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Association between diabetes mellitus and cirrhosis mortality: The Singapore Chinese Health Study

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Abstract

Background and Aim—Diabetes mellitus has been linked to liver cirrhosis-related mortality in Western populations, but less is known about this relationship in Asian populations. We studied the impact of diabetes on the risk of cirrhosis mortality in a population-based cohort among Chinese in Singapore.

Methods—We used data collected and analysed from the Singapore Chinese Health Study, a prospective community based cohort of 63,275 subjects aged 45 to 74 years during enrolment between 1993 and 1998. Information on diet, lifestyle and medical history was collected via structured questionnaire. Mortality cases from cirrhosis in the cohort were identified via linkage with nationwide death registry up to 31 December 2014. Cox proportional regression models were used to estimate the associations with adjustment for risk factors of cirrhosis.

Results—After a mean follow-up of 16.9 years, there were 133 deaths from cirrhosis. Diabetes was associated with an increased risk of cirrhosis mortality [hazard ratio (HR): 2.80; 95% confidence interval (CI): 2.04-3.83], and for both viral (HR: 2.20; 95% CI: 1.18-4.11) and non-

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Contributions of authors

The authors declare the following contributions to the preparation of the manuscript study: conception and design (WPK and GGB), acquisition of data (WPK and JMY), data analysis (WPK and GGB), interpretation of data (all authors), drafting of intellectual content (all authors) and final approval of manuscript (all authors). GGB and WPK take responsibility for the integrity of the work as a whole.

viral hepatitis related cirrhosis mortality (HR: 3.06; 95% CI: 2.13-4.41). The association between diabetes and non-viral hepatitis-related cirrhosis mortality was stronger among participants of body mass index less than 23 kg/m^2 (HR: 7.11; 95% CI: 3.42-14.79) compared to heavier individuals (HR: 2.28; 95% CI: 1.20-4.35) ($P_{interaction}$=0.02).

Conclusion—Diabetes is a risk factor for cirrhosis mortality, especially for non- viral hepatitis related cirrhosis in population with body mass index considered low or normal in Asia.

Keywords

Diabetes mellitus; cirrhosis mortality; body mass index; Singapore

Introduction

Type 2 diabetes mellitus has become an increasingly prevalent disease with 415 million people estimated to be affected in 2015 and anticipated to rise to 642 million people in 2040 (1)(2). Emerging evidence suggests that diabetes and liver disease often coexist and are correlated (3). Compared to the general population, patients with chronic liver disease/ cirrhosis have a higher prevalence of diabetes (4). Chronic hepatitis C patients with diabetes have increased risk for fibrosis and poorer response to treatment for hepatitis C compared to patients without diabetes (5, 6). Furthermore, between 40 to 70% of patients with diabetes have non-alcoholic fatty liver disease [NAFLD] (7), and are at increased risk of subsequent non-alcoholic steatohepatitis [NASH], advanced fibrosis and cirrhosis (8, 9). In a cohort of NAFLD patients, liver related mortality in patients with diabetes was about 20 times relative to those without diabetes (8). Other studies based on Western cohorts of patients with diabetes have demonstrated a two to three-fold increased risk in liver related mortality compared to general population (10, 11). On the other hand, less is known about the relationship between diabetes and liver-related mortality in Asian populations, where infection due to hepatitis B or C virus remain the most important risk factor for liver cirrhosis (12, 13). Given that Asia remains one of the major epicentres of the diabetes epidemic, the evaluation of the relationship between diabetes and liver related mortality in Asia takes on added urgency (14). In our study, we explored the impact of diabetes on the risk of cirrhosis mortality in a population-based cohort of Chinese participants in Singapore.

