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Increased body mass index is a risk factor for end stage renal disease in the Chinese Singapore population

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Abstract

The relationship between body mass index (BMI) and end stage renal disease (ESRD) is confounded by co-morbidities associated with both conditions. Furthermore, the association at low range BMI is controversial. We studied this association in the Singapore Chinese Health Study, a population-based prospective cohort that recruited Singaporean Chinese men and women 45–74 years of age from 1993 to 1998. Self-reported weight, height, lifestyle factors, usual diet and medical history were collected via an interviewer-administered questionnaire. Incident ESRD cases were identified via record linkage with the nationwide ESRD registry. The computed Cox proportional hazard regression was adjusted for potential risk factors. After an average follow up of 15.5 years, 827 incident ESRD cases were identified. Compared with a normal BMI of 18.5 to under 23 kg/m², the hazard ratios and (95% confidence intervals) of ESRD risk for BMIs under 18.5, 23 to under 27.5, and 27.5 kg/m² or more were 0.54 (0.37–0.79), 1.40 (1.20–1.64) and 2.13

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(1.74–2.59), respectively. This significantly trended, linear, dose-dependent association was only present among those with no history of diabetes, hypertension, coronary heart disease and stroke at baseline, but not significantly among those with any of these co-morbidities. Thus, BMI itself is a risk factor for ESRD in the general population and this association is present in those without preexisting diabetes, hypertension, coronary heart disease and stroke.

Keywords

End stage renal disease; Body mass index; epidemiology; Singapore Chinese Health Study

Introduction

Obesity is associated with increased risk of hypertension and diabetes,^{1,2} and cardiovascular disease (CVD).^{3–5} Paradoxically, overweight and obese patients with established CVD,³ and end stage renal disease (ESRD),⁶ have better prognosis when compared with normal weight patients. Many studies nested in general populations have shown that compared to normal range body mass index (BMI), those with higher BMI had increased risk of chronic kidney disease (CKD)^{7–10} and ESRD.^{11–18} Since hypertension, diabetes and cardiovascular disease are also known co-morbidities of CKD^{19–23} and ESRD,^{24–28} these co-morbidities could confound the association between BMI and renal disease. Moreover, it remains unclear if the effect of increased BMI on the development of ESRD is different between generally healthy individuals and in those with the aforementioned co-morbidities.

The majority of previous studies examining the association between BMI and risk of ESRD were conducted in Europe and North America,^{11–15} where the mean BMI in the general population is higher compared to the Asian populations.^{13–15} In addition, increased risks of diabetes and cardiovascular diseases in Asians have been observed to occur at lower BMI cut-offs.^{29–32} A study in China suggested that the risk of ESRD was increased in the underweight individuals compared to those in the normal range.¹⁶ Hence, studies in Asian populations are needed to investigate the association of low range BMI with the risk of developing ESRD.

In this study, we used data from the Singapore Chinese Health Study, a prospective cohort of middle-aged or older Chinese men and women in Singapore, to study the risks of ESRD associated with BMI categories ranging from <18.5 to 27.5 kg/m². We also explored whether pre-existing co-morbidities could interact with BMI to affect its effect on risk of ESRD.

Results

Study population characteristics

After a mean 15.5 (SD 4.3) years of follow-up among 52,777 subjects (815,795 person-years), there were 827 incident ESRD cases. According to the data from the nationwide ESRD Registry, 822 out of 827 subjects who developed ESRD in this cohort had their underlying causes identified. Among them, 60.4% subjects developed ESRD secondary to diabetes (diabetic nephropathy), 16.6% were secondary to renal vascular disease, including

hypertensive nephropathy, and the remaining 23% were due to miscellaneous causes that included glomerulonephritis (15.4%) and polycystic disease (2.2%).

