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A 48-month Prospective Study of the Effects of Multifactorial Interventions on Cardiovascular Risk Factors in Patients with Type 2 Diabetes Mellitus in an Urban Community: The Beijing Communities Diabetes Study 12

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Abstract

Objective: To assess whether multifactorial interventions have long-term effects on the risk of diabetes-related macrovascular complications in patients with type 2 diabetes mellitus living in urban communities of Beijing.

Design, setting and participants: A total of 2926 patients with type 2 diabetes from 15 community health centers were divided into a diabetes mellitus (DM) group (n=824), a hypertension (HTN) group (n=1267), and a cardiovascular disease (CVD) group (n=835). By applying Framingham risk scores (FRS), patients in the 3 groups were subdivided into low (FRS <10%), medium (FRS 10%-20%), and high (FRS >20%) Framingham risk strata. After 48 months, patients were followed-up to assess the long-term effects of the multifactorial interventions.

Results: At baseline, the patients' mean neck circumference (NC) was significantly higher in the HTN and CVD groups than in the DM group (P<0.05). After 48 months of follow-up, the CVD and HTN groups both had higher blood pressures and lipid levels than the DM group (both P<0.01). Although there was no significant change in the FRS versus baseline in the low and medium

Framingham risk strata, a significant reduction in FRS was noted in the high Framingham risk strata. In Cox multivariate analyses, the HTN and CVD groups had higher incidences of endpoint events than the DM group.

Conclusions: This study has demonstrated for the first time a relationship between NC and CVD in diabetic patients. Multifactorial interventions for CVD risk factors over 48 months lowered the estimated 10-year risk for CVD events in diabetes. FRS score influences the incidence of CVD events in diabetic patients. Aggressive risk reduction should be focused on these individuals who had high FRS score.

Keywords: Type 2 diabetes mellitus; Cardiovascular disease; Hypertension; Framingham risk score

Introduction

The Beijing Communities Diabetes Study (BCDS) is a prospective clinic research project designed to investigate whether multifactorial interventions have a long-term effect on the risk of diabetes-related macrovascular complications in patients with type 2 diabetes mellitus living in urban communities of Beijing. This project, which is similar to the Diabetes Prevention Program (DPP) in 1993 [1], is the first of its kind to be performed in China. It is hoped that the community-based prevention protocol, which is described below, is reproducible, though with some local modifications, throughout China. The significance of this research is paramount as the prevalence of diabetes mellitus in China has reached a record level, with a diagnosed diabetic population of 113.9 million, resulting in increased burdens on individuals and healthcare systems worldwide. The BCDS project lends support to emphasis on the critical need to conduct and publish reports on well-designed community-based diabetes interventions, despite the low response rates and lack of information on nonresponders [2].

Subjects and Methods

Details of the BCDS study have been published previously [3]. For the present study (BCDS 12), the patients were all residents of 15 community health centers who were recruited between August 2008 and July 2009. They were aged between 20 and 80 years, and all had been diagnosed with type 2 diabetes mellitus. The patients' likelihood of moving away from that their Beijing community was taken into account when enrolling patients. The study was conducted according to the declaration of Helsinki. The Medical Ethics Committee of Beijing Tongren Hospital approved the study protocol, and all participants provided their written informed consent.

The patients enrolled in BCDS were monitored by 130 GPs on a one-to-one basis during the 48-months multi-factorial intervention. The GPs were systemically educated by six professors of endocrinology that come from top tier hospital, and enhancing the level of patient care by stepping up regular clinical consultation.

Goals of treatment in BCDS are in accordance with 2007 and 2010 China guideline for type 2 diabetes: a stepwise implementation of diet control, behavior modification and the optimum management strategy that targeted hyperglycemia, hypertension, dyslipidemia and microalbuminuria. A major focus on comprehensive cardiovascular risk reduction includes blood glucose, blood pressure and lipid profiles. Patients who failed to achieve target goals would be required to carry out intensive life style control under the direction of GPs; medication did can be increased and/or a drug from a different class can be added to treatment. When encountered difficult and complicated cases or the patients were in poor compliance, in order to optimize for treatment during multi-factorial intervention, the GPs would request consultation repeatedly. Where possible, all treatment decisions should involve the patient, with a focus on patient preferences, needs, and values.

Approaches to prevention of diabetic complications in BCDS include the following: Patients were seen at clinic visits every 2 months; HbA1c every 3-6 months; Annual micro-albumin checks; Yearly dilated eye examinations; Measurements of the lipid profile and ECGs were performed 6-monthly or yearly.

Type 2 diabetes mellitus was defined according to the criteria of the World Health Organization. The study population consisted of patients with or without CVD. CVD was diagnosed in a top tier hospital and included coronary heart disease, myocardial infarction, angina pectoris, cerebrovascular disease or other clinical manifestations of CVD. Cerebrovascular disease included ischemic attacks or strokes. Patients were considered hypertensive if they reported current use of antihypertensive medications and/or had a systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg.

