Associations of General and Central Adiposity With Incident Diabetes in Chinese Men and Women

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OBJECTIVE

We assess associations of general and central adiposity in middle age and of young adulthood adiposity with incident diabetes in adult Chinese and estimate the associated population burden of diabetes.

RESEARCH DESIGN AND METHODS

The prospective China Kadoorie Biobank enrolled 512,891 adults 30–79 years of age from 10 localities across China during 2004–2008. During 9.2 years of follow-up, 13,416 cases of diabetes were recorded among 482,589 participants without diabetes at baseline. Cox regression yielded adjusted hazard ratios (HRs) for incident diabetes associated with measures of general (e.g., BMI and BMI at 25 years) and central (e.g., waist circumference [WC]) adiposity.

RESULTS

The mean (SD) BMI was 23.6 kg/m^2 (3.4 kg/m^2), and 3.8% had a BMI ≥30 kg/m^2. Throughout the range examined (19–32 kg/m^2), BMI showed a positive log-linear relationship with diabetes, with adjusted HRs per SD higher usual BMI greater in men (1.98; 95% CI 1.93–2.04) than in women (1.77; 1.73–1.81) (*P* for heterogeneity <0.001). For WC, HRs per SD were 2.13 (95% CI 2.07–2.19) in men and 1.91 (1.87–1.95) in women (*P* for heterogeneity <0.001). Mutual adjustment attenuated these associations, especially those of BMI. BMI at age 25 years was weakly positively associated with diabetes (men HR 1.09 [95% CI 1.05–1.12]; women 1.04 [1.02–1.07] per SD), which was reversed after adjustment for baseline BMI. In China, the increase in adiposity accounted for ∼50% of the increase in diabetes burden since 1980.

CONCLUSIONS

Among relatively lean Chinese adults, higher adiposity—general and central—was strongly positively associated with the risk of incident diabetes. The predicted continuing increase in adiposity in China foreshadows escalating rates of diabetes.

China has the largest number of adults with diabetes of any country worldwide, after a rapid increase in prevalence (1). Between 1980 and 2010, diabetes prevalence increased 2.2-fold in the U.S. and 1.2-fold worldwide (2) but increased almost 10-fold in China (3,4). The reasons for the escalating rates of diabetes in China have still not been properly characterized but likely reflect a combination of demographic changes (e.g., population aging) and increasing levels of adiposity due to lifestyle changes

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*A complete list of the China Kadoorie Biobank (CKB) Collaborative Group can be found in the Supplementary Data online.

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(e.g., increased consumption of energy-dense foods and declining physical activity) associated with rapid economic development and urbanization (5).

Adiposity is an established causal risk factor for type 2 diabetes (6,7). However, much existing evidence comes from Western populations and focuses mainly on BMI, a measure of general adiposity. Questions remain about the relative importance of general versus central (e.g., waist circumference [WC]) adiposity for type 2 diabetes and about the relevance of adiposity at different points during the life course. Although the mean population BMI in China has increased by almost 1 kg/m^2 per decade since the mid-1980s, it remains much lower than in the West (8). However, for a given BMI, Chinese adults are reported to have a higher proportion of body fat and a greater propensity to central adiposity than their Western counterparts (9). Previous studies of adiposity and type 2 diabetes in China have been limited by small sample size, cross-sectional design, examination of later adulthood BMI only, or restriction to occupational or urban cohorts (10–14). We assess the associations of general and central adiposity in middle age, and of young adulthood adiposity, with incident diabetes in the prospective China Kadoorie Biobank (CKB) study of 0.5 million adult men and women and estimate the associated burden of diabetes in the general population.

RESEARCH DESIGN AND METHODS

Study Population

Details of the CKB study design, methods, and population have been reported previously (http://www.ckbiobank.org/) (15,16). Briefly, study participants were recruited from 10 diverse areas (5 urban and 5 rural) of China, selected to ensure diversity in exposure and disease patterns, while taking account of population stability and death and disease registry quality. Permanent, nondisabled residents of 100–150 rural villages or urban committees in each study area, 35–74 years of age, were invited to participate. A response rate of ~30% was achieved (16), and 512,891 men and women were enrolled (including ~10,000 slightly outside the target age range of 35–74 years).

Local, national, and international ethical approval was obtained prior to commencement of the study. All participants provided written informed consent.

Data Collection

The baseline survey took place between June 2004 and July 2008. Trained health workers administered laptop-based questionnaires and undertook physical examinations. Data were collected on sociodemographic status; lifestyle factors, including smoking, alcohol consumption, diet, and physical activity (leisure, household, occupational, and commuting); personal and family medical history; and, using calibrated instruments with standard protocols, anthropometric measures, lung function, blood pressure, and heart rate. A nonfasting venous blood sample was collected, and the time that had passed since participants last ate was recorded. Immediate on-site testing of plasma glucose level was undertaken using the Johnson & Johnson SureStep Plus Meter (LifeScan, Milpitas, CA). Participants with a glucose level $\geq$140 mg/dL and $<$200 mg/dL were invited to return the following day for fasting plasma glucose testing. Resurveys of 5% randomly selected samples of surviving participants were undertaken in 2008 and 2013–2014, collating the same data as at baseline, including anthropometric data.