Materials and Methods

Study population

We analysed data from the Singapore Chinese Health Study [SCHS], which has been previously described (15). In summary, the study was a population-based prospective cohort established from April 1993 to December 1998. A total of 63,257 participants between the ages of 45 and 74 years (about 85% of eligible participants approached) were enrolled. They were drawn from permanent residents or citizens of Singapore who resided in the government-built housing estates, which entailed 86% of the Singapore population who resided in such facilities during the recruitment period. Recruitment was restricted to the two major dialect groups of Chinese in Singapore, the Hokkiens and the Cantonese. The study

was approved by the Institutional Review Board of the National University of Singapore and written informed consent was obtained from each participant.

Assessment of diabetes status and other characteristics

At recruitment, trained interviewers conducted an in-person interview with each participant in his/her home. Using a structured questionnaire, information encompassing demographics, weight, height, dietary information, lifetime use of tobacco, current physical activity, menstrual/reproductive history (for women), occupational exposure and family history of cancer was obtained. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. For those with missing weight and/or height, BMI was calculated using imputed weight and/or height derived from the linear regression equation: Weight = y-intercept + gradient × height, where values for the y-intercept and gradient were derived from gender-specific weight-height regression lines obtained from all cohort participants with known heights and weights (16). The participants were asked whether they had a history of physician-diagnosed diabetes during the interview, and positive respondents were then asked for their ages at time of diagnosis. The robustness and accuracy (98.9%) of the self-reported diabetes data in this cohort has been validated in a separate study analysing 1651 cohort participants (17).

A follow-up interview of the SCHS cohort was conducted between 1999 and 2004, and 83% of the original cohort was re-interviewed. Information on self-reported medical history (diabetes, coronary heart disease, and stroke), weight and height was obtained again using the same questions asked during the baseline interview at recruitment.

Ascertainment of mortality

Record linkage with the Singapore Registry of Births and Deaths allowed the identification of deaths among cohort members, with mortality data updated through December 31, 2014. In addition, as of December 31, 2014, only 52 subjects (0.08%) were known to be lost to follow-up due to migration out of Singapore or for other reasons. This suggests that emigration among the study population was negligible and that vital statistics at follow-up was virtually complete.

Underlying causes of death were coded according to the International Classification of Diseases, Ninth Revision. Code 070 was used for viral hepatitis-related mortality while code 571 was used for chronic liver disease and cirrhosis-related mortality. For all deaths identified with these two codes, all causes of death for each case, direct and contributing, were reviewed and verified by two gastroenterologists (GBB Goh, WC Chow). A total of 141 cirrhosis-related deaths were initially identified via the linkage. After excluding eight cases with a co-diagnosis of HCC identified via database linkage with the nationwide cancer registry, 133 cases of cirrhosis mortality were included as cases in this study.

Statistical analysis

For each study participant, person-years were counted from the date of baseline interview to the date of death, migration or 31 December 2014, whichever occurred first. Cox proportional hazards regression models were used to explore the relationship between

diabetes and cirrhosis mortality within the entire cohort. The magnitude of the associations was assessed by the hazard ratios (HRs), their corresponding 95% confidence intervals (CIs) and P values. All models adjusted for age at recruitment (year), year of study enrolment (1993-1995, 1996-1998), gender, dialect group (Hokkien, Cantonese), educational level (no formal education, primary school, secondary school or higher), BMI (kg/m^2, continuous), smoking status (never, former, current), alcohol intake (non/monthly, weekly, daily) and coffee consumption (less than daily, 1 cup/day, 2-3 cups/day, ≥4 cups/day). Since we had information about diabetes status and BMI at both baseline and follow-up interview for most of the participants (n=52,322), we included these two factors as time-varying covariates, in addition to baseline values of all other study covariates, in order to take into account changes in diabetes status and BMI at the follow-up visit. Subgroup analysis was performed for viral and non-viral hepatitis cirrhosis related deaths, and also for non-specified cirrhosis deaths. We further examined the diabetes-cirrhosis mortality association stratified by duration of diabetes and BMI subgroup at baseline (<23 and ≥23 kg/m^2). Heterogeneity of the diabetes-BMI subgroup risk association was tested using a product term between diabetes status and BMI subgroup in the Cox model.

