JAMA | Original Investigation

Association Between Diabetes and Cause-Specific Mortality in Rural and Urban Areas of China

Fiona Bragg, DPhil; Michael V. Holmes, PhD; Andri Iona, MSc; Yu Guo, MSc; Huaidong Du, PhD; Yiping Chen, DPhil; Zheng Bian, MSc; Ling Yang, PhD; William Herrington, MD; Derrick Bennett, PhD; Iain Turnbull, MRCP; Yongmei Liu, MBBS; Shixian Feng, MBBS; Junshi Chen, MD; Robert Clarke, FRCP; Rory Collins, FRS; Richard Peto, FRS; Liming Li, MPH; Zhengming Chen, DPhil; for the China Kadoorie Biobank Collaborative Group

IMPORTANCE In China, diabetes prevalence has increased substantially in recent decades, but there are no reliable estimates of the excess mortality currently associated with diabetes.

OBJECTIVES To assess the proportional excess mortality associated with diabetes and estimate the diabetes-related absolute excess mortality in rural and urban areas of China.

DESIGN, SETTING, AND PARTICIPANTS A 7-year nationwide prospective study of 512 869 adults aged 30 to 79 years from 10 (5 rural and 5 urban) regions in China, who were recruited between June 2004 and July 2008 and were followed up until January 2014.

EXPOSURES Diabetes (previously diagnosed or detected by screening) recorded at baseline.

MAIN OUTCOMES AND MEASURES All-cause and cause-specific mortality, collected through established death registries. Cox regression was used to estimate adjusted mortality rate ratio (RR) comparing individuals with diabetes vs those without diabetes at baseline.

RESULTS Among the 512 869 participants, the mean (SD) age was 51.5 (10.7) years, 59% (n = 302 618) were women, and 5.9% (n = 30 280) had diabetes (4.1% in rural areas, 8.1% in urban areas, 5.8% of men, 6.1% of women, 3.1% had been previously diagnosed, and 2.8% were detected by screening). During 3.64 million person-years of follow-up, there were 24 909 deaths, including 3384 among individuals with diabetes. Compared with adults without diabetes, individuals with diabetes had a significantly increased risk of all-cause mortality (1373 vs 646 deaths per 100 000; adjusted RR, 2.00 [95% CI, 1.93-2.08]), which was higher in rural areas than in urban areas (rural RR, 2.17 [95% CI, 2.07-2.29]; urban RR, 1.83 [95% CI, 1.73-1.94]). Presence of diabetes was associated with increased mortality from ischemic heart disease (3287 deaths; RR, 2.40 [95% CI, 2.19-2.63]), stroke (4444 deaths; RR, 1.98 [95% CI, 1.81-2.17]), chronic liver disease (481 deaths; RR, 2.32 [95% CI, 1.76-3.06]), infections (425 deaths; RR, 2.29 [95% CI, 1.76-2.99]), and cancer of the liver (1325 deaths; RR, 1.54 [95% CI, 1.28-1.86]), pancreas (357 deaths; RR, 1.84 [95% CI, 1.35-2.51]), female breast (217 deaths; RR, 1.84 [95% CI, 1.24-2.74]), and female reproductive system (210 deaths; RR, 1.81 [95% CI, 1.20-2.74]). For chronic kidney disease (365 deaths), the RR was higher in rural areas (18.69 [95% CI, 14.22-24.57]) than in urban areas (6.83 [95% CI, 4.73-9.88]). Among those with diabetes, 10% of all deaths (16% rural; 4% urban) were due to definite or probable diabetic ketoacidosis or coma (408 deaths).

CONCLUSIONS AND RELEVANCE Among adults in China, diabetes was associated with increased mortality from a range of cardiovascular and noncardiovascular diseases. Although diabetes was more common in urban areas, it was associated with greater excess mortality in rural areas.

JAMA. 2017;317(3):280-289. doi:10.1001/jama.2016.19720

Editorial page 264

Supplemental content

CME Quiz at jamanetworkcme.com

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The China Kadoorie Biobank Collaborative Group members are listed in the Supplement.

Corresponding Authors: Zhengming Chen, DPhil, University of Oxford, Nuffield Department of Population Health, Richard Doll Building, Old Road Campus, Oxford OX3 7LF, England (zhengming.chen@ctsu.ox.ac.uk); Liming Li, MPH, Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing 100191, China (lmlee@vip.163.com).

The prevalence of diabetes in China has more than quadrupled in recent decades, with an estimated 110 million adults having diabetes in 2010 and 490 million adults estimated to have prediabetes.[1-4] A previous study estimated that diabetes accounted for 5% to 7% of overall adult mortality or disability-adjusted life-years in China in 2010.[5] However, such estimates were derived mainly from extrapolation of risk estimates from studies conducted in high-income countries where many patients with diabetes have reasonably good control of blood glucose and take cardiovascular-protective medications.[6-9] Previous studies of diabetes and mortality in China have been limited by small sample size, enrollment of participants many decades ago (when the prevalence of diabetes was relatively low), or restriction to local occupational or urban cohorts.[10-12]

CKB *China Kadoorie Biobank*

CKD *chronic kidney disease*

IHD *ischemic heart disease*

RR *rate ratio*

In China, many cases of diabetes are undiagnosed,[1,3,4] and among persons diagnosed with diabetes, many are not adequately managed,[4] particularly in rural areas, thereby increasing the risk of premature death. Because the increase in diabetes prevalence in China is recent, the full effect on mortality and morbidity is unknown. Moreover, the main adult disease patterns in China differ appreciably from those in Western countries (eg, more people die of stroke than of ischemic heart disease [IHD] in China) and also vary greatly between different regions.[13] Therefore, reliable estimates of the emerging epidemic of mortality associated with diabetes are needed nationally and regionally to plan prevention and treatment programs. This nationwide prospective study examined the association of diabetes with cause-specific mortality in rural and urban areas in China.

Key Points

Question What is the excess mortality risk associated with diabetes in rural and urban areas of China?

Findings In this 7-year nationwide prospective study of 512 869 adults, diabetes was more common in urban than rural areas (8.1% vs 4.1%, respectively), and individuals with diabetes had significantly increased risk of mortality from all causes and from a range of cardiovascular and noncardiovascular diseases.

Meaning In China, diabetes is more common in urban than rural areas, and is associated with increased mortality. With an increasing adult population and rising prevalence of diabetes among young adults, the burden of diabetes-associated mortality will increase further.

Methods

Details of the China Kadoorie Biobank (CKB) design, its methods, and its participants have been reported previously.[14,15] Briefly, the 2004-2008 baseline survey took place in 10 (5 urban and 5 rural) localities across China, chosen from China's nationally representative Disease Surveillance Points system to retain geographic and social diversity. All 1 801 200 registered residents thought to be aged 35 to 74 years in the study areas were identified through local residential records and invited by letters and information leaflets to attend study clinics between June 2004 and July 2008. Of these registered residents, 512 869 participated, including 12 665 just outside this age range (making the actual baseline age range from 30-79 years). Because a substantial minority of registered residents would be disabled or living elsewhere, it was estimated that about one-third of the nondisabled invitees actually living in the study areas participated. Prior to commencement of the study, ethics approval was obtained from the Oxford University Tropical Research Ethics Committee and the Chinese Center for Disease Control and Prevention Ethical Review Committee and all participants provided written informed consent.