A total of 2926 adults with diabetes were recruited for analysis. The participants were divided into 3 study groups: a hypertension (HTN) group (n=1267), a cardiovascular disease (CVD) group (n=835) and a no-complications diabetes mellitus (DM) group that had normal blood pressures and no CVD (n=824). By using Framingham risk scores (FRS) [4], in the present study, prediction of CHD risk was performed in all patients at baseline using the following glycated hemoglobin (HbA1c) risk categories: score 0 = HbA1c ≤ 7.0% ; score 1=7.0% <HbA1c ≤ 7.9%; score 2=8.0% <HbA1c ≤ 8.9%; and score 3=HbA1c >9.0%. Subsequently, the effects of the interventions applied in reducing the FRS was evaluated by comparing the 48-month follow-up scores with baseline scores.

On the basis of the baseline FRS, patients in the 3 study groups were subdivided into risk categories of <10% (low Framingham risk strata), 10% to 20% (medium Framingham risk strata) and >20% (high Framingham risk strata) to evaluate the 10-year risk of CVD. For the lower risk populations with a 10-year risk between 10% to 20%, limited data were available on the recommended management strategies.

For the present study, cardiovascular events were defined as the first nonfatal or fatal cardiovascular events, including

myocardial infarction, sudden death, nonfatal stroke, or amputation.

Patients excluded from analysis in the present study included those with type 1 diabetes, urinary infections, hematuria, severe disabilities, hepatic failure, renal failure, schizophrenia, goiter or fever, sleep apnea syndrome. Patients with evidence of microvascular disease (retinopathy, peripheral neuropathy and nephropathy) were also excluded.

Study procedures

Baseline information on sociodemographic variables included age, gender, smoking habits, history of diabetes and parental history of diabetes. Data obtained from clinical evaluations included height, body weight, body mass index (BMI), and waist circumference (WC) and hip circumference (HC). Overweight was defined as a BMI >24 kg/m^2. The neck circumference (NC) at the upper margin of the laryngeal prominence was also measured with the patients' heads erect and eyes facing forward. SBP and DBP values in all participants were also obtained.

Laboratory data

Blood samples in all patients were drawn after an overnight fast. Laboratory measurements (using established methods) included:

1. Fasting plasma glucose (FPG), 2-hour postprandial blood glucose (2hPG), and fasting serum insulin concentrations. HbA1c was measured by a central endocrinology laboratory in Beijing Tongren Hospital using a Bio-Rad Variant hemoglobin analyzer. Insulin resistance (determined by the homeostatic model assessment [HOMA] method) was calculated as the product of fasting insulin multiplied by fasting glucose divided by 22.5.
2. Serum lipid concentrations (total cholesterol, low- and high-density lipoprotein [LDL and HDL]-cholesterols, and triglycerides.
3. Alanine aminotransferase (ALT), blood urea nitrogen, and serum creatinine concentrations.
4. Urinary albumin excretion rate (UAER), which was performed via a centralized 8-hour overnight urine collection.

After blood sampling, all patients underwent a resting 12-lead ECG. Angina pectoris and/or >0.1 mV ST segment deviation during a treadmill maximal exercise stress test were recorded. Nonstereoscopic photographs of the central fundus were taken for all eyes (Camera CR-DGi; Canon Inc, Tokyo, Japan).

On December 31, 2012, participants were informed of the final results and asked to continue with normal medical care every year.

Statistical analysis

The BCDS database was set up using EpiData 3.0 software. Statistical analysis was performed using SAS® software (version 9.0, SAS Institute Inc., Cary, USA). The results were expressed as means ± SD or medians and interquartile range (IQR; Q1,Q3). The baseline characteristics of the study participants with and without CVD or hypertension were compared using a t-test for proportions, and were compared with a paired t-test or unpaired Student's t-test or Mann-Whitney U test for means. Kaplan-Meier estimates of the risk for the final clinical endpoints were made.

Nonparametric Mann-Whitney tests were used to test the differences in FRS among the groups after 48 months of follow-up. A Kaplan-Meier analysis was used to indicate the prognostic value of the FRS for patients. Hazard ratios and 95% CIs were determined for the study groups with scores <10%, between 10% and 20% and >20%. These time-varying HRR models were fitted using Cox regression. A P value <0.05 in a 2-tailed test was considered to indicate statistical significance.

Results

Among the 2926 patients with type 2 diabetes who were included in the analysis, 1267 of mean age 64.0 ± 10.0 years had hypertension and comprised the HTN group, 835 of mean age 67.7 ± 8.8 years had cardiovascular disease and comprised the CVD group, and 824 of mean age 59.1 ± 11.0 years with diabetes but with a normal blood pressure (<140/90 mmHg) and without CVD comprised the DM group. More than half of the study population (78.84%) had a FRS between 10% to 20%, while 6.56% had a FRS <10% and 14.59% a FRS >20%.

Patients' clinical characteristics and comorbidities

Low Framingham risk strata: the baseline and follow-up demographic and clinical characteristics of the DM, HTN and CVD groups for patients in the low Framingham risk strata are shown in **Table 1**. At baseline and the post-intervention evaluation, patients in the CVD and HTN groups had higher SBP and DBP levels than the DM group (P<0.01).

Table 1 Demographic and clinical characteristics of the DM group, HTN group and CVD group in low Framingham risk strata at baseline (2008) and end of study follow up (2012) in the Beijing Communities Diabetes Study (Report 12).

