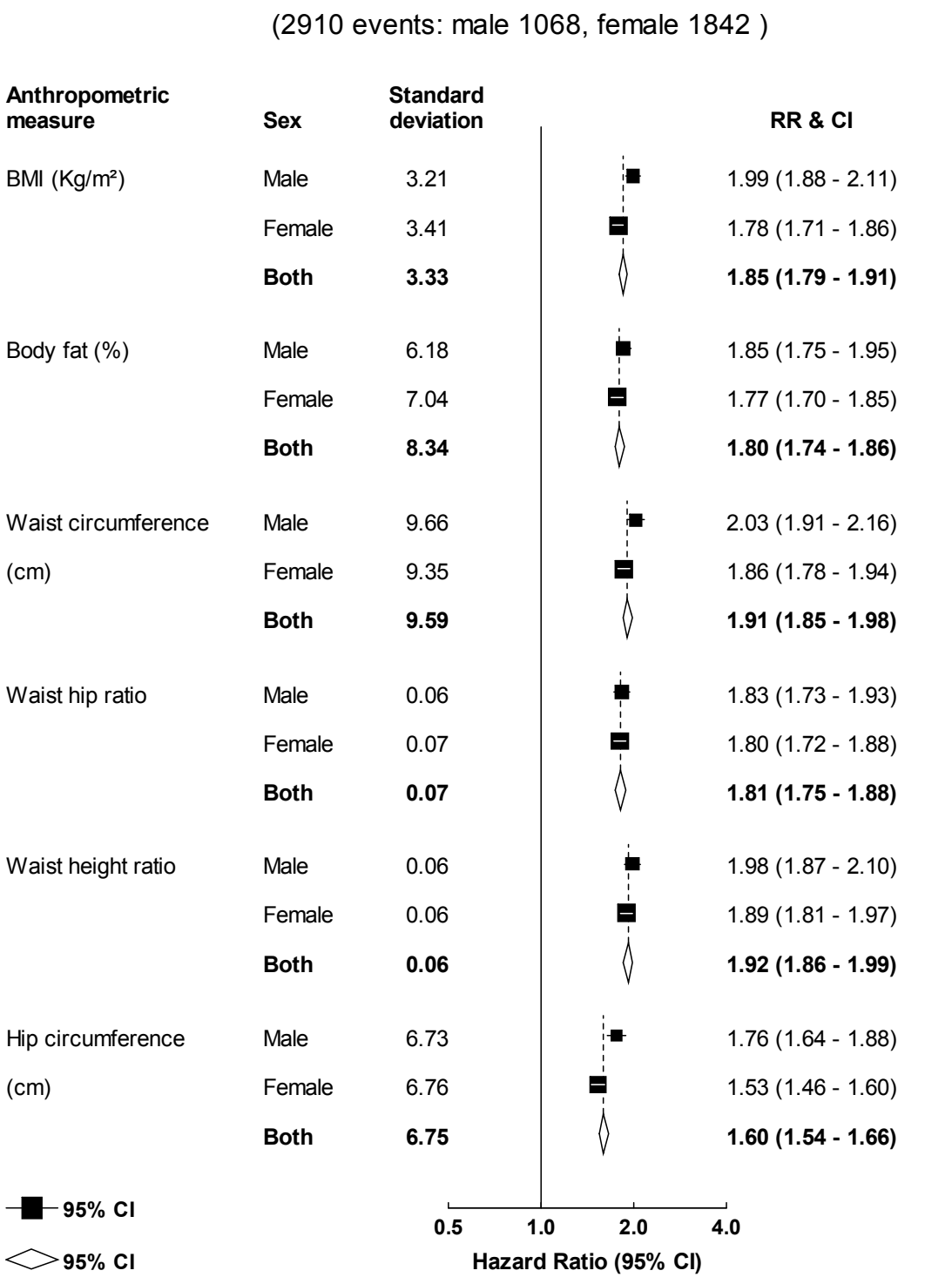
*Adjusted for age, area, education, household income, alcohol use, smoking status, physical activity and family history of diabetes

Figure 4.3.7 Hazard ratios* for incident diabetes by baseline waist height ratio, by sex



*Adjusted for age, area, education, household income, alcohol use, smoking status, physical activity and family history of diabetes

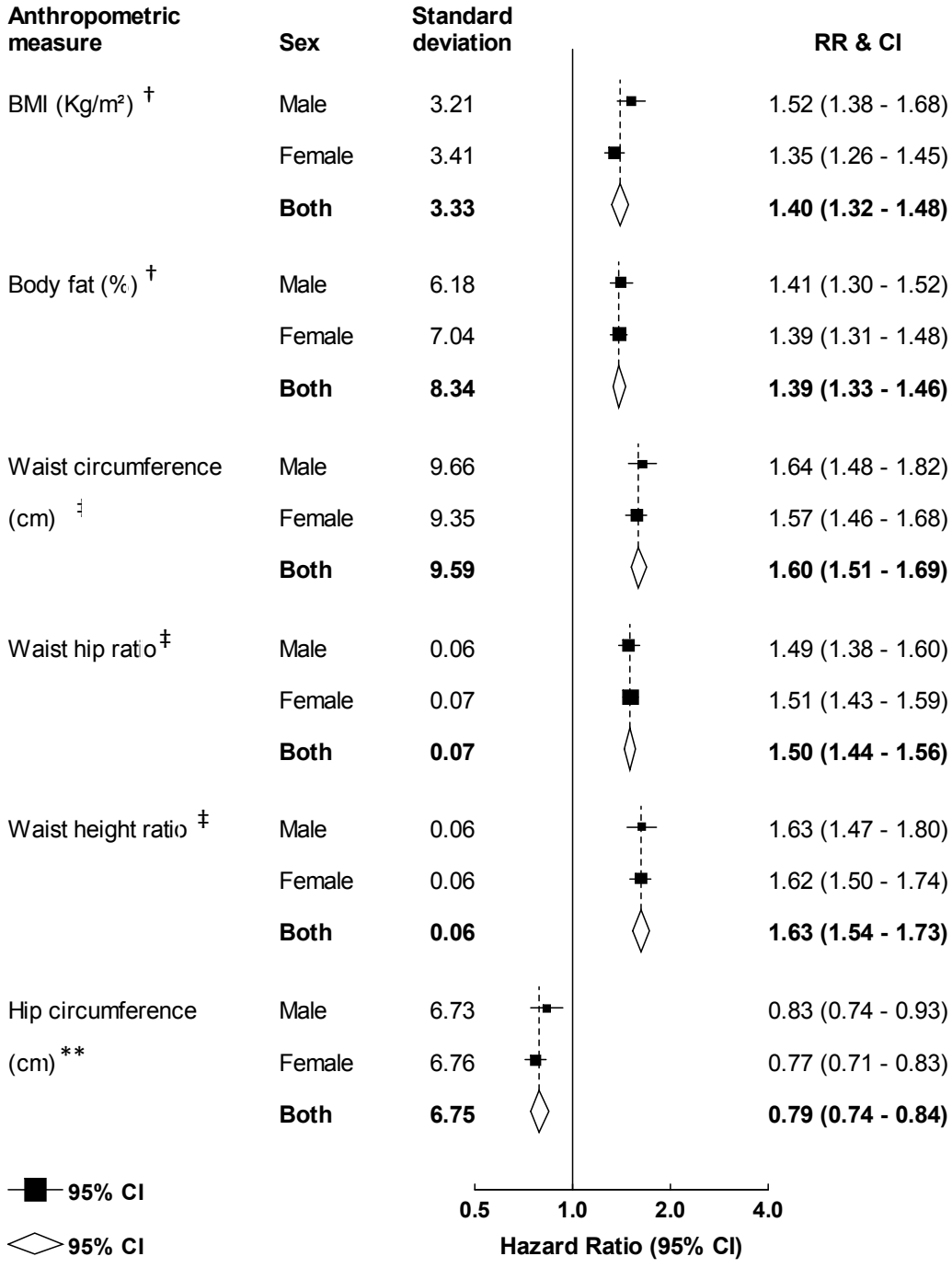
Figure 4.3.8 Hazard ratios* for 1-SD increment in different measures, not adjusted for other adiposity measures



*Adjusted for age, area, education, household income, alcohol use, smoking status, physical activity and family history of diabetes

Figure 4.3.9 Hazard ratios* for 1-SD increment in different measures, adjusted for other adiposity measures

(2910 events: male 1068, female 1842)



* Adjusted for age, area, education, household income, alcohol use, smoking status, physical activity and family history of diabetes;

† Additional adjustment for waist circumference;

‡ Additional adjustment for BMI;

** Additional adjustment for BMI and waist circumference

5. Discussion

Both cross-sectional and prospective findings from this largest ever cohort study in China provided powerful evidence that adiposity was an important risk factor for diabetes in adult Chinese men and women, irrespective of which adiposity measures were used. In particular, we observed log-linear associations between various adiposity measures and diabetes risk: above 18.5 kg/m^2, every 2 kg/m^2 higher BMI was associated with 44% (95%CI: 41%-47%) increased risk of diabetes; and throughout the entire range, every 5 cm larger waist circumference was associated with 41% (95%CI: 38%-44%) increased risk of diabetes. In the entire range of normal adiposity (excluding malnutrition, i.e. BMI<18.5 kg/m^2), we found no evidence of any apparent "threshold", below which, lower adiposity was no longer associated with lower risk of diabetes. Rather, the relative risk of diabetes increased linearly even within the conventionally "normal range" of adiposity (i.e. BMI< 25 kg/m^2 or WC < 90 cm).

In the present study, measures of central adiposity, such as waist circumference, waist hip ratio or waist height ratio, were shown consistently to be more strongly associated with diabetes prevalence than were measures of overall adiposity, such as BMI and percentage body fat. However, the prospective data suggested, perhaps more appropriately, that both central and overall adiposity measures were equally strong predictors of new-onset of type 2 diabetes, although some adiposity measures (i.e. waist circumference, waist height ratio, BMI) were somewhat moderately stronger than others (i.e. waist hip ratio and percentage body fat). Among all the measures of adiposity, waist-hip ratio was the most strongly associated with diabetes prevalence, whereas waist circumference was the most predictive of diabetes incidence.

After controlling for overall adiposity, central adiposity measures remained strongly associated with diabetes prevalence, while the associations were significantly attenuated for overall adiposity measures after adjusting for central adiposity. In prospective associations, however, both central and overall adiposity measures remained strongly independent predictors of diabetes incidence after adjusting for each other. In both analyses, we demonstrated that adding both central and overall adiposity measures together could further improve risk prediction.

Given waist circumference, hip circumference was inversely associated with both diabetes prevalence and incidence. Every 5 cm larger hip circumference was associated with 16% (95%CI: 12%-20%) reduced risk of diabetes, implying a protective effect of the adipose depot in the hip region.

In addition, for many of the above associations, there was possible effect modification by age and sex. The effects of adiposity seemed stronger in men and in people in younger age groups.

5.1 Strengths and weaknesses of the study

5.1.1 Study size and measures of adiposity

A major strength of the CKB Study is its large sample size. It is one of the largest biobank studies in the world, and is the largest single cohort study ever conducted in China. In terms of number of participants involved (n=512,000 participants), it is larger than all of the previous China National Diabetes Surveys[22,75] combined (i.e. ranging from 46,000 to 224,000 participants in previous surveys, refer to Table 2.2), which significantly increases the power of the study and reduces the influence of random error. To our

knowledge, only a limited number of prospective studies have been conducted in China,[84,98,127,128] and most of them were small with a sample size of up to several thousand (i.e. normally ranging from 1,500 to 6,000 participants, refer to Table 2.3). Even in a moderately large study of Shanghai women (about 73,000 participants), the published prospective results were based on merely 100 incident diabetes cases.[98] In comparison, the present CKB Study is much more robust to provide precise effect estimates.

The present study also provides one of the most comprehensive assessments of multiple anthropometric measures in relation to diabetes prevalence and incidence in the Chinese population. Unlike many other studies which used self-reported questionnaires and measures,[58,95,129] the baseline information of the CKB participants was collected by trained interviewers using electronic questionnaire. The physical measurements of different anthropometric indicators were all performed by health professionals using standard instruments and protocols. With a high consistency of the anthropometric measures between baseline and the resurvey of 5% participants (e.g. correlation coefficient=0.93 for BMI), the measurement error of the present study has been proven to be minimal. The high correlation of anthropometric measurements between baseline and resurvey also reduces the potential for regression dilution bias to a minimal level.

5.1.2 Diagnosis of diabetes and completeness of follow-up

The prevalent diabetes cases were identified at baseline by both self-report (supported by evidence of diabetic medication) and random plasma glucose testing (confirmed by a follow-up fasting plasma glucose test). This ensured the accurate and almost complete identification of all potential prevalent cases in the study population. For incident

diabetes, all cases were diagnosed by local hospitals and were reported by professional public health staff or the health insurance bureau. Compared to the collection of disease outcomes by self-reported in many previous cohort studies, the follow-up procedures of the CKB Study provides a more comprehensive and reliable approach for identifying true cases among the study participants.

The diagnostic accuracy of the diabetes incidence was confirmed in the event verification sub-study. In the surveyed sample of 831 incident diabetes, 93.1% were adjudicated as "definite diabetes", 5.4% were "probable diabetes" and only 1.4% were refuted as "non-diabetes". The level of true positive of the diabetes cases in the present study is compatible or better than most major Chinese[84,98] and Western[58,95,129] cohort studies. The high quality of diabetes endpoint report ensures reliable estimation of the exposure-disease association in the prospective analysis of the present study.

In addition, despite the large community-based sample, loss to follow up of the CKB participants remains exceptionally low at 0.2%, which is another important strength of the study.

5.1.3 Effects of confounding and potential biases

The potential confounding effects of demographic, socioeconomic and lifestyle factors on the association between adiposity and diabetes were carefully considered and controlled for in the present study. All models were commonly adjusted for age,[28] education level,[31] annual household income,[25] alcohol consumption,[33,34] smoking status,[35-37] physical activity,[32] and family history of diabetes,[29] which were selected based on evidence from previous studies and independent assessment of the CKB data. In

addition, in view of the geographic heterogeneity of the cohort, study area was also adjusted for in all analyses. A number of other factors were adjusted for as confounders in previously cross-sectional or cohort studies, like marital status,[24] cardiovascular disease history,[83] blood pressure,[22,82,87] cholesterol,[84,92,106] and lung function.[106] However, these "confounders" were either remotely related to exposure and outcome (e.g. marital status, lung function), or were on the causal pathway as an intermediate factor (e.g. blood pressure). Therefore, they were not included in the models to help avoid any undue over-adjustment of unrelated factors.

Potential confounders like dietary composition or total energy intake were not included in our analyses. This was largely because of potential for recall bias and the complexity of evaluating the calorie containment of vast variety of Chinese food. Since both confounders are hard to assess adequately even when the best instruments are available, they have not been included in most other studies.