Trained health workers administered laptop-based questionnaires at local study clinics to collect sociodemographic factors (eg, smoking, alcohol consumption, diet, physical activity); medical history; measured height, weight, and waist and hip circumference; lung function; blood pressure; and heart rate. A nonfasting venous blood sample was collected (with record of the time since last ate) for storage and onsite random plasma glucose testing using the SureStep Plus system (LifeScan). Participants without a prior diabetes diagnosis plus an onsite random plasma glucose level between 140 mg/dL and 200 mg/dL (7.8-11.0 mmol/L) were invited for a fasting plasma glucose test the following day.[16]

Previously diagnosed diabetes was defined by a "yes" response to the question, "Has a doctor ever told you that you had diabetes?" These individuals were asked to provide additional information about age at first diagnosis and current use of certain medications for diabetes (eg, insulin and metformin), which were used to differentiate between type 1 and 2 diabetes (which was not asked specifically).

Respondents were also asked to provide information regarding use of medications for cardiovascular disease (eg, aspirin, agents to lower lipid levels and blood pressure). Among those without previously diagnosed diabetes, diabetes detected by screening was defined as (1) a random plasma glucose level of 126 mg/dL or greater (≥7.0 mmol/L) with time since last ate food of 8 hours or longer or 200 mg/dL or greater (≥11.1 mmol/L) with time since last ate of less than 8 hours or (2) a fasting plasma glucose level of 126 mg/dL or greater (≥7.0 mmol/L) on subsequent testing.

Cause-specific mortality was monitored through China's Disease Surveillance Points system[17] and electronic health insurance records, with annual active confirmation of survival through local residential and administrative records. The Disease Surveillance Points system provides reasonably complete and reliable death registration, in which almost all adult deaths were medically certified. For the few (<5%) without medical attention prior to death, standardized procedures were used to determine probable causes of death from symptoms or signs described by relevant informants (usually family members).[18]

The trained Disease Surveillance Points system staff coded all diseases on the death certificates and assigned underlying causes using the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision.* For deceased participants, the information entered into the study follow-up system (including scanned images of the original death certificates) was reviewed centrally by study clinicians, who were unaware of baseline information, who classified diabetes as the underlying cause only for deaths from diabetic ketoacidosis or coma or from diabetes with no other (eg, vascular or renal) antecedent cause on the death certificates (eTable 1 in the Supplement).

Mean and prevalence values for baseline variables by diabetes status were standardized for 5-year age groups, sex, and study area as were mortality rates using the total CKB study population as the standard. Cox proportional hazard models were used to determine the relationship between baseline diabetes and cause-specific mortality. Mortality rate ratio (RRs) and 95% CIs were adjusted for baseline covariates (education level, smoking, alcohol consumption, physical activity, and body mass index [calculated as weight in kilograms divided by height in meters squared]) and stratified by location (5 urban and 5 rural areas), age at risk (5-year groups), and sex.

In the analyses of mortality by duration of diabetes, the floating absolute risk method was used such that the RR for each category of duration (0 [screening-detected diabetes], <5, 5-<10, 10-<15, and ≥15 years) was accompanied by a 95% CI derived only from the variance of the log risk in that 1 category. Hence, each RR, including the one for the reference group, is associated with a group-specific 95% CI that reflects the amount of data in only that 1 category.[19] The group-specific 95% CI for RR is (RR/T, $RR \times T$), where T = exp ($1.96\sqrt{v}$) and v is the variance of the log risk, and RR − 1 gives the proportional excess risk.

Comparison of RRs for the first 4 years and for the subsequent years of follow-up revealed no evidence of departure from the proportional hazards assumption for all-cause mortality. Adjusted RRs were compared across strata of other covariates, and χ^2 tests for trend and heterogeneity were applied to the log RRs and their standard errors. The population-attributable fraction was calculated using $P(RR - 1)/(1 + P[RR - 1])$[20] where P is the prevalence of diabetes in this study. Two-sided P values were used and $P < .05$ denotes statistical significance; no correction was made for multiple testing. All analyses used SAS version 9.3 (SAS Institute Inc).

Results

Of the 512 869 participants (mean age, 51.5 years), 5.9% (3.1% previously diagnosed, 2.8% detected by screening) had diabetes at baseline and the prevalence was higher in urban areas than in rural areas (8.1% vs 4.1%, respectively). Individuals with diabetes were older and better educated, especially in urban areas, and after adjustment for age, they were less physically active and had higher measurements for body mass index, waist circumference, and blood pressure (**Table 1**). They were also more likely to have a history of hypertension, cardiovascular disease, chronic kidney disease, and chronic liver diseases and to have a family history of diabetes. Based on age at diagnosis (<30 years) and insulin use, less than 1% of cases were likely to have been type 1 diabetes and were included in the analyses. Diabetes prevalence increased with age (from 1.3% at aged 30-39 years to 11.4% at aged 70-79 years; **Figure 1**).

Among those with previously diagnosed diabetes (n = 16 142; n = 5617 in rural areas and n = 10 525 in urban areas), the median age at diagnosis was 53 years and the median time since diagnosis was 6 years. Overall, 77% of those previously diagnosed as having diabetes reported use of antidiabetic medications (65% taking oral medications, 15% taking insulin, and 4% taking both). Use of oral agents was higher in rural areas than urban areas (75% vs 60%, respectively), whereas the opposite was true for insulin (7% vs 18%).

Despite widespread use of treatments for diabetes, their mean plasma glucose levels remained elevated (eFigure 1 in the Supplement). However, at the time of the baseline survey, few of those with diabetes, either previously diagnosed or diagnosed based on screening, were taking statins or medications for hypertension (Table 1), this was particularly true for those with previously diagnosed diabetes (1.1% and 14.5%, respectively) (eTable 2 in the Supplement).

During 3.64 million person-years of follow-up (until January 1, 2014), 24 909 (4.9%) participants died (3384 with diabetes and 21 525 without diabetes) at age of risk of 35 to 79 years and 2204 (0.4%) were lost to follow-up. Overall, individuals with diabetes had a significantly elevated all-cause mortality compared with individuals without diabetes (1373 vs 646 deaths per 100 000, respectively; adjusted RR, 2.00 [95% CI, 1.93-2.08]). Compared with persons without diabetes, all-cause mortality for persons with diabetes increased with age, with absolute mortality rates of 716 vs 253 per 100 000, respectively, at the ages of 35 to 59 years (adjusted RR, 2.41 [95% CI, 2.22-2.62]), 1666 vs 916 per 100 000 at the ages of 60 to 69 years (RR, 2.01 [95% CI, 1.88 to 2.14]), and 3760 vs 2435 per 100 000 at the ages of 70 to 79 years (RR, 1.84 [95% CI, 1.75 to 1.95]).

The adjusted RRs comparing those with diabetes vs those without diabetes were greater in rural areas than urban areas both overall (RR for rural areas, 2.17 [95% CI, 2.07-2.29] vs RR for urban areas, 1.83 [95% CI, 1.73-1.94]) and at each specific age group (Figure 1) as were the absolute excess mortality rates among those with diabetes (ages 35-59 years: 737 per 100 000 in rural areas vs 290 per 100 000 in urban areas; ages 60-69 years: 1295 per 100 000 vs 545 per 100 000, respectively; ages 70-79 years: 2443 per 100 000 vs 1317 per 100 000).