Statistical computing was conducted using SAS version 9.1 (SAS Institute Inc., Cary, NC) statistical software package. All P values quoted were two-sided, and P values of <0.05 were considered statistically significant.

Results

There were 5,696 participants who reported history of diabetes mellitus at recruitment (9.0%). Compared to those without diabetes, participants with history of diabetes were older, more likely to be women, had higher BMI, and had lower level of education. They were also more likely to be ever smokers but less likely to be daily drinkers of alcohol or coffee (Table 1) There were 133 cirrhosis-related deaths identified from the study during mean follow-up of 16.9 years [standard deviation (SD) 5.1 years]. The mean age of death among cases of cirrhosis death was 68.6 (SD 9.4) years, and the mean follow-up period among cases was 9.3 (SD 5.4) years. Among these 133 cases, 34 cases (25%) had chronic hepatitis B, 2 cases had chronic hepatitis C (2%), 16 cases (12%) had chronic alcoholic liver disease and 3 cases (2%) had biliary cirrhosis. The rest of the 78 cases were classified as cryptogenic or unspecified cirrhosis (59%).

After adjusting for other risk factors of cirrhosis and potential confounders, including BMI categories, participants with a history of diabetes at baseline had an approximately three-fold risk of mortality from cirrhosis, and this association was materially unchanged in the analysis that included update of diabetes status and BMI using follow-up data (HR: 2.80; 95% CI: 2.04-3.83). The positive association between history of diabetes and cirrhosis mortality was present among both viral hepatitis related cases (HR: 2.20; 95% CI: 1.18-4.11) and non-viral hepatitis-related cases (HR: 3.06; 95% CI: 2.13-4.41). We further limited our analysis to cases with cryptogenic cirrhosis by excluding cases of alcoholic cirrhosis (16 cases), primary biliary cirrhosis (3 cases), viral hepatitis-B related cirrhosis (34 cases) and viral-hepatitis C related cirrhosis (2 case), and the association between diabetes and cryptogenic cirrhosis mortality remained (Table 2).

The mean BMI in the study population at baseline was 23.1 (SD 3.3); 48% of study participants had BMI<23 kg/m^2. Nonetheless, only 6.4% (3.1% among those with diabetes and 6.8% among those without diabetes) of this cohort could be considered underweight (BMI<18.5 kg/m^2). In the whole cohort analysis, a higher BMI≥23 kg/m^2 was associated with increased risk of death from cirrhosis compared to lower BMI. In stratified analysis, the increased risk with higher BMI was only observed in those without diabetes at baseline (HR: 1.53; 95% CI: 1.03-2.28), and only limited to non-viral hepatitis related or cryptogenic cirrhosis mortality (Table 3).

In the stratified analysis by BMI group (<23 and ≥23 kg/m^2) at baseline, although the approximately 2-fold increase in associations between diabetes and viral-hepatitis related mortality did not reach statistical significance in either groups, the risk estimates were not statistically different. Conversely, for non-viral hepatitis related or cryptogenic cirrhosis, diabetes was a much stronger risk factor with a higher risk estimate in participants with BMI<23 kg/m^2 than in participants with higher BMI (p for interaction <0.04). Specifically, the association between diabetes and risk of non-viral hepatitis related cirrhosis mortality among participants with BMI<23 kg/m^2 (HR: 7.11; 95% CI: 3.42-14.79) was much stronger than the association observed among those with BMI≥23 kg/m^2 (HR: 2.28; 95% CI: 1.20-4.35) (Table 4).

Finally, we examined the joint effect of BMI and diabetes at baseline on risk of cirrhosis mortality. For viral-hepatitis related mortality, although none of the risk estimates reached statistical significance due to small case numbers, higher BMI (≥23 kg/m^2) did not seem to be a risk factor and the association of diabetes between low/normal weight and heavier participants were similar. However, for non-viral hepatitis related cirrhosis, compared to low/normal weight subjects without diabetes, while participants with either higher BMI or baseline history of diabetes displayed significantly higher risk, the risk was essentially highest in low/normal weight subjects with diabetes (HR: 7.00; 95% CI: 3.42-14.30). The findings were similar when the analysis was limited to cryptogenic cirrhosis related mortality (Table 5).