One of our major concerns with regards to the present cross-sectional and prospective analyses is the reverse causation. It is commonly observed that diabetes can cause weight loss as the disease progresses,[130] and hypoglycaemic agents such as metformin and thiazolidinedione have been reported to decrease adipose tissue mass[131] or change regional body fat distribution.[132] A reverse causation could, therefore, exist especially in the cross-sectional analyses as both exposure and the outcome variables were collected at the same time.

The reverse causation bias may also influence the prospective analyses due to the relatively short follow-up period in the present study. As weight loss and change in body fat distribution is likely to occur before diabetes is diagnosed, the anthropometric values

recorded at baseline may underestimate the usual values. Consequently, the biased results could potentially exhibit a weaker strength of association between adiposity and diabetes. Nevertheless, in a sensitivity analysis that excluded the first two years of follow-up, there was no material change in the study findings.

An additional potential concern is the relatively low incidence rate of diabetes outcome in the present study. During the 5.1 years of follow-up, there were less than 3,000 incident diabetes cases reported, largely through the chronic disease reporting system. The incidence rate was much lower than that reported in other studies in Chinese populations, e.g. the Beijing Project 5-Year Follow-up Study (crude incidence rate: 705.8 per 100,000 person years),[92] and the Singaporean Chinese Study (crude incidence rate: 897.9 per 100,000 person years).[133] The primary reason for the low incidence rate is that the CKB cohort was still at its early stage when the present analyses were conducted. The chronic disease reporting system in some study areas were not completely established until 2 or 3 years after the baseline survey.

The low incidence rate was likely a result of under-reporting. The present CKB Study involves three follow-up strategies, including chronic disease reporting system, health insurance data, and death registry. All the three strategies were combined to maximise incident case report. However, due to the unavailability of health insurance (HI) data by the time this thesis was completed (the HI data only became available in March 2013, yielding a further 2,842 new cases), the incident cases from the health insurance data weren't incorporated into the prospective analyses of the present study. As certain proportion of incident diabetes would have been expected to be misclassified as non-diabetic cases, such random misclassification was likely to bias the exposure-outcome

association towards the null. A further ad hoc analysis based on chronic disease data and the latest HI data produced results which were essentially the same as those presented in this thesis (data not shown).

In addition, the under-reporting of diabetes is also likely to be a systematic bias in the CKB Study. Since the chronic disease reporting system covers only hospitalised cases (i.e. inpatient visits), outpatient diabetes cases are not routinely reported to our database. Likewise, the health insurance in most study sites covers only inpatient visits (except for Zhejiang). Consequently, most outpatient diabetes cases are undetectable in the current disease follow-up strategies. As most initial onset of type 2 diabetes is likely to be diagnosed through outpatient visits, the under-reporting of incident diabetes cases is a major limitation with the current study design.

Meanwhile, the low incidence rate may also be partly due to “healthy volunteer effect” usually seen in cohort studies, which is particularly common with a relatively short follow-up period. As those who volunteered to participate in the CKB cohort were systematically less likely to be chronically ill, the diabetes prevalence and the incidence in the first few years of follow up is likely to be low among the participants. As this observed phenomenon is diminishing over time, the incidence rate of diabetes will potentially increase in the next few years of follow up.

The response rate was also low (up to 30%) at baseline. There may be multiple reasons involved, e.g. the target populations, especially in urban areas, were hard to mobilise; the access to health centres were limited to rural residents where physical examinations were performed; and perhaps more importantly, the healthy volunteer effect. The low response rate would affect the baseline prevalence estimates to a certain extent.

Consequently, the interpretation of the baseline prevalence needs to be with caution and avoid overly extrapolate to a national estimate. The different response rates by sex and by rural/urban location at baseline (data unavailable in the CKB International Coordinating Centre in Oxford) are unlikely to bias the diabetes incidence in the follow-up period, as the follow-up procedures are completely independent of baseline recruitment. We consider the under-reporting at this early stage of the CKB cohort may still be the main reason for the different diabetes incidence rates observed in different study areas.

5.1.4 Generalisability of study findings

Despite the large sample size, one of the potential critiques of the present CKB Study is that the sample population is not nationally representative, arguing that this could possibly limit the generalisability of the results. Indeed, the prevalence of diabetes in the present study (5.2%) was much lower than the most recent national estimate in the 2009 National Diabetes Survey (9.7%)[25]. Since the objective of the study is not to determine the population prevalence or incidence of diabetes, it is likely that the present estimate in the CKB Study is different from other results because of different sampling strategies between studies. Moreover, with a relatively low response rate (~30%) and potential healthy volunteer effect, the present estimate may not fully reflect the prevalence of diabetes in the entire Chinese population. Nevertheless, comparing to the diabetes prevalence reported by the 1994 National Diabetes Survey (2.09%)[70], and 2002 China National Nutrition and Health Survey (2.70%)[91], our result showed a consistent trend of increasing diabetes prevalence in the Chinese population, and the estimate was quantitatively compatible to the InterAsia Study (5.49%)[102] of a nationally

representative sample of the Chinese populations, which was conducted during the same period as the CKB Study.

On the other hand, the national prevalence reported in the 2009 National Diabetes Survey is highly questionable. First of all, the estimate was based on a fairly small sample size (n=46,239), compared to all previous surveys. The smaller sample size may directly affect the prevalence estimate by selection bias. Secondly, the 2009 National Diabetes Survey only recruited people who lived in their current residence for 5 years or longer. As there were a large number of "young migrant workers" in China (229.78 million, age below 50 years), the residents surveyed in this study, particularly in rural areas, were likely to be elderly left at home villages. The significantly higher diabetes prevalence in the elderly population could possibly inflate the overall estimates (this may explain the higher incidence rate of diabetes among rural participants in the present CKB Study). Thirdly, the 1994 National Diabetes Survey (2.07% in both sexes)[70] and the 2002 China National Nutrition and Health Survey (male: 2.5%; female 2.8%)[91], as well as the present CKB Study (male: 5.0%; female 5.4%) all reported an equal or higher prevalence of diabetes in females (this fact may also support the higher diabetes incidence rate in women, as observed in the prospective results of this thesis), while the opposite was reported in the 2009 National Diabetes Survey (male: 10.6%; female: 8.8%)[25]. All these pieces of evidence suggest a potentially flawed sampling and selection bias, hence a limited generalisability of the 2009 National Diabetes Survey.

In brief summary, the large population sample of the CKB Study covers diverse demographic, geographic, socioeconomic and lifestyle characteristics. Although the study is explicitly not a representative sample of the Chinese population, the lack of

national representativeness is not considered to have a major impact on the external validity of results. As with many other important cohort studies like the British Doctors Study, the Framingham Study and the Nurses' Health Study, we believe the lack of national representativeness will not prevent the CKB cohort from producing important findings that are relevant for disease prevention and predication not only to Chinese but also to other populations.[134,135]

5.2 Consistency of findings

5.2.1 Direction and strength of associations

5.2.1.1 BMI

The results from the CKB Study provided compelling and reliable evidence about the causal link between BMI and diabetes, which were also suggested by many other cross-sectional and prospective studies of Chinese populations. In general, our cross-sectional results were quantitatively compatible to most previous cross-sectional studies.[20,22,75,82,83] The prospective association, on the other hand, was quantitatively consistent with the findings of the Singaporean Chinese Study,[87] but much stronger than that of the two small cohort studies conducted in China. In the Shanghai Diabetes Study (n=4,907, 128 incident DM), high BMI (>28kg/m^2) was associated with 128% increased diabetes risk[114] and in the Beijing Project 5-Year Follow-up Study (n=1,566, 126 incident diabetes), people with a BMI over 25 kg/m^2 had a 100% increased diabetes risk.[84] Whereas in the present study, those with a BMI>28 kg/m^2 had a 225% increased risk of diabetes, and those with a BMI>25kg/m^2 had a 206% increased risk of diabetes.

In the CKB, the strength of association between BMI and diabetes incidence was similar to that in several cohort studies of Western populations, particularly in men. For example, in the 21.3 mean years of follow-up in the British Regional Heart Study (n=7,735, 449 incident cases), moderately overweight (BMI: 25-27.5 kg/m^2), considerably overweight (BMI: 27.5-29.9 kg/m^2) and obese (BMI: ≥30 kg/m^2) were found to associate with 2.2-fold (RR=2.24, 95%CI: 1.71-2.94), 3.6-fold (RR=3.57, 95%CI: 2.68-4.74) and 6.2-fold (RR=6.20, 95%CI: 4.58-8.38) increased risks of type 2 diabetes,[106] whereas in the present study the hazard ratios for the same BMI categories were 2.41 (95%CI: 2.25-2.58), 3.79 (95%CI: 3.48-4.14) and 5.58 (95%CI: 4.96-6.27). Our finding is also quantitatively compatible to the U.S. Health Professionals Follow-up Study (n=51,529, 884 incident cases),[136] suggesting that the strength of the association between BMI and diabetes was essentially the same in both Chinese and the U.S. male populations.

In female populations, however, the risks of diabetes in different BMI categories were inconsistent between the present study and some Western cohort studies. Using BMI<21 kg/m^2 as the reference group, the U.S. Nurses' Health Study (aged 30-55, n=42,492, 705 incident cases) reported that the hazard ratios increased from 1.2 (95%CI: 0.8-1.7) in lower BMI level (21-23 kg/m^2) to 18.1 (95%CI: 12.8-25.7) in the highest BMI level (>31 kg/m^2).[58] We applied the same cut-offs to the CKB Study and found that the strength of association was much weaker in Chinese women of the same age range, with a hazard ratio of 8.8 (95%CI: 7.4-10.5) in the highest BMI level. Similarly, in the U.S. Iowa Women's Health Study in which older women were recruited (age >55 years, n=31,702, 1,578 incident cases),[129] the strength of the association between BMI and self-reported

incident diabetes was consistently stronger compared to the Chinese women of the same age range in the CKB Study. On the other hand, the British Women's Heart and Health Study (n=3,404, 128 incident cases) reported that the hazard ratio associated with 1 kg/m^2 increment in BMI was 1.13 (95%CI: 1.10-1.16),[61] whereas it was 1.18 (95%CI: 1.17-1.20) in the present study. This, in contrast to other western cohorts, suggests a stronger effect of BMI in the Chinese women population than in the British women population.

Comparing our findings with a meta-analysis of 32 prospective studies published between 1985 and 2004 (including 21 U.S.- and Europe-based studies), the relative risk of diabetes incidence for per 1 kg/m^2 increment in BMI was significantly higher in the current CKB Study (HR=1.20, 95%CI:1.19-1.21) than the pooled relative risk of the published data (HR=1.16, 95%CI:1.13-1.19).[65]

Although this meta-analysis may support the notions of some previous studies,[87,99] that the lean Chinese populations had a greater risk of diabetes than the Western populations. Nonetheless, this conclusion was not fully supported when comparing our results with current prospective evidence of major Western prospective studies. And the meta-analysis itself may be largely affected by strong cross-population heterogeneity and publication bias. Without more robust data from Western cohorts of a comparable sample size and quality, it seems inappropriate to draw any conclusion about between-population difference in the strength of the association between adiposity and risk of diabetes.

5.2.1.2 Percentage body fat

There is a paucity of evidence for the association between percentage body fat and type 2 diabetes. To our knowledge, only one small Chinese cohort study estimated the total body fat percentage using bioelectrical impedance analysis (i.e. TANITA Body Composition Analyzer). In the Shanghai Diabetes Studies of 2,638 people with 128 incident cases of diabetes, the age and sex-adjusted relative risks for type 2 diabetes were 2.35 (95%CI: 1.23-4.48) and 2.89 (95%CI: 1.43-5.81), respectively in people with intermediate (BF%: 20.1%-25% for men, 30.1%-35% for women) and high (BF% > 25% for men and >35% for women) body fat percentage.[127] With a wide confidence interval of its results, it was hard to compare these findings with the present Study. Nevertheless, the point estimates of hazard ratios at different levels of percentage body fat were somewhat higher for the CKB Study, in which, the hazard ratios for the intermediate and high BF% levels being 2.16 (95%CI: 1.93-2.42) and 4.35 (95%CI: 3.98-4.77), respectively.

In the Western populations, there is also limited data about the association of percentage body fat with diabetes prevalence or incidence. In a cross-sectional study of 4,828 people in Spain, Gómez-Ambrosi et al. observed that body fat percentage had a stronger cross-sectional association with diabetes than BMI.[137] However, with limited information provided in the report, we are unable to directly compare the relative risk of body fat percentage in that study with the CKB population.

5.2.1.3 Waist circumference

The association between waist circumference and diabetes in China was mostly from cross-sectional studies,[24,82,138] as previously described in the Section 2.3.1. Most of these studies showed similar findings with the present CKB Study, except for the CNNHS

2002,[91] which suggested a stronger association between waist circumference and diabetes prevalence. This steeper association was probably due to the relatively younger age (mean: 48.6 years) of the study participants compared to other studies.

The results from the present CKB Study was also consistent with the prospective evidence from the Hong Kong Cardiovascular Risk Factor Prevalence Study, which followed around 2,000 participants for an average of 6.4 years. It reported that the adjusted hazard ratio for people with central obesity (≥90 cm for male, ≥80 cm for female) was 3.3 (95%CI: 2.2-4.8),[128] same as that seen in the CKB Study. Comparatively, a much lower relative risk was reported by the Beijing Project 5-Year Follow-up Study, with only a 40% increased risk of diabetes for the centrally obese group (≥90 cm for male, ≥80 cm for female).[84] Again, the findings of the Beijing Project 5-Year Follow-up Study was probably unreliable due to its small sample size, limited incident cases and a significant proportion of people loss to follow-up.

The association of diabetes with waist circumference in the CKB male population appeared similar to some European and the U.S. male cohorts, such as the U.S. Health Professionals Follow-up Study[95] and the MONICA/KORA Augsburg Cohort Study (n=6,012, 401 incident cases).[59] By contrast, waist circumference appeared to have a stronger effect in Western female populations. In the Iowa Women's Health Study of an older U.S. female population (55-69 years),[139] the strength of association across waist circumference quintiles was twice as strong as that found in the same age group in the present CKB Study. Similarly, a stronger effect of waist circumference for diabetes was also observed in the U.S. Nurses' Health Study of younger female adults. In this study, the relative risks increased from 1.0 (reference) in the lowest waist circumference group

(WC<71 cm) to 22.4 (95%CI: 14.8-33.9) in the highest group (WC>96.4 cm).[58] When applying the same waist circumference cut-offs and age group, it only increased to 5.0 (95%CI: 4.5-5.6) in the CKB Study. The stronger effect was also observed in the British Women's Heart and Health Study, although the difference was not statistically significant. The hazard ratio for every 5 cm increment in waist circumference was 1.45 (95%CI: 1.36-1.54) in this British cohort,[61] while the same hazard ratio was 1.40 (95%CI: 1.38-1.43) in the present study.

