Diabetes and 15-year Cardiovascular Mortality in a Chinese Population: Differential Impact of Hypertension and Metabolic Syndrome

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Background: It remains unclear if the risk for cardiovascular (CV) mortality in patients with diabetes mellitus (DM) is equivalent to that in patients with a history of cardiac disease in Asian populations. The aims of the present study were to investigate whether or not non-heart disease (HD) DM subjects have a similar risk of CV mortality as HD patients without DM (non-DM HD), and whether or not hypertension (HT) or metabolic syndrome (MS) is a CV mortality marker for diabetic subjects identified from a community-based population.

Methods: We followed 11,058 Chinese people aged ≥ 30 years on Kinmen island for a median of 15.0 years.

Results: The age-, sex- and smoking-adjusted hazard ratios for CV mortality were 3.56 [95% confidence interval (CI): 1.99–6.36] for DM subjects with HD, 1.64 (95% CI: 1.25–2.16) for DM without HD (non-HD DM) subjects, and 1.63 (95% CI: 1.09–2.44) for non-DM HD patients, when compared with subjects without DM and HD. Among the 827 non-HD DM subjects identified at the baseline survey, the age-, sex- and smoking-adjusted hazard ratios for CV mortality were 2.36 (95% CI: 1.30–4.28) for the presence versus absence of HT, and 1.23 (95% CI: 0.65–2.34) for the presence versus absence of MS.

Conclusion: Non-HD DM subjects had a similar risk of CV mortality to non-DM HD subjects in this Chinese population. The presence of HT but not MS substantially increased CV mortality risk in the DM subjects. [*J Chin Med Assoc* 2010;73(5):234–240]

Key Words: cardiovascular mortality, cardiovascular risk equivalent, diabetes mellitus

Introduction

Diabetes mellitus (DM) has long been recognized as a major risk factor of cardiovascular (CV) morbidity and mortality.[1] DM subjects suffer at least 2 times more coronary heart disease (HD) and ischemic stroke mortality than subjects without DM.[2] DM subjects without a prior history of myocardial infarction at baseline may be equivalent to nondiabetic subjects with prior myocardial infarction in terms of future risk for fatal and nonfatal myocardial infarction.[3] Therefore, recent guidelines have recommended aggressive targets for blood pressure control and management of dyslipidemia in all DM patients, as in patients with established coronary HD.[4,5] However, the novel concept that DM is a coronary HD equivalent has not always been supported by subsequent epidemiological studies,[6–9] and a recent meta-analysis showed that DM subjects without prior myocardial infarction have a 43% lower risk of developing total coronary HD events compared with nondiabetic subjects with prior myocardial infarction.[2] Furthermore, it remains unclear if the concept extends to other CV outcomes and applies to Asian populations. We hypothesized that DM is equivalent to a prior history of HD in the prediction of CV mortality in Chinese, and that the risk of CV mortality in DM subjects can further be stratified by the presence of hypertension (HT) and metabolic syndrome (MS).

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Therefore, the aims of the present study were to investigate whether or not DM patients without prior HD have a similar risk of CV mortality as HD without MD (non-DM HD) patients, and whether or not the presence of HT or MS enhances CV mortality risk in DM subjects identified from a community-based population of homogeneous Chinese.

Methods

Baseline surveys for all residents over 30 years of age in Kinmen County of Taiwan were performed during the period of 1991–1995, with an overall response rate of 62.5%, based on a target population of 20,185 by household registration.[10,11] For the present study, subjects with missing information in any 1 of the components of MS were excluded; the baseline characteristics stratified by the presence or absence of DM and HD for the final 11,058 eligible study subjects are presented in Table 1.

Details of the data collection in the surveys have been previously reported.[10,11] Briefly, demographic and clinical parameters were collected during face-to-face interviews with structured questionnaires. Anthropometric measurements including body weight, height, and waist circumference were carried out with the subjects wearing light clothing and no shoes. Three blood pressure measurements separated by at least 5 minutes from the right arm of subjects after they were seated for at least 5 minutes were taken manually using a mercury sphygmomanometer and a standard-sized cuff by well-trained medical students or public health nurses. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. All participants were volunteers and had given consent to participate in this survey. However, no written consent forms were obtained from the participants.

