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A curvilinear association of body mass index with cardiovascular diseases in Chinese patients with type 2 diabetes mellitus – A population-based retrospective cohort study

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ABSTRACT

Aims: This epidemiological and longitudinal study aimed to confirm the association between BMI and CVD and determine the optimal BMI range for Chinese patients with T2DM.
Method: A retrospective cohort study was conducted on 113,194 Chinese adult primary care T2DM patients without prior CVD history at baseline, and had a documented BMI in 2008–2010. Using the average of the annual mean of BMI records (updated BMI) over a median follow-up of 4.2 years, the risk of CVD associated with BMI by gender, age group, smoking status and presence of chronic kidney disease group was evaluated using multivariable Cox proportional hazard regression adjusted by socio-demographics and clinical characteristics.
Results: The updated BMI value and the incidence of CVD showed a J-shaped curvilinear relationship. Low (<18.5 kg/m^2) or high (≥25 kg/m^2) BMI range was associated with higher risk of CVD and the optimal BMI range associated with the lowest likelihood of CVD was 20–22.9 kg/m^2 in overall cohort and all selected groups.
Conclusions: There was no evidence of benefit of underweight or adiposity with regard to the risk of CVD and thus the maintenance of a normal weight should be emphasized as an integral part of preventive intervention in the diabetes management.

1. Introduction

Diabetes mellitus (DM) is an important public health issue, affecting 387 million people and costing US $376 billion in global health expenditures worldwide (International Diabetes Federation, 2015; Zhang et al., 2010). Excess adiposity is a well-recognized risk factor for cardiovascular disease (CVD) and mortality (Hubert, Feinleib, McNamara, & Castelli, 1983). According to the World Health Organization (WHO), at population level, body mass index (BMI) is the recommended indicator for thinness and fatness and suggests the threshold for underweight of BMI < 18.5 kg/m^2, normal of BMI between 18.5 and 24.9 kg/m^2, overweight of BMI between 25 and 29.9 kg/m^2 and obesity of BMI ≥ 30 kg/m^2 (World Health Organization, 2004). Due to genetic variation and the variation in the body build of various ethnicities, there was a separate BMI cut-off for overweight and obesity in China (Hong Kong) at BMI of 23 kg/m^2 and 27 kg/m^2, respectively, by WHO cross sectional study (World Health Organization, 2004). In many international guidelines for diabetes management, the key objective is to minimize the risk of CVD by controlling BMI (American Diabetes Association, 2014; International Diabetes Federation Guideline Development Group, 2014). However, some studies have been reported that there is an obesity paradox which associates with better survival and fewer CVD events in obesity patients compared to those without obesity (Hainer & Aldhoon-Hainerová, 2013). In fact, there has been an ongoing debate on the association between BMI and mortality in diabetic population where several studies demonstrated positive linear relationship (Katzmarzyk, Hu, Cefalu, Mire, & Bouchard, 2013; Tobias et al., 2014), while some showed inverse, U-shaped or null relationship (Carnethon et al., 2012; Logue et al., 2013; McEwen et al., 2012). Nevertheless, an in-depth investigation on how BMI is associated with the incidence of CVD among patients with type 2 DM (T2DM) is rarely conducted and thus the evaluation for the optimal BMI level for the prevention of CVD is important and highly relevant in clinical practice and policy planning.

There has never been a territory-wide study investigating the relationship between BMI and CVD for Chinese diabetic patients under primary care. Current literature focuses on investigating BMI

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associated with CVD in general population, rather than solely in the diabetic population. Diabetic patients were around 2–4 times more likely to have CVD than non-diabetic patients (Fox et al., 2004; Franco, Steyerberg, Hu, Mackenbach, & Nusselder, 2007) and thus the effect of obesity for diabetic patients may be extrapolated from those for non-diabetic patients. Moreover, although China shares the largest proportion (25%) of diabetic patients around the world, accounting for around 100 million Chinese adults (International Diabetes Federation, 2015), there is a lack of studies on the Chinese population. Due to different body proportions, fat distribution patterns, genetic and environmental factors including lifestyle and health behaviours, substantial differences in BMI distribution and disease risk across racial and ethnic groups were identified (Byrne & Wild, 2011; Forouhi & Sattar, 2006; World Health Organization, 2004). Therefore, the findings from non-Chinese population may not be generalized to Chinese populations.

Due to the importance of BMI control on the management of DM, and the fact that BMI is a modifiable risk factor for diabetic patients, understanding the effects of BMI on CVD among diabetic patients can assist clinicians in setting BMI targets in the management plan for diabetic patients and determine the achievable risk reduction through controlling BMI. Hence, this study aims to investigate the association between BMI and CVD events and determine the optimal BMI range for effective diabetes management in Chinese patients with T2DM. It can also reveal if there is any discrepancy between Chinese and non-Chinese populations when the relationship between BMI and CVD events with relevance to clinical practice is compared. The hypotheses of our study were that: (1) there is no obesity paradox which associates with better survival and fewer CVD events in obesity patients compared to those without obesity; (2) there is a curvilinear association between BMI and the risk of CVD and (3) the optimal BMI range should be similar among Chinese patients with T2DM, irrespective of gender, age group, smoking status and presence of hypertension and chronic kidney disease.

