Risk of non-fatal cardiovascular diseases in early-onset versus late-onset type 2 diabetes in China: a cross-sectional study

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Summary

Background **The age of onset of type 2 diabetes is decreasing. Because non-Chinese patients with early-onset type 2 diabetes (defined here as diagnosis at <40 years) have increased risk of vascular complications, we investigated effects of early-onset versus late-onset type 2 diabetes on risk of non-fatal cardiovascular diseases in China.**

Methods **We did a cross-sectional survey using data from the China National HbA_{1c} Surveillance System (CNHSS), including 222773 Chinese patients with type 2 diabetes in 630 hospitals from 106 cities in 30 provinces of China in 2012. We documented demographic information and clinical profiles. Non-fatal cardiovascular disease was defined as non-fatal coronary heart disease or non-fatal stroke. Prevalence of non-fatal cardiovascular diseases was standardised to the Chinese population in 2011. We did logistic regression analysis to obtain odds ratios (ORs) for the risk of cardiovascular disease in patients with early-onset versus late-onset type 2 diabetes. Because the CNHSS did not contain patients on diet or lifestyle treatment alone, and did not capture information on smoking or lipid or antihypertensive treatment, we validated our findings in another dataset from a cross-sectional, multicentre observational study (the 3B study) of outpatients with type 2 diabetes to confirm that exclusion of patients with diet treatment only and non-adjustment for lipid-lowering and antihypertensive drugs did not introduce major biases in the main analysis.**

Findings **Of 222773 patients recruited from April 1, 2012, to June 30, 2012, 24316 (11%) had non-fatal cardiovascular disease. Patients with early-onset diabetes had a higher age-adjusted prevalence of non-fatal cardiovascular disease than did patients with late-onset diabetes (11·1% *vs* 4·9%; p<0·0001). After adjustment for age and sex, patients with early-onset type 2 diabetes had higher risk of non-fatal cardiovascular disease than did those with late-onset type 2 diabetes (OR 1·91, 95% CI 1·81–2·02). Adjustment for duration of diabetes greatly attenuated the effect size for risk of non-fatal cardiovascular disease (1·13, 1·06–1·20). Results of the validation study showed that exclusion of patients with diet only and non-adjustment for lipid-lowering and antihypertensive drugs resulted in marginal changes in ORs for risk of non-fatal cardiovascular disease in patients with early-onset versus late-onset type 2 diabetes. Early-onset type 2 diabetes remained associated with increased risk of cardiovascular disease, attributable to longer duration of diabetes.**

Interpretation **Chinese patients with early-onset type 2 diabetes are at increased risk of non-fatal cardiovascular disease, mostly attributable to longer duration of diabetes.**

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Introduction

Prevalence of type 2 diabetes is increasing worldwide, and care for the disease and its complications is becoming a substantial health burden, especially for developing countries.[1] The age at which diabetes is diagnosed is decreasing, and many people now develop type 2 diabetes when they are younger than 40 years.[2] Non-Chinese patients with early-onset type 2 diabetes are at high risk of vascular complications.[3–8]

During the past three decades, China has experienced a rapid shift towards westernised lifestyles, and the prevalence of diabetes increased from 1·3% in 1986 to 11·6% in 2010, which translates into 113·9 million Chinese people aged 18 years or older with diabetes.[9,10] 5·7% of these people were younger than 40 years at diagnosis. In Hong Kong, early-onset diabetes (defined here as <40 years at diagnosis) greatly increased risk of cardiovascular and renal complications compared with patients with late-onset type 2 diabetes of similar ages.[11] Our group reported that early-onset type 2 diabetes among patients treated at accredited 3A hospitals in select cities in China substantially and significantly increased risk of microvascular diseases compared with late-onset diabetes.[12] We used China's largest diabetes database, derived from the China National HbA_{1c} Surveillance System (CNHSS), to investigate the risk of non-fatal cardiovascular disease in patients with early-onset versus late-onset type 2 diabetes in mainland China.

Methods

Study design and participants

We combined two studies to provide a sample and a validation cohort to assess risk of non-fatal cardiovascular disease in patients with early-onset and late-onset type 2 diabetes.

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Research in Context

Evidence before this study

We searched PubMed between July 1, 1985, and Aug 26, 2015, with the terms "young onset", "early onset", "type 2 diabetes", and "cardiovascular disease". We included only original studies with patients with young-onset or early-onset type 2 diabetes as the study participants, and use of cardiovascular disease (either coronary heart disease or stroke or both) as the clinical outcome. We excluded studies of gene mutations and familial diabetes and review articles.

Two studies examined the risk of cardiovascular disease in early-onset versus late-onset type 2 diabetes. A cross-sectional survey reported that early-onset type 2 diabetes slightly increased risk of cardiovascular disease (odds ratio 1·05, 1·01–1·10). Another study reported that the risk of cardiovascular-renal complications was significantly higher in patients with early-onset type 2 diabetes compared with late-onset type 2 diabetes in Chinese people (hazard ratio 1·48, 1·17–1·88). Early-onset type 2 diabetes seemed to be associated with increased risk of cardiovascular disease compared with type 1 diabetes and late-onset type 2 diabetes. The effects of early-onset type 2 diabetes on the risk for cardiovascular disease in mainland China were mostly unkown.

Added value of this study

Using the largest database of patients with type 2 diabetes in China (n=222 773), we provided data regarding whether Chinese patients with early-onset type 2 diabetes in mainland China are at increased risk of cardiovascular diseases compared with those with late-onset type 2 diabetes, and whether the increased risks of cardiovascular diseases are attributable to increased duration of diabetes.

Implications of all the available evidence

Increased risk of cardiovascular disease among patients with early-onset type 2 diabetes is an unaddressed gap in China. Owing to the preventable nature of type 2 diabetes and the few medical resources available for prevention of diabetes in China, priority should be given to prevention of diabetes among young patients. Since intensive intervention reduces risk of cardiovascular disease, more medical resources should be shifted to management of this group. Further research into the effectiveness and cost-effectiveness of such interventions is warranted.