Characteristic	2008			2012		
Total	DM (n=119)	HTN (n=57)	CVD (n=16)	DM (n=119)	HTN (n=57)	CVD (n=16)

Age (years)	45.2 ± 7.9	45.1 ± 9.3	49.0 ± 9.9			
Gender (male/female)	62/57	31/26	13-Mar			
Duration of diabetes (years)	2.00(0.00, 5.92)	1.50(0.00, 4.00)	1.33(0.00, 3.88)			
Height (cm)	165.8 ± 8.0	163.7 ± 8.2	167.5 ± 7.2			
Weight (kg)	70.1 ± 12.6	70.0 ± 12.2	76.4 ± 11.8			
Body mass index (Kg/m²)	25.4 ± 3.8	26.1 ± 4.4	27.1 ± 3.0	25.5 ± 3.7	26.6 ± 6.2	26.6 ± 3.0
Waist circumference (cm)	88.6 ± 10.4	87.3 ± 8.8	91.5 ± 10.4	88.7 ± 10.5	88.7 ± 9.3	92.1 ± 11.3
Hip circumference (cm)	100.0 ± 9.0	99.1 ± 9.2	101.0 ± 5.8	100.2 ± 8.9	100.0 ± 9.7	102.2 ± 5.6
Waist-hip ratio	0.89 ± 0.06	0.88 ± 0.06	0.91 ± 0.08	0.88 ± 0.06	0.89 ± 0.06	0.90 ± 0.08
Neck circumference (cm)	36.7 ± 3.5	36.2 ± 4.1	38.9 ± 4.1*†	36.8 ± 3.5	35.9 ± 3.5*	38.5 ± 4.1*†
Systolic blood pressure (mmHg)	116.7 ± 10.2	127.2 ± 12.4*	125.9 ± 11.4*	121.1 ± 8.3	123.0 ± 8.0*	128.9 ± 15.5*†
Diastolic blood pressure (mmHg)	77.3 ± 7.2	80.6 ± 9.0*	79.4 ± 10.0*	75.2 ± 5.6	75.9 ± 6.3	78.7 ± 9.3
Smoker (%)	12.61	3.51	0			
FPG (mmol/L)	7.76 ± 2.65	7.17 ± 2.46	6.71 ± 1.37	7.53 ± 2.51	6.54 ± 1.58*	6.89 ± 1.90†
Hpg (mmol/L)	10.08 ± 3.37	9.79 ± 3.61	10.55 ± 3.79	9.06 ± 2.72	8.26 ± 1.45	9.09 ± 1.64
HbA1c (%)	7.33 ± 1.78	6.74 ± 1.83	7.06 ± 1.40	7.16 ± 1.52	6.47 ± 0.80*	7.05 ± 1.11
Fasting plasma insulin (μU/ml)	8.93(5.67, 29.52)	8.70(4.54, 23.20)	9.45(4.48, 38.32)			
HOMA-IR	3.58(1.74, 8.01)	2.86(1.44, 7.50)	3.13(1.19, 12.09)			
Triglycerides (mmol/l)	1.41(1.00, 2.30)	1.56(1.01, 2.05)	1.48(1.11, 2.10)	1.30(1.00, 2.10)	1.40(1.00, 1.80)	1.35(0.90, 1.90)
Total cholesterol (mmol/l)	4.54 ± 0.84	4.44 ± 1.08	4.44 ± 1.11	4.78 ± 0.92	4.56 ± 1.09	4.37 ± 1.28
HDL-cholesterol (mmol/l)	1.20 ± 0.33	1.27 ± 0.28	1.19 ± 0.33	1.22 ± 0.35	1.29 ± 0.45	1.32 ± 0.43
LDL-cholesterol (mmol/l)	2.51 ± 0.82	2.54 ± 0.70	2.78 ± 0.77	2.86 ± 0.73	2.62 ± 0.97	2.63 ± 0.77
Alanine aminotransferase (U/L)	19.54	24.2	22	20	20	21
	(15.10, 25.40)	(16.00, 30.26)	(19.30, 29.75)	(15.50, 28.00)	(12.90, 30.00)	(19.00, 33.00)
Blood urea nitrogen (mmol/L)	4.82(3.90, 6.10)	4.80(3.71, 5.98)	5.40(5.00, 7.14)	5.30(4.60, 6.20)	5.20(4.15, 6.20)	4.65(3.50, 5.40)
Creatinine (mmol/L)	72.82 ± 20.41	78.57 ± 38.03	78.29 ± 27.46	74.36 ± 18.19	71.32 ± 25.66	74.92 ± 15.45
Urine acid (mmol/l)	251.40 ± 100.26	286.24 ± 106.00*	325.04 ± 109.39*	282.79 ± 100.06	306.83 ± 89.68	308.73 ± 109.32
Framingham risk score (FRS)	6.33 ± 2.91	6.30 ± 3.90	7.81 ± 1.60	8.08 ± 4.48	8.81 ± 4.31	9.54 ± 3.64

N = number of individuals. Values are expressed as mean ± SD, median (Q1,Q3) or number (%). P statistical significance of the differences among the three groups. *-vs. DM group; †- vs. HTN group. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; FPG, fasting plasma glucose; Hpg, 2-hour postprandial blood glucoseHbA1c, hemoglobin A1c; FRS, Framingham risk score

The CVD group showed a tendency towards a markedly higher NC than the DM and HTN groups both at baseline (38.9 ± 4.1 cm vs. 36.7 ± 3.5 cm and 36.2 ± 4.1 cm, respectively; P<0.05) and after 48 months of follow-up (38.5 ± 4.1 cm vs. 36.8 ± 3.5 cm and 35.9 ± 3.5 cm, respectively; P<0.05). For glucose metabolism parameters and a number of the hemodynamic values (lipid and serum creatinine concentratons), there were no significant differences among the 3 groups. However, the CVD and HTN groups had higher baseline uric acid levels than the DM group (P<0.05).