Overnight fasting serum and plasma samples were drawn for glucose, lipids, and other biochemical measurements. Serum triglycerides were measured by automated enzymatic methods with a Hitachi auto-analyzer (Hitachi, Tokyo, Japan) and Boehringer Mannheim Diagnostics (Mannheim, Germany) reagents. Serum high-density lipoprotein cholesterol was measured using a precipitation method (Kodak Ektachem HDL Cholesterol kit; Eastman Kodak, Rochester, NY, USA). Plasma glucose concentrations were determined by a hexokinase/glucose-6-phosphate dehydrogenase method (Gilford Glucose HK Reagent kit; Gilford Systems, Oberlin, OH, USA). DM was defined as fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L) or on drug treatment for DM.[12] HD was defined by a "yes" response to the questionnaire of "Do you have HD?". HT was defined as a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or being on drug treatment for HT.[4] MS was defined when ≥ 3 of the following 5 components were present:[13] (1) waist circumference ≥ 90 cm in men and ≥ 80 cm in women;[14] (2) triglyceride levels ≥ 1.7 mmol/L (150 mg/dL); (3) high-density lipoprotein cholesterol levels < 1.0 mmol/L (40 mg/dL) in men and < 1.3 mmol/L (50 mg/dL) in women; (4) systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, or on drug treatment for HT; (5) fasting glucose ≥ 5.5 mmol/L (100 mg/dL) or on drug treatment for DM. Cigarette smoking was defined by "yes" to the question of "Do you have a habit of smoking?".

The dates and causes of death for those who died within a median of 15.0 years after the baseline survey were collected for all of the 11,058 participants by linking our database with the National Death Registry through a unique personal identification number. Participants who were not present in the National Death Registry at the study time point were considered as surviving. The National Death Registry database registers valid death information based on the certified death certificates for every Taiwanese person who has been given a unique and life-long personal identification number. The death certificates were coded according to the International Classification of Disease, Ninth Revision (ICD-9). The relevant ICD-9 codes used for CV death were 390–459.

Statistical analysis

Data are presented as mean ± standard deviation. The Student's t test and χ^2 test were used for between-group comparisons when appropriate. Mortality rates were calculated by dividing the number of deaths by the person-years of observation. The period of observation was defined as the interval between the baseline survey and the date of death or the last entry date of the National Death Registry when surviving. The Cox proportional hazards model was used to estimate the relative risks of mortality, adjusting for covariates. The covariates included age, sex and smoking, since smoking is a well established risk factor of CV disease. The percentages of current smoking differed significantly among all groups ($p = 0.0218$). The Kaplan-Meier estimate and log-rank test were used to preliminarily compare survival curves of all-cause and CV mortality for the subgroups. All statistical significance was set at $p < 0.05$. Statistical analyses were performed using the statistical package SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

Table 1. Baseline characteristics of participants stratified by diabetes mellitus and heart disease in 1991–1995 surveys*