The adjusted RRs were greater in women than in men older than 60 years (eFigure 2 in the Supplement). The excess mortality associated with diabetes accounted for 4.7% of the male deaths (absolute death rate of 2043 per 100 000 for men with diabetes vs 930 per 100 000 for men without diabetes) and 6.9% of the female deaths (absolute death rate

Table 1. Baseline Factors by Diabetes Status of Individuals Living in Rural and Urban Areas of China[a]

Characteristic[b]	Rural Areas		Urban Areas		Total	
	No Diabetes (n = 274 838)	Diabetes (n = 11 854)	No Diabetes (n = 207 751)	Diabetes (n = 18 426)	No Diabetes (n = 482 589)	Diabetes (n = 30 280)
Age and socioeconomic factors						
Age, mean (SD), y	50.7 (10.4)	56.3 (9.4)	51.8 (10.7)	58.5 (9.8)	51.2 (10.6)	57.2 (10.1)
Female, %	58.5	58.5	59.6	59.6	59.0	59.0
≥6 y of education, %	34.3	33.7	67.7	70.7	48.7	54.8
Lifestyle factors						
Ever regular smoker, %	65.7	66.8	70.0	68.9	67.6	68.1
Ever regular alcohol drinker, %	84.5	84.6	81.8	81.9	83.3	82.8
Physical activity, mean (SD), MET h/d	23.3 (12.4)	20.6 (16.6)	18.6 (10.5)	16.7 (17.0)	21.2 (11.6)	18.9 (17.6)
Anthropometry and blood pressure, mean (SD)						
Standing height, m	1.58 (0.05)	1.58 (0.07)	1.60 (0.05)	1.60 (0.08)	1.59 (0.05)	1.59 (0.08)
Body mass index[c]	23.1 (3.1)	24.5 (4.8)	24.2 (3.3)	25.4 (5.2)	23.6 (3.2)	24.9 (5.2)
Waist circumference, cm	78.7 (9.0)	84.0 (13.0)	81.7 (8.9)	85.9 (12.8)	80.0 (9.0)	84.8 (13.7)
Waist-to-hip ratio	0.88 (0.06)	0.92 (0.09)	0.87 (0.06)	0.91 (0.11)	0.88 (0.06)	0.92 (0.10)
Systolic blood pressure, mm Hg	132.2 (19.7)	139.3 (25.7)	128.7 (19.1)	136.9 (26.8)	130.6 (19.5)	138.3 (27.5)
Diastolic blood pressure, mm Hg	78.0 (10.9)	80.8 (14.6)	77.2 (10.7)	80.0 (15.7)	77.7 (10.8)	80.5 (15.8)
Random plasma glucose, mg/dL	100.8 (19.8)	234.0 (133.2)	104.4 (19.8)	216.0 (142.2)	102.6 (19.8)	226.8 (144.0)
Medical history and medications, %						
Hypertension	9.4	20.6	12.7	24.0	10.8	22.4
Cardiovascular disease	1.6	3.3	4.2	7.9	2.7	6.0
Chronic renal	1.4	1.7	1.6	2.3	1.4	2.1
Chronic liver	1.2	1.5	1.2	1.3	1.2	1.4
Cardiovascular disease medications[d]						
Statin	3.2	2.6	1.1	0.6	2.1	1.3
Aspirin	12.0	5.1	7.7	4.6	9.8	4.7
Blood pressure lowering[e]	29.7	16.1	28.0	17.4	28.8	16.8
Antidiabetic medications						
Chlorpropamide or metformin		75.2		59.8		65.1
Insulin		7.4		18.2		14.5
Both		3.5		3.7		3.6
Any		79.9		75.3		76.9
Family history of diabetes, %	4.1	15.3	10.0	26.8	6.7	21.9

Abbreviation: MET, metabolic equivalent task.

SI conversion factors: To convert glucose to mmol/L, multiply by 0.0555.

[a] Participants (n = 22) with missing or implausible values for key variables (eg, blood pressure, anthropometric measures, and duration of diabetes) were excluded, leaving 512 869 for the analyses. The comparisons between the diabetes and no diabetes groups were significant at *P* < .01 except for smoking, alcohol drinking, standing height, waist-to-hip ratio, and history of chronic liver disease.

[b] Adjusted for age, sex, and region.

[c] Calculated as weight in kilograms divided by height in meters squared.

[d] Among participants with hypertension, cardiovascular disease, or diabetes at baseline (n = 88 738).

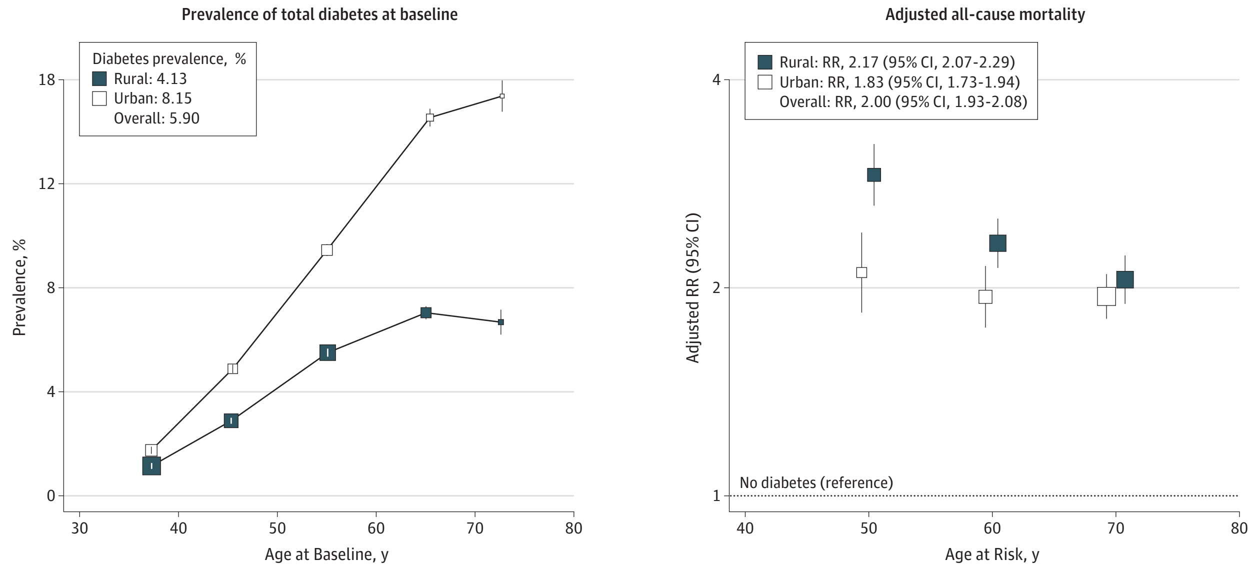
[e] Included angiotensin-converting enzyme inhibitors, β-blockers, diuretics, and calcium antagonists.

of 1416 per 100 000 for women with diabetes vs 418 per 100 000 for women without diabetes). Moreover, among those without diabetes at baseline, the random plasma glucose test level was associated positively with all-cause mortality (RR, 1.11 [95% CI, 1.10-1.12] per 18 mg/dL [1 mmol/L] higher usual random plasma glucose level).