The mean BMI in this population at baseline was 23.1 (SD 3.6), and 52.0% had BMI <23 kg/m². Nonetheless, only 7.7% of the study population could be considered underweight (BMI <18.5 kg/m²). The distributions of selected characteristics and dietary exposures by BMI categories are shown in Table 1. Compared to the lightest subjects (BMI < 18.5 kg/m²), subjects who were obese (BMI ≥ 27.5 kg/m²) were slightly younger at recruitment, more likely to be women, have lower education levels, and less likely to have ever smoked or consumed alcohol daily. They also had much higher prevalence of self-reported physician-diagnosed history of hypertension and diabetes, as well as a higher daily intake of total protein and red meat, when compared to their leaner counterparts.

BMI and ESRD risk

BMI was significantly associated with increased risk of developing ESRD in a dose-dependent manner (Table 2). In a multivariable model that adjusted for demographic, lifestyle and dietary factors, compared with normal BMI 18.5–<23 kg/m², the HRs (95% CIs) of ESRD risk for BMI <18.5, 23–<27.5, and ≥ 27.5 kg/m² were 0.54 (0.37–0.79), 1.40 (1.20–1.64) and 2.13 (1.74–2.59), respectively ($P_{\text{trend}} < 0.0001$). After additional adjustment for self-reported history of diabetes, hypertension, stroke or coronary heart disease, this linear, dose-dependent relationship was considerably attenuated ($P_{\text{trend}} = 0.079$).

When we stratified the cohort by baseline history of self-reported physician diagnosed co-morbidities including diabetes, hypertension, coronary heart disease and stroke, we found that among those without any of these pre-existing co-morbidities, the risk of ESRD increased in a stepwise manner with increasing BMI, but the relationship was null in those with any of the known co-morbidities ($P_{\text{interaction}} = 0.009$) (Table 3). Similarly, when stratified by baseline status of diabetes or hypertension, the dose-dependent association between BMI categories and risk of ESRD was only observed among those without history of diabetes ($P_{\text{interaction}} < 0.001$) or hypertension ($P_{\text{interaction}} = 0.026$).

When we limited the analysis to those without diabetes, hypertension, coronary heart disease and stroke at baseline, and divided them into 10 successive BMI groups with approximately 1 kg/m² increment in BMI per successive group, using <18 kg/m² as the referent category, the risk of ESRD increased in a dose-dependent manner with increasing BMI, with HRs ranging from 1.06 (95% CI: 0.46–2.49) in the 18–<20 kg/m² group to 2.84 (95% CI: 1.55–5.23) in the highest BMI group (≥ 27 kg/m²) ($P_{\text{trend}} < 0.0001$). Conversely, there was no linear association between increasing BMI and the risk of ESRD among those with one or more co-morbidities at baseline. In participants without co-morbidities, restricted cubic spline analysis showed a linear relationship between BMI and ESRD risk regardless of number of knots (P for nonlinearity = 0.17 [3 knots], 0.35 [4 knots], and 0.51 [5 knots]; Figure 1a) while the association between BMI and ESRD risk in individuals with co-morbidities was null (Figure 1b). The best model fit was obtained with 3 knots (AIC=3917) compared to 4 (AIC=3919) or 5 knots (AIC=3920); thus we chose this with first knot as reference (BMI=18.8 kg/m²). The results remained essentially the same using the 2nd knot

as reference. The difference in the BMI-ESRD risk association between individuals with and those without co-morbidities was statistically significant ($P_{\text{interaction}}=0.009$).

In lag-time analysis when we only included subjects with more than 4 years of followup, the increased risk in the heaviest subjects was more pronounced: in a multivariable model that adjusted for demographic, lifestyle and dietary factors, compared with normal BMI 18.5– $<23 \text{ kg/m}^2$, the HRs (95% CIs) of ESRD risk for BMI <18.5 , 23– <27.5 , and $\geq 27.5 \text{ kg/m}^2$ were 0.53 (0.35–0.82), 1.45 (1.22–1.71), 2.18 (1.76–2.70), respectively ($P_{\text{trend}} < 0.0001$). After additional adjustment for self-reported history of diabetes, hypertension, stroke or coronary heart disease, this linear dose-dependent relationship was considerably attenuated ($P_{\text{trend}}=0.025$) (Supplementary Table 1). Again, this increased ESRD risk with increased BMI was observed only among those without pre-existing co-morbidities (Supplementary Table 2).