For the sample cohort, we used data from the CNHSS, an initiative launched by the Chinese Diabetes Society in 2009 to monitor glycaemic control in outpatients with type 2 diabetes in China. In this analysis, we used data collected from April 1, 2012 to June 30, 2012. The methods and inclusion and exclusion criteria have been published previously.[12] Briefly, 630 hospitals participated and recruited patients to the survey, including 12 primary care hospitals, 132 secondary care hospitals, and 486 tertiary care hospitals from 106 cities in 30 provincial administrative regions. A primary hospital was a com—munity medical institution and provided primary health services; a secondary hospital was a local medical institution and provided comprehensive health services; and a tertiary hospital was a regional medical institution and provided comprehensive and specialist health services (see appendix p 1 for details). During this period, research nurses or fieldworkers invited the first seven patients each day who met the inclusion criteria from patients seeking care at the outpatient clinics of the department of endocrinology of the hospitals involved. The process continued until a total of 400 patients were recruited from each hospital during the 3-month recruitment period unless the recruitment period ended on June 30, 2015.

See Online for appendix

The inclusion criteria included the following: being an outpatient with type 2 diabetes diagnosed by the 1999 World Health Organization's criteria[13] for diagnosis of diabetes and being treated with antidiabetic drugs; aged 18 years or older; having at least one previous outpatient medical record for diabetes; and being a local resident for at least 6 months consecutively before participation in the study. The exclusion criteria included the following: having type 1 diabetes, defined as acute presentation with diabetic ketoacidosis, heavy ketonuria, or continuous need for insulin within 1 year of diagnosis; having diabetes secondary to other diseases; being on diet and other lifestyle therapy or Chinese herbal medicine only; inpatients; pregnancy or breastfeeding; being unable to complete the survey owing to mental illness; being unconscious or unable to communicate.

The validation study (the 3B study) was an observational, cross-sectional, multicentre study of outpatients with established type 2 diabetes. 25 817 patients were recruited from at least 100 hospitals at different levels (ie, tertiary hospitals, secondary hospitals, and primary hospitals) from six major geographical regions of China from Aug 18, 2010, to March 30, 2011. The investigators of every participating hospital aimed to recruit 250 consecutive outpatients during the study period. Participants were attending clinics in community hospitals (primary), secondary city level hospitals (secondary), and teaching or comprehensive central hospitals (tertiary) across China. Inclusion criteria were type 2 diabetes for at least 6 months and age 18 years or older. Exclusion criteria were type 1 diabetes, pregnancy, participating in any other clinical studies, or unable to report their medical history. Because of representativeness, detailed documentation of lifestyle and clinical factors, and availability for analysis, the 3B study was used to confirm that non-inclusion of patients on diet treatment only and non-adjustment for smoking and use of lipid-lowering drugs and antihypertensive drugs would not introduce major bias in the main analysis.

Ethical approval for the CNHSS was obtained from the Ethics Committee of the Chinese People's Liberation Army General Hospital and approval for the 3B study was obtained from the Ethics Committee of Peking University People's Hospital. Written informed consent was obtained before collecting data from the patients.

Procedures

Health professionals reviewed the medical notes, including results of laboratory assays, and recorded data in a form. Data included sex, height, weight, blood pressure, and date of diagnosis of diabetes. Patients reported whether they were diagnosed with any concomitant diseases or diabetes complications, including hypertension, coronary heart disease, dyslipidaemia, cerebrovascular disease, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, and diabetes-related foot ulcers. All laboratory assessments were done in local hospitals, where the patients were interviewed. High-density lipoprotein cholesterol (HDL-C) was calculated with Friedewald's equation.[14] Laboratory data for HbA_{1c} and lipids were recorded at this visit. Specific information about treatments used for management of type 2 diabetes was documented, including use of oral antidiabetic drugs, including DPP-4 inhibitors, glucagon-like peptide-1 receptor agonists, different types of insulin, and combinations of these drugs. Staff members entered and uploaded all data to a central database.

Additional data for the validation study included demographics, socioeconomic status (education level, marital and employment status, individual and family income, and medical insurance), health behaviours (smoking, drinking, and exercise patterns), and use of lipid-lowering and antihypertensive drugs. Laboratory measurements within 30 days before or 7 days after screening were retrieved and recorded, including HbA_{1c}, fasting serum glucose, total cholesterol, low-density lipoprotein cholesterol (LDL-C), HDL-C, triglycerides, serum creatinine, and urine creatinine.

Outcomes

Previous coronary heart disease and date of diagnosis were retrieved from the patient database. Medical records from secondary or tertiary hospitals were used to define previous coronary heart disease, including ischaemic heart disease with abnormal electrocardiogram or stress test, myocardial infarction with typical changes in electrocardiogram and plasma enzyme testing, coronary revascularisation, percutaneous transluminal coronary angioplasty, or coronary atherectomy. Previous diagnosis of stroke was ascertained by reviewing medical records from secondary or tertiary hospitals, and included ischaemic or haemorrhagic stroke—ie, subarachnoid haemorrhage, intracerebral haemorrhage, and other or unspecified intracranial haemorrhage, irrespective of whether the patient had completely or incompletely recovered. Cardiovascular disease was defined as having either coronary heart disease or stroke.

Peripheral vascular disease was defined as intermittent claudication, foot ulcer, or amputation. Albuminuria was defined as urinary albumin of more than 20 mg/L or urinary albumin to creatinine ratio 2·5 mg/mmol or more in men and 3·5 mg/mmol or more in women.