Diabetes was associated with a RR of 2.13 (95% CI, 2.01-2.26) for death from cardiovascular disease (**Table 2**), including IHD (RR, 2.40 [95% CI, 2.19-2.63]), stroke (RR, 1.98 [95% CI, 1.81-2.17]; 71.8% of stroke deaths were due to intracerebral hemorrhage; RR, 1.87 [95% CI, 1.67-2.09]), and other vascular diseases (RR, 1.96 [95% CI, 1.71-2.26]). The RRs for vascular mortality were greater at younger ages than older ages (RR, 2.62 [95% CI, 2.28-3.02] for ages 35-59 years vs RR, 1.98 [95% CI, 1.83-2.15] for ages 70-79 years) and greater in women than in men (RR, 2.36 [95% CI, 2.18-2.56] for women vs RR, 1.93 [95% CI, 1.77-2.10] for men), but did not differ significantly between rural areas and urban areas (eFigures 3-5 in the Supplement).

Similarly, diabetes was associated with an increased RR of 2.32 (95% CI, 1.76-3.06) for mortality from chronic liver disease, infections (RR, 2.29 [95% CI, 1.76-2.99]), liver cancer (RR, 1.54 [95% CI, 1.28-1.86]), pancreatic cancer (RR, 1.84 [95% CI, 1.35-2.51]), female breast cancer (RR, 1.84 [95% CI,

Figure 1. Prevalence of Total Diabetes at Baseline and Adjusted Rate Ratio (RR) for All-Cause Mortality by Age at Risk and Urban vs Rural Area



No. of individuals					
Rural	57 517	85 756	86 201	45 787	11 442
Urban	36 113	68 570	65 385	42 111	14 007

No. of person-years			
Rural			
No diabetes	1 379 479	422 725	181 234
Diabetes	40 085	28 026	12 172
Urban			
No diabetes	970 075	304 379	182 027
Diabetes	51 128	41 702	31 592

The overall prevalence was adjusted for age, sex, and geographical area. The prevalence in urban areas and in rural areas were adjusted only for age and sex. The size of each box is proportional to the number of participants with diabetes and the error bars indicate the 95% CI. All-cause mortality was adjusted for age, geographic area (5 within each of rural and urban region), sex, education level, smoking, alcohol consumption, physical activity, and body mass index. Age at risk was calculated according to baseline age and length of follow-up, with a censoring date of January 1, 2014, or age of death if earlier. An individual could contribute person-time to more than 1 age category. Each RR has a 95% CI that reflects the variance of the log risk in that 1 group, taking into account the variance of the log risk in the reference group without diabetes (shown with a dotted line). Each box has an area inversely proportional to the effective variance of the log RR. The analyses were restricted to those who died between the ages of 35 and 79 years, excluding 5 deaths at ages younger than 35 years and 1014 deaths at ages of 80 years or older. The reference group for the urban analyses was individuals without diabetes in urban areas and the reference group for the rural analyses was individuals without diabetes in rural areas. Because there are 2 reference groups represented by the dotted line, the 95% CIs are not shown. To avoid overlap of 95% CI lines, the boxes and their 95% CIs for rural and urban areas in the right panel were moved apart slightly from the actual positions.

1.24-2.74]), and female reproductive system cancer (RR, 1.81 [95% CI, 1.20-2.74]). Diabetes was not associated with increased mortality from cancers of lung, stomach, esophagus, and intestine. For chronic respiratory disease, mainly chronic obstructive pulmonary disease, the RR was 1.29 (95% CI, 1.10-1.51). For deaths from external (eg, accident, suicide, and violence) and other medical causes, diabetes was associated with significant excess risk.

Among individuals with diabetes at baseline, definite diabetic ketoacidosis or coma accounted for 3.8% (128 of 3384) (6.3% [109 of 5617] in rural areas vs 1.1% [19 of 10 525] in urban areas) of the deaths compared with 0.07% (15 of 21 525) of the deaths among those without diabetes at baseline (because some developed diabetes during follow-up) (RR, 181.85 [95% CI, 103.95-318.14]). A further 6.4% (217 of 3384) (9.6% [166 of 5617] in rural areas vs 3.1% [51 of 10 525] in urban areas) of deaths were due to probable diabetic ketoacidosis or coma (ie, unspecified diabetic deaths) with an RR of 75.96 (95% CI, 54.68-105.52).

For the comparison of individuals with diabetes vs those without diabetes, the RR for mortality from diabetic ketoacidosis or coma was greater in rural areas (RR, 115.29 [95% CI, 84.31-157.65]) than in urban areas (RR, 47.43 [95% CI, 25.19-89.32]) (eFigure 3 in the Supplement). Similarly, the absolute death rate from diabetic ketoacidosis or coma was higher in rural areas (3.49 per 1000 individuals vs 0.56 per 1000 individuals for urban areas) and increased with age (**Figure 2**). Among those with diabetes, 10% of all deaths (16% rural; 4% urban) were due to definite or probable diabetic ketoacidosis or coma (408 deaths).

Individuals with diabetes had a significantly elevated RR of 13.10 (95% CI, 10.45-16.42) for mortality from chronic kidney disease (CKD), mainly diabetes-related CKD (RR, 83.29 [95% CI, 53.15-130.51]) rather than other or unspecified kidney disease (RR, 1.72 [95% CI, 1.13-2.60]). The RR for CKD was greater in rural areas (RR, 18.69 [95% CI, 14.22-24.57]) than in urban areas (6.83 [95% CI, 4.73-9.88]) (eFigure 3 in the Supplement), as were absolute death rates from CKD among those with diabetes both overall (1.2 per 1000 individuals in rural areas vs 0.4 per 1000 individuals in urban areas) and at each age group (Figure 2).

Table 2. Number of Deaths, Standardized Mortality Rates, and Adjusted Rate Ratio for Cause-Specific Mortality by Diabetes Status at Baseline