Variables	DM and HD ($n=76$)	Non-HD DM					Non-DM HD ($n=415$)	No DM or HD ($n=9,740$)
		DM + HT + MS ($n=389$)	DM + HT ($n=89$)	DM + MS ($n=195$)	DM alone ($n=154$)	Total ($n=827$)		
Age (yr)	61.8 ± 10.3	60.3 ± 11.7†	58.5 ± 11.1†	56.8 ± 12.1†	53.5 ± 11.5	58.0 ± 11.9	55.1 ± 12.8‡	48.4 ± 13.0
Male sex	31.6	35.6†	82.0†	33.3†	50.0	44.1	42.4	44.4
WC (cm)	91.7 ± 10.7	92.4 ± 9.2†	82.4 ± 5.7	92.5 ± 8.5†	82.8 ± 8.9	89.6 ± 9.7	85.6 ± 10.7‡	82.4 ± 9.8
BMI (kg/m^2)	26.2 ± 4.2	25.9 ± 3.3†	22.5 ± 2.7	26.0 ± 3.2†	22.8 ± 2.9	25.0 ± 3.4	23.8 ± 3.5‡	23.2 ± 3.3
TG (mg/dL)	146.4 ± 92.8	161.6 ± 107.0†	88.1 ± 29.1	158.5 ± 93.1†	89.8 ± 50.8	139.6 ± 95.1	97.5 ± 65.9‡	88.1 ± 54.6
HDL-C (mg/dL)	48.3 ± 12.9	48.4 ± 16.0†	60.4 ± 19.1	46.2 ± 13.8†	60.0 ± 18.1	51.3 ± 17.2	54.2 ± 16.3‡	56.2 ± 16.9
LDL-C (mg/dL)	138.3 ± 44.0	144.5 ± 44.2†	135.7 ± 40.3	140.2 ± 40.9	134.3 ± 40.0	140.6 ± 42.3	132.8 ± 44.6‡	126.9 ± 36.8
CHOL (mg/dL)	215.5 ± 50.9	223.1 ± 47.1†	213.7 ± 41.5	217.5 ± 46.2	211.4 ± 42.5	218.6 ± 45.7	205.5 ± 48.1‡	200.2 ± 38.3
SBP (mmHg)	148 ± 23	157 ± 18†	154 ± 17†	126 ± 10†	120 ± 11	143 ± 22	136 ± 24‡	128 ± 20
DBP (mmHg)	87 ± 15	91 ± 14†	91 ± 11†	77 ± 9	75 ± 8	85 ± 14	82 ± 14‡	80 ± 12
FPG (mg/dL)	152.3 ± 44.1	166.1 ± 55.1	151.1 ± 60.7	161.4 ± 65.8	163.9 ± 65.4	163.0 ± 60.4	95.4 ± 12.2‡	94.6 ± 12.9
MS	84.2	100	0	100	0	70.6	29.9‡	20.7
HT	59.2	100	100	0	0	57.8	46.0‡	30.9
Smoking	18.4	21.3	39.3	23.6	30.5	25.5	18.1‡	23.4

**Data presented as mean ± standard deviation or %; †$p<0.05$ for comparison with the subgroup of DM alone; ‡$p<0.05$ for comparison between people with non-HD DM and those with HD non-DM. DM = diabetes mellitus; HD = heart disease; HT = hypertension; MS = metabolic syndrome; WC = waist circumference; BMI = body mass index; TG = triglycerides; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; CHOL = total cholesterol; SBP = systolic blood pressure; DBP = diastolic blood pressure; FPG = fasting plasma glucose.*

Results

There were 903 (8.17%) subjects with DM and 491 (4.44%) subjects with self-reported HD at baseline. The mean values of waist circumference, BMI, triglycerides, systolic blood pressure, diastolic blood pressure, and the percentages of MS and HT were decreased in the following 4 subgroups: (1) DM and HD ($n=76$); (2) subjects with DM but without HD [(non-HD DM), $n=827$]; (3) HD but without DM ($n=415$); and (4) without either DM or HD ($n=9,740$) (Table 1, all $p<0.05$ for trend). The mean values of high-density lipoprotein cholesterol were increased for the 4 subgroups ($p<0.05$).

Subjects with DM but without HD had a significantly older age, greater waist circumference and BMI, higher levels of total cholesterol, triglycerides, low-density lipoprotein cholesterol, and fasting plasma glucose, and higher systolic and diastolic blood pressure, prevalence of HT and smoking, and lower high-density lipoprotein cholesterol than did subjects with HD and non-DM (Table 1).

Among subjects with DM and non-HD, 4 subgroups were defined according to the presence or absence of HT and MS. The subgroup of DM + HT had a significantly older age, more males, and higher systolic and diastolic blood pressure than the subgroup of DM alone. In contrast, the subgroup of DM + MS had a significantly older age, more males, greater waist circumference and BMI, higher levels of triglycerides, higher systolic blood pressure, and lower high-density lipoprotein cholesterol levels than the subgroup of DM alone (Table 1).

There were 1,660 total deaths (10.83 per 1,000 person-years) and 369 CV deaths (2.41 per 1,000 person-years) during the follow-up period (median: 15.0 years). Men had higher total (13.64 *vs.* 8.67 per 1,000 person-years, $p<0.0001$) and CV (2.70 *vs.* 2.19 per 1,000 person-years, $p=0.0418$) mortality than women.