	Early-onset (n=26 992)	Late-onset (n=195 781)	p value
Age (years)	40·9 (7·9)	60·7 (9·6)	<0·0001
Age of diabetes diagnosis (years)	34·5 (5·0)	55·3 (8·9)	<0·0001
Male sex	15 642 (58%)	104 143 (53%)	<0·0001
Duration of diabetes (years)	6·4 (6·3)	5·4 (4·9)	<0·0001
BMI (kg/m^2)	24·5 (3·4)	24·5 (3·0)	0·65
BMI groups			
≤23·9	12 315 (46%)	86 514 (44%)	<0·0001
24·0–27·9	11 345 (42%)	88 822 (45%)	<0·0001
≥28·0	3332 (12%)	20 445 (10%)	<0·0001
HbA_{1c} (%)	7·9 (1·8)	7·7 (1·5)	<0·0001
HbA_{1c} (mmol/mol)	63·0 (19·5)	60·8 (16·8)	<0·0001
Targets of glycaemic control achieved*	8067 (30%)	58 957 (30%)	0·45
SBP (mm Hg)	128·6 (14·2)	132·0 (14·5)	<0·0001
DBP (mm Hg)	80·8 (10·4)	81·6 (10·2)	<0·0001
Targets of blood pressure control achieved*	17 927 (66%)	116 405 (59%)	<0·0001
Triglyceride (mmol/L)	1·8 (1·3–2·7)	1·8 (1·3–2·7)	0·092
LDL-C (mmol/L)	2·9 (1·6)	3·0 (1·6)	<0·0001
HDL-C (mmol/L)	1·3 (0·9)	1·4 (0·9)	<0·0001
Targets of lipid control achieved*	4963 (18%)	33 286 (17%)	<0·0001
Diabetes medications (p<0·0001)			
One OAD only	5370 (20%)	39 429 (20%)	0·35
Two OADs	5548 (21%)	53 229 (27%)	<0·0001
Three OADs	1297 (5%)	13 617 (7%)	<0·0001
Four or more OADs	74 (<1%)	556 (<1%)	0·78
OADs plus insulin	6936 (26%)	45 929 (23%)	<0·0001
OADs plus GLP-1	81 (<1%)	341 (<1%)	<0·0001
Insulin only	7634 (28%)	42 354 (22%)	<0·0001
Hospital levels (p<0·0001)			
Primary	326 (1%)	3955 (2%)	<0·0001
Secondary	4854 (18%)	41 476 (21%)	<0·0001
Tertiary	21 812 (81%)	150 350 (77%)	<0·0001
Non-fatal macrovascular complications			
Non-fatal coronary heart disease	1668 (6%)	22 648 (12%)	<0·0001
Non-fatal stroke	575 (2%)	8404 (4%)	<0·0001
Non-fatal cardiovascular disease	2060 (8%)	28 047 (14%)	<0·0001
Microvascular complications			
Diabetic retinopathy	2339 (9%)	16 589 (8%)	0·29
Diabetic nephropathy	1722 (6%)	10 336 (5%)	<0·0001

Data are mean (SD), median (IQR), or n (%). p values were derived from χ^2 test or Student's *t* test. SBP=systolic blood pressure. DBP=diastolic blood pressure. OAD=oral antidiabetic drug. LDL-C=low-density lipoprotein cholesterol. HDL-C=high-density lipoprotein cholesterol. Cardiovascular disease was defined as having either coronary heart disease or stroke. *Targets of glycaemic control were defined as HbA_{1c} of less than 7% whether patients were on OADs or insulin. Targets of blood pressure control were defined as SBP/DBP less than 140/90 mm Hg whether patients were on antihypertensive drugs or not. Targets of lipid control were defined as LDL-C less than 2·6 mmol/L, HDL-C greater than 1·0 mmol/L in men and 1·3 mmol/L in women, and triglyceride less than 1·7 mmol/L whether patients were on lipid-lowering drugs or not.

Table 1: **Clinical and biochemical characteristics of patients with early-onset versus late-onset type 2 diabetes**

Statistical analysis

After checking the distribution of continuous variables with a normality test, we used Student's *t* test to compare continuous variables if normal distributions were not rejected, and Kruskal-Wallis test if normal distributions were rejected. We used the χ^2 test to compare categorical variables between patients with early-onset and late-onset type 2 diabetes. We used ANCOVA to compare adjusted means of metabolic variables between early-onset and late-onset type 2 diabetes in different age groups. Because the CNHSS survey over-represented tertiary care patients and under-represented primary care patients, we calculated age-standardised and hospital level-specific age-standardised prevalence of cardiovascular disease to the Chinese population in 2011 with the direct method.[15] We used binary logistic regression and separate binary