Discussion

In this prospective cohort of Singapore Chinese adults, we found a positive linear association between BMI and the risk of developing ESRD. The risk increase began at BMI levels that are generally considered to be normal or lean. Furthermore, the BMI-ESRD risk association was only present in individuals who had no history of diabetes, hypertension, stroke, and chronic heart disease at baseline, which minimized the potential confounding effect of these pre-existing conditions on the BMI-ESRD association. We also replicated the linear dose-dependent association between BMI and risk of ESRD after excluding all ESRD events and follow-up years that occurred within the first 4 years post enrolment into the cohort study, which reduced the potential effect of undiagnosed ESRD on the BMI-ESRD risk association. These results provide additional evidence that support BMI as a risk factor for ESRD.

In our study, diabetes and renal vascular disease accounted for majority of the ESRD cases in our cohort (77%), and this is comparable to the 73% in USA according to the US Renal Disease Systems 2016 report.³³ Our observations of increased ESRD risks at elevated BMI are consistent with prior studies.^{10–18} The association between low-range BMI and ESRD was poorly studied in most studies because a) subjects with low BMI ($< 18.5 \text{ kg/m}^2$) were excluded,^{13–15} b) the BMI cut off for definition of the lowest or reference category was set at a higher range^{17,18} than the one used in this study, or c) the number of outcomes in the low-range BMI categories were low.¹¹ As the population in this study was relatively lean at recruitment, we were able to examine the association between BMI and ESRD risk along the continuum of BMI from <18.5 to $\geq 27.5 \text{ kg/m}^2$.

The Northern California study observed that underweight subjects (i.e. BMI $< 18.5 \text{ kg/m}^2$) had decreased risks of ESRD when compared to subjects with normal BMI,¹² which is in accordance with the results of our study. Similarly, an Austrian study showed a significant continuous dose-dependent association between BMI and ESRD, but only after a follow up time of more than 10 years, and it was suggested that the duration of obesity could play an additional role in the development of ESRD.¹¹ In contrast, the underweight subjects in the China National Hypertension Study had increased risks of ESRD when compared to normal

weight subjects.¹⁶ This study involved a cohort of mid-adulthood Chinese participants who had a mean follow up time less than 10 years,¹⁶ and the authors attributed the increased risk of ESRD among the underweight subjects to a higher prevalence of either poor nutrition or protein-wasting as a result of their disease progression from pre-existing CKD to ESRD. However, we are cognizant that in our study population, the sample size for those <18.5 kg/m² was small (<8%) and we cannot be confident about the association between BMI and risk of ESRD among those who were severely underweight.

The biological mechanism underlying the positive association between BMI and risk of ESRD remains largely unknown. It is suspected that increased body mass leads to glomerular hyperfiltration and hyperfusion, leading to increased microalbuminuria and eventual proteinuria and focal segmented glomerulosclerosis.³⁴ Renal biopsies have demonstrated focal segmental glomerulosclerosis in subjects with obesity-related CKD.^{35–37} Coupled with the observation that angiotensin converting enzyme (ACE) inhibitors was able to retard the progression of CKD among obese patients with proteinuria in the American African Study of Kidney disease (AASK),³⁸ these findings suggest that hyperfiltration may be the biological mechanism underlying obesity and the development of ESRD.