The 4 groups of DM and HD, DM and non-HD, HD and non-DM, and non-DM and non-HD had decreased total ($p<0.0001$) and CV ($p<0.0001$) mortality (Table 2). The survival curves of CV death for the 4 groups were significantly different (p value of log-rank test <0.0001). Compared with the group of non-DM and non-HD, the other 3 groups of DM and HD, DM and non-HD, and HD and non-DM had significantly increased hazard ratios for total and CV mortality, with or without adjustment for age, sex, and smoking (Table 2). Compared with the group of HD and non-DM, the groups of DM and HD, and DM and non-HD had significantly increased adjusted hazard ratios for total mortality (Table 2). In contrast, compared with the group of HD and non-DM, the group of DM and HD, but not the group of DM and non-HD, had significantly increased adjusted hazard ratios for CV mortality (Table 2).

We also carried out an analysis for the event of coronary artery disease (CAD) mortality (ICD-9 codes: 410–414). Because the case numbers of CAD mortality were very small ($n=58$), the calculated hazard ratios for CAD mortality were extremely unstable [DM and HD: 1.12 (CAD = 1); DM and non-HD: 1.42 (CAD = 15); HD and non-DM: 0.18 (CAD = 1); non-DM and non-HD: 0.30 (CAD = 41)]. The between-group

Table 2. Total and cardiovascular mortality and hazard ratios according to the status of diabetes mellitus and heart disease at baseline*

	DM and HD ($n=76$)	Non-HD DM ($n=827$)	Non-DM HD ($n=415$)	No DM or HD ($n=9,740$)
PY	894	10,555	5,642	136,135
Total deaths	29	263	89	1,279
Total mortality, 1/1,000 PY	32.4	24.9	15.8	9.4
cHR (95% CI)	**3.46 (2.39–5.00)**	**2.66 (2.33–3.04)**	**1.68 (1.35–2.08)**	1.0 (reference)
aHR (95% CI)	**2.04 (1.41–2.96)**	**1.62 (1.42–1.86)**	**1.26 (1.01–1.56)**	1.0 (reference)
aHR (95% CI)	**1.61 (1.06–2.46)**	**1.30 (1.02–1.66)**	1.0 (reference)	
aHR (95% CI)	1.21 (0.82–1.79)	1.0 (reference)		
CV deaths	12	64	26	267
CV mortality, 1/1,000 PY	13.4	6.1	4.6	2.0
cHR (95% CI)	**7.00 (3.92–12.48)**	**3.14 (2.39–4.12)**	**2.35 (1.57–3.52)**	1.0 (reference)
aHR (95% CI)	**3.56 (1.99–6.36)**	**1.64 (1.25–2.16)**	**1.63 (1.09–2.44)**	1.0 (reference)
aHR (95% CI)	**2.10 (1.05–4.17)**	1.04 (0.66–1.65)	1.0 (reference)	
aHR (95% CI)	**2.02 (1.08–3.78)**	1.0 (reference)		

**Numbers in bold indicate statistical significance. DM = diabetes mellitus; HD = heart disease; PY = person-years; cHR = crude hazard ratio; CI = confidence interval; aHR = hazard ratio adjusted for age, sex, and smoking; CV = cardiovascular.*

differences of CAD mortality rate did not reach statistical significance.

The 4 subgroups of DM + HT + MS, DM + HT, DM + MS, and DM alone had decreased CV mortality ($p = 0.0004$; Table 3, Figure 1A). Compared with the subgroup of DM alone, the subgroups of DM + HT + MS and DM + HT but not DM + MS had significantly increased hazard ratios for total and CV mortality (Table 3). The increased hazard ratios for total and CV mortality became non-significant when adjusted for age, sex, and smoking status (Table 3).

When the 827 non-HD DM subjects were stratified only by HT, subjects with DM with HT had significantly increased adjusted hazard ratios for total (1.59; 95% CI = 1.21–2.09) and CV (2.36; 95% CI = 1.30–4.28) mortality when compared with subjects with DM but without HT. The Kaplan-Meier estimate and log-rank test for CV mortality are shown in Figure 1B. In contrast, when the non-HD DM subjects were stratified only by MS, subjects with DM with MS had similar adjusted hazard ratios for total mortality (0.95; 95% CI = 0.71–1.26) and non-significantly increased CV mortality (1.23; 95% CI = 0.65–2.34) when compared with subjects with DM but without MS. The Kaplan-Meier estimate for CV mortality was not significant (log-rank test p value = 0.1039).