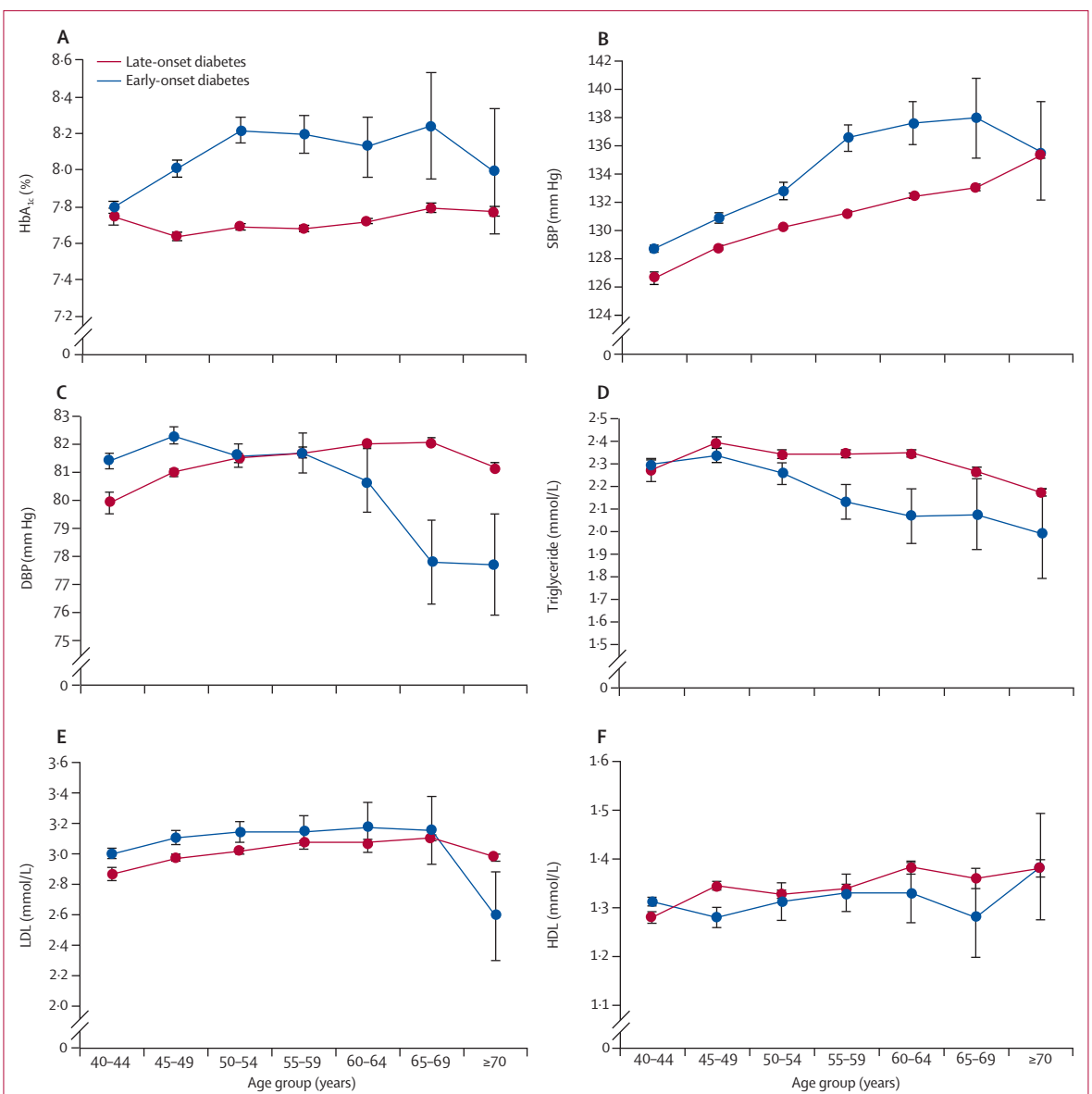

Figure 1: **Profile of cardiovascular risk factors in early-onset and late-onset type 2 diabetes**
SBP=systolic blood pressure. DBP=diastolic blood pressure. LDL-C=low-density lipoprotein cholesterol. HDL-C=high-density lipoprotein cholesterol. Means of HbA_{1c}, blood pressure, and lipids in the ANCOVA were adjusted for age, sex, and level of hospital. p<0·0001 for HbA_{1c} for all age groups except for the 40–44 years group (p=0·1010; A). p<0·0001 for SBP at all age groups except for age 70 years or older (p=0·8710; B). p<0·0001 for DBP for all age groups except groups aged 50–54 years (p=0·7770) and 55–59 years (p=0·6820; C). p<0·0001 for triglyceride except for the group aged 40–44 years (p=0·4520; D). p<0·0001 for LDL-C in all groups except the group aged 55–59 years (p=0·2400) and 65–69 years (p=0·7680; E). For HDL-C, p=0·0660 for the age 40–44 years group, p=0·5130 for the group aged 50–54 years, p=0·7850 for the group aged 55–59 years, p=0·3520 for the group aged 60–64 years, p=0·9660 for the group aged older than 70 years, and p<0·0001 for the groups aged 45–49 years and 65–69 years (F).

logistic regression by hospital level to estimate the odds ratio (OR) of non-fatal cardiovascular disease in early-onset versus late-onset type 2 diabetes to show overall and different effect sizes by level of hospital. We used a structured adjustment scheme to control confounding effects of traditional risk factors, with attention to whether these adjustments attenuated effect sizes. Specifically, model 1 was adjusted for age and sex; model 2 was adjusted for variables in model 1 and duration of diabetes; model 3 was adjusted for variables in model 2, subsequent worsened metabolic profile (increased HbA_{1c}, high blood pressure, and increased LDL-C or decreased HDL-C), and other traditional risk factors; and model 4 was adjusted for targets of glycaemic control (HbA_{1c}<7·0% or 53 mmol/mol) and lipid control (LDL-C<2·6 mmol/L) in place of levels and other variables in model 3.

To observe the age at which the cumulative incidence of non-fatal cardiovascular disease started to rise, we transformed the cross-sectional survey into a retrospective cohort with follow-up time calculated as time in years from birth to the date of occurrence of the disease or the date of the survey, whichever came first. We used Kaplan-Meier analysis to plot cumulative incidence of non-fatal cardiovascular disease by age, stratified by early-onset versus late-onset type 2 diabetes among primary, secondary, and tertiary care patients. A two-tailed p value of less 0·05 was considered to be significant. The CNHSS excluded patients who received diet treatment only and did not document lifestyle factors such as smoking status and use of lipid-lowering and antihypertensive drugs.

We applied the same analysis in the validation study to check the consistency of the effect of early-onset versus late-onset type 2 diabetes on the risk of non-fatal cardiovascular disease in the CNHSS. We examined the effects of adjustments for treatment with diet only and use of lipid-lowering drugs and anti-hypertensive drugs in multivariable analysis. We did additional analysis to assess the effect of including peripheral vascular disease in the definition of non-fatal cardiovascular disease on the effect size of early-onset versus late-onset type 2 diabetes on non-fatal cardiovascular disease risk.

All statistical analyses were done with SAS, version 9.1 or SPSS 22.

Role of the funding source

The funders of the study had no role in study design, data analysis, data interpretation, or writing of the report. Novo Nordisk China coordinated collection of data in the CNHSS. Merck Sharp & Dohme had no role in data collection in the 3B study. The corresponding authors had full access to all the data in the study and had the final responsibility to submit for publication.

Results

Among 223 612 enrolled patients, 839 with missing key variables were excluded, and the remaining 222 773 were used in the analysis (table 1). These patients had a mean age of 58·3 years (SD 11·3), with a mean duration of diabetes of 5·6 years (SD 5·1). 54% of patients were male.