Discussion

This study showed that diabetes was associated with a three-fold increase in risk of cirrhosis mortality among Chinese in Singapore, and this association was observed in both non-viral and viral hepatitis-related cirrhosis. Furthermore, the association between diabetes and non-viral hepatitis-related cirrhosis mortality was much stronger in participants with BMI <23 kg/m^2 compared to the heavier participants.

A few studies have shown that type 2 diabetes is associated with an increased risk of cirrhosis mortality. The Verona Diabetes Study, a population-based study of 7,148 participants with diabetes reported a 2.5-fold increase in mortality from chronic liver disease and cirrhosis after 5 years of follow-up compared to the general population (10, 18). The Freemantle diabetes study, based on 1,294 diabetic participants, also showed a 2-fold increase in risk of cirrhosis mortality (19). Small prospective cohort studies based in Japan and Mexico both observed that patients with concurrent cirrhosis and diabetes had

significantly higher mortality risk than patients who only had cirrhosis, and the predominant cause of death was either cirrhosis or hepatocellular carcinoma (20, 21). A separate study by Younossi et al reported that in NAFLD, patients with diabetes had higher all-cause and liver-related mortality risk compared to those without diabetes (8). The diabetes-cirrhosis mortality association in our study, which is the first analysis from a Chinese population, is thus consistent with the literature.

In our analysis, diabetes was a risk factor for both viral and non-viral related cirrhosis mortality, including cryptogenic cirrhosis. Diabetes has been proven to be an important risk factor for cirrhosis development, complications and liver – related mortality in both chronic hepatitis B and C cohorts (22-26). We assume that NAFLD would account for the majority of the participants in the non-viral or cryptogenic cirrhosis group, since it has been demonstrated in other population-based studies that NAFLD represents most of cirrhosis mortality in this group (11, 27, 28). NAFLD is characterised by insulin resistance and hepatic fat accumulation, with a spectrum of disease ranging from the relatively benign simple hepatic steatosis to the aggressive, more progressive non-alcoholic steatohepatitis [NASH] (29, 30). Diabetes doubles the risk of development of NAFLD compared to controls and, more importantly, is a strong predictor of NASH and advanced fibrosis/cirrhosis (8, 9, 31-33). The pathogenic pathways and mechanisms underlying the direct role of diabetes in liver injury have not been fully established (3). The core theory is that insulin resistance leads to up-regulation of pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α). This is accompanied by a corresponding down-regulation of insulin-sensitizing and anti-inflammatory cytokines such as adiponectin, and ultimately perpetuation of the inflammatory pathways and consequently liver injury (34). Moreover, hyperinsulinemia stimulates the activation and proliferation of hepatic stellate cells, which produce collagen required for hepatic fibrosis (35). Similarly, hyperglycemia and hyperinsulinemia has been shown to stimulate connective tissue growth factor synthesis in stellate cells, which has in turn been implicated in the development and progression of hepatic fibrosis (36).

Increased BMI is an established risk factor of NAFLD/NASH (37, 38). Similarly, even in this population that could be considered lean relative to Western population, we also observed a higher risk of cirrhosis mortality in those with higher BMI. However, interestingly, this increased risk with higher BMI was only observed in those without diabetes at baseline. An unexpected finding of our study is that the association between diabetes mellitus and cirrhosis mortality was stronger in participants with BMI <23 kg/m^2 as opposed to heavier subjects. The increased risk with diabetes was only observed in those who had lower BMI, and the participants who had normal/low BMI and history of diabetes concurrently turned out to the ones at highest risk of non-viral hepatitis related cirrhosis mortality. We have proposed four possible explanations for our observation. The first postulation is that earlier medical care and aggressive risk factor screening/treatment targeted on heavier participants with diabetes may have contributed to better outcomes. Secondly, others have suggested that normal weight or lean diabetics may have different pathogeneses or genetic profiles, which may be associated with a predilection for liver injury and phenotypically, a more aggressive liver disease progression (38-40). Thirdly, studies have also suggested that BMI is an imperfect surrogate marker for measurement of adiposity, as it cannot discriminate between lean body mass and fat mass. In these studies,