Table 3. Total and cardiovascular mortality and hazard ratios in subjects with diabetes mellitus and no heart disease according to the status of hypertension and metabolic syndrome at baseline*

	DM + HT + MS ($n = 389$)	DM + HT ($n = 89$)	DM + MS ($n = 195$)	DM alone ($n = 154$)
PY	4,805	1,085	2,591	2,074
Total deaths	152	36	40	35
Total mortality, 1/1,000 PY	31.6	33.2	15.4	16.9
cHR (95% CI)	**1.99 (1.31–2.74)**	**1.99 (1.25–3.17)**	0.92 (0.58–1.44)	1.0 (reference)
aHR (95% CI)	1.32 (0.90–1.92)	1.55 (0.97–2.49)	0.76 (0.48–1.20)	1.0 (reference)
CV deaths	42	8	9	5
CV mortality, 1/1,000 PY	8.7	7.4	3.5	2.4
cHR (95% CI)	**3.70 (1.46–9.34)**	**3.14 (1.03–9.59)**	1.44 (0.48–4.28)	1.0 (reference)
aHR (95% CI)	2.44 (0.95–6.26)	2.82 (0.91–8.76)	1.09 (0.36–3.29)	1.0 (reference)

**Numbers in bold indicate statistical significance. DM = diabetes mellitus; HT = hypertension; MS = metabolic syndrome; PY = person-years; cHR = crude hazard ratio; CI = confidence interval; aHR = hazard ratio adjusted for age, sex, and smoking; CV = cardiovascular.*

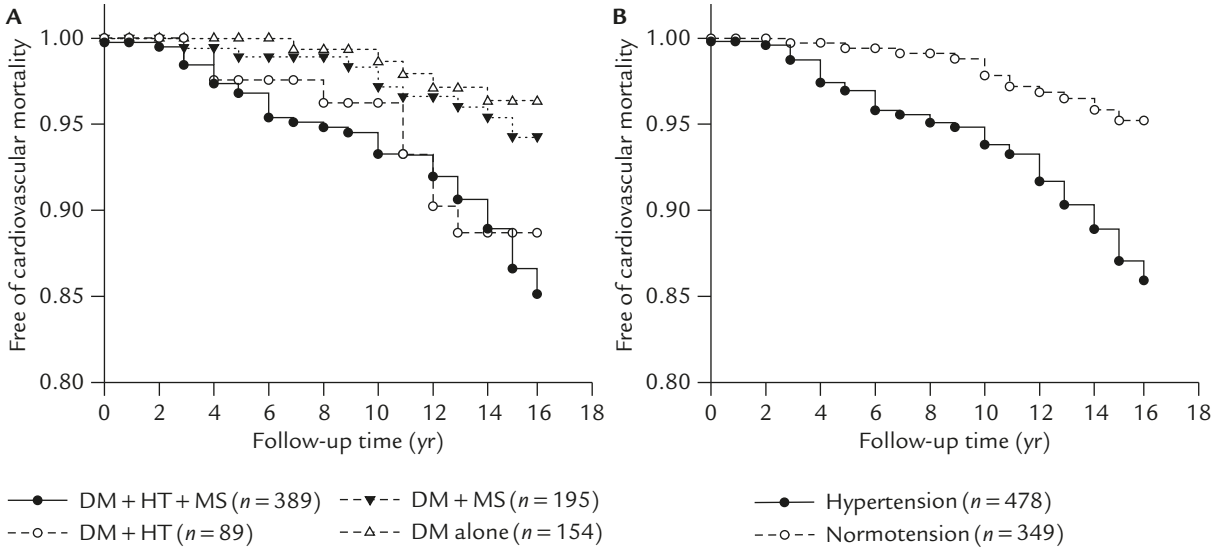

Figure 1. (A) Survival curves of cardiovascular mortality among 827 subjects with diabetes mellitus (DM) and no heart disease stratified by the presence or absence of hypertension (HT) and metabolic syndrome (MS). (B) Differential impact of HT on the survival functions of cardiovascular mortality in subjects with DM and no heart disease.