Anthropometric Measurements

Standing height was measured to the nearest 0.1 cm using a portable stadiometer. Weight was measured to the nearest 0.1 kg using the scale function of the TBF-300 Body Composition Analyzer (Tanita Inc., Tokyo, Japan), and the estimated weight of clothing was subtracted (summer 0.5 kg; spring/autumn 1.0 kg; winter 2.0–2.5 kg). Height and weight were measured without shoes. The TBF-300 Body Composition Analyzer used foot-to-foot bioelectrical impedance analysis to measure body fat percentage (BF%) using its built-in proprietary algorithm. WC and hip circumference (HC) were measured to the nearest 0.1 cm with a nonstretchable tape measure, as follows: WC was measured at the midpoint between the lowest rib margin and the iliac crest; HC was measured around the maximum circumference of the buttocks. WC and HC were measured unclothed or 1–2 cm was subtracted from the WC reading to account for undergarments and 1 and 2.5 cm were subtracted from the HC reading to account for skirt and trousers, respectively. BMI was calculated as weight in kilograms divided by height in meters squared. BMI at 25 years (BMI25) used self-reported weight at age 25 years and measured height at baseline. BMI change was calculated by subtracting BMI25 from BMI. The proportional change in BMI was BMI change as a percentage of BMI25. Waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR) were calculated as the WC divided by HC and standing height, respectively.

Follow-up for Morbidity and Mortality

Information on nonfatal disease outcomes was collected through linkage with established disease surveillance systems for certain diseases (diabetes, cancer, ischemic heart disease, and stroke), and, via unique national identification, with the national health insurance system, which includes details of ICD-10–coded diagnoses resulting in, or during, hospitalization. The vital status of participants was monitored through death registries and was checked annually against local residential and health insurance records, and by active confirmation. Deaths were ICD-10 coded by trained staff blinded to baseline information. Cases of incident diabetes were identified through the disease surveillance system for diabetes and through diabetes diagnoses (ICD-10 codes E10 to E14) recorded in the health insurance databases or as underlying or contributing to death on death certificates. By 1 January 2016, 37,289 participants (7.3%) had died and 4,098 (0.8%) were lost to follow-up.

Statistical Analysis

The current study excluded participants with missing BMI (n = 2) data or with previously diagnosed or screen-detected diabetes (17) at baseline (n = 30,300), leaving 482,589 participants (198,574 men, 284,015 women) for inclusion in the main analyses.

All analyses were performed separately for men and women. The prevalence and mean values of baseline characteristics were calculated across BMI categories (9), standardized by 5-year age groups and study area. Cox proportional hazards models were used to estimate hazard ratios (HRs) for the associations of baseline general (BMI, BF%) and central (WC, WHR, WHtR) adiposity measures and BMI25 and BMI change with incident diabetes, stratified by age at risk (5-year groups) and study area, and adjusted for education, income, occupation, smoking,

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alcohol consumption, physical activity, and family history of diabetes. Further analyses additionally adjusted for selected adiposity measures to examine independent effects. Adiposity measures were categorized (cut points: 20th, 40th, 60th, 80th, 90th, and 95th percentiles) to examine the full distribution, while ensuring adequate cases in each category. If the shape of the association was log linear, adiposity measures were also investigated as continuous variables. The associations of BMI and WC with incident diabetes were examined across international and Asia-specific categories (9,18). The "floating absolute risk" method was used when examining adiposity measures as categorical variables (19); this does not alter the value of the HRs but provides a 95% CI for each HR based on the amount of data in that category.

Single adiposity measurements may not accurately reflect an individual's usual level because of random measurement error, including within-person variation or change over time (20). Repeat adiposity measurements available for 18,750 participants who attended the resurvey 3 years after baseline were used to estimate regression dilution ratios, calculated as the slope of the regression line between baseline and resurvey measurements adjusted for age and study area (21). Log HR estimates for baseline BMI and WC (and other adiposity measures), which were examined as continuous variables, were multiplied by the reciprocal of the regression dilution ratio to estimate associations of usual BMI and WC with incident diabetes risk (20). Comparison of HRs for the first 4 years and for subsequent years of follow-up revealed no clear deviation from the proportional hazards assumption. Adjusted HRs were calculated across strata of other covariates, and χ^2 tests for trend and heterogeneity were applied to log HRs and their SEs (22).

All analyses used SAS version 9.4. Figures were produced using R version 3.3.2.