Median Framingham risk strata: the baseline and follow-up demographic and clinical characteristics of the DM, HTN and CVD groups for patients in the medium Framingham risk strata are shown in the **Table 2**. The CVD group were older, had a longer duration of diabetes, and higher baseline SBP than the DM group (66.5 ± 8.1 vs. 61.3 ± 9.3 years; 4.75 (range 0.00-10.42) vs. 3.25 (range 0.00-9.67) years; and 128.3 ± 13.6 vs. 121.6 ± 9.8 mmHg; all P <0.01). In addition, there were other statistically significant differences in baseline characteristics between the 3 groups, including gender, BMI, and waist circumference (all P<0.01) and there was also a

significant difference in the percentages of smokers between the HTN and DM groups (P<0.01). Significant differences for some parameters were also detected after 48 months of follow-up, including BMI, waist circumference, and blood pressure.

As shown in **Table 2**, The CVD group had a significantly higher mean NC than the DM group at baseline (36.8 ± 4.0 vs. 35.9 ± 3.7 cm; P<0.01), as did the HTN group (36.7 ± 3.6 vs. 35.9 ± 3.7 cm; P<0.001). On the other hand, lower fasting glucose, HbA1c and lipid levels were noted in the CVD and HTN groups in comparison with the DM group (all P<0.01), although fasting insulin and insulin resistance (HOMA-IR) values were similar in the 3 groups (P>0.05). In terms of serum uric acid, blood urea nitrogen and creatinine levels, patients in the DM group had a more adverse risk profile than the other groups (all P<0.01).

Table 2 Demographic and clinical characteristics of the DM group, HTN group and CVD group in median Framingham risk strata at baseline (2008) and end of study follow up (2012) in the Beijing Communities Diabetes Study (Report 12).

Characteristic	2008			2012		
Total	DM (n=689)	HTN (n=973)	CVD (n=645)	DM (n=689)	HTN (n=973)	CVD (n=645)
Age (years)	61.3 ± 9.3c	63.1 ± 8.7*	66.5 ± 8.1*†			
Gender (male/female)	300/389	405/568	336/309*†			
Duration of diabetes (years)	3.25(0.00, 9.67)	3.58(0.00, 8.33)	4.75(0.00,10.42) *†			
Height (cm)	163.0 ± 7.8	162.8 ± 7.9*	164.2 ± 7.8*†			
Weight (kg)	65.8 ± 10.5	67.9 ± 11.3*	68.6 ± 11.1*†			
Body mass index (Kg/m²)	24.7 ± 3.3	25.6 ± 3.5*	25.4 ± 3.4*	24.9 ± 4.6	25.6 ± 3.7*	25.4 ± 3.7*
Waist circumference (cm)	86.7 ± 9.0	89.6 ± 9.3*	90.1 ± 8.9*	86.6 ± 8.9	89.2 ± 9.4*	89.6 ± 9.4*
Hip circumference (cm)	97.8 ± 8.1	100.0 ± 8.7*	99.9 ± 8.4*	98.0 ± 8.1	99.8 ± 8.4*	100.1 ± 8.6*
Waist-hip ratio	0.89 ± 0.06	0.90 ± 0.07*	0.90 ± 0.06*	0.88 ± 0.06	0.90 ± 0.07*	0.90 ± 0.06*
Neck circumference (cm)	35.9 ± 3.7	36.7 ± 3.6*	36.8 ± 4.0*	35.9 ± 3.5	36.7 ± 3.6*	36.8 ± 3.7*
Systolic blood pressure (mmHg)	121.6 ± 9.8	131.4 ± 14.0*	128.3 ± 13.6*†	123.3 ± 9.4	126.6 ± 9.7*	126.8 ± 9.5*
Diastolic blood pressure (mmHg)	76.0 ± 7.16	79.7 ± 9.2*	77.0 ± 8.7†	75.1 ± 6.8	75.9 ± 6.9*	75.0 ± 7.0†
Smoker (%)	19.01	13.67*	18.14			
FPG (mmol/L)	8.11 ± 2.78	7.62 ± 2.47*	7.41 ± 2.33*	7.34 ± 2.10	7.23 ± 1.95	7.11 ± 1.92
Hpg (mmol/L)	10.90 ± 4.23	10.45 ± 6.33	10.25 ± 3.83	9.19 ± 2.69	9.17 ± 2.79	9.27 ± 2.80
HbA1c (%)	7.47 ± 1.74	7.09 ± 1.54*	7.04 ± 1.34*	7.09 ± 1.29	6.89 ± 1.15*	6.90 ± 1.08*
Fasting plasma insulin (μU/ml)	7.78(4.36, 18.60)	9.48(5.60, 19.80)	11.30(5.50, 23.40)			
HOMA-IR	2.81(1.49, 6.31)	3.17(1.85, 6.71)	3.55(1.92, 8.07)			
Triglycerides (mmol/l)	1.50(1.06, 2.14)	1.45(1.02, 2.15)	1.52(1.06, 2.15)	1.40(1.00, 1.90)	1.30(1.00, 1.90)	1.40(1.10, 2.00)
Total cholesterol (mmol/l)	5.28 ± 1.26	5.16 ± 1.24*	4.98 ± 1.10*†	5.03 ± 1.15	4.96 ± 1.09	4.73 ± 1.03*
HDL-cholesterol (mmol/l)	1.38 ± 0.45	1.34 ± 0.44	1.29 ± 0.39*†	1.35 ± 0.39	1.31 ± 0.38*	1.28 ± 0.35*
LDL-cholesterol (mmol/l)	2.98 ± 0.87	2.92 ± 0.82*	2.84 ± 0.83*†	3.00 ± 0.85	2.93 ± 0.88	2.81 ± 0.76*†
Alanine aminotransferase (U/L)	20.1	20	19.00*†	19	19	19
	(14.50, 28.00)	(14.00, 28.00)	(14.00, 25.30)	(14.30, 24.00)	(14.20, 26.00)	(14.00, 24.00)
Blood urea nitrogen (mmol/L)	5.10(4.10,6.30)	5.16(4.28,6.50)	5.61(4.63, 6.68) *†	5.28(4.50, 6.30)	5.40(4.50, 6.40)	5.80(4.90, 6.80) *†
Creatinine (mmol/L)	70.19 ± 25.98	74.79 ± 28.98*	76.56 ± 29.97*†	73.04 ± 39.40	74.80 ± 29.11	78.70 ± 30.82*†
Urine acid (mmol/l)	256.97 ± 103.40	283.24 ± 105.45*	290.52 ± 115.45*	282.47 ± 84.29	297.57 ± 95.38*	306.96 ± 88.46*†