Alternatively, studies also reported increased levels of leptin, a peptide primarily produced in adipose tissue that stimulates glomerulosclerosis and proteinuria, in those with CKD, suggesting a hormonal mechanism for the association between obesity and ESRD.³⁹ In addition, abdominal adiposity has been associated with reduction in adiponectin levels⁴⁰ and increase in urine albumin excretion.^{41–43} This observation may be explained by the adiponectin receptors residing on podocytes and likely playing a role in podocyte morphology and/or function.⁴⁴ In support of this hypothesis, experimental studies have shown that mice lacking adiponectin expression showed effacement of podocyte foot processes and proteinuria,^{45,46} and adiponectin knockout mice treated with adiponectin have been shown to have reduced proteinuria and podocyte effacement.^{45,46}

Our study also observed that the positive and linear relationship between BMI and ESRD risk existed only among those who did not report diabetes, hypertension, stroke or coronary heart disease at baseline. Prior cohort studies, such as the Northern California cohort study,¹² the Woman's Health Initiative¹³ and the Reason for Geographic and Racial Differences in Stroke (REGARDS) study,^{14,15} found an overall increased risk of ESRD with increased BMI, but observed that the association was either attenuated^{12,13} or nullified^{14,15} after adjusting for obesity-related co-morbid conditions such as diabetes and hypertension. Our study similarly observed that the BMI-ESRD association was attenuated after adjusting for these underlying co-morbid conditions. Hence, the effect of BMI on renal function in patients may be mediated via its effect on increasing the risk of diabetes or hypertension, and is therefore attenuated after accounting for these co-morbid conditions.

Prior studies of cohorts with pre-existing hypertension and cardiovascular disease did not observe a relationship between increased BMI and ESRD risk,^{47,48} and these observations are similar to the null BMI-ESRD relationship we observed in our stratified cohort with preexisting co-morbid conditions. We hypothesize that these studies on populations with co-morbid conditions related to ESRD were likely to have significant proportion with

underlying CKD, and this may have contributed to the null or inverse BMI-ESRD relationship that was observed. This hypothesis is supported by a study on CKD patients that showed a reverse J-shaped association between BMI and all-cause mortality in men.⁴⁹ In dialysis patients, the relationship between excess weight and death also appears to be reversed.^{50–52} Together, these findings suggest that the effects of BMI on the risk of ESRD are attenuated in the presence of stronger co-morbid risk factors that worsen kidney function. Another explanation is that in patients with underlying CKD, low BMI could be a marker of poor nutrition or protein wasting as a result of disease progression.

The strengths of our study are its large sample size, prospective design and a high follow up rate over a long period of time. We were also able to objectively assess ESRD morbidity using the nationwide Singapore Renal Registry, which strictly follows international guidelines of ESRD and has a high rate of follow up.^{53,54} Lag sensitivity analysis on a sub-cohort of subjects with more than 4 years of follow up from baseline yielded similar results to those derived from the entire cohort, supporting our findings that BMI is a risk factor for ESRD. In addition, we also analysed the relationship between BMI and ESRD risk using the BMI “trigger points” of risks for an Asian population^{29–32} which are more useful observational categories for our population compared to the international categories.

The limitations of our study are, in general, those related to the nature of observational studies. First, height and weight were assessed by self-report, and some levels of measurement error were inevitable. This would most likely result in non-differential misclassification and likely underestimation of risk between BMI and ESRD. However, self-reports of body weight and height to assess BMI have been reported to correlate well with actual measurements and have been validated for use in health risk estimates.^{55–57} Additionally, we have previously published the associations between BMI and other disease outcomes in this cohort, including risk of diabetes,⁵⁸ cancer⁵⁹ and mortality.⁶⁰

Second, although components of the metabolic syndrome, namely abdominal obesity, hypertension, diabetes mellitus, hypertriglyceridemia, and decreased high density lipoprotein levels, have been associated with increased risks of developing CKD,⁶¹ and ESRD,⁶² in other studies, we were only able to conduct stratified analysis to examine the modification of the BMI-ESRD risk association by diabetes and hypertension. Specifically, in our study, we noted that the positive, dose-dependent association between BMI and risk of ESRD was only present among participants without baseline diabetes or hypertension. Unfortunately, we do not have data on hip-waist ratio or blood lipid measurements to see if other components of the metabolic syndrome, namely abdominal obesity, hypertriglyceridemia, and high density lipoprotein levels, modified the BMI-ESRD risk association.