RESULTS

Among the 482,589 participants, the mean BMI was 23.6 kg/m^2 (SD 3.3 kg/m^2), 4.5% were underweight (<18.5 kg/m^2), 28.1% were overweight (25.0–29.9 kg/m^2), and 3.8% were obese (≥30.0 kg/m^2) (Table 1). Men with higher BMI were more likely to have higher socioeconomic status and to be alcohol drinkers and were less likely to be regular smokers. These associations were not evident in women. In both sexes, BMI was strongly positively associated with random plasma glucose level and family history of diabetes, and measures of both general and central adiposity tended to correlate strongly with each other (Supplementary Fig. 1 and Supplementary Table 1). BMI25 was positively associated with BMI at baseline but was only weakly correlated with baseline adiposity measures. Mean BMI and WC values were higher in urban than in rural areas. Between the baseline survey and the 2013 resurvey (i.e., ~8 years after baseline), there were modest increases in mean BMI (men 23.4 to 24.0 kg/m^2; women 23.8 to 24.2 kg/m^2) and WC (men 82.0 to 86.3 cm; women 79.1 to 83.4 cm), which were more marked in rural than urban areas (Supplementary Table 2).

During ~4.3 million person-years (mean 9 years) of follow-up, 13,416 participants (2.8%) were newly diagnosed with diabetes (13,198 nonfatal, 218 fatal) at age at risk of 35–79 years. The overall diabetes incidence was 314 per 100,000 person-years, which was similar in urban and rural areas (320 vs. 312 per 100,000 person-years), in contrast to higher diabetes prevalence in urban areas at baseline (Supplementary Fig. 2). Among those in whom incident diabetes developed during follow-up, the mean baseline BMI (25.5 kg/m^2 [SD 3.6 kg/m^2] vs. 23.5 kg/m^2 [SD 3.3 kg/m^2]) and WC (85.2 cm [SD 10.1 cm] vs. 79.8 cm [SD 9.6 cm]) were higher than among those in whom diabetes did not develop.

Compared with men with so-called "normal" weight, overweight or obese men had adjusted HRs of 2.87 (95% CI 2.76–2.98) and 6.10 (5.54–6.72), respectively, for incident diabetes (Table 2). Among women, the corresponding HRs were 2.35 (95% CI 2.28–2.42) and 4.36 (4.09–4.65). Individuals who were underweight had significantly lower risk (men: HR 0.64 [95% CI 0.52–0.77]; women: HR 0.61 [0.53–0.71]). When Asia-specific BMI cut points (9) were applied, the magnitude of HRs associated with overweight and obesity were similar (Supplementary Table 4). There was a fourfold to fivefold higher risk associated with grade 2 abdominal obesity (18) compared with a "normal" WC (Table 2).

There were positive log-linear associations of baseline BMI and WC with the risk of incident diabetes (P for trend <0.001) (Fig. 1). For BMI, each 1-SD increment was associated with HRs of 1.91 (95% CI 1.86–1.96) in men and 1.70 (1.67–1.73) in women (P for heterogeneity <0.001), whereas for WC they were 1.99 (1.94–2.04) and 1.78 (1.75–1.81) (P for heterogeneity <0.001), respectively. After mutual adjustment, the HRs for BMI were attenuated by >60% (men 66%; women 61%) and for WC by ~40% (men 43%; women 44%). For both BMI and WC, the HRs per SD increment were greater in men than in women at all ages (overall P for heterogeneity <0.001) (Supplementary Fig. 3) and at younger rather than older ages in both sexes (P for trend <0.001) (Supplementary Figs. 4 and 5).

The strength of associations of BMI and WC with diabetes were consistent between study areas (Supplementary Fig. 6), but overall they were stronger in rural than in urban areas (P for heterogeneity <0.001) and in individuals without a family history of diabetes, although the difference reached significance only in men (P for heterogeneity = 0.01) (Supplementary Figs. 4 and 5). Among men, there was evidence of a stronger association of WC with diabetes in ever-regular than in never-regular smokers (P for heterogeneity = 0.02) (Supplementary Fig. 4).

After applying regression dilution ratios (men 0.95; women 0.93), each 1-SD higher usual BMI was associated with adjusted HRs of 1.98 (95% CI 1.93–2.04) and 1.77 (1.73–1.81) in men and women, respectively (Supplementary Table 5), whereas for usual WC the corresponding HRs were 2.13 (2.07–2.19) and 1.91 (1.87–1.95) (regression dilution ratios: men 0.91; women 0.89).

There were strong, positive log-linear associations of other measures of adiposity with risk of diabetes (Supplementary Figs. 7 and 8 and Supplementary Table 5). HC was positively associated with incident diabetes after basic adjustment (P for trend <0.001), with a greater HR in men than in women (1.76 [95% CI 1.71–1.82] vs. 1.49 [1.46–1.53] per 1 SD) (P for heterogeneity <0.001). After additional adjustment for WC, this association was reversed, and the sex difference attenuated (men 0.87 [95% CI 0.83–0.92]; women 0.86 [0.83–0.89]) (P for heterogeneity = 0.7). For WHR, each 1-SD increment was associated with adjusted HRs of 1.33 (95% CI 1.31–1.35) in men and 1.27 (1.26–1.29) in women (P for

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Table 1—Baseline characteristics of participants by BMI