those with seemingly normal BMI could still have increased waist circumference, which is generally considered a better marker for visceral fat and more relevant to the pathogenesis of NAFLD (40-42). We postulate that this could be the case for those with diabetes. Finally, we cannot rule out that the diabetics who were lean in this population could have more problem with malnutrition or poorer control of their disease, and hence at higher risk of cirrhosis mortality. Nonetheless, only a small minority of our study population could be considered underweight.

The strengths of this study include the prospective study design in a population-based cohort with a long-term follow-up among cohort participants. Singapore is a small city-state with a system for easy access to specialized medical care. Robust data on causes of death were ascertained from the nationwide registry, where mortality assessment can be considered complete and reliable. However, there are a number of potential limitations in our study. First, non-differential misclassification in using self-report of physician-diagnosed diabetes status could potentially result in under estimating the effect of diabetes on cirrhosis mortality. Second, we did not have data on treatment of diabetes, including type of medications used or the adequacy of disease control. Indeed, some oral hypoglycemic agents such as the glitazones have been useful in the treatment of NAFLD (43). Third, viral hepatitis diagnosis were only ascertained from death records and may be under-reported, leading to an inadvertent inclusion of such cases in the non-viral hepatitis related group. This could again cause an underestimation the diabetes-cirrhosis mortality association, especially for non-viral hepatitis related cirrhosis.

In conclusion, the present study demonstrates a strong, positive association between diabetes and cirrhosis mortality. Paradoxically, diabetic patients who are of low/normal weight may be more prone to liver fibrosis and cirrhosis-related mortality than those with higher BMI. The findings of the present study bear important public health implication given a rapid increase in diabetes prevalence in developing countries of Asia where people have relatively low body weights. The impact of diabetes on cirrhosis mortality would be bigger in the developing countries than the developed world.

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List of abbreviations

HR	hazard ratio
CI	confidence interval
BMI	body mass index

NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
SCHS	Singapore Chinese Health Study
SD	standard deviation

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Key Points

- Diabetes mellitus is associated with a three-fold increased risk in mortality from cirrhosis.
- The relationship between diabetes mellitus and cirrhosis mortality is present for both viral and non-viral related etiologies.
- The association between diabetes and non-viral hepatitis-related cirrhosis mortality was stronger in participants with body mass index <23 kg/m^2 than their heavier counterparts.
- The findings of the present study bear important public health implication given a rapid increase in diabetes prevalence in developing countries of Asia where people have relatively low body mass index.

TABLE 1

Description of selected demographic and lifestyle characteristics by history of diabetes at baseline

	History of diabetes at baseline	No history of diabetes at baseline
Number of subjects	5,696	57,561
Age (year), mean (SD)	60.1 (7.7)	56.2 (8.0)
BMI (kg/m^2), mean (SD)	24.0 (3.3)	23.0 (3.3)
<18.5 kg/m^2, n (%)	178 (3.1)	3,901 (6.8)
18.5-22.9 kg/m^2, n (%)	1,880 (33.0)	24,407 (42.4)
≥23.0 kg/m^2, n (%)	3,638 (63.9)	29,253 (50.8)
Men, n (%)	2,425 (42.6)	25,529 (44.4)
Dialect, n (%)		
Cantonese	2,614 (45.9)	26,670 (43.6)
Hokkien	3,082 (54.1)	30,891 (53.4)
Level of education, n (%)		
No formal education	2,006 (35.2)	15,327 (26.6)
Primary school	2,502 (43.9)	25,548 (44.4)
Secondary school or above	1,188 (20.9)	16,686 (29.0)
Ever smoker, n (%)	1,825 (32.0)	17,502 (30.4)
Daily drinker of alcohol (%)	118 (2.1)	2,087 (3.6)
Daily coffee drinking (%)	3,649 (64.1)	40,792 (70.9)