	Diabetes at Baseline (n = 30 208)		No Diabetes at Baseline (n = 482 589)		
Cause of Death	No. of Deaths	Standardized Mortality Rate per 100 000 (95% CI)[a]	No. of Deaths	Standardized Mortality Rate per 100 000 (95% CI)[a]	Rate Ratio (95% CI)[b]
Diabetic ketoacidosis or coma	345	185.07 (159.37-210.77)	63	1.90 (1.43-2.37)	99.59 (75.13-132.01)
Definite	128	75.06 (57.19-92.93)	15	0.45 (0.22-0.68)	181.85 (103.95-318.14)
Probable	217	110.01 (91.54-128.49)	48	1.45 (1.04-1.87)	75.96 (54.68-105.52)
Chronic renal disease	177	82.81 (66.90-98.71)	188	5.64 (4.83-6.44)	13.10 (10.45-16.42)
Cardiovascular disease	1461	538.42 (504.14-572.69)	7804	235.61 (230.37-240.85)	2.13 (2.01-2.26)
Ischemic heart disease	634	207.94 (187.13-228.74)	2653	81.06 (77.96-84.15)	2.40 (2.19-2.63)
Stroke	580	246.45 (222.98-269.92)	3864	115.41 (111.76-119.06)	1.98 (1.81-2.17)
Other cardiovascular disease	247	84.03 (70.21-97.85)	1287	39.14 (37.00-41.29)	1.96 (1.71-2.26)
Respiratory disease	167	76.53 (62.50-90.56)	1943	58.30 (55.71-60.90)	1.29 (1.10-1.51)
Chronic obstructive pulmonary disease	145	68.00 (54.79-81.21)	1796	53.80 (51.31-56.30)	1.26 (1.06-1.50)
Other respiratory disease	88	31.72 (21.81-41.62)	425	13.12 (11.87-14.37)	2.00 (1.58-2.54)
Cancer	790	300.39 (274.04-326.73)	7789	234.31 (229.09-239.53)	1.27 (1.18-1.37)
Lung	198	64.82 (54.05-75.59)	1897	57.77 (55.16-60.38)	1.20 (1.03-1.39)
Liver	133	61.96 (48.35-75.56)	1192	35.44 (33.42-37.46)	1.54 (1.28-1.86)
Pancreas	50	14.57 (9.65-19.48)	307	9.33 (8.29-10.38)	1.84 (1.35-2.51)
Esophagus	51	22.52 (15.31-29.72)	936	27.83 (26.04-29.61)	0.92 (0.69-1.23)
Stomach	98	36.14 (27.62-44.65)	1105	33.25 (31.29-35.22)	1.16 (0.94-1.44)
Colorectal	57	18.83 (12.81-24.85)	540	16.39 (15.00-17.78)	1.11 (0.84-1.46)
Female breast	31	10.35 (6.05-14.65)	186	5.55 (4.75-6.35)	1.84 (1.24-2.74)
Female reproductive system	28	10.74 (5.47-16.01)	182	5.44 (4.65-6.23)	1.81 (1.20-2.74)
Other types	144	60.47 (47.75-73.20)	1444	43.31 (41.07-45.55)	1.21 (1.01-1.44)
Chronic liver disease	63	34.25 (23.71-44.78)	418	12.33 (11.14-13.51)	2.32 (1.76-3.06)
Liver cirrhosis	33	16.44 (9.34-23.54)	189	5.63 (4.82-6.43)	2.36 (1.61-3.46)
Viral hepatitis	21	12.16 (5.93-18.39)	169	4.95 (4.20-5.70)	2.10 (1.32-3.35)
Other chronic liver disease	9	5.65 (0.99-10.32)	60	1.75 (1.31-2.20)	2.89 (1.39-6.00)
Infection	72	22.56 (16.35-28.78)	353	10.82 (9.69-11.95)	2.29 (1.76-2.99)
Pneumonia	55	15.15 (10.37-19.94)	190	5.98 (5.12-6.83)	2.47 (1.80-3.38)
Infection excluding pneumonia	17	7.41 (3.44-11.38)	163	4.84 (4.10-5.59)	1.83 (1.09-3.05)
External	139	75.29 (59.79-90.79)	1760	51.07 (48.68-53.47)	1.55 (1.30-1.85)
Other medical cause	170	57.64 (46.42-68.87)	1207	36.37 (34.31-38.43)	1.66 (1.41-1.96)
All-cause mortality[c]	3384	1372.96 (1313.84-1432.08)	21 525	646.35 (637.70-655.01)	2.00 (1.93-2.08)

[a] Standardized to age, sex, and study area structure of China Kadoorie Biobank population.

[b] Stratified by age, sex, and study area and adjusted for education level, smoking, alcohol use, physical activity, and body mass index.

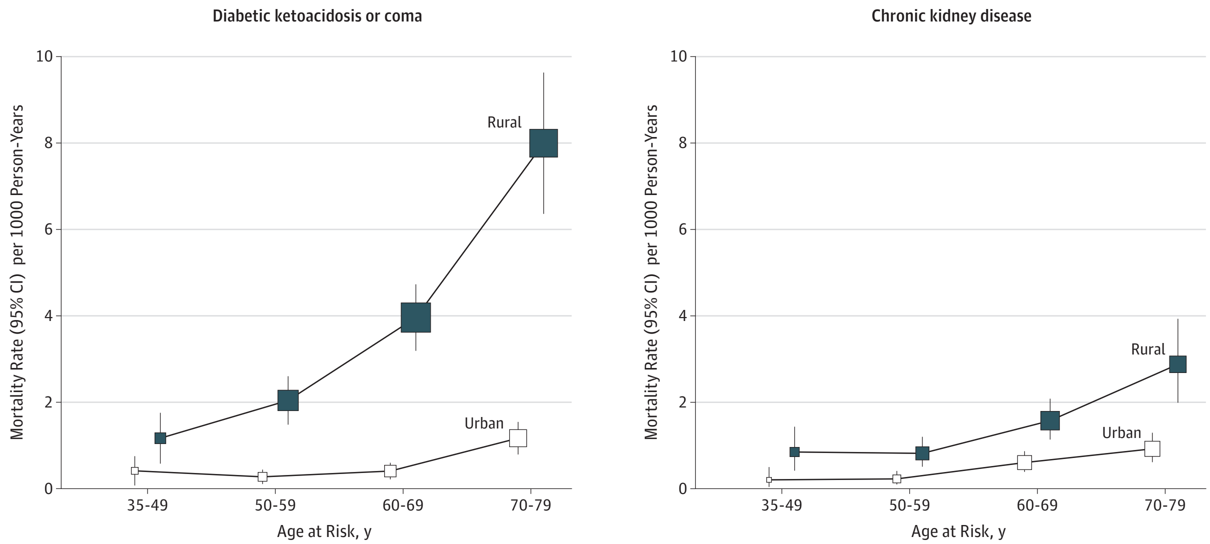
[c] The analyses were restricted to those who died between the ages of 35 and 79 years, excluding 5 deaths at ages younger than 35 years, and 1014 deaths at ages of 80 years or older. Overall a total of 248 deaths between the ages of 35 and 79 years were attributed to unknown causes and the adjusted RR associated with diabetes was 1.53 (95% CI, 1.10-2.23).

For all-cause mortality, the RRs were higher with previously diagnosed diabetes (RR, 2.20 [95% CI, 2.11-2.30]) than with screening-detected diabetes (RR, 1.76 [95% CI, 1.67-1.86]) (eTable 3 in the Supplement). For mortality from several specific diseases, including diabetic ketoacidosis or coma, the RRs were higher with previously diagnosed diabetes compared with screening-detected diabetes (RR, 164.35 [95% CI, 143.02-188.86] vs 46.33 [95% CI, 36.99-58.03], respectively), CKD (RR, 18.88 [95% CI, 15.78-22.59] vs RR, 6.31 [95% CI, 4.54-8.78]), IHD (RR, 2.76 [95% CI, 2.51-3.05] vs RR, 1.91 [95% CI, 1.67-2.18]), stroke (RR, 2.16 [95% CI, 1.93-2.41] vs RR, 1.79 [95% CI, 1.58-2.03]), and infection (RR, 2.88 [95% CI, 2.19-3.79] vs RR, 1.45 [95% CI, 0.91-2.30]).

Among those with diabetes, the risk increased with time since first diagnosis and each 5-year increase was associated with a 13% higher overall mortality (RR, 1.13 [95% CI, 1.09-1.17]; $P < .001$ for trend) (**Figure 3**). This trend was driven mainly by diabetic ketoacidosis or coma, CKD, and cardiovascular mortality, especially in rural areas (eFigure 6 in the Supplement).

The all-cause mortality RRs also varied by several additional baseline risk factors (eFigure 7 in the Supplement), especially among those with previously diagnosed diabetes. Among those with screening-detected diabetes the RRs also varied by area, body mass index (mainly for nonvascular mortality; eFigure 8 in the Supplement), and systolic blood pressure (mainly for vascular mortality; eFigure 9 in the Supplement), but not by sex.