	Men					Women				
	BMI (kg/m^2)					BMI (kg/m^2)				
Characteristics*	<18.5	18.5–24.9	25.0–29.9	≥30	Total	<18.5	18.5–24.9	25.0–29.9	≥30	Total
No. of participants	9,108	129,855	54,161	5,450	198,574	12,528	177,202	81,426	12,859	284,015
Age and socioeconomic factors										
Mean age (SD), years	56.4 (14.4)	52.2 (11.0)	50.9 (11.0)	49.7 (13.1)	52.1 (10.9)	53.1 (14.7)	49.7 (10.4)	51.2 (9.7)	52.1 (10.9)	50.5 (10.4)
≥6 years of education, %	56.9	58.5	62.5	62.9	57.5	42.1	43.5	41.0	38.3	43.7
Living in urban area, %	29.0	36.2	56.4	66.0	42.2	33.6	41.8	48.5	51.5	43.7
Occupation, %										
Agriculture and related	47.4	45.8	38.0	34.5	44.7	44.2	41.9	39.3	37.1	41.6
Other	32.0	36.5	41.8	42.7	36.4	21.7	24.1	23.1	20.8	24.1
Retired/housewife/unemployed	20.6	17.6	20.2	22.8	18.9	34.0	34.0	37.6	42.1	34.3
Annual household income, %										
<10,000 yuan	33.5	27.4	22.3	19.8	26.4	34.5	30.0	29.4	30.2	29.9
10,000–19,999 yuan	29.3	28.9	27.7	28.6	28.3	29.6	29.0	29.8	30.1	29.4
>19,999 yuan	37.2	43.6	50.1	51.6	45.3	35.9	41.0	40.8	39.7	40.6
Lifestyle factors										
Ever-regular smoker, %	79.9	75.4	70.7	70.4	74.5	5.1	3.3	2.8	3.3	3.1
Ever-regular alcohol drinker, %	36.6	41.3	43.0	44.1	41.8	2.7	3.0	3.2	2.8	3.0
Mean physical activity (SD), MET-h/d	22.1 (18.7)	23.4 (13.6)	21.5 (14.0)	19.6 (16.1)	22.4 (15.3)	20.4 (13.7)	20.7 (10.5)	20.1 (11.0)	19.1 (12.7)	20.8 (12.8)
Anthropometry, blood pressure, and plasma glucose, mean (SD)										
BMI, kg/m^2	17.7 (0.9)	22.0 (1.7)	26.7 (1.4)	31.5 (1.9)	23.3 (3.2)	17.5 (1.0)	22.2 (1.7)	26.8 (1.4)	31.9 (2.3)	23.7 (3.4)
WC, cm	67.6 (6.0)	78.3 (6.5)	90.7 (6.3)	102.1 (8.8)	81.7 (9.7)	64.3 (6.4)	75.3 (6.3)	86.0 (6.2)	96.5 (8.4)	78.7 (9.4)
HC, cm	81.9 (5.7)	88.5 (4.4)	95.7 (4.5)	102.9 (6.7)	90.5 (6.8)	81.6 (4.7)	88.7 (4.4)	95.6 (4.6)	103.5 (6.5)	91.0 (6.8)
WHR	0.83 (0.08)	0.88 (0.06)	0.95 (0.05)	0.99 (0.07)	0.90 (0.06)	0.79 (0.08)	0.85 (0.06)	0.90 (0.06)	0.93 (0.07)	0.86 (0.07)
WHtR	0.41 (0.04)	0.47 (0.04)	0.55 (0.04)	0.62 (0.05)	0.49 (0.06)	0.42 (0.04)	0.49 (0.04)	0.56 (0.04)	0.63 (0.05)	0.51 (0.06)
BF%†	12.8 (4.1)	20.0 (4.4)	27.3 (4.7)	32.5 (7.0)	21.9 (6.2)	19.2 (3.3)	29.2 (4.5)	37.8 (4.5)	45.3 (6.4)	31.9 (7.1)
BMI25‡, kg/m^2	20.0 (2.5)	21.6 (2.1)	22.5 (2.5)	23.8 (3.5)	21.9 (2.3)	20.0 (2.8)	21.5 (2.6)	22.7 (2.9)	23.9 (3.8)	21.8 (2.7)
BMI change‡, kg/m^2	−2.3 (2.5)	0.6 (2.5)	4.3 (2.7)	7.7 (3.7)	1.6 (3.4)	−2.4 (2.8)	0.7 (2.8)	4.1 (3.0)	8.0 (4.2)	2.0 (3.6)
Proportional change in BMI (%)	−10.7 (11.4)	3.5 (12.2)	20.2 (13.8)	34.1 (20.2)	8.0 (16.3)	−11.1 (12.6)	4.6 (13.6)	19.7 (15.8)	35.7 (23.4)	10.1 (17.0)
SBP, mmHg	121.7 (23.0)	129.5 (18.1)	137.5 (19.8)	144.8 (27.7)	132.4 (19.9)	120.5 (25.3)	127.3 (19.8)	134.6 (20.8)	141.3 (24.7)	129.0 (21.6)
RPG§, mg/dL	99.0 (27.0)	99.0 (19.8)	102.6 (23.4)	106.2 (32.4)	100.8 (21.6)	100.8 (27.0)	102.6 (19.8)	106.2 (21.6)	108.0 (27.0)	102.6 (19.8)
Family history of diabetes, %	4.6	5.5	7.4	8.2	6.0	4.2	6.2	7.4	8.0	6.7