2. Materials and methods

2.1. Study design

This was a territory-wide retrospective cohort study on Chinese subjects aged ≥ 18 years old who were clinically diagnosed with T2DM and no prior history of CVD, and their DM was under the management of primary care. Clinical data between 1 August 2008 and 31 December 2010 were obtained from patients who had received primary care services from one of the 74 General Out-Patient Clinics under the Hong Kong Hospital Authority (HA). The HA is the governing organization of all public-sector hospitals and primary care clinics in Hong Kong, managing over 50% of DM patients under primary care. The data were made available from a territory-wide study for the evaluation of local diabetic programmes (Fung et al., 2012). With the aid of the administrative database of HA, the clinical diagnosis of T2DM was identified by the International Classification of Primary Care-2 (ICPC-2) code of 'T90'. Each patient was observed from their earliest records of BMI, as baseline date, to the date of incidence of CVD event, all-cause mortality, or last follow-up as censoring until 31 December 2013, whichever came first.

2.2. Cardiovascular diseases identification

The outcome of interest was CVD event with one of the following subtype diagnoses: coronary heart disease (CHD), stroke, or heart failure. The diagnosis of comorbidities was identified using the diagnosis coding system of ICPC-2 and International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) (World Health Organization, 1998, 2003). CHD including, ischaemic heart disease, myocardial infarction, coronary death and sudden death, was identified as ICPC-2 of K74–K76 or ICD-9-CM of 410.x, 411.x–414.x, 798.x. Heart failure was identified as ICPC-2 of K77 or ICD-9-CM of 428.x. Stroke, including fatal and non-fatal, was identified as ICPC-2 of K89–K91 or ICD-9-CM of 430.x–438.x.

2.3. Updated BMI and measurements

The BMI readings in the patient records were used and retrieved for data analysis. The updated BMI value was defined as the average of the annual mean BMI measurements, generated for each individual from baseline to each year follow-up before the last follow-up date. For example, if the follow-up period for a particular patient is 4 years, then the updated BMI value is defined as the average of the means of baseline, first, second, third and fourth year BMI values. The updated BMI was widely used to investigate the association between clinical parameter and the incidence of morbidity and mortality (Adler et al., 2000; Zhao et al., 2013, 2014). The average and standard deviation of number of BMI measurements during the follow-up period was 7.3 and 5.4 times, respectively.

The baseline covariates included the socio-demographics, clinical parameters, disease characteristics and treatment modalities of the patients. Socio-demographics consisted of gender, age, smoking status and drinking habit. Clinical parameters were haemoglobin A1c (HbA1c), blood pressure (BP), lipid profile (low-density lipoprotein-cholesterol (LDL-C) and total cholesterol to high-density lipoprotein cholesterol ratio (TC/HDL-C ratio)), triglyceride (TG) and urine albumin to creatinine ratio (ACR). Disease characteristics included self-reported duration of diabetes mellitus and family history of diabetes mellitus. Hypertension was identified as the clinical diagnosis with ICPC-2 code of "K86" or "K87". The presence of chronic kidney disease was indicated by the estimated glomerular filtration rate below 60 ml/min/1.73 m^2. Treatment modalities included the usage of anti-hypertensive drug, oral anti-diabetic drug, insulin and lipid-lowering agent. All laboratory assays were performed in accredited laboratories by the College of American Pathologists, the Hong Kong Accreditation Service or the National Association of Testing Authorities, Australia.

2.4. Data analysis

Missing data, with the exception of BMI, was handled by multiple imputation technique (Royston, 2004). The method aims at increasing the power of the analysis and producing more reliable and applicable models within clinical practice (Moons, Donders, Stijnen, & Harrell, 2006; Schafer & Graham, 2002; Steyerberg & van Veen, 2007). It also avoids unnecessary biases by considering subjects with incomplete data (Clark & Altman, 2003; Royston, 2004). In this study, each missing value was imputed five times by the chained equation method, equivalent to attain a relative efficiency of 95% (Rubin, 2004; Van Buuren, Boshuizen, & Knook, 1999). For each of the five imputed datasets, we performed the same analysis, with the five sets of results and combined based on Rubin's rules (Rubin, 2004).

All study subjects were categorized into one of the following nine groups according to the updated BMI value (<18.5 kg/m^2, 18.5–19.9 kg/m^2, 20–22.9 kg/m^2, 23–24.9 kg/m^2, 25–27.4 kg/m^2, 27.5–29.9 kg/m^2, 30–32.4 kg/m^2, 32.5–34.9 kg/m^2 and ≥35 kg/m^2). For each subgroup of BMI, descriptive statistics were displayed after multiple imputation. Differences in baseline characteristics between groups were tested by univariate linear regression for continuous variables or univariate logistic regression for categorical variables. The incidence rate was estimated by an exact 95% confidence interval (CI) based on a Poisson distribution (Ulm, 1990). The differences in the incidence of CVD between groups were assessed using log-rank tests. The BMI groups associated with the incidence of CVD were examined using multivariable Cox proportional hazards regressions, adjusted by all baseline covariates. The proportional hazards assumption was

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