Framingham risk score (FRS)	14.06 ± 2.28	15.45 ± 2.31*	15.60 ± 2.20*	14.21 ± 2.92	15.45 ± 2.98*	15.66 ± 2.65*

N = number of individuals. Values are expressed as mean ± SD , median(Q1,Q3) or number (%). P statistical significance of the differences among the three groups. *-vs. DM group; †- vs. HTN group. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cho¬lesterol; FPG, fasting plas¬ma glucose; Hpg, 2-hour postprandial blood glucoseHbA1c, hemoglobin A1c; FRS, Framingham risk score.

High Framingham risk strata: the baseline and follow-up demographic and clinical characteristics of the DM, HTN and CVD groups for patients in the high Framingham risk strata are shown in **Table 3**. The CVD group had the highest mean age. At baseline, the CVD and HTN groups had a significantly higher SBP than the DM group (P<0.01). On the other hand, the CVD and HTN groups were more likely than DM group to have lower fasting glucose, HbA1c, fasting insulin, and HOMA-IR levels (all P<0.01-0.05), and a more adverse lipid profile. After 48 months of follow-up, there were no significant differences in these variables between the 3 groups.

Table 3 Demographic and clinical characteristics of the DM group, HTN group and CVD group in high Framingham risk strata at baseline (2008) and end of study follow up (2012) in the Beijing Communities Diabetes Study (Report 12).