Compared to the same meta-analysis mentioned in Section 5.2.1.1, the effect of waist circumference appeared somewhat stronger in the Western populations. For every 5 cm increment of waist circumference, there was a 45% (95%CI: 31%-62%) increased risk of diabetes for both sexes combined in the pooled analysis of the Western populations,[65] while there was a 41% (95%CI: 38%-44%) increased risk in the CKB Study.

By comparing our findings with the currently available data from major prospective studies and meta-analysis, there was suggestive evidence that the association between waist circumference and diabetes may be stronger in the Western populations, particularly in females, although some of the evidence lacks statistical significance. Again, it is still yet to reach a conclusion as more prospective evidence from the Western populations is needed for a more thorough comparison between Chinese and the Western populations.

5.2.1.4 Waist hip ratio

Several studies analysed the cross-sectional association between waist hip ratio and the diabetes prevalence in the Chinese populations and their findings were broadly similar to that seen in the present CKB data. In the Shanghai Women's Health Study, the odds

ratios for diabetes were 1.58 (95%CI: 1.00-2.51), 3.36 (95%CI: 2.21-5.09) and 6.05 (95%CI: 4.05-9.04) in the 2nd, 3rd, and 4th quartiles, respectively,[82] which was highly compatible to those found in the present CKB Study. A similar strength of cross-sectional association was also observed in the Guangzhou Biobank Study baseline analysis.[83] Comparatively, the InterAsia Study reported a weaker association across WHR tertiles.[24] Such association reported was probably less reliable due to its failure to control for possible confounders as described previously in Section 2.5.1.

Only two Chinese cohort studies examined the prospective association between waist hip ratio and diabetes, each with relatively small sample size or a significant loss to follow up. In the Beijing Project Follow-up Study, the relative risk of diabetes in people with a higher WHR (≥0.90 for men, ≥0.85 for women) was 2.91 (95%CI: 1.46-5.80),[84] as opposed to 3.19 (95%CI: 2.77-3.69) in men and 3.31 (95%CI: 2.92-3.76) in women in the CKB Study. In the Shanghai Women's Health Study (n=72,773, 99 incident cases), on the other hand, the relative risks for diabetes were only found statistically significant in the last quintile (HR=2.45, 95%CI: 1.10-5.48),[98] and the strength of association was much weaker than the CKB Study, due chiefly to the small number of incident diabetes cases involved.

Unlike other anthropometric indicators, the strength of association between WHR and diabetes incidence were highly consistent between the present CKB Study and other major Western cohort studies.[58,59,95] Moreover, the relative risk associated with per 0.05 increment in WHR found in the CKB Study (HR=1.53, 95%CI: 1.49-1.57) was also highly consistent with the findings of a meta-analysis of 32 prospective cohort studies (HR=1.56, 95%CI: 1.41-1.75).[65]

5.2.1.5 Waist Height Ratio

Waist height ratio, as another central adiposity indicator, is less well studied in the Chinese populations. The CNNHS 2002 Study only analysed the association between waist height ratio and metabolic syndromes,[100] which was hardly comparable to the current CKB Study. The meta-analysis of the DECODA Study reported that for 1-SD increment in WHtR, the pooled odds ratios for diabetes were 1.62 (95%CI: 1.40-1.87) in men and 1.57 (95%CI: 1.38-1.76) in women,[90] much weaker than 1.91 (95%CI: 1.81-2.01) and 1.96 (95%CI: 1.91-2.10) seen in the CKB Study.

No prospective study on the WHtR-diabetes association has previously been reported for the Chinese population. There is also limited prospective evidence from Western populations. With five years of follow-up, the U.S.-based Insulin Resistance Atherosclerosis Study (n=1,073, 146 incident cases) found that the relative risk for 1-SD increment in waist height ratio was 1.79 (95%CI: 1.49-2.15).[140] Compared to our findings, it appeared that the strength of association between waist height ratio and diabetes was stronger in the Chinese population than in the U.S. population, as for per 1 standard deviation increment in waist height ratio, there was a 92% (95%CI: 88%-95%) increased risk of diabetes for both sexes combined.

5.2.1.6 Hip circumference

Several studies of the Western populations have shown that hip circumference was inversely associated with diabetes risks for any given levels of waist circumference.[141-144] In a recent meta-analysis of 11 studies, people in the highest category of hip circumference were reported to have a 43% reduced risk for diabetes, compared to those in the lowest category.[145] Since the hip circumference cut-offs were not clearly

elucidated in this meta-analysis, it is therefore difficult to compare it directly to our results.

In the Chinese population, the independent effect of hip circumference for diabetes has not been thoroughly studied. One cross-sectional[82] and one prospective study[146] found a positive association between hip circumference and diabetes in Chinese populations. However, neither study accounted for waist circumference or BMI. The recent Shanghai Women and Shanghai Men's Health Studies (n=124,373 for both studies combined, 2,754 incident cases) provided the only prospective evidence, in which, there was a protective effect of hip circumference for diabetes after adjusting for both waist circumference and BMI.[147] Despite a similar declining trend across hip circumference quintiles, the strength of the inverse association was not as strong as what we found in the current CKB Study: for men and women in the highest hip circumference quintile, there was a 22% and 35% reduced risk for diabetes in the Shanghai Women and Shanghai Men's Health Studies, while in the present study there was a 50% reduced risk for both men and women. Such a difference may be accounted for by difference in age between the two studies (mean: 56.4 years versus 52.1 years). And perhaps more importantly, the Shanghai Women and Shanghai Men's Health Studies used the urine glucose test to identify and exclude baseline diabetes cases. The low sensitivity of the urine test in diagnosing diabetes could result in misclassification of baseline cases, hence biased the prospective association towards the null.

5.2.2 The best single predictor for diabetes

The cross-sectional analysis of the current CKB Study suggested that central adiposity measures had a stronger association with diabetes prevalence, compared to the overall

adiposity measures. We also found that among central adiposity measures, the strongest association was observed for waist hip ratio, followed by waist circumference and waist height ratio. These findings confirmed those reported in most of the previous cross-sectional studies in China.

For example, both the Shanghai Women's Health Study[82] and the Guangzhou Biobank Study[83] reported in their baseline analyses that type 2 diabetes prevalence was more strongly related to waist hip ratio than that with waist circumference; and the association with BMI was the weakest of the three measures. In the InterASIA Study in which a nationally representative sample of Chinese adult population was recruited, central obesity was again found more closely related to diabetes than was overall obesity.[102] Same finding was also shown in the Obesity in Asia Collaboration Study.[67] However, in both the InterASIA and the Obesity in Asia Collaboration studies, waist hip ratio was found only marginally better than other indicators in discriminating prevalent diabetes cases. This was probably because of the small sample size involved in the InterAsia Study, and poor controlling for possible confounders in both studies, as previously described. The meta-analyses of the DECODA Study[90] (which involved five Chinese studies) and the EpiDREAM Study[96] (which involved non-Chinese populations from 191 centres in 21 countries) both showed a significantly stronger association between central adiposity measures and diabetes prevalence; however, due to the large heterogeneity and possible publication bias involved, neither meta-analysis was conclusive in identifying the best indicator among all central adiposity measures.

While current cross-sectional evidence was strongly in favour of central adiposity measures, especially the WHR, in association with diabetes prevalence, little prospective

evidence in Chinese populations was available about the relative importance of different adiposity measures in association with incident diabetes. Most available prospective evidence was based on Western populations, with mixed findings.

In comparing central and overall adiposity measures, the MONIKA/KORA Augsburg Cohort Study found that the association with type 2 diabetes incidence was weaker for waist circumference than for BMI in men, and both waist circumference and BMI were equal in women.[59] However, in the British Regional Heart Study, the British Women's Heart and Health Study and the EPIC-Potsdam Study, BMI and waist circumference both showed similar associations in men, while waist circumference appeared to be a stronger predictor in women.[60,148] This ambiguity of the relative importance of different adiposity measures possibly reflected a lack of power due to the small sample sizes of these studies. The U.S.-based Iowa Women's Health Study and the Health Professionals Follow-Up Study, on the other hand, both found that waist circumference was the strongest predictor for diabetes.[95,95,139] Although the better indicator between waist circumference and BMI was still controversial, WHR was consistently suggested by the above studies,[59,59,95,139,148] as the weakest predictor of diabetes.

Meanwhile, there were also a number of studies which suggested an equivalent ability among different adiposity measures in predicting diabetes. In the 9-year follow-up of the Atherosclerosis Risk in Communities cohort in the U.S. (n=12,814, 1,515 incident cases), no one measure was found significantly better than others.[149] The same conclusion was found for another comparative study of 4 British cohorts.[61] A relatively strong piece of evidence was from a meta-analysis of 32 cohort studies across Asia, Europe and the U.S. It confirmed that all the adiposity measures had similar associations

with incident diabetes, and therefore central adiposity indicators showed no obvious advantage over BMI.[65]

As few large scale cross-sectional or prospective cohort studies measured body composition using bioimpedance, substantial uncertainty remained about the relative importance of percentage body fat. In an analysis of the combined data from the TULIP Study, the EPIC-Potsdam Study and the MONIKA/KORA Augsburg Cohort Study, percentage body fat was not directly measured but a surrogate derived from other adiposity measures. The surrogate of percentage body fat was found not as strong a predictor of diabetes as BMI, while waist circumference was the strongest.[150] This study provided only weak evidence as the validity of the surrogate was still yet to be established. The only direct evidence was from one small cohort study of Pima Indians (n=1,614, 322 incident cases), which compared the bioelectrical impedance measure of percentage body fat with other anthropometric measures in association to diabetes. It showed that the predictive value of percentage body fat for diabetes was less strong compared to BMI, waist circumference and waist height ratio.[151] Despite the relatively small sample size, this study was consistent with the present CKB findings.

In comparison to previous studies, the CKB Study provided a unique opportunity to systematically assess the relative importance of different anthropometric measures in predicting diabetes in the Chinese populations. Despite some previous cross-sectional evidence, the present study added important and reliable prospective evidence to this particular population. Moreover, the present study also allowed for reliable comparison between the Chinese populations and other populations. Our results from the prospective analyses confirmed the findings of many Western studies and suggested

that both central and overall adiposity measures were equally important in predicting future diabetes. Similar to several Western cohort studies, our results also provide strong evidence that some measures, i.e. waist circumference and waist height ratio, were moderately more strongly associated with incident diabetes than were others, i.e. BMI, waist hip ratio and percentage body fat.

5.2.3 Independent and joint associations of central and overall adiposity with diabetes

In the present CKB Study, we found that central adiposity measures were strongly associated with diabetes prevalence that was largely independent of BMI; but overall adiposity was no longer associated with diabetes prevalence after controlling for central adiposity. The prospective analyses, on the other hand, showed that both central and overall adiposity were independently associated with incident diabetes after adjusting for each other, and the independent associations with diabetes appeared somewhat stronger for central adiposity than for overall adiposity.

Several cross-sectional studies in China have assessed the independent association of central adiposity. These studies, in particular the InterASIA Study, Shanghai Women's Health Study and Guangzhou Biobank Study, all found that central adiposity measures (WC or WHR) were strongly associated with diabetes prevalence at any given level of BMI.[82,83,101] In accord with the present CKB study, BMI was no longer associated with diabetes after controlling for central adiposity in all the three studies.

Despite the limited evidence in China, the prospective associations found in the present CKB Study agreed with most available Western studies. Two large Europe-based cross-

sectional studies showed that central and overall adiposity measures were both significantly associated with diabetes after mutual adjustment.[96,152] This was well supported by the prospective evidence from four cohort studies, including the U.S.-based Nurses' Health Study, the Health Professionals Follow-Up Study, as well as the joint analysis of the British Regional Heart Study and the British Women's Heart and Health Study. In addition, all the four cohort studies indicated that among central adiposity measures, waist circumference appeared to be a stronger independent predictor for diabetes than other indicators,[58,95,148,153] which was also highly consistent with our present finding. We found only one piece of evidence in the Iowa Women's Health Study, which suggested that the independent effect of BMI was stronger than that of waist hip ratio.[129] In that study, however, both central and overall adiposity were not directly measured but based on self-report. This could potentially involve measurement error and may therefore largely affect the validity of waist hip ratio.

In addition to the independent effects, the present CKB Study also showed the joint effects of central and overall adiposity. In both cross-sectional and prospective analyses, the increasing waist circumference, waist hip ratio and waist height ratio were all shown to be associated with higher diabetes risks within low, medium and high BMI categories. These findings were consistent with those of major cross-sectional studies of the Chinese,[82,101] American,[154] and European[96,152] populations. They were also highly consistent with the prospective evidence from the Nurses' Health Study,[58] Health Professionals Follow-Up Study,[95] Iowa Women's Health Study,[129] and the MONICA/KORA Augsburg Cohort Study.[59]

5.2.4 Effect modification of age and sex

Age

The present CKB Study provided strong evidence that the effects of adiposity for diabetes were significantly modified by age, with participants at younger age having a greater excess risk for a given difference of adiposity. At age 35-49 years, each 1 standard deviation increase in BMI was associated with a hazard ratio of 1.97 (95%CI: 1.85-2.11), compared with 1.71 (95%CI: 1.59-1.84) at age 65-79 years. Similarly, for waist circumference, the difference in the risks between the two age groups was about 40%, being 2.15 (95%CI: 2.00-2.31) and 1.75 (95%CI: 1.62-1.89), respectively. Similar but less reliable findings have also been reported previously in both Chinese and the Western populations: in the Singaporean Chinese Health Study of 52,000 people, the strength of the BMI-diabetes association was greatly attenuated with increasing age.[87] The U.S.-population based Cardiovascular Health Study found that people with higher adiposity (measured by BMI, WC and WHR) in the age group of 65-74 years generally doubled the risks of diabetes to those of 75 years of age or older.[155] Comparing the findings of the Iowa Women's Health Study (aged 55-69 years) with the Nurses' Health Study (aged 30-55 years), same level of elevated central or overall adiposity was consistently associated with lower diabetes risks in the Iowa cohort of elderly women.[58,139]

Sex

In the present CKB Study of Chinese populations, we also found that the association between adiposity and diabetes appeared somewhat stronger in men than in women,

although such sex difference was only significant for BMI (males: HR=1.99, 95%CI: 1.88-2.11; females: HR=1.78, 95%CI 1.71-1.86). The current evidence from other studies was somewhat inconsistent. In the Nurses' Health Study and the Health Professional Study, Hu et al. claimed that BMI, waist circumference and waist hip ratio were a stronger predictor of diabetes in women than in men in the U.S. population.[153] Similar pattern was also observed in the British Regional Heart Study and the British Women's Heart and Health Study,[148] but the difference between sexes was not statistically significant. In Asian populations, the DECODA Study of cross-sectional data from 16 Asian cohorts reported a stronger risk of diabetes for per 1 standard deviation increment in both central and overall adiposity measures in women (OR_{BMI}=1.59, 95%CI: 1.48-1.70), compared to men (OR_{BMI}=1.52, 95%CI: 1.41-1.64).[90] The finding may not be fully reliable because of the cross-sectional study design and a strong heterogeneity in Asian populations. In addition, as only a limited number of Chinese studies were included in this study, the finding may not be generlisable to Chinese populations. Another meta-analysis of prospective evidence suggested that diabetes was more strongly associated with BMI and waist hip ratio in women, while it was more strongly associated with waist circumference in men.[65] However, since neither of the two meta-analyses provided results that were of statistical significance, there was still no concrete conclusion of the effect modification by sex.