Discussion

In the present community-based study, subjects with DM without self-reported HD had a similar adjusted risk of CV mortality as subjects with self-reported HD without DM. This finding indicates that DM imposes a risk of CV mortality equivalent to that for the self-reported HD in this homogeneous Chinese population. Among subjects with DM without self-reported HD, there appeared to be a gradient of risk for total and CV mortality, with the highest risk in the subgroup of DM + HT + MS, followed by DM + HT. The presence of HT but not MS substantially increased the risk of CV mortality in subjects with DM without self-reported HD.

Although there have been many studies investigating the role of DM as a CV disease equivalent, discrepant results have been reported because of differences in the characteristics of the study population, follow-up duration, criteria for the diagnosis of coronary HD or CV disease.[2] Briefly, studies in the Finnish population,[15] Scottish men,[16] and American women[17] suggested that patients with non-HD DM have a similar CV disease risk as non-DM HD patients. In contrast, the Atherosclerosis Risk in Communities study,[18] an Australian population-based study,[19] the Nurses' Health study,[20] the Physicians' Health study,[7] and the Health Professionals Follow-up study[21] indicated that patients with DM without a prior history of myocardial infarction have a lower risk of coronary HD events compared with patients with a history of myocardial infarction without DM. Although a recent meta-analysis involving 13 studies with 45,108 patients followed up for a duration of 5–25 years concluded that patients with DM without prior myocardial infarction have a 43% lower risk of developing total coronary HD events compared with patients without DM but with previous myocardial infarction, the meta-analysis findings cannot be extrapolated to Asian populations because no relevant Asian studies were included in the meta-analysis.[2]

Our study clearly shows that a self-reported HD increases the risk of CV mortality in subjects with DM, and the CV mortality risk varies substantially in subjects with non-HD DM, according to the presence of HT and MS. It has been recognized that in females, DM confers a greater risk of coronary HD risk than in males,[22] and the risk increases with the duration of DM.[20] The coronary HD risk may begin to exceed that of prior myocardial infarction after 15 years of DM.[20] Therefore, it is clear that not all patients with DM have an equivalent risk of future CV disease, and that it may not be justified to treat all patients with DM as a secondary prevention, especially when resources of health care are limited.[2]

To determine CV disease risks in patients with DM, individual risk assessment may be necessary.[2] In the present study, the presence of HT substantially increased the risks of total and CV mortality in subjects with non-HD DM. Therefore, HT may be considered as a simple and useful marker to stratify risk for these patients.[23] In contrast, the presence of MS may not substantially increase the risks of total and CV mortality in subjects with non-HD DM. Although an increasing prevalence of MS is expected in Asian populations,[24] our previous study suggested that the development of HT and/or DM is a necessary step before MS causes CV mortality.[25]

The limitations of the present study are as follows. Subjects with or without HD were categorized based on a questionnaire. The general public does not know exactly what HD is and usually considers HD a serious disease diagnosed only by a physician. Most subjects who label themselves as having "HD" may have obtained this impression from some medical professionals. Most people who do not know about HD or are not sure if they have HD may simply pick the answer "I don't know". Therefore, a self-reported history of "HD" usually implies the presence of certain heart problems that may increase the risk of CV mortality. In our community surveys, the reply of the presence of HD from participants might actually imply the presence of certain heart problems previously suggested or diagnosed by a medical professional. Although the diagnosis of HD was not specified in the questionnaire and not ascertained by medical records, the results clearly demonstrated that subjects with self-reported HD but without DM had a significantly increased risk for total and CV mortality compared with subjects without DM or HD. Furthermore, we also observed that the presence of self-reported HD significantly increased the risk for CV mortality in subjects with DM.[20]

In the present study, the diagnosis of DM was based on fasting plasma glucose and a history of medication used to facilitate the field work. This approach might have led to slightly lower estimates of prevalence than would be obtained from the combined use of fasting plasma glucose and the oral glucose tolerance test.[26] A long duration of DM is associated with dramatically increased risks of death from all causes and fatal CAD.[20] Because the duration of DM was not available, we were not able to assess its impact on all-cause and CV mortality.

In conclusion, non-HD DM subjects have similar risks of CV mortality to non-DM HD subjects in a

Chinese population. The presence of HT but not MS substantially increases CV mortality risk in DM subjects.

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