Characteristic	**2008**			**2012**		
Total	DM (n=16)	HTN (n=237)	CVD (n=174)	DM (n=16)	HTN (n=237)	CVD (n=174)
Age (years)	71.0 ± 6.5	71.7 ± 6.6	73.3 ± 5.6*†			
Gender (male / female)	0/16	8/229*	0/174†			
Duration of diabetes (years)	1.21(0.00, 14.08)	5.00(0.00, 11.17)	5.00(0.92, 11.67)			
Height (cm)	154.6 ± 4.9	157.3 ± 5.4	157.5 ± 5.2			
Weight (kg)	58.7 ± 9.6	62.4 ± 9.2	63.1 ± 9.0			
Body mass index (Kg/m²)	24.5 ± 3.4	25.2 ± 3.5	25.4 ± 3.3	24.4 ± 3.6	25.3 ± 3.7	25.3 ± 3.4
Waist circumference (cm)	87.5 ± 13.6	88.7 ± 9.3	89.4 ± 9.5	87.3 ± 12.1	88.2 ± 9.1	88.0 ± 9.5
Hip circumference (cm)	97.9 ± 8.7	99.8 ± 9.1	99.7 ± 8.0	99.9 ± 8.9	99.4 ± 9.5	99.2 ± 8.2
Waist-hip ratio	0.89 ± 0.12	0.89 ± 0.06	0.90 ± 0.07	0.87 ± 0.08	0.89 ± 0.06	0.89 ± 0.07
Neck circumference (cm)	34.1 ± 2.4	35.5 ± 3.3	35.9 ± 3.6	35.1 ± 2.5	35.5 ± 3.3	35.4 ± 3.5
Systolic blood pressure (mmHg)	127.1 ± 10.3	140.6 ± 14.4*	138.7 ± 11.8*	123.5 ± 11.0	130.4 ± 9.9*	129.03 ± 11.4*
Diastolic blood pressure (mmHg)	74.7 ± 5.0	78.4 ± 9.4	77.3 ± 8.6	71.9 ± 5.7	74.7 ± 7.7	74.4 ± 7.6
Smoker (%)	18.75	10.13	9.77			
FPG (mmol/L)	9.96 ± 4.02	8.21 ± 2.68*	7.65 ± 2.16*†	7.87 ± 2.09	7.44 ± 2.22	7.13 ± 1.65
Hpg (mmol/L)	13.67 ± 5.63	11.24 ± 4.60*	10.39 ± 3.98*	10.75 ± 3.93	9.54 ± 2.97	9.26 ± 2.78
HbA1c (%)	9.74 ± 2.45	7.64 ± 1.47*	7.30 ± 1.42*	7.59 ± 0.93	7.22 ± 1.21	7.01 ± 1.12
Fasting plasma insulin (μU/ml)	7.86(3.66, 16.70)	10.83(6.05, 19.70) *	8.81(5.67, 16.35) *			
HOMA-IR	3.17(2.05, 7.60)	3.75(2.32, 6.53) *	2.92(1.69, 6.20) *			
Triglycerides (mmol/l)	1.30(1.20, 1.80)	1.60(1.20, 2.00)	1.60(1.20,2.00)	1.41(1.06, 1.80)	1.71(1.29, 2.31)	1.63(1.20, 2.18)
Total cholesterol (mmol/l)	6.05 ± 1.12	5.76 ± 1.16*	5.46 ± 1.27*	5.59 ± 0.96	5.24 ± 1.13	5.05 ± 1.13
HDL-cholesterol (mmol/l)	1.51 ± 0.58	1.43 ± 0.45	1.34 ± 0.41	1.57 ± 0.88	1.37 ± 0.38	1.34 ± 0.42
LDL-cholesterol (mmol/l)	3.75 ± 0.91	3.23 ± 0.92*	3.15 ± 0.90*	3.47 ± 0.96	3.06 ± 0.93	3.04 ± 0.85
Alanine aminotransferase (U/L)	19	16	17	20	18	16.7
	(12.20, 21.00)	(13.00, 23.00)	(12.00, 22.54)	(14.00, 27.00)	(12.40, 24.00)	(13.00, 20.50)
Blood urea nitrogen (mmol/L)	5.70(5.00, 6.03)	5.53(4.51, 6.61)	5.71(4.62, 6.90)	5.65(4.60, 7.90)	5.60(4.70, 6.71)	5.75(4.80, 7.00)

Creatinine (mmol/L)	68.00 ± 18.02	69.25 ± 24.60	70.41 ± 25.41	68.92 ± 18.30	72.99 ± 21.60	73.02 ± 24.20
Urine acid (mmol/l)	232.22 ± 91.30	274.06 ± 107.65	287.07 ± 117.74	294.75 ± 80.61	291.60 ± 82.47	291.41 ± 96.59
Framingham risk score (FRS)	20.75 ± 1.00	21.29 ± 1.44	21.41 ± 1.33	19.00 ± 1.96	20.09 ± 2.13	19.99 ± 2.15

N = number of individuals. Values are expressed as mean ± SD , median(Q1,Q3) or number (%). P statistical significance of the differences among the three groups. *-vs. DM group; †- vs. HTN group. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cho¬lesterol; FPG, fasting plas¬ma glucose; Hpg, 2-hour postprandial blood glucoseHbA1c, hemoglobin A1c; FRS, Framingham risk score.

Changes in patients' Framingham risk scores (FRS)

For patients in the medium Framingham risk strata, the FRS was significantly higher in the CVD and HTN groups than in the DM group at baseline and after 48 months of follow-up (both P<0.01). Interestingly, a significant change in the FRS from baseline to the 48-month follow-up score was not found in any of the 3 groups **(Table 2)**. In all 3 groups, the post-intervention FRS was significantly reduced compared with the baseline score (P<0.01 for each). Thus, while the FRS was significantly decreased at the end of 48 months of follow-up in the high Framingham risk strata, this correlation was not detected in either the low or medium Framingham risk strata.

All-cause endpoint events after 48 months of follow-up

During the 48-month follow-up period, there were a total of 85 endpoint events, 15 of which were attributed to a tumor and 13 to nephropathy. Among the total study population, valid follow-up information was available for 50 first cardiovascular events (including 25 strokes and 25 myocardial infarctions). In the 3 study groups, the cumulative cardiovascular event rate was 4.6% for the CVD group and 2.2% for HTN group. In comparison, the cumulative cardiovascular event rate was significantly lower in the DM group (1.1%; P<0.001). No first cardiovascular events were diagnosed only by ECG, as all had previously been diagnosed clinically.

Factors analysis was performed to explore the variables contributing to the incidence of endpoint events **(Table 4)**. In the initial regression model, age and gender were considered as potential confounding factors. In the multivariate analyses that were controlled for age and clustering by clinic, patients in the CVD and HTN groups had a higher incidence of endpoint events than those in the DM group (HR 16.497, 95% CI 2.378−11.965; and HR 4.117, 95% CI 1.030−5.506, respectively).