5.3 Interpretation

5.3.1 Plausibility of the association between adiposity and diabetes

At present, the exact pathogenic mechanisms underlying any association between obesity and insulin resistance and pancreatic β-cell failure are yet to be understood. There are, however, a number of theories and hypotheses based on experimental and clinical evidence. One of the important mechanisms linking adiposity with diabetes is described in the "lipotoxicity theory", in which non-esterified fatty acids (NEFAs) and triglycerides have long been viewed as one of the determining factors of insulin resistance and NIDDM.[156] By targeting the liver, NEFAs could enhance certain gluconeogenic and glycogenolysis enzymes, leading to hyperglycaemia.[81] Meanwhile, NEFAs could directly suppress β-cell insulin secretion,[157] and promote apoptosis of these cells.[158] In addition, excessive NEFA β-oxidation has been shown to affect skeletal muscle metabolism through several pathways (e.g. inhibition of glycogen synthase and hexokinase, and GLUT4 synthesis and translocation), leading to insulin resistance in myocytes.[159]

Similar to the "lipotoxicity theory", is the recently developed "ectopic fat storage hypothesis". This proposes that positive energy balance, in combination with inadequate adipose tissue mass, could lead to impaired fat oxidation and divert lipids for storage in non-adipose organs like the liver,[160] skeletal muscle,[161] and pancreatic β-cells.[162] This ectopic fat storage is believed to eventually cause insulin resistance, glucose intolerance and diabetes.[163]

Excess fat has also been found to cause insulin resistance through various other mechanisms.[161,164] In particular, there is a more systematic view of adipose tissue as an "endocrine organ"; through responding to various hormone systems and the central nervous system, as well as expressing and secreting important factors like leptin, adiponectin and resistin etc., both central and peripheral adipose tissues contribute to regulation of whole body metabolism and energy homeostasis.[165]

Another major mechanism proposed to underlie the association between adiposity and diabetes is the "inflammatory state theory". This suggests that adipose tissue could induce a "low-grade inflammatory state" throughout the body by producing pro-inflammatory molecules like C-reactive protein, TNF-α, transforming growth factor β and interleukins (IL-6, IL-8 and IL-10).[166] It then deregulates nutrient homeostasis through the cross-talk between insulin receptor signalling and the inflammatory pathways, leading to development of insulin resistance and type 2 diabetes.[167]

Although further study is needed for a clearer understanding of the underlying mechanisms, current clinical and laboratory evidence has provided some pivotal insights and helped to explain the associations of obesity with diabetes, as observed in the present study.

5.3.2 Best single predictor

Although no adiposity measure was found to be statistically superior to others in relation to future diabetes in the CKB Study, some central adiposity measures appeared to be moderately better than others. The relative importance of each adiposity measure

may be accounted for by its underlying biological mechanisms as well as its ability to accurately represent the different adipose depots.

A number of studies have suggested that abdominal adiposity, and visceral fat in particular, may play a vital role in the development of diabetes.[81,168-170] Central adiposity measures are more strongly correlated with abdominal fat mass (including both visceral and abdominal subcutaneous fat) as a surrogate index, compared to the overall adiposity measures.[171] With regards to central adiposity measures, waist circumference has been repeatedly reported to be more closely correlated with abdominal visceral adipose tissue than the WHR.[172-174] This may explain the relatively stronger risk of diabetes observed for waist circumference and waist height ratio (which takes into account both waist circumference and body frame) in several Western cohort studies,[95,95,139] as well as in the present CKB Study.

Fat depots elsewhere are also considered metabolically active. The evidence of non-portal mechanisms for insulin resistance,[166] along with the theories of "endocrine organ"[165] and "inflammatory state",[167] underlie the biological plausibility of overall adiposity in relation to the development of diabetes. Nevertheless, the measure of BMI appears to be an imperfect surrogate of overall adiposity: firstly, BMI cannot accurately detect the individual variation in total body adiposity as well as regional adiposity distribution;[175] and secondly, it reflects fat body mass, lean body mass and bone mass altogether. While bone mass is neutral to diabetic risks, lean body mass, especially the skeletal muscle, is the major metabolic organ responding to insulin to regulate plasma glucose homeostasis.[176] The protective effect of lean body mass, in theory, could attenuate the risk of diabetes associated with BMI. These properties of the index may

therefore explain why BMI was somewhat, if not significantly, weaker than central adiposity measures in predicting diabetes.

The findings from the present CKB Study as well as several other studies[150,151] suggested that the percentage body fat was probably less strong than other anthropometric measurements in predicting diabetes. This could possibly be explained by the nature of the measure. Like BMI, percentage body fat is also unable to detect variation in regional adiposity distribution. Moreover, the percentage body fat derived from bioelectrical impedance analysis is not considered the "gold standard" to reflect actual body fat composition. It has been reported that the measure may be heavily influenced by dehydration,[177] diet[178] and physical exercise right before the measure was taken.[179] This likely misclassification of exposure probably explains, in particular, why percentage body fat is a less sensitive indicator of overall adiposity than others.

As with many other studies[59,59,95,139,148], waist hip ratio consistently appeared to be a weaker predictor for diabetes in the present study. Although WHR is considered a valid measure of central adiposity, the relation with abdominal fatness (measured by dual-energy X-ray absorptiometry, DXA) was found to be weaker for WHR than for waist circumference.[180] WHR is also believed to be less predictive for visceral fat then other central adiposity measures.[181,182] Because of the high correlation between waist and hip circumferences, individuals with the same WHR can have different adiposity levels and metabolic profiles. It potentially misclassifies adiposity, therefore underestimating the association with diabetes. The insensitivity of this compound index is a major limitation for using this to predict future diabetes outcome.

5.3.3 Independent and joint association of central and overall adiposity measures

Our data showed that at any given level of overall adiposity, measures of central adiposity were significant predictors of diabetes, and vice versa. In the joint analyses, both central and overall adiposity measures added additional information on diabetes risks on top of each other. These findings, again, suggest the independent effects of overall and central fat accumulation on the development of type 2 diabetes.

As previously discussed in Section 5.3.1 and 5.3.2., the observed independent effect of central and overall adiposity may be explained by the different pathophysiological mechanisms involved in the development of diabetes. For example, the lipotoxicity mechanism is one of the major theories to link central adiposity with diabetes.[81] Among different adiposity depots, visceral fat is considered both metabolically and lipolytically more active than peripheral adipose tissues,[168] as it is closely located around essential metabolic organs like the liver and pancreas. Visceral fat is therefore believed to have a significant role in releasing NEFAs into the liver and blood stream through the portal vein, causing lipotoxicity (also known as the portal hypothesis).[183] In addition, central adiposity may play a role in the "ectopic fat storage hypothesis". Specific to this theory, a critical visceral adipose tissue threshold (CVATT) has been hypothesized,[170] beyond which, lipids begin to store in other non-adipose tissues, and cause insulin resistance.

Despite the "portal hypothesis", current clinical evidence suggests visceral adipose tissue contributes about 15% of the total NEFAs in systemic circulation (up to 40% in extremely obese cases); and the majority of NEFAs (up to 75%) were released from the

subcutaneous adipose tissues of the trunk and upper extremities.[184] In keeping with this finding, it was argued that other fat depots may have a stronger impact on peripheral insulin sensitivity than visceral fat.[185] In addition, the theories of "endocrine organ"[165] and "inflammatory state",[167] as previously discussed, both suggest a more integrated metabolic role of adiposity as a whole, rather than isolated compartments with different functions.

The above evidence, therefore, strongly associates diabetes with both overall and central adiposity. In the shared and independent pathophysiological pathways, both adiposity measures could contribute independently and jointly to the development of diabetes, as was observed in the present study.

5.3.4 Inverse association of diabetes with hip circumference

The mechanisms underlying a possible protective effect of hip circumference on diabetes have not yet been established. Nevertheless, a number of hypotheses, in combination with laboratory evidence, could potentially explain the protective effect of hip circumference observed in the CKB Study, as well as in many other large population studies.[141-144]

Skeletal muscle is a major regulator of systemic insulin sensitivity and larger hip circumference may indicate a greater skeletal muscle mass in the gluteal region.[186] Larger hip circumference may also reflect increased femoral and gluteal subcutaneous fat mass, hypothesized to act as a "sink" for NEFAs. The low level of basal lipolysis and lipolytic stimulation in the femoral and gluteal subcutaneous fat masses[169] could "trap" fatty acids and reduce the rate of free fatty acid release into the blood stream. It is thus

postulated to protect the liver and muscle from high exposure to NEFAs,[110] a major risk factor for insulin resistance. Moreover, a recent review of *in vivo* and *in vitro* studies concluded that a beneficial adipokine profile (e.g. a higher leptin and adiponectin levels, and lower levels of inflammatory cytokines) was associated with gluteal and femoral fat, which could reduce the risks of insulin resistance and diabetes.[187]

The current hypotheses and evidence could perhaps partly explain the inverse association between hip circumference and diabetes, but more research is needed to thoroughly understand the metabolic function of this specific adiposity depot.

5.3.5 Modifying effects of age and sex

Age

The weaker association of adiposity measures with diabetes risk among elderly people observed in the present study has been found in several other studies.[87,155] Older age is generally considered to be associated with a substantial decline in lean body mass and a relative increase in fat mass,[188] especially visceral fat,[189] at a given BMI. This phenomenon is also observed in the CKB Study. In theory, the change in body composition and increase in fat mass should increase the risk for diabetes in people of older age. We consider two possible explanations for our findings: (1) different pathophysiological pathways may be involved in elderly-onset diabetes, which are independent of adiposity. Increasing evidence has demonstrated that the ageing process is directly linked to multiple β-cell disorders[190,191] and apoptosis.[192] These age-related pathways could bypass body adiposity and directly affect insulin secretion and regulation, therefore potentially attenuating the adiposity-diabetes association in

elderly people; (2) possible selection bias may be involved; healthy elderly participants were recruited to the CKB Study at baseline, and these non-diabetic volunteers may have better insulin sensitivity or β-cell function despite their older age, or may be genetically resistant to diabetes. Such selection bias could also affect the association between adiposity and diabetes.

Nevertheless, the weaker association observed for the elderly group does not undermine the absolute effect of adiposity for diabetes. With a high diabetes incidence rate among the elderly people, the absolute diabetic risk associated with excess adiposity remains high for this specific age group.

Sex

Despite epidemiological evidence suggesting the association between adiposity and diabetes is stronger in women than in men[65,148,153], the opposite was observed in the present study. Based on computed tomography or MRI, it has been consistently reported in Western populations that men generally had significantly larger visceral depots than did women,[193-196] and hence, were at higher risk of metabolic and cardiovascular diseases. Similarly, Chinese men have been reported to have greater levels of visceral adipose tissue than women at any given age, BMI and total fat mass.[197,198] Because of the important pathogenic role of visceral adipose tissues in insulin resistance and hyperglycaemia, a more centrally obese (particularly if due to excess visceral fat) male population may be at higher risk for diabetes, as was observed in the present study. Furthermore, laboratory evidence exists to support our findings, suggesting there may be distinct differences between the sexes in fatty acid mobilization

(i.e. gender-specific adrenoceptor sensitivity, and enhanced hormone-sensitive lipase in visceral fat cells in obese men),[199] and storage (i.e. a larger subcutaneous fat depot in women and visceral fat depot in men),[200] which potentially protect women from over exposure to free fatty acids, thus reducing the risk of diabetes.

5.4 Clinical and public health implications

With a more than five-fold increase in the prevalence of diabetes in China over the past 30 years, it is imperative that a reliable understanding of the association between obesity and diabetes is established to quantify the level of risk, to provide clinical guidance and to enable important prevention strategies. Based on the findings of this thesis, we consider several major clinical and public health implications.

Firstly, despite the debates over the "best anthropometric indicator" for diabetes amongst different central and overall adiposity measures in the Chinese population, we demonstrate that all anthropometric measures (BMI, percentage body fat, waist circumference, waist hip ratio and waist height ratio) perform broadly similar in defining obesity and predicting diabetes risk. Appropriate anthropometric measures should, therefore, be selected based on individual clinical settings, preference and availability of measurement instruments. All indicators, irrespective of whether measure for central or overall adiposity, should provide similar prediction abilities for diabetes risk.

Nonetheless, waist circumference seems to be a useful adiposity measure for public health purposes. It is moderately more strongly associated with diabetes risk and it is a cost-effective "one-step" measure that can be easily performed in population-based diabetes surveillance and prevention programmes. As China has a large population and

an increasing pandemic of diabetes, such a relatively simple measure is especially valuable when targeting public health interventions at a population level. Moreover, compared with compound indices such as BMI and waist hip ratio, waist circumference is easy to interpret and is understood by the public. This makes it a powerful tool for public health education and self-monitoring of individuals' diabetes risks.

Secondly, the finding that central adiposity contributes independently to the development of diabetes has strong clinical and public health implications. Obtaining information of central obesity (e.g. waist circumference) in addition to BMI could provide important extra information to evaluate individual patient's diabetes risk. This may be particularly important in Chinese populations where there is a greater susceptibility to central obesity at any given level of BMI. With the evidence shown in this study, it is advisable that the Chinese clinical guidelines should incorporate both central and overall adiposity measures in assessing individual risk for diabetes.

On the other hand, knowing waist circumference over and above BMI may also benefit other clinical interventions. For example, when a patient needs to go through metabolic surgery, a current threshold of BMI > 35 kg/m^2 is normally applied. Since the combined effect of both central and overall adiposity on cardiovascular disease risk and other complications is beyond BMI alone, it is plausible that additional central adiposity measures should be incorporated into the clinical decision making process.

The additional assessment of waist circumference could also help identify diabetes risk at population level. With both central and overall adiposity measures, it will be more accurate for diabetes prevention and education programmes to target on high risk populations.

Thirdly, we observed a linear association with diabetes risk for people with a BMI ≥ 18.5 kg/m^2 and across the entire range of waist circumference in the CKB. Despite the recommended anthropometric cut-offs for Chinese populations by the World Health Organization[201] and the International Diabetes Federation,[202] we did not find a specific point at which there was a sharp increase in the risk of diabetes in this large cohort. This implies that clinical guidelines and public health interventions should not solely target on specific anthropometric values. Effective diabetes prevention and treatment should always aim for reducing adiposity at individual and population levels.