MET-h/d, metabolic equivalent of task hours per day; RPG, random plasma glucose; SBP, systolic blood pressure. SI conversion factor: to convert glucose to mmol/L, divide by 18. *Standardized to age and study area structure of the study population. †Data missing for 226 participants. ‡Data missing for 77,745 participants. §Data missing for 7,975 participants.

Table 2—Number of cases of diabetes, standardized diabetes incidence rates, and adjusted HRs by BMI and WC at baseline

	Men			Women		
	No. of cases	Standardized rate per 100,000 (95% CI)*	HR (95% CI)†	No. of cases	Standardized rate per 100,000 (95% CI)*	HR (95% CI)†
BMI (kg/m^2)						
Underweight (<18.5)	104	112.4 (84.7–140.2)	0.64 (0.52–0.77)	182	117.9 (89.9–145.9)	0.61 (0.53–0.71)
Normal weight (18.5–24.9)	2,183	195.4 (188.6–202.2)	1.00 (0.96–1.05)	3,492	200.1 (193.2–206.9)	1.00 (0.97–1.04)
Overweight (25.0–29.9)	2,366	537.3 (519.4–555.1)	2.87 (2.76–2.98)	3,680	528.8 (511.2–546.3)	2.35 (2.28–2.42)
Obese (≥30.0)	431	1,055.9 (1,023.7–1,088.1)	6.10 (5.54–6.72)	978	1,047.6 (1,015.2–1,080.0)	4.36 (4.09–4.65)
WC (cm)						
Normal‡	3,781	178.6 (169.7–187.5)	1.00 (0.96–1.04)	2,914	116.7 (109.9–123.5)	1.00 (0.96–1.04)
Abdominal obesity grade 1§	947	713.8 (663.8–763.8)	3.06 (2.87–3.26)	2,690	408.2 (392.4–423.9)	2.19 (2.11–2.27)
Abdominal obesity grade 2‖	356	1,379.9 (1,309.3–1,450.6)	5.16 (4.65–5.73)	2,728	843.7 (829.8–857.6)	3.94 (3.78–4.10)

*Standardized to age and study area structure of CKB population. †Stratified by age and study area and adjusted for education, income, occupation, smoking, alcohol consumption, physical activity, family history of diabetes. ‡Men ≤94.0 cm; women ≤80.0 cm. §Men 94.1–102.0 cm; women 80.1–88.0 cm. ‖Men >102.0 cm; women >88.0 cm. Analyses were restricted to participants in whom diabetes developed between 35 and 70 years of age, excluding 7 incident cases of diabetes at <35 years of age and 236 at ≥80 years of age.

heterogeneity <0.001), which were moderately attenuated by additional adjustment for BMI.

Further adjustment for blood pressure or dietary factors (fresh fruit, fresh vegetables, meat, rice, soybean products, and wheat consumption), or in women for menopausal status, did not materially alter the associations, nor did the exclusion of individuals in whom cancer developed (which could cause significant weight change) prior to the diagnosis of diabetes (Supplementary Table 6). Sensitivity analyses based on the resurvey population (n = 14,881) revealed no significant differences in the strength of associations of BMI (P for heterogeneity: men 0.4; women 0.5) or WC (P for heterogeneity: men 0.3; women 0.4) with incident diagnosed diabetes and undiagnosed diabetes (Supplementary Fig. 9).

There was a weak positive log-linear association between BMI25 and the risk of diabetes in later adulthood (men HR 1.09 [95% CI 1.05–1.12] and women 1.04 [1.02–1.07] per 1 SD higher) (P for trend <0.001) (Supplementary Fig. 10). However, after additional adjustment for BMI at baseline, a higher BMI25 was associated with a lower risk of incident diabetes (P for trend <0.001). Likewise, there was no clear association of BMI25 with incident diabetes within each baseline BMI category, whereas the converse was true for baseline BMI levels within each BMI25 category (Supplementary Table 7). Absolute (Supplementary Fig. 10) and proportional (Supplementary Fig. 11) changes in BMI between 25 years of age and baseline (mean 26.1 years) were strongly positively associated with the risk of diabetes, but these associations were markedly attenuated after additional adjustment for BMI at baseline.