	n	Prevalence of non-fatal coronary heart disease			Prevalence of non-fatal stroke			Prevalence of non-fatal cardiovascular disease			
		Early-onset	Late-onset	p value	Early-onset	Late-onset	p value	Early-onset	Late-onset	p value	Extra disease cases
Rates by age among the whole study patients											
<35 years	4688	91 (1·9%)	0	..	28 (0·6%)	0	..	112 (2·4%)	0	..	112
35–39 years	6840	224 (3·3%)	0	..	51 (0·8%)	0	..	262 (3·8%)	0	..	260
40–44 years	12 635	359 (4·6%)	125 (2·6%)	<0·0001	114 (1·5%)	32 (0·6%)	<0·0001	447 (5·8%)	142 (2·9%)	<0·0001	224
45–49 years	25 644	399 (8·8%)	893 (4·2%)	<0·0001	136 (3·0%)	294 (1·4%)	<0·0001	495 (10·9%)	1090 (5·2%)	<0·0001	259
50–54 years	29 225	261 (13·9%)	1793 (6·6%)	<0·0001	104 (5·5%)	555 (2·0%)	<0·0001	330 (17·6%)	2230 (8·2%)	<0·0001	176
55–59 years	41 217	176 (21·3%)	3640 (9·0%)	<0·0001	78 (9·4%)	1062 (2·6%)	<0·0001	221 (26·7%)	4388 (10·9%)	<0·0001	131
60–64 years	34 475	92 (29·6%)	3862 (11·3%)	<0·0001	41 (13·2%)	1421 (4·2%)	<0·0001	111 (35·7%)	4862 (14·2%)	<0·0001	67
65–69 years	30 116	31 (28·4%)	3975 (13·3%)	<0·0001	11 (10·1%)	1495 (4·9%)	<0·0001	41 (37·6%)	4938 (16·5%)	<0·0001	23
≥70 years	37 933	35 (42·7%)	8360 (22·1%)	<0·0001	12 (14·6%)	3545 (9·4%)	0·1020	41 (50·0%)	10 397 (27·5%)	<0·0001	18
p_{trend}*	222 773	<0·0001	<0·0001	..	<0·0001	<0·0001	..	<0·0001	<0·0001	..	..
Crude rate	222 773	1668 (6·2%)	22 648 (11·6%)	<0·0001	575 (2·1%)	8404 (4·3%)	<0·0001	2060 (7·6%)	28 047 (14·3%)	<0·0001	1270
Standardised rate†	222 773	9·0%	4·0%	<0·0001	3·4%	1·4%	<0·0001	11·1%	4·9%	<0·0001	1674
Age-standardised rates by level of hospital											
Primary hospitals	4281	11·4%	4·8%	<0·0001	6·6%	1·2%	<0·0001	14·2%	5·5%	<0·0001	28
Secondary hospitals	46 330	11·2%	4·9%	<0·0001	2·7%	1·4%	<0·0001	12·5%	5·7%	<0·0001	330
Tertiary hospitals	172 162	8·8%	3·5%	<0·0001	3·6%	1·4%	<0·0001	11·2%	4·4%	<0·0001	1482

Cardiovascular disease was defined as having either coronary heart disease or stroke. *p value for χ^2 test of prevalence between early-onset versus late-onset type 2 diabetes in each age category. †Prevalence was standardised to the population of mainland China in 2011.

Table 2: **Age-standardised prevalence of non-fatal cardiovascular diseases among patients with early-onset versus late-onset type 2 diabetes**

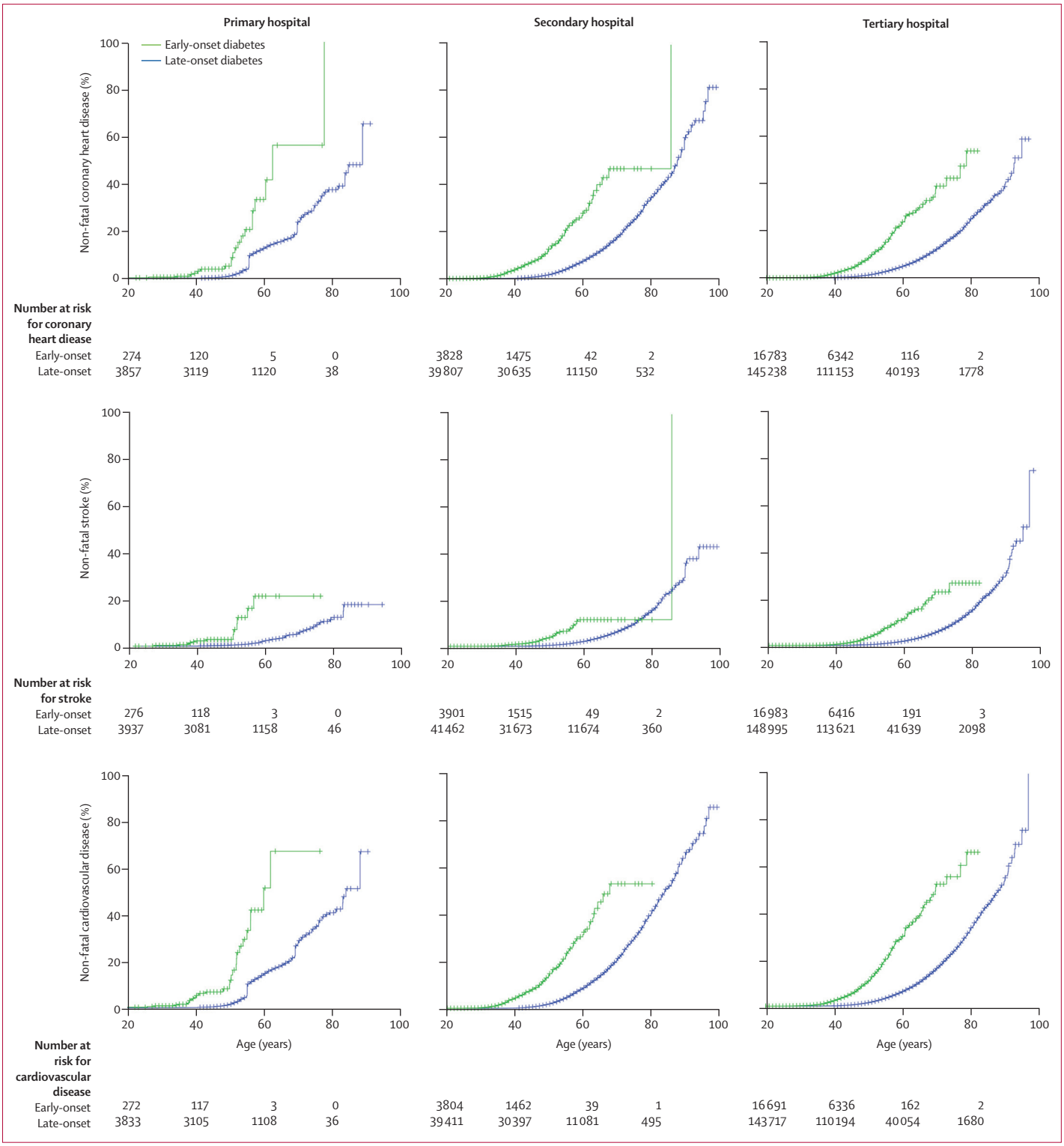

***Figure 2*: Kaplan-Meier plot of non-fatal cardiovascular diseases stratified by early-onset and late-onset diabetes in patients attending primary, secondary, and tertiary hospitals, by age**
Non-fatal coronary heart disease (A). Non-fatal stroke (B). Non-fatal cardiovascular disease (C; either non-fatal coronary heart disease or non-fatal stroke). Log-rank test p<0·0001 for differences between early-onset and late-onset type 2 diabetes for all age groups.