Figure 2. Rural and Urban Mortality Rates for Diabetic Ketoacidosis or Coma (Definite or Probable) and Chronic Kidney Disease Among People With Diabetes by Age at Risk



Diabetic ketoacidosis or coma

	35-49	50-59	60-69	70-79
Rural				
No. of deaths	15	53	109	98
No. of person-years	13 028	27 057	28 026	12 172
Urban				
No. of deaths	6	10	17	37
No. of person-years	15 053	36 075	41 702	31 592

Chronic kidney disease

	35-49	50-59	60-69	70-79
Rural				
No. of deaths	11	22	44	35
No. of person-years	13 028	27 057	28 026	12 172
Urban				
No. of deaths	3	8	25	29
No. of person-years	15 053	36 075	41 702	31 592

The mortality rates by risk in the 4 age groups were standardized for sex, using the total population with diabetes in the China Kadoorie Biobank as the standard. The age at risk was calculated according to baseline age and length of follow-up, with a censoring date of January 1, 2014, or age of death if earlier. The analyses were restricted to those who died between the ages of 35 and 79 years, excluding 0 deaths at ages younger than 35 years and 5 deaths for diabetic ketoacidosis or coma and 8 deaths for chronic kidney disease at ages of 80 years or older. The size of each box is proportional to the number of deaths in each group and the error bars indicate the 95% CI. To avoid overlap of 95% CI lines, the boxes and their 95% CIs for rural and urban areas were moved apart slightly from the actual positions. An individual could contribute person-time to more than 1 age category.

Apart from the rural vs urban differences, the RRs did not differ significantly across the 10 geographic regions (eFigure 10 in the Supplement) and were largely unaffected by additional adjustment for blood pressure and several dietary factors (eg, consumption of fresh fruit, vegetables, or meat), by exclusion of individuals with major prior diseases (eg, cardiovascular disease, cancer, chronic obstructive pulmonary disease, and chronic liver disease) at baseline (RR, 2.03 [95% CI, 1.93-2.14]), or exclusion of the first 3 years of follow-up (RR, 1.92 [95% CI, 1.84-2.02]) or those with new-onset diabetes during follow-up (RR, 1.93 [95% CI, 1.85-2.03]). Additional adjustment for use of medications also had little statistical effect on all-cause mortality (RR, 1.83 [95% CI, 1.75-1.93]).

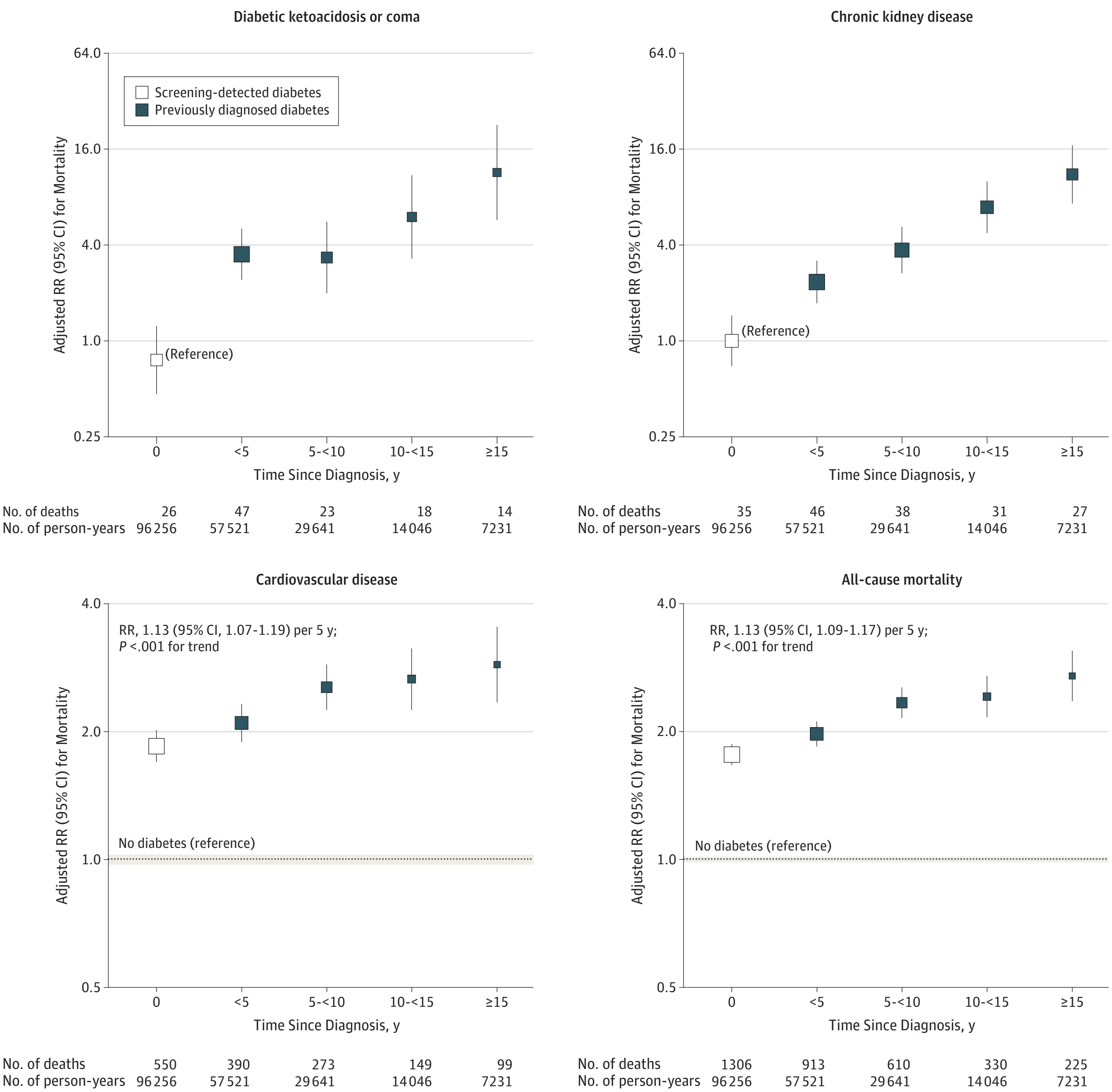
Discussion

This large prospective study of adults from rural and urban areas in China showed that diabetes was associated with significantly increased mortality from a wide range of diseases, with the greatest proportional excess mortality from diabetic ketoacidosis or coma and CKD, followed by IHD, stroke, other vascular, chronic liver disease, infection, certain cancers (mainly liver, pancreatic, female breast, and endometrial cancers), and external causes. Even though the prevalence of diabetes was higher in urban areas, diabetes was associated with greater excess mortality in rural areas.

Several large prospective studies and meta-analyses have provided reliable evidence about the relevance of diabetes for total and certain cause-specific mortality.[7-9] However, most of these previous studies were conducted in high-income countries where people with diabetes were generally well managed and mainly assessed the effects of previously diagnosed diabetes. Overall, the all-cause mortality RRs associated with previously diagnosed diabetes were more modest in these studies[7-9] than those observed in the present study; however, the differences in the study characteristics could partially account for the differences. The low use of cardiovascular-protective medications (eg, statins) in the CKB diabetes population would be expected to yield even greater excess cardiovascular mortality than those reported in high-income countries, but this may have been offset by the relatively short durations of diabetes.