CONCLUSIONS

This is the largest ever prospective cohort study in China examining the relationship between adiposity and incident diabetes. In this relatively lean adult population, there were strong, positive, apparently log-linear, associations between measures of central and general adiposity and incident diabetes, and general overweight and obesity were associated with twofold to sixfold greater risks of diabetes. Relative risk estimates appeared to be somewhat greater among men than women and for measures of central than general adiposity. Assuming a causal association and an increase in mean population BMI of 1 kg/m^2 per decade, as has occurred in China (8), and applying our relative risk estimates to national diabetes prevalence, it was estimated that adiposity accounted for almost 50% of the increase in diabetes burden since 1980 and that 40 million prevalent cases of diabetes (men 21.5 million; women 18.5 million) (36%) could be attributed to excess general adiposity (BMI ≥25 kg/m^2) in China in 2010 (Fig. 2).

Previous large prospective studies, or meta-analyses of such studies, have demonstrated clearly that adiposity is the strongest modifiable risk factor for type 2 diabetes. In a large pooling project of Western prospective cohorts, including 5,500 cases of diabetes, each 5 kg/m^2 increment in BMI was associated with a 2.7-fold higher risk of diabetes (23). This is comparable with findings from the European Prospective Investigation into Cancer and Nutrition (EPIC)-InterAct nested case-control study of >12,000 cases of type 2 diabetes, which showed a doubling of the risk of type 2 diabetes per SD (~4 kg/m^2) higher BMI (24). Our study shows reliably that risk estimates for BMI in Chinese adults are largely comparable with those from previous Western studies, thus further extending the positive log-linear association with diabetes to well below the range of BMI typically seen in Western populations (9). Central adiposity measures, indicating the degree of visceral adiposity, are proposed to be more important indicators of cardiometabolic risk than general adiposity measures (25). However, previous large studies in Western populations, and limited data from East Asia (24,26), have found largely comparable strengths of association of WC (e.g., 2-fold to 2.5-fold higher risk per SD higher after minimal adjustment for confounding) and BMI with the risk of diabetes (24). Importantly, however, these studies did not take account of regression dilution bias, which would be expected to be somewhat greater for WC than for BMI. In the CKB study, more marked attenuation of the association of baseline BMI with incident diabetes after adjustment for baseline WC than vice versa and the stronger association of usual WC than usual BMI, after accounting for measurement error, suggest a somewhat stronger association of WC with the risk of diabetes.

Previous findings on sex differences in the strength of association between adiposity and type 2 diabetes are inconsistent (13,23,27,28). One prospective study in

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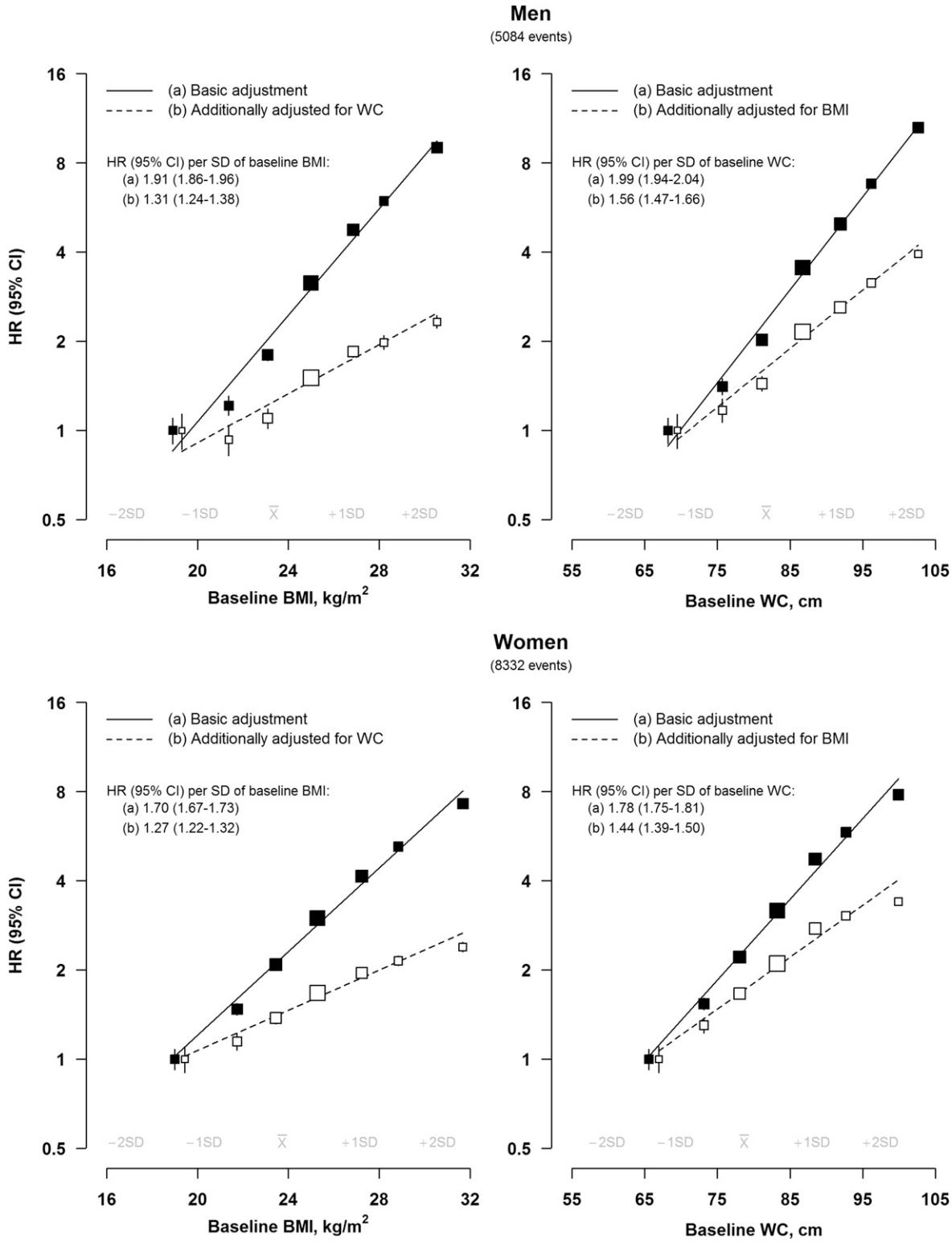