In addition to these implications, it should be noted that the CKB cohort comprises a relatively older generation, for whom the exposure to over-nutrition often took place later in their adult life--the problem of overweight and obesity in the Chinese population is still a relative recent phenomenon. However, this will be much different for the younger Chinese generation, who will experience more prolonged exposure to increased adiposity and a greater diabetes risk throughout their life course. The strong impact of obesity on the younger generations requires immediate public health actions at both policy and programme levels to avoid a future pandemic of diabetes in the Chinese population.

5.5 Implication for future research

As the present study was based on a relatively short period of follow-up and the health insurance data was not available by the time all the prospective analyses were conducted, future research should be primarily focused on validating the findings of this thesis with the latest and more complete follow-up data (including both the update-to-

date chronic disease reporting data and the recently available health insurance data). A significantly larger number of incident diabetes cases will strongly increase the statistical power and the precision of the risk estimates. Moreover, it will also reduce reverse causation by excluding the first few years of follow-up.

With more incident diabetes cases, it is also important to investigate other potential effect modifications by conducting subgroup analyses. For example, after stratifying the participants by levels of physical activity, alcohol use and smoking status, the strength of association between adiposity and diabetes could be explored within each subgroup. The stratified analyses will not only increase precision of the effect estimation by taking into account subgroups that may be affected differently, but also help develop potential causal hypotheses of the underlying biological mechanisms.

As an important next step, the CKB Study offers a unique opportunity to explore the genetic association between obesity-related genes and diabetes. With the planned genome sequencing projects, the future genetic analyses will provide strong evidence to assess whether the observed associations in this thesis are reliable and causal.

6. Conclusion

With the data from this well-characterised and well-phenotyped large cohort of the Chinese men and women, we identified a strong positive link between adiposity and diabetes, irrespective of which measure is used. The association between anthropometric measures and diabetes risk is generally linear across the normal adiposity ranges in this particular population.

Although different anthropometric measures have similar relations with diabetes, measures of central obesity (e.g. waist circumference or waist-height ratio) appear moderately more strongly associated with diabetes, compared with measures of overall adiposity (e.g. BMI, percentage body fat). Among the measures of central obesity, waist circumference seemed to be the most informative in predicting future diabetes risk and waist-hip ratio is the most informative in indicating prevalent diabetes.

In addition, this thesis demonstrates reliably that both central and overall adiposity contribute independently to the development of diabetes, and the joint measurement and consideration of both overall and central adiposity can better predict diabetes risks than either individually.

Furthermore, evidence from this thesis suggests a significant protective effect of hip circumference on diabetes in the Chinese population. This finding supports an increasing amount of evidence from many other populations.

Despite the many hypotheses regarding the mechanisms underlying obesity-induced diabetes, no firm conclusion has been reached. Further research is needed to explore the different effects of various adipose depots through pathological, molecular and perhaps genetic studies.

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8. Appendix

Appendix I: Baseline Survey Questionnaire

25 March 2004

Kadoorie Study of Chronic Disease in China

【Questionnaire】

Section 1: Background information

1.1 Study ID: ☐☐☐☐☐☐☐☐☐ *(The date & time of interview will be recorded by computer)*

1.2 Name_____, Sex：Male ☐ Female ☐ , **Name of spouse**_____

1.3 Date of birth: ☐☐☐☐ar ☐☐onth ☐☐

1.4 National ID number (if no, put #) ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

1.5 Home address：_____ Province _____ City_____ District/County _____ Street/Village

Home telephone: Not available ☐， Y☐☐☐-☐☐☐☐☐☐☐☐☐☐

1.6 What is the highest level of school education you ever received?

- ☐ No formal school
- ☐ Primary School
- ☐ Middle School
- ☐ High School
- ☐ Technical school / college
- ☐ University

1.7 What is your current occupation?

- ☐ Agriculture & related workers
- ☐ Factory worker
- ☐ Administrator / manager
- ☐ Professional / technical
- ☐ Sales & service workers
- ☐ Retired
- ☐ House wife / husband
- ☐ Self-employed
- ☐ Unemployed
- ☐ Other or not stated

1.8 How many people living together in the household? ☐☐ sons

1.9 What is your current marital status?

- ☐ Married
- ☐ Separated / divorced
- ☐ Widowed
- ☐ Never married

1.10 What is the total income last year in your household?

- ☐ <2,500 yuan
- ☐ 2,500-4,999 yuan
- ☐ 5,000-9,999 yuan
- ☐ 10,000-19,999 yuan
- ☐ 20,000-34,999 yuan
- ☐ ≥35,000 yuan

1.11 Do you have any health care cover and following items in your household?

	Yes	No
Health care cover	☐	☐

☐ ☐ Own house / apartment

☐ ☐ Toilet for private use

☐ ☐ Telephone or mobile phone

☐ ☐ Motor vehicle (e.g. car or motorbike)

☐ ☐ Holiday during last five years

Section 2: Tea drinking

2.1 During the past 12 months, how often did you drink any tea?

☐ Never or almost never
☐ Only occasionally
☐ Only at certain seasons
☐ Every month but less than weekly
☐ Usually at least once a week → ***Go to Q2.2***

2.1a In the past, did you ever have a period of at least 1 year during which you usually drank tea at least once a week?

☐ Yes → 2.1b if so, how long ago did it end? ☐☐ s } ***Go to section 3***
☐ No

2.2 During the past 12 months, on how many days did you drink tea in a typical week?

☐ 1-2 days/week
☐ 3-5 days/week
☐ Daily or almost every day

2.3 At about what age did you start drinking tea in most weeks? ····· ☐☐ ears

---

2.4 On days when you drink tea, how many cups do you usually drink? (choose one only)

Green /Jasmine tea ····· ☐☐ lay

Oolong tea ····· ☐☐ day

Black tea ····· ☐☐ /day

Other tea ····· ☐☐ ·· cups/day

2.5 How often do you change tea leaves during a day? …… ☐☐ times

2.6 About how much tea leaves do you usually add each time? …… ☐☐ Grams

2.7 What strength of tea do you usually prefer to drink?

- ☐ Weak
- ☐ Moderate
- ☐ Strong

2.8 At about what temperature do you usually drink your tea?

- ☐ Room temperature / warm
- ☐ Hot
- ☐ Burning hot

2.9 Has your tea consumption changed significantly compared with that some years ago?

☐ About the same as before, ☐ Has increased a lot, ☐ Has decreased a lot

Section 3: Alcohol consumption

3.0 Have you drunk any alcohol today? ☐ Yes, ☐ No

3.1 During the past 12 months, how often did you drink any alcohol?

- ☐ Never
- ☐ Only occasionally
- ☐ Only at certain seasons
- ☐ Every month but less than weekly
- ☐ Usually at least once a week → ***Go to Q3.2***

3.1a In the past, did you ever have a period of at least 1 year, during which you usually drank some alcohol at least once a week?

☐ Yes, → if so, how long ago did it end? ☐☐ ars } ***Go to section 4***

☐ No

3.2 During the past 12 months, on how many days did you drink alcohol in a typical week?

- ☐ 1-2 days/week

☐ 3-5 days/week

☐ Daily or almost every day

3.3 At about what age did you start drinking some alcohol in most weeks? ☐☐

3.4 On days when you drink, how much alcohol do you usually drink in a day?
(Can choose up to 3 types of alcohol for special occasions; for beer, 1 large bottle=2 small ones**)**

Alcohol type	**On a typical day (choose one)**	**On a special day when you drink a lot**	**Last time when you drank**
Beer (large)	☐☐ Bottle	☐☐ Bottle	☐☐ Bottle
Rice Wine	☐☐ liang	☐☐ liang	☐☐ liang
Wine	☐☐ liang	☐☐ liang	☐☐ liang
Spirit (≥50% alcohol)	☐☐ liang	☐☐ liang	☐☐ liang
Spirit (<50% alcohol)	☐☐ liang	☐☐ liang	☐☐ liang

3.5 On a typical day when you drink alcohol, when do you usually take the drink?

☐ Usually drink with the meal

☐ Usually drink between or after the meals

☐ No regular pattern

3.6 After drinking alcohol, do you usually experience hot flushes or dizziness?

☐ Yes, soon after first mouthful

☐ Yes, after drinking small amount of alcohol

☐ Yes, but only after drinking large amount of alcohol

☐ No

3.7 During the past month, how often have you drunk alcohol in the morning?

- ☐ Never
- ☐ <1 day/week
- ☐ A few days a week
- ☐ Daily or almost daily

3.8 During the past month, have you ever had the following experiences?

Yes	No	
☐	☐	Unable to work or to do anything because of drinking
☐	☐	Felt depressed, irritated or couldn't control yourself after drinking
☐	☐	Could not keep away from drinking
☐	☐	Had shakes when you stopped drinking

3.9 Has your alcohol consumption changed significantly compared with that some years ago?

- ☐ About the same as before
- ☐ Has increased a lot
- ☐ Has decreased a lot

Section 4: Smoking history

4.0 Have you smoked any tobacco today? ☐ **Yes,** ☐ **No,** →if yes how many: __ total, __in last hour

4.1 How often do you smoke tobacco now?

- ☐ Do not smoke now
- ☐ Only occasionally
- ☐ Yes, on most days
- ☐ Yes, daily or almost every day

} → ***Go to Q4.5***

4.2 In the past, how frequently did you smoke?

- ☐ Did not smoke
- ☐ Smoked only occasionally
- ☐ Smoked on most days
- ☐ Smoked daily or almost every day

} → ***Go to Q 4.3***

4.2a In your life time, have you smoked a total of at least 100 cigarettes or equivalent?

- ☐ Yes
- ☐ No

} ➔ ***Please go to section 5***

4.3 How many years ago did you last stop smoking regularly? ☐☐ Years

4.4 What was your main reason for stopping?

- ☐ Physical illness that you already had
- ☐ Money
- ☐ Health concerns (about future illness)
- ☐ Family against
- ☐ Other

4.5 At about what age did you first start smoking on most days? ☐☐ ears

4.6 What tobacco did you use when you first started smoking on most days?

Mainly cigarette ☐, Mainly non-cigarette ☐, Mixed types ☐

↳ 4.6a If so, have you always smoked some cigarettes on most days, never having a month or more without them? Yes ☐, No ☐

4.7 How much tobacco do you usually smoke (or did you smoke before giving up)?

Filter cigarettes (factory) …… ☐☐ nber/day

Non-filter cigarettes (factory)…… ☐☐ nber/day

Hand-rolled cigarettes …… …… …… ☐☐ liang/month

Pipe or water pipe …… ☐☐ ang/month

Cigars …… ☐☐ nber/day

4.9 How deeply do you usually inhale the smoke?

☐ Mouth only
☐ Throat
☐ Lung ➔ 4.9a Have you nearly always inhaled a lot of smoke into your lung when smoking? Yes ☐, No ☐

4.10 Has your tobacco consumption changed significantly compared with that some years ago?

☐ About the same as before, ☐ Has increased a lot, ☐ Has decreased a lot

Section 5: Diet

5.2 During the past 12 months, about how often did you eat the following foods?

	Daily	4-6 days per week	1-3 days per week	Monthly	Never/rarely
Rice	☐	☐	☐	☐	☐
Wheat	☐	☐	☐	☐	☐
Other staple food (corn, millet etc.)	☐	☐	☐	☐	☐
Meat	☐	☐	☐	☐	☐
Poultry	☐	☐	☐	☐	☐
Fish/sea food	☐	☐	☐	☐	☐
Fresh eggs	☐	☐	☐	☐	☐
Fresh vegetables	☐	☐	☐	☐	☐
Soybean products	☐	☐	☐	☐	☐
Preserved vegetables	☐	☐	☐	☐	☐
Fresh fruit	☐	☐	☐	☐	☐
Dairy products (milk, yogurt)	☐	☐	☐	☐	☐

5.3 During the past 12 months, have you taken the following supplements regularly?

Yes	No	
☐	☐	Fish oil/cod liver oil
☐	☐	Vitamins
☐	☐	Calcium/iron/zinc
☐	☐	Ginshen (at least 5 or more times during a year)
☐	☐	Other herbal products

5.3a Have you ever experienced any severe food shortage? ☐ Yes, ☐ No ➔ *Go to Q5.3c*

5.3a1 What year was the worst food shortage you experienced? _____ years

5.3b During the most severe food shortage you experienced:

– did you lose weight? ☐ No, ☐ Yes, → **If yes, about how much?** _____ *jing*,

– did you develop any specific disease related to food shortage? ☐ No, ☐ Yes

5.3c How many years have you had a refrigerator in your home? ☐☐ Years

---

5.4 During the past month, about how often did you eat hot spicy food?

☐ Never or almost never
☐ Only occasionally
☐ 1-2 days/week
} → ***Go to section 6***
☐ 3-5 days/week
☐ Daily or almost every day

5.5 At what age did you start to eat spicy food at least once a week? ☐☐ Years

5.6 What strength of spicy food do you usually prefer to eat?

☐ Weak, ☐ Moderate, ☐ Strong

5.7 On day when you eat spicy food, what are the main sources of spice usually used?

Yes	**No**	
☐	☐	Chili sauce
☐	☐	Chili oil
☐	☐	Dried chili pepper
☐	☐	Fresh chili pepper
☐	☐	Other or don't know

Section 6: Passive smoking & indoor air pollution

6.1 Have you ever lived with smoker in the same house for at least 6 months?

- ☐ Never
- ☐ Yes, but not now
- ☐ Yes, at present

} → ***If yes, duration of living together*** ☐☐

6.2 How frequently are you exposed to other people's tobacco smoke either at home, workplace or in public places? *(i.e. a minimum of 5 consecutive minutes each time)*

- ☐ Never or almost never
- ☐ Occasionally (<1 time/week)

} → ***Go to Q6.4***

- ☐ 1-2 days/week
- ☐ 3-5 days/week
- ☐ Daily or almost every day

6.3 What is the usual duration of your exposure per week? ☐☐ Hours

---

6.4 During past year, how long did you store pesticides at home? ☐☐ Months

---

6.4a Please tell us the duration you lived in 3 most recent houses (each for at least 1 year)?

Present house ☐☐ years

Previous house ☐☐ years

The house before previous ☐☐

6.5 In your present & two previous houses, how often did you cook at home?

- ☐ Daily
- ☐ Weekly
- ☐ Monthly
- ☐ Never/Rarely → ***Go to Q6.8***
- ☐ No cooking facility → ***Go to Q6.11***

6.6 In your present & two previous houses, what was the main cooking fuel used?

- ☐ Gas
- ☐ Coal
- ☐ Wood
- ☐ Eletricity
- ☐ Other

6.7 In your present & two previous houses, what was the main cooking oil used?

☐ Rapeseed ☐ Lard

☐ Peanut ☐ Other

☐ Soybean

6.7a How much time have you spent on cooking so far today? | | | ninutes

---

6.8 In your present & two previous houses, did your stove(s) all have a chimney / extractor?

☐ Yes ☐ Not all stoves ☐ No

6.9 In your present & two previous houses, was your stove always kept under slow burning throughout the day?

☐ Yes, always ☐ Yes, sometimes ☐ No → if ticked, ***Go to Q6.11***

— If yes, types of the fuel most commonly used?