Table 2

Diabetes in relation to risk of liver cirrhosis mortality

Characteristics	Person-year	Cases	HR (95% CI)[a]	HR (95% CI)[b]
All cirrhosis mortality				
No diabetes	987,885	105	1.00	1.00
Diabetes	78,179	28	3.01 (1.96-4.61)	2.80 (2.04-3.83)
Viral hepatitis related cirrhosis mortality (34 cases of HBV and 2 cases of HCV)				
No diabetes	987,885	31	1.00	1.00
Diabetes	78,179	5	1.89 (0.72-4.93)	2.20 (1.18-4.11)
Non-viral hepatitis related cirrhosis mortality				
No diabetes	987,885	74	1.00	1.00
Diabetes	78,179	23	3.47 (2.14-5.62)	3.06 (2.13-4.41)
Cryptogenic cirrhosis mortality[c]				
No diabetes	987,885	62	1.00	1.00
Diabetes	78,179	16	2.66 (1.52-4.67)	2.60 (1.73-3.89)

Hazard ratio (HR) adjusted for age at recruitment (year), year of study enrolment (1993-1995, 1996-1998), gender, dialect group (Hokkien, Cantonese) educational level (no formal education, primary school, secondary school or higher), smoking status (never, former, current), alcohol intake (non/monthly, weekly, daily), coffee consumption (less than daily, 1 cup/day, 2+ cups/day) and body mass index (kg/m^2)

[a] Using body mass index and status of self-reported, physician-diagnosed diabetes at baseline interview

[b] Including information of updated body mass index and status of self-reported, physician-diagnosed diabetes at follow-up interview

[c] Excluding alcoholic cirrhosis (16 cases), primary biliary cirrhosis (3 cases), viral hepatitis-B related cirrhosis (34 cases) and viral-hepatitis C related cirrhosis (2 cases).

Table 3

Body mass index in relation to risk of liver cirrhosis mortality

Characteristics	Whole cohort		With baseline diabetes		Without baseline diabetes	
	Cases	HR (95% CI)[a]	Cases	HR (95% CI)[a]	Cases	HR (95% CI)[a]
All cirrhosis mortality						
<23 kg/m^2	54	1.00	13	1.00	41	1.00
≥23 kg/m^2	79	1.31 (0.92-1.86)	15	0.71 (0.33-1.51)	64	1.53 (1.03-2.28)
Viral hepatitis related cirrhosis mortality (34 cases of HBV and 2 cases of HCV)						
<23 kg/m^2	17	1.00	2	1.00	15	1.00
≥23 kg/m^2	19	1.05 (0.54-2.04)	3	0.93 (0.14-6.03)	16	1.08 (0.53-2.20)
Non-viral hepatitis related cirrhosis mortality						
<23 kg/m^2	37	1.00	11	1.00	26	1.00
≥23 kg/m^2	60	1.43 (0.94-2.17)	12	0.69 (0.30-1.59)	48	1.79 (1.1-2.91)
Cryptogenic cirrhosis mortality[b]						
<23 kg/m^2	30	1.00	8	1.00	22	1.00
≥23 kg/m^2	48	1.36 (0.86-2.17)	8	0.58 (0.21-1.55)	40	1.72 (1.02-2.92)

[a]Hazard ratio (HR) adjusted for age at recruitment (year), year of study enrolment (1993-1995, 1996-1998), gender, dialect group (Hokkien, Cantonese) educational level (no formal education, primary school, secondary school or higher), smoking status (never, former, current), alcohol intake (non/monthly, weekly, daily), coffee consumption (less than daily, 1 cup/day, 2+ cups/day) and baseline diabetes status (for whole cohort analysis only).