The present study also showed that the main causes of death associated with diabetes differed between China and elsewhere. In many Western populations, diabetes is associated with more deaths from IHD than from stroke, whereas in China the opposite is true, even though the mortality RRs for IHD and stroke in the present study were similar to those reported previously.[7-9] Moreover, existing evidence relating hemorrhagic stroke to diabetes is more limited. In a meta-analysis

Figure 3. Adjusted Rate Ratio (RR) for All-Cause Mortality and Selected Disease-Specific Mortality by Duration Since Diabetes Diagnosis at Baseline



The adjusted RRs are relative to screening-detected diabetes (for diabetic ketoacidosis or coma and chronic kidney disease) or to those without diabetes (for cardiovascular disease and all-cause mortality). The dotted line indicates the RR for the reference group with shading indicating group-specific 95% CI. These 95% CIs were derived using the floating absolute risk method.[19] An individual could contribute person-time to more than 1 age category.

of more than 100 prospective studies with approximately 1200 hemorrhagic strokes, individuals with diabetes had an approximately 50% excess risk.[6] This study included more deaths (>3200) from hemorrhagic stroke than in the previous meta-analysis and provided reliable evidence of positive associations of diabetes with death from hemorrhagic stroke. For several major nonvascular conditions examined, the risk estimates also appeared to be similar in magnitude to previous reports, including cancer, infection, chronic liver diseases, and deaths from external causes.[7,9] However, for deaths from diabetic ketoacidosis or coma and CKD, the excess risks in the present study, particularly in rural areas, were much greater than those reported in high-income countries.

Few previous prospective studies provided information about deaths from diabetic ketoacidosis or coma, perhaps reflecting the rarity of such deaths. Available population-based registry data suggested that less than 1% of deaths in the United States among people with diabetes were due to diabetic ketoacidosis or coma.[21] Even though a high proportion of diabetes cases was treated with antidiabetic medications in rural areas, approximately 16% of all deaths among them were due to definite or probable diabetic ketoacidosis or coma, with the absolute death rate being almost 10 times as high as in urban areas, though the absolute number of deaths remains low. A recent nationwide survey in China, which had a similar treatment rate with antidiabetic medications as in the present study, reported that only about one-third of the treated diabetes cases had achieved adequate glycemic control,[4] as opposed to three-quarters in the United States.[22]

Similarly, for CKD mortality, the observed RR in the present study was about 4 times as high as those reported in previous studies,[8,9] reflecting poor management of diabetes and its complications, particularly in rural areas where both the RR and absolute rates were almost 3 times as great as in urban areas. Consistent with the present study findings, the mortality from diabetes-related CKD in China has more than doubled since 1990.[13] By contrast, the proportional all-cause excess mortality risk among individuals with type 2 diabetes declined significantly in most Western populations during that period (eg, to only about 15% in Sweden; RR, 1.15),[23] attributed largely to better glycemic control and routine use of cardioprotective agents (eg, aspirin, statins, and antihypertensive treatment).

As in many previous studies,[7-9,24,25] greater all-cause and cardiovascular mortality RRs were seen among women than men, especially in those older than 60 years. The differences were seen mainly in individuals with previously diagnosed diabetes rather than in those with screening-detected diabetes, suggesting that the sex difference in excess risk associated with diabetes was probably driven mainly by factors related to detection and management of diabetes, which few previous studies were able to investigate fully.

The probability of death associated with diabetes in the general population could be estimated by combining the age-specific all-cause mortality RRs in this study with 2010 age-specific mortality rates from China,[26] accounting for the duration of diabetes at the same time. Based on the 2010 Chinese death rates, the 25-year probability of death was 69% among those diagnosed with diabetes at the age of 50 years and 38% among those who remained free of diabetes at the age of 75 years, corresponding to an estimated loss of a median of 9 years of life (10 years of life in rural areas and 8 years of life in urban areas) for individuals with diabetes diagnosed at the age of 50 years (eFigure 11 in the Supplement), assuming the excess mortality is largely causal.

This study has several strengths. Although not nationally representative with a relatively low participation rate at baseline, the large sample size, diversity of areas covered, and broadly consistent findings across study population subgroups means that the present RR estimates are likely not biased and can be generalizable to the population at large. Moreover, the study has several other strengths, including standardized approaches and stringent quality control for data collection, availability of information on previously diagnosed and screening-detected diabetes, duration and management of diabetes, central review of death certificates, and completeness of follow-up.

However, the study also has several limitations. First, the prevalence of diabetes in this study was only about half of that reported in a 2010 nationally representative survey in China, arising mainly from a difference in the prevalence of screening-detected diabetes (2.8% in CKB vs 8.1% in national survey), rather than previously diagnosed diabetes (3.1% in CKB vs 3.5% in national survey).[4] Apart from difference in sampling methods and effects of temporal trends in diabetes prevalence, the 2010 China national survey used 3 different tests (ie, hemoglobin A_{1c}, fasting glucose, and 2-hour glucose) to identify screening-detected diabetes, whereas the present study used random plasma glucose and fasting plasma glucose. However, prevalence estimates in the present study were similar to those reported in other contemporaneous, representative Chinese surveys during the 2000s that used similar approaches,[2,27] and the 2009-2010 China survey of CKD that reported a prevalence of 7.0% in urban areas and 4.3% in rural areas.[28] Nevertheless, it is likely that a proportion of diabetes cases in the present study were undetected at baseline, which could result in underestimation of diabetes-associated risk, even though exclusion of those who had new-onset diabetes during follow-up did not alter the proportional risk estimates. Second, it was not possible to determine the prevalence of type 1 diabetes. However, based on age at diagnosis (<30 years) and insulin use, less than 1% of cases were likely to have been type 1 diabetes. Future studies are also needed to confirm whether diabetes detected by different approaches would have similar mortality risk, which may affect the reliability of our estimates on absolute mortality associated with diabetes in China. Third, it was not possible to adjust for lipid and other blood-related factors, so residual confounding may still persist. Fourth, no detailed information was available about severity and complications of diabetes, which may modify mortality risk estimates.

China's 2030 Sustainable Development Goals include reducing noncommunicable disease mortality by one-third, and monitoring the changes over time. In China, mortality rates for adults aged 69 years or younger are decreasing due to many dietary, social, occupational, and health care changes, and declined by about 15% during 2000-2010.[5,29] This decreasing trend may be slowed or even halted by increasing tobacco-attributed mortality in men,[30] and the increasing prevalence of diabetes in both sexes.

Moreover, among people of a given age, the risk of death is strongly associated with the duration of diabetes, so the lifetime hazards will be even greater for people who develop diabetes during early adult life than for those who do so after they reach the age of 50 years. As the prevalence of diabetes in young adults increases and the adult population grows,[31] the annual number of deaths related to diabetes is likely to continue to increase, unless there is substantial improvement in prevention and management.

Conclusions

Among adults in China, diabetes was associated with increased mortality from a range of cardiovascular and noncardiovascular diseases. Although diabetes was more common in urban areas, it was associated with greater excess mortality in rural areas.

ARTICLE INFORMATION

Author Affiliations: Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, England (Bragg, Holmes, Iona, Du, Y. Chen, Yang, Herrington, Bennett, Turnbull, Clarke, Collins, Peto, Z. Chen); Medical Research Council Population Health Research Unit, University of Oxford, Oxford, England (Holmes, Iona, Du, Y. Chen, Yang); Chinese Academy of Medical Sciences, Beijing, China (Guo, Bian, Li); Qingdao Center for Disease Control and Prevention, Qingdao, China (Liu); Henan Provincial Center for Disease Control and Prevention, Henan, China (Feng); National Center for Food Safety Risk Assessment, Beijing, China (J. Chen); School of Public Health, Peking University, Beijing, China (Li).