4281 (2%) of 222773 were primary care hospital patients, 46330 (21%) were secondary care hospital patients, and 172162 (77%) were tertiary care hospital patients. 26992 (12%) had early-onset type 2 diabetes. Excluded patients did not differ from the patients included in the analysis in age, sex, and disease duration (data not shown). Patients with early-onset type 2 diabetes were younger, had a longer duration of diabetes, and were more likely to be treated with insulin alone or insulin combined with oral antidiabetic drugs compared with patients with late-onset type 2 diabetes (table 1). Use of drug classes by the two groups is shown in the appendix p 2.

After adjustment for sex and level of hospital, patients with early-onset type 2 diabetes had increased HbA_{1c}, systolic blood pressure, and LDL-C compared with patients with late-onset type 2 diabetes in almost every age group, although some differences were not statistically significant (figure 1). Diastolic blood pressure was significantly higher in patients with early-onset type 2 diabetes than in those with late-onset type 2 diabetes when aged younger than 50 years, but was significantly lower in those with early-onset type 2 diabetes than in those with late-onset type 2 diabetes after age 60 years (figure 1). HDL-C was significantly lower in patients with early-onset type 2 diabetes than in those with late-onset type 2 diabetes in the 45–49 years and 65–69 years age groups. Triglyceride concentrations decreased with increasing age in both groups, but the decrease was more rapid in patients with early-onset type 2 diabetes than in those with late-onset type 2 diabetes, resulting in significantly lower triglyceride concentrations in patients with early-onset diabetes after age 45 years (figure 1).

Patients with early-onset type 2 diabetes had a significantly higher prevalence of non-fatal cardiovascular disease at each age group at all levels of hospital (table 2). Although crude prevalence of non-fatal coronary heart disease, stroke, and cardiovascular disease was higher in the late-onset group than in the early-onset group (table 1), the age-standardised prevalence of non-fatal coronary heart disease, stroke, and cardiovascular disease was significantly higher among patients with early-onset type 2 diabetes than in those with late-onset type 2 diabetes (table 2). Kaplan-Meier plots showed that the prevalence of non-fatal coronary heart disease, stroke, and cardiovascular disease was significantly increased in patients with early-onset type 2 diabetes compared with those with late-onset type 2 diabetes from 40 years of age onward (figure 2).

After adjustment for age and sex, early-onset type 2 diabetes was associated with 1·91 times (95% CI 1·81–2·02) increased risk of non-fatal cardiovascular disease compared with late-onset type 2 diabetes. The differences in risk of non-fatal cardiovascular disease and coronary heart disease (but not non-fatal stroke) was mainly driven by tertiary and secondary care patients (table 3; appendix pp 3–4). The increased risk of non-fatal cardiovascular disease was attenuated after further adjustment for duration of diabetes (OR 1·13, 1·06–1·20; table 3). Additional adjustment for other factors only slightly attenuated effect sizes, with the overall association remaining significant (non-fatal cardiovascular disease 1·13, 1·07–1·20; table 3).

	Primary	Secondary	Tertiary	Overall
Multivariable model 1				
Early versus late onset	1·41 (0·97–2·07)	1·90 (1·69–2·12)	1·98 (1·85–2·10)	1·91 (1·81–2·02)
Model fit (C)	0·625	0·679	0·686	0·700
Multivariable model 2				
Early versus late onset	0·93 (0·62–1·41)	1·18 (1·05–1·33)	1·14 (1·06–1·22)	1·13 (1·06–1·20)
Duration of diabetes (years)	1·05 (1·03–1·06)	1·07 (1·06–1·07)	1·07 (1·07–1·08)	1·07 (1·06–1·07)
Model fit (C)	0·631	0·701	0·713	0·712
Multivariable model 3				
Early versus late onset	1·05 (0·66–1·69)	1·17 (1·03–1·32)	1·13 (1·06–1·21)	1·12 (1·06–1·19)
Duration of diabetes (years)	1·03 (1·01–1·05)	1·05 (1·04–1·05)	1·06 (1·06–1·06)	1·06 (1·05–1·06)
Model fit (C)	0·824	0·733	0·743	0·759
Multivariable model 4				
Early versus late onset	0·98 (0·63–1·52)	1·17 (1·04–1·32)	1·14 (1·06–1·22)	1·13 (1·07–1·20)
Duration of diabetes (years)	1·01 (1·00–1·03)	1·05 (1·04–1·05)	1·06 (1·05–1·06)	1·05 (1·05–1·06)
Model fit (C)	0·856	0·749	0·757	0·744

Data are odds ratio (95% CI). Cardiovascular disease was defined as either coronary heart disease or stroke. Multivariable model 1 was adjusted for age and sex. Multivariable model 2 was adjusted for age, sex, and duration of diabetes. Multivariable model 3 was adjusted for age, sex, duration of diabetes, BMI, self home glucose monitoring, diabetes medications (as listed in table 1), diabetic nephropathy, HbA_{1c}, low-density lipoprotein cholesterol, and the blood pressure control target. Multivariable model 4 was adjusted for age, sex, duration of diabetes, BMI, self home glucose monitoring, diabetes medications (as listed in table 1), diabetic nephropathy, targets of glycaemic control, targets of blood pressure control, and targets of lipid control.

Table 3: **Odds ratio of early-onset versus late-onset type 2 diabetes for non-fatal cardiovascular disease by level of hospital**

Prevalence of coronary heart disease and cardiovascular disease was significantly higher in women than in men, although we identified no difference in the prevalence of stroke (appendix pp 5–6). Triglyceride concentration was negatively associated with duration of diabetes (appendix pp 7–8). Increased risk of cardiovascular disease in early-onset versus late-onset type 2 diabetes was mainly driven by patients with a BMI of less than 24·0 kg/m² and duration of diabetes of 10 years or more (appendix pp 9–10). Kaplan-Meier analysis showed an increase in the cumulative incidence of non-fatal cardiovascular disease with increasing disease duration, with the most rapid increase after 10 years duration of diabetes (appendix p 11).