Figure 1—Adjusted HRs (95% CI) for diabetes by baseline BMI and WC. Basic adjustment results are stratified by age and study area and are adjusted for education, household income, occupation, smoking, alcohol consumption, physical activity, and family history of diabetes. Squares represent the HR with area inversely proportional to the variance of the log HR, and error bars indicate the 95% CI. Adjusted HRs are plotted against mean BMI and WC levels in each category. To avoid overlap of 95% CI lines, the boxes and their 95% CIs for the reference groups were moved apart slightly from the actual positions. Continuous associations reflect sex-specific BMI and WC SDs.

China (13) showed a stronger association of BMI and WC in women, but the number of women included was small (~20%; n = 16,680). Several Western population studies (24,29) have shown a stronger association of WC, but less clearly of BMI, among women than men. The CKB study provides robust evidence of a stronger association of BMI among men, which was

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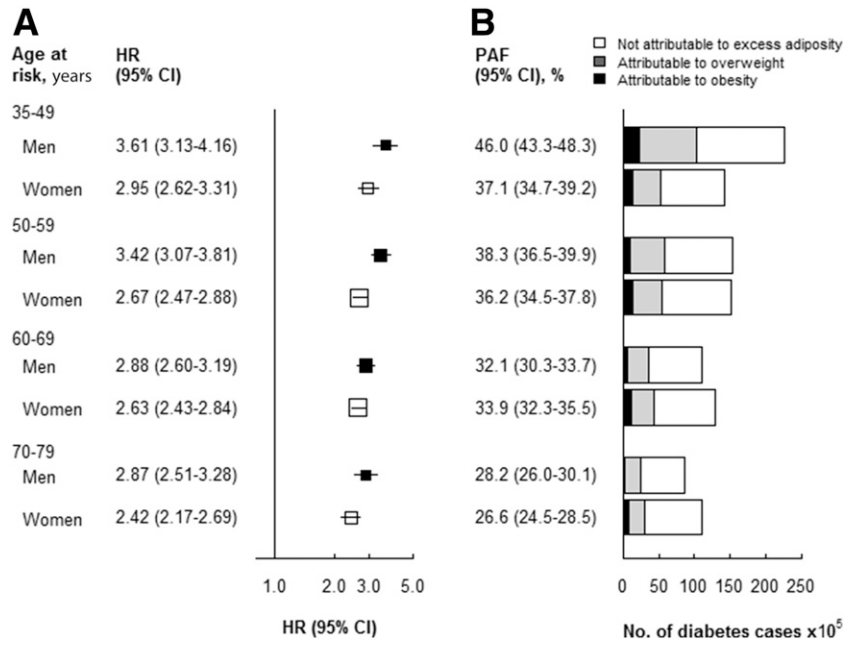

Figure 2—Adjusted HRs for diabetes and cases of diabetes caused by excess adiposity (BMI ≥25 kg/m^2). *A*: Adjusted HR for diabetes associated with excess adiposity (BMI ≥25 kg/m^2) by age and sex. HRs are calculated for overweight or obese (BMI ≥25 kg/m^2) participants versus the absence of overweight or obese (BMI <25 kg/m^2) participants. HRs are stratified by age and study area and are adjusted for education, household income, occupation, smoking, alcohol consumption, physical activity, and family history of diabetes. Squares represent the HR with the area inversely proportional to the variance of the log HR, and error bars indicate the 95% CI. *B*: Diabetes cases attributable to excess adiposity (BMI ≥25 kg/m^2) in 2010. Age- and sex-specific prevalence of overweight and obesity in the CKB study are comparable with contemporaneous nationally representative surveys (32), and the population attributable fraction (PAF) was calculated as P(HR−1) divided by HR, where P is the prevalence of excess adiposity among those in whom incident diabetes developed. By applying age- and sex-specific HRs to nationally representative, age- and sex-specific diabetes prevalence (4), we estimated the number of diabetes cases attributable to excess adiposity.

attenuated by additional adjustment for WC. This is consistent with the apparently stronger association of WC among men observed in the CKB study, likely reflecting a greater propensity of men than women for visceral fat accumulation (18) and for higher levels of insulin resistance (30). Explanations for the discrepancy with previous findings in Western population studies, in particular for WC, are unclear but may reflect ethnic differences in the sexual dimorphism in body composition (31) (e.g., predisposition to visceral vs. subcutaneous adiposity), but further investigation is required to understand this fully (31).