Table 4 Cox regression for factors influenced events of BCDS study.

	b	Se	Wald x	P	HR	95%CI for HR	
						Lower	Upper
Model 1							
Group			21.147	0			
HTN vs. DM	0.868	0.428	4.117	0.042	2.381	1.03	5.506
CVD vs. DM	1.674	0.412	16.497	0	5.334	2.378	11.965
Model 2							
Age	0.667	0.162	16.859	0	1.948	1.417	2.677
Gender	-0.678	0.244	7.759	0.005	0.507	0.315	0.818
Group			11.341	0.003			
HTN vs. DM	0.656	0.431	2.315	0.128	1.927	0.828	4.486
CVD vs. DM	1.254	0.42	8.926	0.003	3.504	1.539	7.977

In a subanalysis of the effects of age and gender for the DM group versus the CVD and HTN groups, the 48-month HRs for endpoint events were 8.926 (95% CI 1.539-7.977) and 2.315 (95% CI 0.828−4.486), respectively **(Table 4)**.

Discussion

This longitudinal study lasted 48 months, and was based on the community-hospital integrated management of type 2 diabetes. All treatments administered in the BCDS were in accordance with national guidelines for type 2 diabetes mellitus in China. Furthermore, the regular clinical consultation by Professors in endocrinology from top tier hospitals is the most remarkably specialties. Based on co-operative between the systematically trained GPs and Professors in endocrinology, the multi-factorial intervention had been efficiently implemented during the last 48 months. And the Individualized management employing a variety of treatment options may contribute to improve patient-based compliance and reduce the drop-off rate.

Although around 3 million excess deaths a year are attributable to diabetes worldwide [5], there are few community-based research data available on diabetes management in developing countries, including China. The results of this study, which are similar to those of the Steno-2 study [6], provide novel data on the multifactorial

management of type 2 diabetes mellitus at a community level in China.

The mean HbA1c level in the patients in BCDS was decreased by 0.27%, and the mean FPG was decreased by 0.5 mmol/L over the 48-month follow-up period. The achievement of better glycemic control and better blood pressure and lipid profiles may be explained by the comprehensive interventions that were applied.

Some studies have found that approximately 75% of patients with type 2 diabetes are hypertensive [7]. In China, a report published in 2007 indicated that 34% of patients with type 2 diabetes had hypertension, which was especially prevalent in northern China [8]. In the present study, 70.8% of the BCDS participants had hypertension. These patients were more likely to be older, overweight, or obese. Although diabetes is itself a major cardiovascular risk factor, its presence increases the risk for other factors, particularly hypertension [9,10]. In the UKPDS study, tight blood pressure control in patients with hypertension and type 2 diabetes achieved a clinically important reduction in the risk of death and complications related to diabetes [11]. In Beijing communities, the prevalence of hypertension is high and the blood pressure control rate is low in patients with type 2 diabetes. Thus, the need for multi-risk factor control and effective community-based management for patients with type 2 diabetes and hypertension is clear.

Several follow-up studies have suggested that weight-change is the mechanism of the reduced incidence of diabetes [12]. The BCDS 2 study focused on the clinical characteristics of diabetic patients with metabolic syndrome (MS) and its components living in 15 urban communities in Beijing in 2011 [13]. From the viewpoint of the characteristics of diabetic patients, BMI data from the BCDS suggests that patients in the CVD and HTN groups were usually obese. In factor analyses performed to explore the variables contributing to the incidence of endpoint events, variables related to obesity were considered potential confounding factors.

Visceral adipose tissue (VAT) is recognized as a unique, pathogenic fat depot, conferring a metabolic risk above and beyond standard anthropometric measures such as BMI and WC [14]. As an index for upper-body subcutaneous adipose tissue distribution, NC seems suitable for use in a clinical setting as a strong indicator of central obesity and metabolic abnormalities in type 2 diabetes, and it has been evaluated in relation to cardiovascular risk factors [15,16]. At baseline, the CVD group in the present study showed a tendency towards a markedly higher NC than the DM group, both in the low Framingham risk strata and the medium Framingham risk strata ($P<0.01$-0.05). In the HTN group, the mean NC was significantly higher than in the DM group in the medium Framingham risk strata ($P<0.001$). The study's findings indicate that the reduction in NC seen during the 48-month active intervention period persisted. Even when differences in the above mentioned variables were taken into account, surprisingly, the trend for an increased NC and an increased incidence of CVD persisted in the CVD group. This correlation is important as it can shed some light on the pathogenesis of cardiovascular disease and merits further long-term research.

As complications related to cardiovascular diseases are still a very important health problem, the FRS has become a widely used method to predict the occurrence of CVD over a 10-year period [17] and its usefulness in this regard has been demonstrated [18]. Studies have also shown that the higher the risk for developing CHD, the greater the efficacy of the intervention that is needed. Several primary prevention trials have demonstrated a significant effect of interventions on cardiovascular events in patients with lower risk scores [19].

In our study, participants in the CVD group were more likely to be older, have a longer duration of diabetes, and higher blood pressure than those in DM group. At baseline and at the end of 48 months of follow-up, the FRS was lower in the DM group than in the CVD or HTN groups ($P<0.001$) in the medium Framingham risk strata. After 48 months of follow-up, no significant increase in the FRS was evident in the low and medium Framingham risk strata in comparison with baseline levels. However, a significant reduction in the FRS after 48 months of follow-up was found in the high Framingham risk strata. Thus, it is likely that a multifactorial intervention for CVD risk factors will have a positive, long-term effect on the FRS in type 2 diabetes patients in the community, especially those in the high Framingham risk strata.