In the validation study, 25817 patients with type 2 diabetes were enrolled, 363 patients with missing variables were excluded, and the remaining 25454 were used in the analysis. Characteristics of study patients and prevalence of non-fatal cardiovascular disease in patients with early-onset versus late-onset type 2 diabetes are shown in the appendix (pp 12–14). Of 25454 patients with type 2 diabetes, 5760 (23%) had non-fatal cardiovascular disease (coronary heart disease 3788 [15%]; stroke 2576 [10%]) and 391 (2%) had peripheral vascular disease (patients with both peripheral vascular disease and cardiovascular disease 6026 [24%]). 2809 (11%) patients

	Cardiovascular disease	Cardiovascular disease or peripheral vascular disease
Multivariable model 1		
Early versus late onset	1·34 (1·17–1·53)	1·36 (1·19–1·55)
Multivariable model 2		
Early versus late onset	0·94 (0·81–1·09)	0·95 (0·82–1·09)
Duration of diabetes (years)	1·03 (1·03–1·04)	1·03 (1·03–1·04)
Multivariable model 3		
Early versus late onset	0·94 (0·78–1·13)	0·95 (0·79–1·13)
BMI (kg/m^2)	1·04 (1·03–1·05)	1·03 (1·01–1·05)
SBP (per 10 mm Hg)	1·08 (1·06–1·11)	1·08 (1·06–1·10)
LDL-C (mmol/L)	0·98 (0·96–1·01)	0·98 (0·96–1·01)
Multivariable model 4		
Early versus late onset	0·94 (0·78–1·13)	0·95 (0·79–1·14)
Diet treatment only	0·80 (0·69–0·93)	0·81 (0·70–0·94)
Multivariable model 5		
Early versus late onset	0·92 (0·76–1·11)	0·93 (0·77–1·12)
Use of lipid-lowering drugs	2·18 (2·01–2·36)	2·14 (1·97–2·31)
Use of antihypertensive drugs	2·13 (1·96–2·31)	2·08 (1·92–2·25)

Cardiovascular disease was defined as coronary heart disease or stroke. SBP=systolic blood pressure. LDL-C=low-density lipoprotein cholesterol. Multivariable model 1 was adjusted for age and sex. Multivariable model 2 was adjusted for age, sex, and duration of diabetes. Multivariable model 3 was further adjusted for the variables listed above as well as lifestyle (non-smoker, ex-smoker, 1–5 cigarettes per day, or 6 or more cigarettes per day; and non-drinker, ex-drinker, 1–10 g alcohol per day, or 11 g and more alcohol per day), BMI, diabetes medications (including no diabetes medication, no oral antidiabetic drug [OAD], one OAD, two OADs, three OADs, four or more OADs, and insulin), hypoglycaemia within the past 6 months, albuminuria, HbA_{1c}, SBP, and LDL-C. Multivariable model 4 was adjusted for the variables listed above and whether patients were on diet treatment for hyperglycaemia only. Multivariable model 5 was further adjusted for the variables listed above as well as use of lipid-lowering drugs and use of antihypertensive drugs.

Table 4: **Validation of odds ratios of early-onset versus late-onset type 2 diabetes for non-fatal cardiovascular disease in the 3B study**

were diagnosed with type 2 diabetes when they were aged younger than 40 years. Early-onset type 2 diabetes was associated with increased risk of non-fatal cardiovascular disease (OR 1·34, 95% CI 1·17–1·53), and adjustment for duration of diabetes attenuated the OR (0·94, 0·81–1·09). By contrast, we noted only marginal changes in ORs for non-fatal cardiovascular disease after further adjustment for additional variables including lifestyle and metabolic profile (OR 0·94, 0·78–1·13), lifestyle and metabolic profile and diet only (0·94, 0·78–1·13), or lifestyle and metabolic profile, diet only, and use of lipid-lowering drugs and antihypertensive drugs (0·92, 0·76–1·11; table 4). Inclusion of peripheral vascular disease in the definition of non-fatal cardiovascular disease did not change the effect sizes (table 4).

Discussion

In both the main analysis and the validation study, patients with early-onset type 2 diabetes had a higher risk of non-fatal cardiovascular disease at all age groups compared with patients with late-onset type 2 diabetes. The higher risk among patients with early-onset type 2 diabetes is mostly explained by prolonged duration of diabetes.

Studies have reported a consistent increase in prevalence of early-onset type 2 diabetes worldwide—eg, in the UK,[16] Finland,[17] and Japan.[18] In mainland China, prevalence of early-onset diabetes (younger than age 40 years) in the general population increased from 1·01% in 1997 to 5·7% in 2010.[10,19,20] In our study, early-onset type 2 diabetes accounted for 7·6% of patients recruited from primary care centres, 10·5% of patients recruited from secondary care centres, and 12·7% of patients recruited from tertiary care centres.

Patients with early-onset type 2 diabetes have been suggested to have increased risk of cardiovascular complications compared with those with late-onset diabetes, and more rapid development and progression of complications.[3–8,21,22] A large study[4] in a predominantly white population reported that adults with type 2 diabetes who were diagnosed younger than age 45 years had a 14 times increased risk of developing myocardial infarction compared with patients diagnosed at age 45 years or above. Data from the Hong Kong Diabetes Registry[11] also showed that early-onset type 2 diabetes was associated with a substantially higher risk of cardiovascular-renal complications compared with late-onset type 2 diabetes at all ages. These studies are in agreement with our data showing that Chinese people in mainland China with early-onset type 2 diabetes have sharply increased risk of non-fatal cardiovascular disease.