The diabetes incidence rates observed in the current study were similar in urban and rural areas, in contrast with a higher prevalence of diabetes seen in urban areas at baseline (17). A higher proportion of undiagnosed diabetes in urban areas could explain this pattern; however, evidence from a subset of study participants who attended baseline and two subsequent surveys suggests that the rate of undiagnosed diabetes after baseline was higher in rural (44%) than in urban (35%) areas. This would be expected to result in smaller relative risk estimates in rural areas, but the adiposity-associated diabetes risks, if anything, were somewhat greater in rural than in urban areas, especially among men. The converging urban-rural diabetes incidence trends may in part reflect marked increases in adiposity in rural areas over recent years (32) as well as adverse lifestyle changes beyond adiposity. In combination with poorer diabetes-associated outcomes in rural areas (33), this highlights the need for focused attention on diabetes prevention and management in rural areas of China.

Although some studies have suggested that early adulthood adiposity is an independent risk factor for type 2 diabetes during later adulthood (34,35), this is not supported by larger studies in which the association was attenuated (36,37) or reversed (38) after accounting for later adulthood adiposity. One previous Chinese population study (35), including ~120,000 adults with a diabetes prevalence of 21%, found increasing odds of prevalent diabetes with increasing BMI at age 20 years after controlling for weight change between 20 and 40 years. However, the cross-sectional study design increases the susceptibility of these analyses to biases. With more incident diabetes cases than previous studies combined (n = 11,400 vs. 4,500), we show clearly that adiposity in later adulthood is critical in determining the risk of type 2 diabetes, which is consistent with the more functional—rather than anatomical—abnormalities underlying type 2 diabetes (36) and with observed type 2 diabetes remission (6). Although we used self-reported weight at 25 years, resurvey data demonstrated good correlation between repeated self-reports (Pearson correlation coefficients 0.81 and 0.77, comparing baseline with first and second resurveys, respectively), which is consistent with previous studies showing accurate recall of past body weight (39). These findings highlight the importance of weight management throughout adulthood, although their generalizability to current and future generations of young adults is unclear, given the low average BMI25 in CKB study participants.

Apart from the large population, our study has several strengths. The exclusion of diagnosed and undiagnosed diabetes at baseline reduced the potential for reverse causality, and the relatively lean study population enabled investigation of a uniquely wide adiposity range. The use of standardized protocols and extensive training across study centers ensured the reliability of exposure measurements. A medical record review for almost 1,000 incident cases of diabetes confirmed the validity of the diagnosis (positive predictive value 97%, based on American Diabetes Association diagnostic criteria [40] and medication use), and the estimated diabetes prevalence based on the CKB resurvey population (to enable estimation of undiagnosed diabetes prevalence) was reasonably consistent with nationally representative surveys (4,41) (Supplementary Table 8). Furthermore, the mean BMI and prevalence of overweight and obesity in the CKB study were comparable to contemporaneous nationally representative surveys in China (32). Extremely low loss

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to follow-up and the diversity of the study population limit the potential for biased risk estimates and ensure the generalizability of the findings. Furthermore, the adjustment of estimates for regression dilution bias, using repeat adiposity measures during follow-up, ensures accurate estimates of the association of usual adiposity levels and the risk of diabetes. Although repeat adiposity measurements used for adjustment were slightly earlier than the ideal midpoint of follow-up (intraindividual variation in exposures increases with longer periods of follow-up) (20), any resulting underestimation of intraindividual variation would be expected to be minimal for adiposity measures. However, our study has certain limitations. Incident diabetes was restricted to diagnosed cases, but the presented sensitivity analyses suggest that this would not have a significant impact on risk estimates. Conversely, although the proportion of diabetes cases remaining undiagnosed may be lower in individuals with the highest BMI levels (given the known association of obesity with type 2 diabetes), leading to overestimation of adiposity-associated risks, this would not explain the observed association among individuals without overweight or obesity. Given the age of the cohort, all incident diabetes cases were assumed to be type 2 diabetes; a small proportion may have been type 1 diabetes, and their inclusion would likely underestimate adiposity-associated risks.

In conclusion, the current study provides the first large-scale prospective evidence of strong, positive, independent relationships of general and central adiposity with incident diabetes risk in Chinese adults. Adiposity is the strongest modifiable, and causal (7), risk factor for type 2 diabetes, and projected further increases in adiposity levels in the population will foreshadow still higher diabetes prevalence in coming decades in China, perhaps particularly among rural populations. In the absence of known modifiable causal mediators of the association with type 2 diabetes, tackling adiposity at a whole-population level is imperative for control of the diabetes epidemic in China.

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