Despite the effects of multifactorial interventions on the FRS, we detected an increased incidence of cardiovascular events during the 48-month follow-up period. The cumulative CVD event rate was significantly higher in the CVD and HTN groups than in the DM group. In the Cox regression analysis that was applied for factors influencing endpoint events, after adjusting for several important confounders, age and gender were found to be associated with endpoint events. The observation that CVD events seem to have a reduced incidence in people who had received specific interventions during the follow-up period is encouraging.

The study was a prospective one, and the dataset used for the analyses has considerable strength. A large, ethnically-diverse community population was enrolled, detailed clinical and metabolic characterization of the cohort was able to be achieved, and the important data were centralized and tested in a central laboratory.

As the study was based on a selected population, it has some limitations. Patients with a non-first CVD were mainly treated in accordance with national guidelines for CHD which resulted in lifestyle and body weight changes. However, if the associations that we observed between NC and cardiovascular disease are confirmed in future studies in first-time CVD patients, a higher NC could serve as a risk stratification tool for cardiovascular disease in patients with diabetes mellitus.

Conclusion

In summary, this study has demonstrated for the first time, the relationship between NC and cardiovascular disease in Chinese patients with type 2 diabetes. Increased blood

pressure, abnormal lipid profiles and elevated plasma glucose concentrations were highly significantly associated with CVD in this population. Moreover, it was evident that the FRS was useful for estimating the beneficial effects of multifactorial treatments in the DM, HTN and CVD groups. Especially in diabetic patients with a risk score above 20%, multifactorial treatment could be effective in improving the FRS. Thus, multifactorial interventions for CVD risk factors in the community are important to reduce the incidence of endpoint events in Chinese diabetic patients with hypertension or CVD. Certain groups of patients may benefit from FRS score estimate to help us aiding decision making regarding overall risk reduction. Hence, we suggest the use of FRS score to stratify patients' CVD risk when analyzing the efficacy of management at regular intervals. Aggressive risk reduction should be focused on these individuals who had high FRS score.

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References

1. Diabetes Prevention Program Research Group (2002) Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 346: 393-403.
2. Li G, Zhang P, Wang J, Gregg EW, Yang W, et al. (2008) The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. Lancet 371: 1783-1789.
3. Xu J, Wei WB, Yuan MX, Yuan SY, Wan G, et al. (2012) Prevalence and risk factors for diabetic retinopathy: the Beijing Communities Diabetes Study 6. Retina 32: 322-329.
4. Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, et al. (1998) Prediction of coronary heart disease using risk factor categories. Circulation 97: 1837-1847.
5. Jafar TH, Haaland BA, Rahman A, Razzak JA, Bilger M, et al. (2013) Non-communicable diseases and injuries in Pakistan: strategic priorities. Lancet 381: 2281-2290.
6. Gaede P, Lund-Andersen H, Parving HH, Pedersen O (2008) Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 358: 580-591.
7. Escobar C, Barrios V (2009) Diabetes and hypertension: which is the best approach? Expert Rev Cardiovasc Ther 7: 269-271.
8. Qi W, Pan C, Lin S (2007) A survey of factors influencing prognosis and control rate for patients with hypertension in mainland China. Chin J Cardiol 35: 457-460.
9. Gillespie EL, White CM, Kardas M, Lindberg M, Coleman CI (2005) The impact of ACE inhibitors or angiotensin II type 1 receptor blockers on the development of new-onset type 2 diabetes. Diabetes Care 28: 2261-2266.
10. Bell DS (2000) Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. N Engl J Med 343: 580.
11. Turner R (1998) Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 317: 703-713.
12. Penn L, White M, Lindström J, Boer A, Blaak E, et al. (2013) Importance of weight loss maintenance and risk prediction in the prevention of type 2 diabetes: analysis of European Diabetes Prevention Study RCT. PLoS One 8: e57143.
13. Fu H, Yuan S, Wan G (2011) Clinical characteristics of diabetic patients with metabolic syndrome and its components at 15 urban communities in Beijing. Chin J Gen Practitioners 10: 390-393.
14. Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, et al. (2007) Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. Circulation 116: 39-48.
15. Yang GR, Yuan SY, Fu HJ, Wan G, Zhu LX, et al. (2010) Beijing Community Diabetes Study Group: Neck circumference positively related with central obesity, overweight, and metabolic syndrome in Chinese subjects with type 2 diabetes: Beijing Community Diabetes Study 4. Diabetes Care 33: 2465-2467.
16. Preis SR, Massaro JM, Hoffmann U, D'Agostino RB, Levy D, et al. (2010) Neck circumference as a novel measure of cardiometabolic risk: the Framingham Heart study. J Clin Endocrinol Metab 95: 3701-3710.
17. Pagano E, Gray A, Rosato R, Gruden G, Perin PC, et al. (2013) Prediction of mortality and macrovascular complications in type 2 diabetes: validation of the UKPDS Outcomes Model in the Casale Monferrato Survey, Italy. Diabetologia 56: 1726-1734.
18. Ryoo JH, Cho SH, Kim SW (2012) Prediction of risk factors for coronary heart disease using Framingham risk score in Korean men. PLoS One 7: e45030.
19. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, et al. (1998) Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA 279: 1615-1622.