Author Contributions: Drs Bragg and Chen, Ms Iona, and Mr Li had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Bragg and Holmes and Ms Iona contributed equally to the article.
Concept and design: Bragg, Holmes, Guo, Yang, Herrington, Peto, Li, Z. Chen.
Acquisition, analysis, or interpretation of data: Bragg, Holmes, Iona, Du, Y. Chen, Bian, Yang, Herrington, Bennett, Turnbull, Liu, Feng, J. Chen, Clarke, Collins, Peto, Z. Chen.
Drafting of the manuscript: Bragg, Holmes, Iona, Guo, Peto, Z. Chen.
Critical revision of the manuscript for important intellectual content: Bragg, Holmes, Iona, Du, Y. Chen, Bian, Yang, Herrington, Bennett, Turnbull, Liu, Feng, J. Chen, Clarke, Collins, Peto, Li, Z. Chen.
Statistical analysis: Bragg, Holmes, Iona, Bennett, Feng, Peto.
Obtained funding: Peto.
Administrative, technical, or material support: Guo, Du, Y. Chen, Bian, Yang, Turnbull, Liu, J. Chen, Clarke, Collins, Z. Chen.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Collins reported receiving grant funding from Kadoorie Trust, MRC, Welllcome Trust, Cancer Research UK, British Heart Foundation, GlaxoSmithKline, Merck & Co, Abbott/Solvay/Mylan, AstraZeneca, Bayer Germany, Medical Research Council, National Institute for Health Research, and UK Biobank. No other disclosures were reported.

Funding/Support: Funding for the baseline survey was provided by the Kadoorie Charitable Foundation. Funding for the long-term continuation of the study was provided by grants 088158/Z/09/Z and 104085/Z/14/Z from the UK Wellcome Trust, grant 2011BAI09B01 from the Chinese Ministry of Science and Technology, and grant 81390541 from the Chinese National Natural Science Foundation. The British Heart Foundation, UK Medical Research Council, and Cancer Research UK provided core funding to the Oxford Clinical Trial Service Unit.

Additional Contributions: We acknowledge the participants, the project staff, and the Chinese Center for Disease Control and Prevention and its regional offices for access to death and disease registries. The Chinese National Health Insurance scheme provides electronic linkage to all hospital admission data. Dr Bragg acknowledges the support from the BHF Centre of Research Excellence (Oxford, England). We thank Jonathan R. Emberson, PhD (Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford), for helpful advice on reviewing and coding of diabetes-related deaths. Mr Emberson was not compensated for his contributions.

REFERENCES

1. Pan XR, Yang WY, Li GW, et al. Prevalence of diabetes and its risk factors in China, 1994. *Diabetes Care*. 1997;20(11):1664-1669.

2. Li LM, Rao KQ, Kong LZ, et al. A description on the Chinese national nutrition and health survey in 2002 [in Chinese]. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2005;26(7):478-484.

3. Yang W, Lu J, Weng J, et al. Prevalence of diabetes among men and women in China. *N Engl J Med*. 2010;362(12):1090-1101.

4. Xu Y, Wang L, He J, et al. Prevalence and control of diabetes in Chinese adults. *JAMA*. 2013;310(9):948-959.

5. Yang G, Wang Y, Zeng Y, et al. Rapid health transition in China, 1990-2010. *Lancet*. 2013;381(9882):1987-2015.

6. Sarwar N, Gao P, Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease [published correction appears in *Lancet*. 2010;376(9745):958]. *Lancet*. 2010;375(9733):2215-2222.

7. Seshasai SR, Kaptoge S, Thompson A, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med*. 2011;364(9):829-841.

8. Campbell PT, Newton CC, Patel AV, et al. Diabetes and cause-specific mortality in a prospective cohort of one million US adults. *Diabetes Care*. 2012;35(9):1835-1844.

9. Woodward M, Zhang X, Barzi F, et al. The effects of diabetes on the risks of major cardiovascular diseases and death in the Asia-Pacific region. *Diabetes Care*. 2003;26(2):360-366.

10. Liu J, Grundy SM, Wang W, et al. Ten-year risk of cardiovascular incidence related to diabetes, prediabetes, and the metabolic syndrome. *Am Heart J*. 2007;153(4):552-558.

11. Shen C, Schooling CM, Chan WM, et al. Self-reported diabetes and mortality in a prospective Chinese Elderly Cohort Study in Hong Kong. *Prev Med*. 2014;64:20-26.

12. An Y, Zhang P, Wang J, et al. Cardiovascular and all-cause mortality over a 23-year period among Chinese with newly diagnosed diabetes in the Da Qing IGT and Diabetes Study. *Diabetes Care*. 2015;38(7):1365-1371.

13. Zhou M, Wang H, Zhu J, et al. Cause-specific mortality for 240 causes in China during 1990-2013. *Lancet*. 2016;387(10015):251-272.

14. Chen Z, Lee L, Chen J, et al. Cohort profile. *Int J Epidemiol*. 2005;34(6):1243-1249.

15. Chen Z, Chen J, Collins R, et al. China Kadoorie Biobank of 0.5 million people. *Int J Epidemiol*. 2011;40(6):1652-1666.

16. Bragg F, Li L, Smith M, et al. Associations of blood glucose and prevalent diabetes with risk of cardiovascular disease in 500 000 adult Chinese. *Diabet Med*. 2014;31(5):540-551.

17. Yang GH, Stroup DF, Thacker SB. National public health surveillance in China. *Biomed Environ Sci*. 1997;10(1):1-13.

18. Yang G, Rao C, Ma J, et al. Validation of verbal autopsy procedures for adult deaths in China. *Int J Epidemiol*. 2006;35(3):741-748.

19. Easton DF, Peto J, Babiker AG. Floating absolute risk. *Stat Med*. 1991;10(7):1025-1035.

20. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *Am J Public Health*. 1998;88(1):15-19.

21. Diabetes Public Health Resource. Diabetes complications. http://www.cdc.gov/diabetes/statistics/mortalitydka. Accessed March 10, 2016.

22. Ali MK, Bullard KM, Saaddine JB, et al. Achievement of goals in US diabetes care, 1999-2010. *N Engl J Med*. 2013;368(17):1613-1624.

23. Tancredi M, Rosengren A, Svensson A-M, et al. Excess mortality among persons with type 2 diabetes. *N Engl J Med*. 2015;373(18):1720-1732.

24. Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men. *Lancet*. 2014;383(9933):1973-1980.

25. Peters SA, Huxley RR, Woodward M. Diabetes as risk factor for incident coronary heart disease in women compared with men. *Diabetologia*. 2014;57(8):1542-1551.

26. Chinese Ministry of Health. *China Statistical Yearbook of Health*. Beijing, China: Publishing House of Peking Union Medical College; 2011.

27. Gu D, Reynolds K, Duan X, et al. Prevalence of diabetes and impaired fasting glucose in the Chinese adult population. *Diabetologia*. 2003;46(9):1190-1198.

28. Zhang L, Wang F, Wang L, et al. Prevalence of chronic kidney disease in China. *Lancet*. 2012;379(9818):815-822.

29. Norheim OF, Jha P, Admasu K, et al. Avoiding 40% of the premature deaths in each country, 2010-30. *Lancet*. 2015;385(9964):239-252.

30. Chen Z, Peto R, Zhou M, et al. Contrasting male and female trends in tobacco-attributed mortality in China. *Lancet*. 2015;386(10002):1447-1456.

31. UN Population Division. *World Population Prospects: The 2012 Revision*. New York, NY: United Nations; 2012.