Several epidemiological studies have investigated whether the increased risk of complications associated with early-onset type 2 diabetes is attributable to prolonged exposure to diabetes and subsequent worsened metabolic profiles.[22,23] In the Hong Kong study, increased risk of cardiovascular and renal complications associated with early-onset type 2 diabetes was ascribed to a prolonged duration of diabetes.[11] Similarly, microvascular complications in Chinese people with early-onset type 2 diabetes who were treated in accredited 3A hospitals were almost completely attributable to prolonged duration of diabetes and subsequent metabolic disorders.[12] Consistently, patients with early-onset type 2 diabetes had worse metabolic profiles compared with patients with late-onset type 2 diabetes. Prolonged type 2 diabetes might lead to reduced β-cell function and increased HbA_{1c} concentrations, which might then increase systolic blood pressure and LDL-C concentrations owing to increased oxidative stress and activation of the renin-angiotensin system.[24,25] Prolonged duration of diabetes and worsened metabolic profile could explain most, although not all, increased risk of cardiovascular disease observed in this study. Data from the large JADE registry[26] showed that triglyceride concentrations were higher in patients with early-onset type 2 diabetes than in those with late-onset type 2 diabetes at baseline. In our study, triglyceride concentrations were also significantly lower in patients

with early-onset type 2 diabetes than in those with late-onset type 2 diabetes at similar ages (except for those aged younger than 45 years), although triglyceride concentrations were similar at baseline. Low triglyceride concentrations might result from decreased β-cell function, and decreased β-cell function owing to prolonged duration of diabetes and subsequent metabolic disorder might account for increased risk of cardiovascular disease. This idea is supported by several observations: triglyceride concentrations are positively associated with plasma insulin concentrations;[27] insulin has a selective effect on increasing synthesis of free fatty acids;[28] and patients with early-onset diabetes have higher HbA_{1c} concentrations compared with those with late-onset type 2 diabetes at similar ages. The observed association between early-onset type 2 diabetes and risk of cardiovascular disease was mainly driven by patients with BMI less than 24 kg/m², to a lesser extent, patients with BMI 24 kg/m² and above, and by patients with longer duration of diabetes (eg, 10 years or more). These observations are consistent with the finding that β-cell mass in obese people without diabetes is increased by about 50% compared with people with normal bodyweight.[29] Thus, these findings support the idea that decreased β-cell function might play a key part in the increased risk of cardiovascular disease in patients with early-onset type 2 diabetes, highlighting the importance of maintaining β-cell function in management of early-onset type 2 diabetes. Interestingly, the risk of cardiovascular disease associated with early-onset type 2 diabetes was higher in women than in men. Further research is needed to investigate whether the decline in β-cell function after lengthy exposure to type 2 diabetes is more severe in women than in men.

Our findings have important implications for shaping public health policy regarding prevention of diabetes in China, where its prevalence has escalated during the past three decades, and increasing numbers of people are diagnosed at a young age.[10] Results of several major studies[9,30,31] showed that type 2 diabetes is preventable with lifestyle modification interventions. We showed that risk of cardiovascular disease rapidly increased in the early-onset type 2 diabetes cohort as early as at age 40 years—10 years earlier than the late-onset cohort. Our study suggests that priority should be given to prevention of diabetes among young patients.

Our findings also have important clinical implications. Results of the United Kingdom Prospective Study[32] showed that intensive management of newly diagnosed type 2 diabetes reduced long-term cardiovascular disease. Results of another major study[33] showed that integrated interventions aiming to normalise glycaemia, blood pressure, and lipids reduced diabetes complications, including cardiovascular disease and death. Thus, our findings suggest that more medical resources should be allocated to management of patients at high risk of non-fatal cardiovascular disease.

The strength of our study was its large sample size, with patients recruited from almost all provinces of China, meaning that it was, to some extent, representative of patients with type 2 diabetes throughout China. Our study also has several limitations. First, our study might over-represent tertiary care hospital patients and under-sample primary care hospital patients. Second, coronary heart disease, stroke, and cardiovascular disease cases in our study were ascertained by reviewing medical records. Some medical records were not available and therefore some cardiovascular disease cases might have been missed. Third, although our study covered the different levels of hospitals in China, some economically disadvantaged patients or patients with mild type 2 diabetes might not have sought medical treatment and thus might have been missed. As a result, the true prevalence of macrovascular complications might be underestimated. Fourth, the inclusion and exclusion criteria only recruited patients on hypoglycaemic drug treatments in the CNHSS. Although this procedure minimised misclassification of non-type 2 diabetes as type 2 diabetes, patients on diet management only were missed. Data for lifestyle measures such as smoking status, alcohol consumption, dietary intake, and exercise were also not collected. The study design also has limitations; eg, this was a cross-sectional study, so competing risk of death could not be considered. Since duration of diabetes was associated with death,[34] especially from cardiovascular disease, more deaths were expected in patients with early-onset type 2 diabetes than in those with late-onset type 2 diabetes at the same ages. Therefore the prevalence of non-fatal cardiovascular disease in early-onset versus late-onset type 2 diabetes might be underestimated. We also did not systematically screen for underlying autoimmune diabetes and secondary diabetes, which might have accounted for some cases of type 2 diabetes in our study.[35] Data for peripheral vascular disease were not collected in the CNHSS cohort, nor was use of antihypertensive drugs and lipid-lowering drugs recorded. However, in the validation study, adjustments for these confounding factors and inclusion of peripheral vascular disease in non-fatal cardiovascular disease resulted in only marginal changes in the effect sizes seen between early-onset versus late-onset type 2 diabetes. Therefore, non-inclusion of these factors in the main analysis might not have had major effects on effect sizes. Finally, the 3B study invited hospitals only in selected areas of China and might be less representative than the CNHSS.

In summary, early-onset type 2 diabetes increased the risk of non-fatal cardiovascular disease in Chinese patients, mostly due to prolonged exposure to type 2 diabetes. Because of the preventable nature of type 2 diabetes, and because intensive management can reduce risk of cardiovascular disease in these patients, priority should be given to prevention of diabetes in young people, and intensive management of patients

with early-onset type 2 diabetes should be in place to reduce the burden of both diabetes and cardiovascular disease in China.

Contributors

LJ, XY, XH, and LGa conceived the idea. LJ, JL, XG, JW, and LGu designed the CNHSS. LJ and DH designed the 3B STUDY. LJ, JL, XG, LGu, JW, and WX collected the data for the CNHSS. LJ, DH, LGa, QJ, XR, BS, JW, CH, DZ, HZ, and CP collected the data for the 3B study. XH and LGa analysed the data. XH and LGa, and LGu wrote the first draft. All authors gave critical comments and contributed to the writing of the manuscript. All authors agreed to submit and publish the manuscript. LJ and XY (the corresponding authors) and XH, LGa, and LGu take full responsibility for the work as a whole, including the study design, access to data, and decision to submit.

Declaration of interests

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