☐ Smokeless coal ☐ Coal brick / Coalite

☐ Smoky coal ☐ Other

— And, the place where stove was usually kept?

☐ Inside the house ☐ Outside the house

6.11 In winter, did you normally heat your house?

☐ Yes, ☐ No

— If yes, what was the main heating fuel used?

☐ Central heating ☐ Wood

☐ Gas ☐ Electricity

☐ Coal ☐ Other

6.12 From what year did the inside of your house tend to be coal-smoky in winter?

☐ Never → if ticked, ***Go to next section***

☐ Ever since childhood

☐ Since the year: _____ year

6.13 In what year did the inside of your house stop being really coal-smoky in winter?

☐ In the year: _____ year

☐ Still is

Section 7: Personal & family medical history

7.1 How is your current general health status?

a). Self-rated health status?

- ☐ Excellent
- ☐ Good
- ☐ Fair
- ☐ Poor

b). Compared to someone of your own age?

- ☐ Better
- ☐ About the same
- ☐ Worse
- ☐ Don't know

7.2 If you were walking on level ground with other healthy people of the same age, would you usually:

a). Become short of breath? ☐ Yes
☐ No
☐ Disabled

b). Slow down due to chest discomfort? ☐ Yes
☐ No
☐ Disabled

7.3 During the past 12 months, have you usually had the following symptoms?

a). Cough frequently?

- ☐ No
- ☐ Yes, for <3 months
- ☐ Yes, for ≥3months

b). Cough up sputum after getting up in the morning?

- ☐ No
- ☐ Yes, for <3 months
- ☐ Yes, for ≥3 months

7.4 Has a doctor EVER told you that you had had the following disease?

	Diagnosed disease?		Age at first	Still on treatment?		
	Yes	No	diagnosis	Yes	No	For CHD, stroke, and hypertension what is the current medication:
Diabetes	☐	☐	_____	☐	☐	1. Aspirin
CHD	☐	☐	_____	☐	☐	2. ACE-I
Stroke or TIA	☐	☐	_____	☐	☐	3. Beta-blocker
Hypertension	☐	☐	_____	☐	☐	4. Statins
Rheumatic heart dis.	☐	☐	_____	☐	☐	5. Diuretics
TB	☐	☐	_____	☐	☐	6. Ca^{++} antagonist
Emphysema/bronchitis	☐	☐	_____	☐	☐	

Asthma	☐	☐	_____	☐	☐
Cirrhosis/chronic hepatitis	☐	☐	_____	☐	☐
Peptic ulcer	☐	☐	_____	☐	☐
Gallstone/gallbladder dis.	☐	☐	_____	☐	☐
Kidney disease	☐	☐	_____	☐	☐
Fracture	☐	☐	_____	☐	☐
Rheumatoid arthritis	☐	☐	_____	☐	☐
Psychiatric disorders	☐	☐	_____	☐	☐
Neurasthenia	☐	☐	_____	☐	☐
Head injury	☐	☐	_____	☐	☐
Cancer*	☐	☐	_____	☐	☐

***If yes, please indicate the site of cancer** ☐ *(If more than one, choose the one that occurred first)*

0. Lung 1. Esophagus 2. Stomach 3. Liver 4. Intestine 5. Breast 6. Prostate 7. Cervix 8. Other

7.5 Have many blood transfusions have you ever received? *(If none, put 0)* ☐☐ times

---

7.5a How many times have you ever donated blood for financial payment?

(If none, put 0) ☐☐

7.6 About how often do you have bowel movements each week?

- ☐ More than once on most days
- ☐ About daily
- ☐ Once every 2-3 days
- ☐ Less than 3 times a week

7.7 How often do your gums bleed when you brush your teeth?

- ☐ Occasionally, rarely or never
- ☐ Sometimes
- ☐ Always
- ☐ Brush teeth rarely or never

7.8 How many brothers & sisters do you have? *(Including half siblings. If unknown, put#)* ☐☐

7.9 How many children do you have? *(Including only biological ones)* ☐☐

7.9a Is your mother still alive?

- ☐ Yes → If ticked, current age: ☐☐
- ☐ No → If ticked, age at death: ☐☐
- ☐ Unknown

7.9b Is your father still alive?

- ☐ Yes → If ticked, current age: ☐☐
- ☐ No → If ticked, age at death: ☐☐
- ☐ Unknown

7.10 Did any of your parents, siblings or children have following diseases? *(For sibling and children, please record the number with disease*)

	Stroke	Heart attack	Diabetes	Mental disorder	Cancer
Mother *(tick box)* ☐	☐	☐	☐	☐	
Father *(tick box)*	☐	☐	☐	☐	☐
Siblings *(inclu. half)*	☐	☐	☐	☐	☐
Children	☐	☐	☐	☐	☐

Section 8U: Physical activities (Urban)

8.1 During the past 12 months, how active were you at work?

☐ Mainly sedentary (e.g. office worker)

☐ Standing occupation (e.g. guard, shop assistant)

☐ Manual work (e.g. plumber, carpenter)

☐ Heavy manual work (e.g. miner, construction worker)

☐ Retired or housewife/husband or unemployed or disabled → ***If ticked, please go to Q8.8***

8.1a In a typical week, about how many hours did you usually work? _____ hours

---

8.2 During the past 12 months, how did you usually get to work?

☐ Mainly walk

☐ By motorbike

☐ By bicycle

☐ By bus/car/ferry/train

☐ Mainly stay at home or work near home

↳***If ticked, please go to Q8.8***

8.3 How much time did you spend each day on journey to & from work? _____minutes

---

Section 8F: Physical activities (New section for rural farmers)

8.1 During the past 12 months, did your farming work change seasonally?

☐ No → ***go to Q8.3***

☐ Yes

8.2 During the farming season in the last 12 months:

— How many months did it usually last? ☐☐ month

— What types of work did it usually involve?

☐ manual ☐ Semi-mechanized ☐ Fully mechanized

— How many hours did you usually work each day? ☐☐ hours

— Of which , how many hours did you sweat or have a much faster heartbeat?

☐☐ hours

8.3 In a typical week, how many hours did you usually work in the field? ☐☐ hours

8.4 Apart from agriculture work, did you have any other job?

☐ No → ***go to Q8.7***

☐ Yes

8.5 How active were you at work with other job?

☐ Mainly sedentary ☐ Mainly general manual work

☐ Mainly standing ☐ Mainly heavy manual work

8.6 In a typical week, about how many hours did you work at other job? ☐☐ hours

---

8.7 In a typical day how much time did you usually spend on the journey to and from work on foot or by bicycle? ☐☐☐ Minutes

---

Section 8C: Physical activities (Common to both rural farmers and urban)

8.8 During the past 12 months, how often did you do exercise in your leisure time?

☐ Never or almost never } → ***If ticked, please go to Q8.11***

☐ 1-3 times/month ☐ 3-5 times/week

☐ 1-2 times/week ☐ Daily or almost every day

8.9 What is your main type of exercise? *(tick one box only)*

☐ Taichi / Qigong ☐ Walking

☐ Jogging/aerobic exercise ☐ Swimming

☐ Ball games (basketball, table tennis, etc) ☐ Other (eg. mountain climbing)

8.10 About how many hours per week did you do such exercise in leisure time? ___ hours

---

8.11 In a typical week during the past 12 months, how often did you sweat or have a much faster heartbeat because of heavy physical activities/exercise?

☐ Never or almost never } → ***If ticked, please go to Q8.13***

☐ <1 time / week ☐ 3-5 times/week

☐ 1-2 times/week ☐ Daily or almost every day

8.12 About how many hours per week did you do such activities? _____ **hours**

8.13 About how many hours per week did you do house work? _____ **hours**

8.14 About how many hours per week did you watch TV or read? _____**hours**

8.15 During the past 12 months, has your weight changed significantly?

☐ About the same as before ☐ Yes, gained ≥2.5 kg ☐ Yes, lost ≥2.5 kg

---

8.16 Have you tried to reduce weight in the past 12 months? No ☐, Yes ☐

8.17 How much did you weigh when you were at age 25? (If unknown put #) | | | | jin

---

Section 9: Reproductive history (for women)

9.1 How old were you when you had your first menstrual period? ☐☐ Year

---

9.2 Have you had your menopause?

☐ No
☐ Yes, currently
☐ Yes, had menopause → If so, age of completion of menopause: ☐☐ Year

---

9.3 How many times have you ever been pregnant? (if none, put 0. Go to Q9.6) ☐☐ imes

— Of which,

Live birth ☐☐ times → If none, Go to Q9.6

Still birth ☐☐ times, Spontaneous abortion ☐☐ ıes, Induced abortion ☐☐ s

---

9.4 Age and length of breas☐☐ at each live birth (twins=one birth)?

Live Birth	Age at end of pregnancy	Mont☐☐ eeding
1st		☐☐
2nd	☐☐	
3rd	☐☐	☐☐
	☐☐	
4th		☐☐
5th	☐☐	☐☐

9.6 Have you ever used oral contraceptive pills?

☐ Never → ***If ticked, please go to Q9.9***

☐ Past use → **if ticked,** age when you last stopped the pill: ☐☐

☐ Current use

9.7 How old were you when you first used oral contraceptives? ☐☐ Year

9.8 For how long altogether have you used oral contraceptives? ☐☐ Year

9.9 Have you had a hysterectomy?

☐ No , ☐ Yes → If yes, age when you had the operation

9.10 Have you had one or both ovaries removed?

☐ No , ☐ Yes → If yes, age when you had the most recent operation

9.11 Have you ever had surgery to remove a breast lump?

☐ No, ☐ Yes → If yes, age when you most recently had the operation

Section 10: Sleeping, mood & mental situation

10.1 In general, how satisfied are you with your life?

- ☐ Very satisfied
- ☐ Satisfied
- ☐ Neither satisfied nor dissatisfied
- ☐ Unsatisfied
- ☐ Very unsatisfied

10.2 Over the past two years have you had any of the following major events in your life?

Yes	No		Yes	No	
☐	☐	Marital separation/divorce	☐	☐	Major injury or traffic accident
☐	☐	Loss of job/retirement	☐	☐	Death /major illness of spouse
☐	☐	Business bankrupt	☐	☐	Death/major illness of other close family member
☐	☐	Violence	☐	☐	Major natural disaster (e.g. flood & drought)
☐	☐	Major conflict within family	☐	☐	Loss of income / living on debt

---

10.3 During the past month, did you have any of the following for ≥3 days each week?

Yes	No	
☐	☐	Taking >30 minutes to fall asleep after going to bed or waking up in the middle of the night
☐	☐	Waking up early and not being able to go back to sleep
☐	☐	Needing to take medicine (including herbal or sleeping pills) at least once a week to help sleep
☐	☐	Having difficulty staying alert while at work, eating or meeting people during daytime

---

10.4 Do you usually take a daytime nap? ☐ Yes usually, ☐ Yes ,but only in summer , ☐ No

10.4a Do you snore during sleep? ☐ Yes, Frequently, ☐ Yes, Sometimes, ☐ No / Don't know

10.5 How many hours do you typically sleep per day (incl. naps)? ☐☐ Hours

---

10.6 During the past 12 months, have you had following situations for 2 or more weeks?

(If answer yes to any of the questions, complete CIDI-SF, starting from A1a)

Yes	No	
☐	☐	Feeling much more sad, or depressed than usual
☐	☐	Loss of interest in most things like hobbies or activities that usually give you pleasure

☐ ☐ Felt so hopeless that you had no appetite to eat even your favourite food

☐ ☐ Feeling worthless and useless, everything went wrong was your fault and life is very difficult that there was no way out

---

10.7 During the past 12 months, have you experienced the following situations?

Yes No

☐ ☐ Having a period lasting one month or longer when most of time you felt worried, tense, or anxious and it interfered your life *(if yes, go to CIDI-SF, B1a section)*

☐ ☐ Having a pain or discomfort in your body lasting ≥3 months that interfered with your life

☐ ☐ Having had a spell or an attack when all of sudden felt frightened, anxious, or very uneasy

☐ ☐ Having had inexplicable strong fear in situations such as closed space (cave, elevator, airplane etc), in the crowds or public such that you would avoid such situations

---

Section 11: Physical examination

11.1 Standing height (without shoes) ..... | | | | . |

11.2 Sitting height ..... | | | | . |

11.3 Waist ..... | | | | . |

11.4 Hip ..... | | | | . |

11.5 Weight (without shoes, but in light clothing) ..... | | | | . |

11.6 BMI ..... | | | . | Kg/m²

11.7 Impedance ..... | | | | **Ω**

Staff code

11.8 Fat % (with one decimal point) ..... | | | . | | | |

11.9 Did you take any drugs to lower blood pressure in the last 2 days? ☐ Yes ☐ No

11.10 Blood pressure & heart rate (to be measured after 5 minutes in the seated position)

	First	Second
SBP		

DBP ☐☐☐ ☐☐☐

Heart rate ☐☐☐ ☐☐☐

11.10a Hours since last ate anything (ignore any drinks)? _____ hours

Staff code ☐☐☐

11.11 Blood sample collected: Yes ☐, Failed ☐

11.12 Lung function & CO levels:

	First	Second		
CO	☐☐☐	☐☐☐	**%COHB**	☐☐·☐☐
FEV1	☐·☐☐	☐·☐☐	*Staff code*	
FVC	☐·☐☐	☐·☐☐		☐☐☐

11.13 Assessment of subject's cooperation and the reliability of data collected?

a) Subject's cooperation?

- ☐ Good
- ☐ Fair
- ☐ Poor

b) The reliability of the information collected?

- ☐ Good
- ☐ Fair
- ☐ Poor

Date of interview _____Year_____Month____Day, **Signature of interviewer**_____

Appendix II: Standard Operating Procedure for Event Identification and Validation

China Kadoorie Biobank

Identification and Validation of Stroke, Diabetes, Ischaemic Heart Disease and Cancer Incidence

【Standard Operating Procedure】

Version 1.2, 27 April 2011

International Coordinating Centre, China Kadoorie Biobank,
CTSU, University of Oxford

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   (2) Selection of Events
   (3) Check basic information of events
   (4) Acquire permission for medical record collection and contact hospital for visits
   (5) Retrieve medical notes
   (6) Review medical records and locate key information
   (7) Copy relevant notes
   (8) RC staff collate information periodically and send it electronically to NCC

4．Pilot study at each RC

5．Disease-specific notes on data collection
   (1) Stroke
   (2) Ischaemic Heart Disease
   (3) Diabetes
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1. Background

The China Kadoorie Biobank (CKB), previously known as the Kadoorie Study of Chronic Disease in China (KSCDC), is a large blood-based prospective study of the genetic and environmental causes of common chronic diseases in China. The study is run by a collaboration of CTSU, Oxford University, the Chinese Academy of Medical Sciences (CAMS) and China CDC. It involves over 510,000 participants aged 30-79 who were recruited from 10 different regions in China during 2004-8. All the participants are now being followed up for mortality and morbidity and it is expected that over the next few decades, this study will generate important new findings about the main determinants of common chronic disease in China, including life-style, dietary, physical activities, behaviour, environmental, aspects of physical and blood biochemistry characteristics, as well as genetic susceptibility.