[b]Excluding alcoholic cirrhosis (16 cases), primary biliary cirrhosis (3 cases), viral hepatitis-B related cirrhosis (34 cases) and viral-hepatitis C related cirrhosis (2 cases).

Table 4

Diabetes in relation to liver cirrhosis mortality by BMI status at baseline

Characteristics	Person-year	Cases	HR (95% CI)	P for interaction
All cirrhosis mortality,				
Body mass index <23 kg/m^2				0.04
No diabetes	482,011	41	1.00	
Diabetes	27,134	13	5.20 (2.73-9.90)	
Body mass index ≥23 kg/m^2				
No diabetes	505,874	64	1.00	
Diabetes	51,045	15	2.16 (1.22-3.83)	
Viral hepatitis related cirrhosis mortality (34 cases of HBV and 2 cases of HCV)				
Body mass index <23 kg/m^2				0.84
No diabetes	482,011	15	1.00	
Diabetes	27,134	2	2.06 (0.46-9.19)	
Body mass index ≥23 kg/m^2				
No diabetes	505,874	16	1.00	
Diabetes	51,045	3	1.82 (0.52-6.34)	
Non-viral hepatitis related cirrhosis mortality				
Body mass index <23 kg/m^2				0.02
No diabetes	482,011	26	1.00	
Diabetes	27,134	11	7.11 (3.42-14.79)	
Body mass index ≥23 kg/m^2				
No diabetes	505,874	48	1.00	
Diabetes	51,045	12	2.28 (1.20-4.35)	
Cryptogenic cirrhosis mortality[c]				
Body mass index <23 kg/m^2				0.04
No diabetes	482,011	22	1.00	
Diabetes	27,134	8	5.73 (2.47-13.28)	
Body mass index ≥23 kg/m^2				
No diabetes	505,874	40	1.00	
Diabetes	51,045	8	1.70 (0.79-3.67)	

Adjusted for age at recruitment (year), year of study enrolment (1993-1995, 1996-1998), gender, dialect group (Hokkien, Cantonese) educational level (no formal education, primary school, secondary school or higher), smoking status (never, former, current), alcohol intake (non/monthly, weekly, daily), coffee consumption (less than daily, 1 cup/day, 2+ cups/day) and body mass index (kg/m^2).

Table 5

Joint effects between diabetes and BMI in relation to risk liver cirrhosis mortality

Characteristics	Body mass index < 23 kg/m^2		Body mass index ≥ 23 kg/m^2	
All cirrhosis mortality	Case	HR (95% CI)	Case	HR (95% CI)
No diabetes	41	1.00	64	1.57 (1.05-2.33)
Diabetes	13	5.22 (2.78-9.8)	15	3.39 (1.86-6.19)
Viral hepatitis cirrhosis mortality				
No diabetes	15	1.00	16	1.08 (0.53-2.19)
Diabetes	2	2.15 (0.49-9.49)	3	1.91 (0.55-6.66)
Non-viral hepatitis cirrhosis mortality				
No diabetes	26	1.00	48	1.85 (1.14-3.01)
Diabetes	11	7.00 (3.42-14.30)	12	4.27 (2.13-8.59)
Cryptogenic cirrhosis mortality				
No diabetes	22	1.00	40	1.72 (1.02-2.92)
Diabetes	8	5.48 (2.41-12.44)	8	3.03 (1.33-6.88)

Adjusted for age at recruitment (year), year of study enrolment (1993-1995, 1996-1998), gender, dialect group (Hokkien, Cantonese) educational level (no formal education, primary school, secondary school or higher), smoking status (never, former, current), alcohol intake (non/monthly, weekly, daily) and coffee consumption (less than daily, 1 cup/day, 2-3 cups/day, 4+ cups/day)