The field work for the CKB project includes three major parts: baseline survey, long-term follow-up surveillance and periodical resurvey of a random subset of surviving participants. The baseline survey of 0.5 million participants and the first resurvey of 20,000 participants were completed during 2008. Currently the main emphasis of the field work involves ensuring reliable and complete follow up for vital status, cause-specific mortality and morbidity as well as for any episodes of hospitalization through linkages with health insurance claim database (to start during 2011). In addition, information related to participants' residential status (moved or loss to follow up) is also being collected on a regular basis. At present, the mortality and morbidity surveillance in each regional centre (RC) utilizes existing routine vital registration and disease surveillance systems. The mortality surveillance monitors cause-specific death whereas the disease surveillance monitors the occurrence of four major chronic diseases (stroke, ischaemic heart disease (IHD), diabetes mellitus (DM) and cancer).

By 31 Dec 2010, a total of 10,444 deaths have been reported: 2,118 stoke deaths, 1,187 IHD deaths, 3,767 cancer deaths and 285 DM deaths. In addition, there were 16,518 incident disease events: 7,162 stroke events, 2,708 IHD events, 4,713 DM events and 2,954 cancer events. While for most death or disease events information on the treating hospital, relevant diagnosis (usually using ICD-10), and level of diagnostic criteria were generally available, it is not clear to what extent the information collected through routine registries are reliable and can be used appropriately for research purposes. To help assess the quality of the follow-up data, a validation study is to be

conducted, involving 500 cases of each of the four major conditions, including stroke, IHD, diabetes and cancer (ie, 50 cases for each condition per site). The information generated from this validation study will be of major significance in helping to inform the future event adjudication plan for the whole study over the coming years.

2. Aims

The validation sub-study primarily aims to assess the diagnostic accuracy of events reported by both the mortality and morbidity surveillance systems with respect to a selected number of major diseases: stroke, ischaemic heart disease (IHD), diabetes mellitus (DM) and six types of cancers (lung, stomach, liver, colorectal, oesophageal and female breast cancer). It will involve locating and retrieving the relevant medical notes related to a specific disease or death event already reported in the study follow-up system and taking copies of relevant parts of the notes. These copies will then be reviewed independently by an expert panel to assess the diagnostic accuracy of the events at a later date. This study also aims to assess the general feasibility of retrieving detailed information from medical notes.

3. Practical procedures for data collection

The key steps in the study are as follows:

(1) Consolidate list of hospital names and tier

Before launching of the main study, each RC will be forwarded a spreadsheet with the names of the hospitals which have been the source of the death or disease events in the study from International Coordination Centre (ICC) and National Coordination Centre (NCC). As the names of these hospitals have been entered manually in many cases, it is important that each RC review the list and indicate where several entries refer to a single hospital (e.g. City First Hospital and the First People's Hospital of the City are referring to the same hospital). After the re-check and revision, RCs are to send the list to NCC. This revised list will then be used to select hospitals from which events will then be selected.

(2) Selection of Events

Oxford University International Coordination Centre will generate lists of events based on the revised and standardized hospital names. To help minimise the potential workload and to improve

the efficiency, only events from several hospitals within each RC will be selected, with a good mixture of hospitals at different tiers (including tier 1, 2 and 3 levels). Each RC will be asked to collect detailed clinical information from hospital medical notes on around 50 stroke events, 50 IHD events, 50 DM events and 50 cancer events. Each RC will be given a list of 50 events for each disease; 200 events in total. However, since it is unlikely that each RC will be able to retrieve medical records from all of these events, a 'Back-up Event List' will be provided. Oxford International Coordination Centre will provide each RC with the 'Event List' and the 'Back-up Event List' at the same time. RC staff should aim to have medical notes from 50 events. This is so that there are sufficient cases to adjudicate. In the situation in which the medical notes from less than 50 events have been retrieved and both the event list and the back-up list are exhausted, RC staff should contact NCC for another back-up event list. Also for convenience, recent events will be selected where possible to increase the likelihood of finding the medical notes.

(3) Check basic information of events

For each event, the RC will be sent a data collection checklist form. This form will contain several pre-filled sections that will help RC staff locate the appropriate medical notes. The information provided will include: the unique Kadoorie identification number of the participant who experienced the event, personal information (e.g. name, sex, and date of birth), the diagnosis given as the cause for the event, information on whether the event was reported by death certificate, disease surveillance record or health insurance data, information on hospital name and hospital record number from where the event was reported to have occurred and the date of the event, etc. After the Data Collection Checklist Form is received, each RC should check the pre-filled section with original Death Certificate or Chronic Disease Reporting Card, to ensure the accuracy of relevant information.

(4) Acquire permission for medical record collection and contact hospital for visits

After checking the basic information of events, RCs should inform the local heath administration (e.g. health bureau) of the project. After acquiring permission from provincial or municipal health administration, RC staff members are to contact relevant hospitals departments and arrange data collection visits. Where necessary, supporting letters and consent forms from patients can be provided by the NCC to ensure the data collection to be successfully carried out. It is suggested that RC staff collect information on events of all disease types when visiting hospital so as to minimize re-visits to hospitals. Where there is resistance from hospitals in the data collection, or if there are other significant issues, RC are staff are encouraged to contact the NCC for further advice.

(5) Retrieve medical notes

To increase efficiency, RC staff could send the event list to hospitals before visiting. So the hospitals could retrieve relevant records in advance. RC staff are encouraged to take both the original list of event and the back-up list to minimize the need to revisit the hospitals. If notes relating to an event cannot be found, RC staff should still complete the second part of disease-specific checklist forms and tick "no" under the question "Whether relevant medical records are retrieved?". RC staff should then explain the reason why it has not been possible to retrieve the notes in the section provided. This form should then be sent to the NCC. The data collector should then select a supplementary event from the back-up list of events and collect data.

RC staff do not necessarily have to retrieve and copy the medical notes themselves. They can train hospital staff do this, if the hospital is willing. However, RC staff remain responsible for the quality of medical notes provided for adjudication and as such they should check through the medical notes and sign after a checklist is completed. RC staff should contact the NCC if they encounter major problems with retrieving medical notes.

(6) Review medical records and locate key information

The extraction of medical records is a skilled and complex task; some medical notes might be quite disorganised. It requires strong reading skills to locate the best supporting evidence to be extracted. After a medical record is retrieved, RC staff are encouraged to spend time looking through the contents of folders, and tick relevant medical investigations performed under section of **"The medical records indicate the following investigations were performed".**

The key documents required for each diagnostic type of event (stroke, ischaemic heart disease, diabetes mellitus, cancer) are outlined under the section of **"Medical evidence to be collected (photo or copy)"** in disease-specific checklist forms at the end of this report. These key documents should be copied. On occasion, not all key documents will be available to copy. Each form indicates the minimum set of documents required for the data collection on a specific event to be considered complete.

If the key information on an event is considered incomplete, the clinical information of this event should be still be send to NCC but a further case from the back-up list should be selected. Some judgment will be required when reviewing the notes as to the best sections to copy. There may be additional information that RC staff believe may be useful to include and copying this additional

information is encouraged. Staff should record the type of information under "**Others (please specify)**". On occasion, it may not be clear which admission or set of notes would provide the best clinical information relating to the specific event requested. For instance, the date of the specific event may not exactly match the admission date. Where this occurs, copies should also be made of the notes relating to an admission closest in time to the specific event where a diagnosis of the same type as the specific event was made.

(7) Copy relevant notes

Copies of the relevant sections of the notes should be of a high enough quality to allow the text to be read. It is especially important that the dates of clinical assessments and investigations are legible. Ideally, notes should be scanned. Where this is not possible, notes should be photocopied and scanned later so that all the information relating to an event can then be sent electronically to the NCC. Alternatively, photos of the notes can be taken, provided the quality is sufficiently high. Where it is required by the hospital or other local authorities that copies of the medical notes are anonymised, care should be taken to ensure that a patient's personal details (name, address, telephone number etc.) are obscured when copies of the key documents are made. RC staff can decide on the best way to achieve this. A piece of black card which obscures these details at the top of the page is probably the best way when taking photographs or scanning documents. Alternatively, a black marker pen could be used to obscure the details of photocopies before they are then scanned. All anonymous copies of notes should contain the study ID, in the copy so that it can be linked unequivocally to the event.

(8) RC staff collate information periodically and send it electronically to NCC

RC staff should compile all the collected information into one document for each individual event, covered by the Data Collection Checklist Form as front page. If not electronic, the document should be scanned at RC before sending electronically to NCC. RC staff should not wait until data on all the events has been collected before forwarding information electronically to the NCC – information on each event should be forwarded after it has been retrieved.

4. Pilot study at each RC

RC staff should arrange to visit a hospital and collect abstracts from medical notes based on procedures introduced in this SOP. RC staff send the abstracts from the pilot together with timeline of project to NCC (RC staff informs NCC of any issues that may restrict their work).

RC staff should run through all the procedures of data collection: collecting abstracts, filling in accompanying forms and sending these electronically to the NCC. This should allow the RC to get a broad indication on the time it might take to complete the project and they can inform the NCC of this. It will also allow the NCC to identify if there are any particular issues with the data collection procedures at a particular RC so as to minimise the recollection of data on particular events.

5. Disease-specific notes on data collection

(1) Stroke

Which event should be assessed?

If a stroke event was identified by disease surveillance form, find the hospital admission that occurred as a result of the stroke event identified by the disease record. If there was no record of hospital admission within a month of the date of the stroke event, this event should be considered incomplete, and another stroke event should be selected from the backup list. If a stroke event was identified by a death certificate, the aim is to collect information on the last hospital admission where the disease was diagnosed, prior to death. Some judgment will be required as to what constitutes the last hospital admission. For instance, if the patient died on the way to hospital and a short statement alone is included in the clinical notes, this should be copied together with notes from the most complete admission closest to death where the diagnosis of the same disease was made. Where there is doubt about the best forms to copy, it is best to take copies and indicate your uncertainties in the notes section of form.

Investigations

Indicate by ticking the boxes which investigations were performed in the process of diagnosing a stroke. The investigations do not have to have been performed in the same hospital that admitted the patient. In addition, the official report on the results of the investigation does not have to be available in the notes. We would also like to know if the actual CT/MRI scans for this stroke event are stored electronically by the hospital and there is an item in the investigations list to indicate this.

Documents

Please copy all the documents listed, where available. CT/MRI reports: where more than one CT or MRI scan has been performed please copy the reports from all the scans received during the specific admission. Please also provide copies of all the lumbar puncture and angiography results, if

performed. The lumbar puncture results are likely to be in the biochemistry or pathology section. If the patient has died, please take a copy of the death certificate if it is in the notes. Please also take a copy of the verbal or medical autopsy, if performed.

Is the information complete?

Essential documents include:

- discharge summary/ death summary
- assessment on admission
- plus one of the investigations listed in the documents to copy section

Where one or more of these essential document are not available, the case should be considered incomplete. The information should still be copied and forwarded to the NCC but an additional event should be selected from the back-up list.

The RC member of staff who has made sure the quality of the forms are appropriate should sign the form at the bottom.

Glossary

CT = X-ray computed tomography, MRI= Magnetic resonance imaging, MRA=Magnetic resonance angiography, SAH= subarachnoid haemorrhage

(2) Ischaemic Heart Disease

Medical record abstractors (field staff) are requested to collect as much key medical information as possible in order for the medical consultant to validate the diagnosis. In the section under **"The medical records indicate the following investigations were performed"**, a number of investigations are listed in the column. Read through medical record, and tick "Yes □" or "No □" on each item. After this, abstract key medical information, including medical record front page, hospital admission notes, discharge note, ECG and laboratory examinations, etc., which could be found in the participant's medical records. Photocopy and attach the evidence to this form, then tick "Attached" boxes where appropriate under **"Medical evidence to be collected (photo or copy)"**. If the records are not found, or the tests were not administered, please tick "Unavailable". Scan the abstracted documents and send the electronic file to NCC.

Key medical information to be collected for IHD validation includes the following:

1. Front page of medical records, admission and discharge notes (or death record)
2. Physical examination showing typical/untypical symptoms.
3. Official record and interpretation documented directly on the ECG tracing. This may be the handwritten physician's interpretation on the tracing or the computerized printout on the tracing which has been reviewed and signed by the physician.
4. Key biomarkers tested on the patients: e.g. Troponin I, Troponin T, CK, CK-MB, AST, LDH, etc., whichever is performed. Special attention needs to be paid to the rise and fall of biomarkers during the whole process of treatment.
5. If angiography is performed, please photocopy the result page.
6. Any other information that is useful for diagnosis.

If there are any questions about the medical records, make notes on Checklist, and communicate with CTSU/Regional Center/National Project Office/Medical Consultant for solutions. The contact information for the project-wide communication procedures are listed in the Appendix.

(3) Diabetes

Medical record abstractors (field staff) are requested to collect as much key medical information as possible in order for the medical consultant to validate the diagnosis. In the section under **"The medical records indicate the following investigations were performed"**, a number of investigations are listed in the column. Read through medical record, and tick "Yes □" or "No □" on each item. After this, abstract key medical information, including medical record front page, hospital admission notes, discharge note, plasma glucose test and other laboratory examinations, etc., which could be found in the participant's medical records. Photocopy and attach the evidence to this form, then tick "Attached" boxes where appropriate under **"Medical evidence to be collected (photo or copy)"**. If the records are not found, or the tests were not administered, please tick "Unavailable". Scan the abstracted documents and send the electronic file to NCC.

Key medical information to be collected for diabetes validation includes the following:

1. Front page of medical records, admission and discharge notes (or death record), for outpatient visits, please collect outpatient records if available.

   *Records abstracted should include main physical and clinical symptoms. **For patients with**

repeated visits, RC staff are responsible to retrieve the time of first diabetic diagnosis. This information is normally shown under "previous medical history".

2. Plasma glucose tests (fasting/random/OGTT)

If following tests is included in the medical records, please collect as well:

1. HbA1c test
2. Prescription from medical doctors (anti-diabetic drugs, insulin, etc.)
3. Urine ketone bodies (KET)
4. Islet β cell antibodies (for type 1 diabetes)
5. Any other information that is useful for diagnosis.

If there are any questions about the medical records, make notes on Checklist, and communicate with CTSU/Regional Center/National Project Office/Medical Consultant for solutions. The contact information for the project-wide communication procedures are listed in the Appendix.

6. Future Steps

After the electronic files of 200 events from each RC are collected, the data will be transferred to medical review team at National Coordination Centre for adjudication. The electronic information will be transferred through ASTER system which is currently being used in HPS-2 Study. This system allows an efficient, confidential and high-quality transfer of data. Then the adjudication will be carried out by medical consultants in Beijing. The medical consultants will follow a set of pre-designed survey instruments to go through medical evidence of each individual event. By combining all available evidence, a conclusion will be drawn based on current China national and international diagnostic guidelines. It is expected the adjudication will take place in September right after the data is submitted to NCC.

After the adjudication is completed, data from the adjudication survey instrument will be transferred to Oxford International Coordination Centre for further processing and analysis. The analysis of data will be primarily based on descriptive statistics to summarize the agreement between reported disease incidence and adjudication results. It is expected that through this analysis, we will be able to identify a number of issues in the CKB follow-up data, e.g. the quality and accuracy of reported data, timeliness of data reporting, relevant investigations performed on specific disease, reliability of each disease reporting procedures, etc. These results will provide us with not only scientific

evidence, but also valuable implication for the future steps of the CKB project.

7. Q&A

1. What is the purpose of the study?

The study aims to assess the accuracy of disease diagnoses collected as part of the China Kadoorie Biobank with respect to four major disease groups: stroke, ischaemic heart disease, diabetes mellitus and cancer. The study does not aim to assess the accuracy of diagnoses made at any single hospital. The results of the validation study will primarily be used to inform the analysis of data.

2. How many medical notes does each RC need to collect?

Each RC is asked to collect the 'complete' medical records from 50 events from each of the major disease groups; 200 events in total. This number is required so that there will be sufficient numbers of events to adjudicate. For various reasons, adequate information may not be retrieved for a particular event, for example, the event may not be identified on the hospital records system or the information in the medical records is very limited. In this case, the information on the event is considered 'incomplete' and is not counted as one of the 50 events for that disease that needs to be collected. The disease-specific form should be filled in and another event from the 'Back-up list' should be selected.

3. Why does the RC need to inform the local health bureau before approaching hospitals to collect information?

Hospitals commonly have a data management policy and will not release patient information without a good reason. The permission from the local health bureau to retrieve medical notes will normally ensure access to the notes. If hospitals still refuse access to notes despite permission from the local health bureau please contact the NCC.

4. What if we cannot find the notes to an event?

RC staff are asked to work hard to find the notes to a specific event. Be aware that hospitals

sometimes have two or more computer systems (e.g. admission record system, payment system) which record hospital admissions so both need to be checked. If the notes cannot be found then it is important that RC clearly explain the reason why on the disease-specific form and outline the efforts they made to retrieve the notes.

5. What if the admission for the patient does not match the admission date on the checklist form?

The aim is to collect information on the hospital admission that occurred as a result of the specific disease event. If the dates to not match, then please consult to Section 5 of this SOP, titled "Disease-specific notes on data collection" about which admission to select. Where there is doubt about the best forms to copy, it is best to take copies and indicate your uncertainties in the notes section of form. Alternatively, contact the NCC and explain the problem.

6. What if RC staff do not understand some of the medical terms on the checklist form or in the medical notes?

If a member of the RC staff is not clear about some of the medical terms, it is important that they ask the local hospital staff or alternatively contact the NCC.

7. What if only some of the essential documents are available?

The 'essential' documents vary depending on the type of disease event. These documents are outlined in Section 5 of this SOP, titled "Disease-specific notes on data collection". Where one of the essential documents is not available the case should be considered 'incomplete', the disease specific forms should be filled in and another case of the same disease selected.

8. Where and when should the documents be emailed?

The documents for a particular event should be collated with the disease-specific checklist form at the front. The forms should be made electronic by scanning or taking a photo and emailed to the NCC address given previously following the security procedures outlined. Any paper or electronic copies of the documents should be stored securely at the CDC. Information on events should be sent

as soon as possible after they have been collected rather than sending all the information after all the hospitals have been visited.

8. Flow chart of data collection procedures

Consolidate list of hospital names and tier, select events

- RC to check if the hospital names in CKB system is correct and consistent
- Send the list of hospitals back to NCC after checking and revision
- Oxford University ICC is to generate event list for validation

Check basic information of events

- RC should check the pre-filled section with original Death Certificate or Chronic Disease Reporting Card, to ensure the accuracy of relevant information.
- Contact NCC for any errors or mismatch

Acquire permission for medical record collection and contact hospital for visits

- RC should inform the local heath administration (e.g. health bureau) of the project. After acquiring permission from provincial or municipal health administration
- Contact relevant hospitals departments and arrange data collection visits
- Send the event list to hospitals

Retrieve medical note, locate key information and copy

- RC staff members to outreach to hospitals
- Retrieve medical notes of events listed
- After reading through the entire medical records, tick relevant medical investigations performed under section of "**The medical records indicate the following investigations were performed**"
- Locate key medical information, then tick relevant boxes where appropriate under "**Medical evidence to be collected (photo or copy)**"
- Copy all key medical information and attach to the Checklist

Collate information and send it electronically to NCC

- Compile all the collected information of each case in a single electronic file, the first sheet should be the completed "Checklist form"
- Forward information electronically to the NCC

China Kadoorie Biobank

Data Collection Checklist - Diabetes

RC name: CKB ID no. _____

Basic Information: Name:_____, Sex:_____,Dob:_____/___/___, National ID no._____

Hospital of admission_____ Hospital department_____, Hospital record No_____,

Date of event____/___/___, Date of report____/___/___, Type of report: disease record/health insurance/death certificate

How have you tried and match the Basic Information to the patient's hospital record in this specific case?
□ Through an electronic admissions record
□ Through a paper-based admissions record
□ Through a semi-electronic/paper admission record
□ Other, please specify: _____

Were original medical notes retrieved: □Yes □No
(Please check that the admission date is approximately consistent with date of event)

If "Yes", were electronic records available? □Yes □No If they are available, it includes: □ Whole record □ Just admission summary	If "No", what is the reason: □ Not on the admission record system; □ On the admission record system, but notes of this age are not retrievable; □ On the admission record system, but notes missing; □ Other, please specify: _____

The medical records indicate the following investigations were performed:

Investigations	Yes	No	Comments
1. Detailed medical records	□	□	
2. Fasting plasma glucose	□	□	
3. Random plasma glucose	□	□	
4. Glycosylated hemoglobin (HbA1c)	□	□	
5. Urine test (Urine ketone boclies)	□	□	
6. Laboratory routine blood test	□	□	
7. Liver/kidney function	□	□	
8. Islet β cell antibodies (for type 1 diabetes)	□	□	
9. Other investigation of relevance, please specify:_____	□	□	

Medical evidence to be collected (photo or copy)

Documents	Yes	No	Comments
1. Cover page of medical records	□	□	
2. Discharge summary/ Death summary	□	□	
3. Fasting plasma glucose (and/or) random plasma glucose (and/or) OGTT	□	□	
4. Glycosylated hemoglobin (HbA1c)	□	□	
5. Prescription from medical doctors (anti-diabetic drugs, insulin, etc.)	□	□	
6. Other report of relevance, please specify:_____	□	□	

RC staff member responsible:_____ Method of data collection: photo/photocopy Date of data collection：____/___/___

Appendix III: Event Adjudication Form for Diabetes

CKB event adjudication form for diabetes

General Information

Participant ID	[_____]
Sex	□ M □ F
Date of birth	[ ][ ][ ][ ] / [ ][ ] / [ ][ ]
Date of admission	[ ][ ][ ][ ] / [ ][ ] / [ ][ ]
Date of discharge of death	[ ][ ][ ][ ] / [ ][ ] / [ ][ ]
General legibility of the medical records	□ Good □ Fair □ Poor
Does the participant in the checklist and in the notes refer to the same person?	□ Yes □ No (If no, please stop adjudication)
Does the participant information on the checklist match that on the medical notes?	□ Yes □ No (if no, please record inconsistency in the section of reviewer's remarks)

Discharge diagnoses

Is the discharge summary available? □Yes □ No

Is diabetes considered as:
- □ main diagnosis
- □ other diagnosis, and the main diagnosis is:_____
- □ not mentioned (please stop adjudication)

What subtype was diagnosed?
- □ Type 1 diabetes (incl: latent autoimmune diabetes)
- □ Type 2 diabetes
- □ Gestational diabetes
- □ Not specified

Are there any other diagnoses reported?
- □ IHD
- □ Stroke
- □ Cancer
- □ Other diseases
- □ None

Prior medical history

Does the patient have a prior history of DM? □ Yes □ No/Unknown

If yes, what subtype?
- □ Type 1 diabetes
- □ Type 2 diabetes
- □ Gestational diabetes
- □ Other

How long ago did DM occour? [___] years [___] months

Signs, symptoms and complications

	Yes	No/Unknown
Did the patient have any classic symptoms of hyperglycemia include polyuria, polydipsia, and unexplained weight loss?	□	□
Did the patient have the following complications?		
Diabetic nephropathy	□	□
Diabetic retinopathy	□	□
Diabetic neuropathy	□	□
Diabetic foot	□	□

Other complications □ □

Investigations

Investigations	Yes	No/ Unknown	Value reported	Upper laboratory reference
1. Fasting plasma glucose	□	□		
2. Random plasma glucose	□	□		
3. 2-hr post prandial plasma glucose	□	□		
4. OGTT	□	□		
5. Glycosylated hemoglobin (HbA1c)	□	□		
6. Islet β cell antibodies	□	□		
7. Urine glucose test	□	□		

Medications

Did the patient receive one or more of the following medications while in hospital or at discharge?	Yes	No/Unknown
Oral hypoglycemic agent	□	□
Insulin	□	□
Traditional Chinese medicine	□	□

Vital status at discharge

What was the patient's vital status at discharge from hospital?
□ Alive
□ Dead
□ Unknown

Reviewer diagnosis

Is there sufficient evidence to support the diagnosis of diabetes?
□ Yes, definite
□ Yes, probable
□ No

If yes, what in your opinion is the subtype?
□Type 1 diabetes (incl: LADA)
□ Type 2 diabetes
□ Gestational diabetes
□ Other

When was the diabetes initially diagnosed:
□ The reported date is the initial presentation of diabetes
□ Patient was diagnosed before
□ Date for initial presentation/diagnosis is not clear

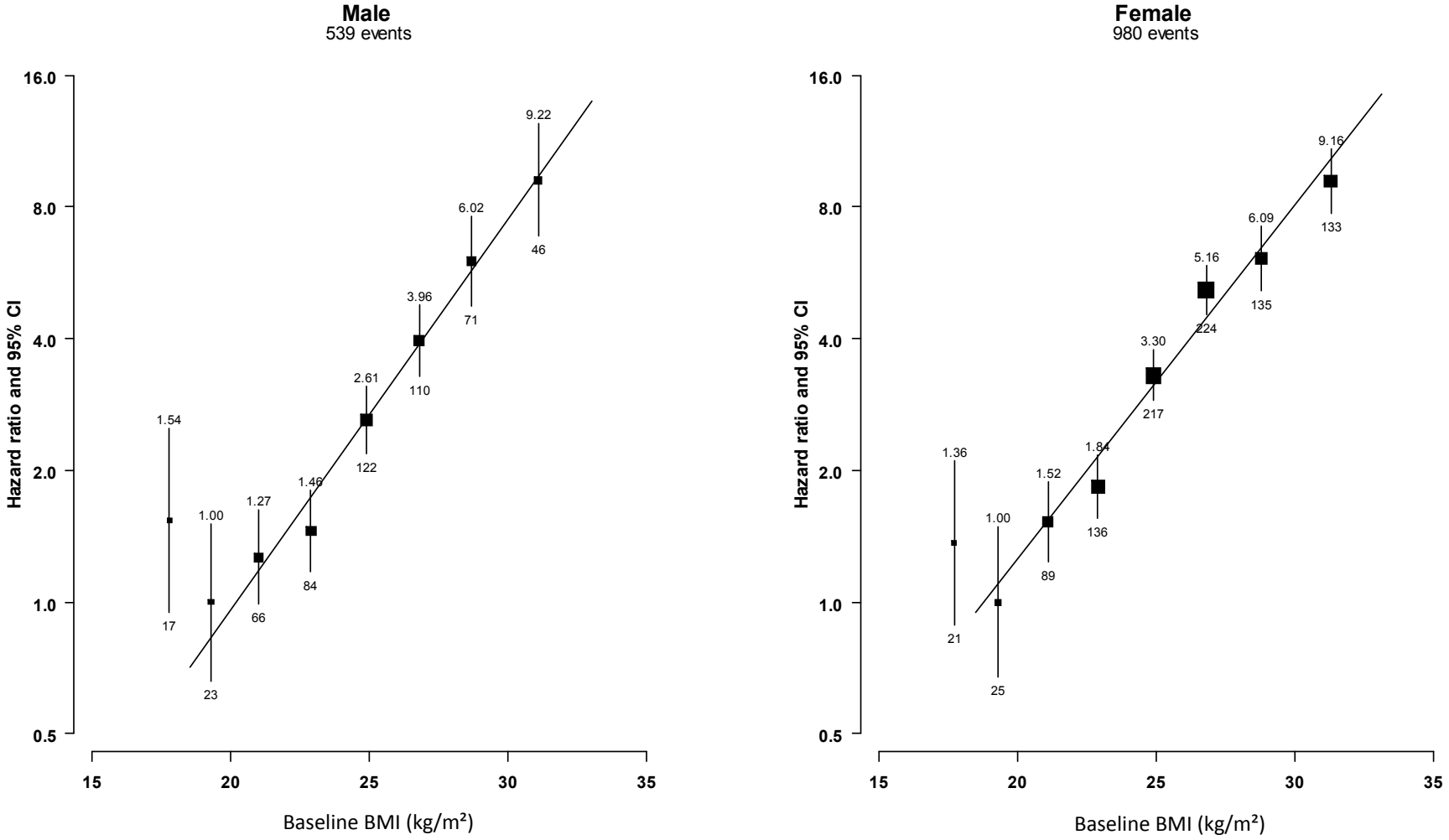
The case needs further review by a medical consultant: □ Yes □No

Comments

Reviewer's name: Date of review: [ ] [ ] [ ] [ ] / [ ] [ ] / [ ] [ ]

Appendix IV: The association between baseline BMI and incident diabetes after excluding data from the study areas of Qingdao and Zhejiang

Appendix IV: Hazard ratios* for incident diabetes by baseline BMI after excluding Qingdao and Zhejiang



*Adjusted for age, area, education, household income, alcohol use, smoking status, physical activity and family history of diabetes