Third, the self-reported baseline co-morbidity status may result in some misclassification and residual confounding. We only inquired about physician-diagnosed co-morbidities, such as diabetes and hypertension, in our study, and it is reasonable to postulate that asymptomatic and unreported cases of these conditions existed in the study population, and could create residual confounding. Nevertheless, although we have no laboratory data to validate the self-report of co-morbidities, we have previously conducted validations of self-

reported diabetes and hypertension in this cohort. A validation study of the self-reported diabetes cases in this cohort was conducted previously using two complementary methods: a hospital-based discharge summary database and a supplementary questionnaire regarding symptoms, diagnostic tests and diabetes treatment during the telephone interview, and positive predictive value of 99% was found in the validation study, suggesting that the self-reported history of physician-diagnosed diabetes was a reliable measure of diabetes status of the study population.⁶³ Additionally, during a follow-up interview conducted within the Singapore Chinese Health Study, 88% of the subjects of a subgroup of 12,646 participants with self-reported physician-diagnosed hypertension also reported taking antihypertensive medications, thus indicating a reasonable validity of this self-reported diagnosis.⁶⁴ Fourth, we did not have any measure of kidney function at baseline and were unable to study the association in those with and without existing CKD separately. Finally, due to the nature of observational studies, causality should be made with caution.

In conclusion, BMI is a dose-dependent risk factor for the development of ESRD, even in low range BMI, and among subjects without history of confounding co-morbidities of diabetes, hypertension, coronary heart disease, and stroke. BMI is a modifiable risk factor in a generally health population to reduce the development of ESRD.

Materials and Methods

Study population

The main objective of the Singapore Chinese Health Study was to build a population-based cohort of Chinese for long-term study of dietary, genetic and environmental determinants of cancer and other chronic diseases in Singapore. The cohort recruited 63,257 Chinese adults who resided in government housing estates, which were facilities where 86% of Singaporeans resided during the recruitment period from April 1993 to December 1998. Participation was restricted to Chinese citizens and permanent residents of the country, of ages 45–74 years at the time of recruitment, and who belonged to either of two major dialect groups: the Hokkien and Cantonese, who originated from the contiguous provinces of Fujian and Guangdong in the southern part of China, respectively. All the 31 housing estates in the country during the period of recruitment were divided by geographical zones and distributed among our team of interviewers. Recruitment occurred by an initial letter informing potential participants of the study and inviting them to participate. Interviewers then went from door-to-door to approach and recruit eligible participants until our desired sample size was achieved. Approximately 85% of eligible subjects who were invited responded positively. The study was approved by the Institutional Review Boards of the National University of Singapore.

Exposure Assessment

At recruitment, we first obtained written informed consent. Trained interviewers carried out in-person interviews with subjects by using a structured, scanner-readable questionnaire that ascertained baseline information on demographics, height, weight, current alcohol and tobacco use, habitual physical activity and self-reported medical history. Habitual diet in the preceding year was captured using a previously described validated 165-item food frequency

questionnaire.⁶⁵ BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2).

Incident ESRD cases

ESRD cases were identified by linking the cohort database with the population-based Singapore Renal Registry. The Singapore Renal Registry defines ESRD as meeting at least one of the following criteria: 1) serum creatinine level of more than or equal to $880 \mu\text{mol/l}$ (10 mg/dl), 2) estimated glomerular filtration rate (eGFR) of less than $15 \text{ ml/min/1.73 m}^2$ (based on either the Modification of Diet in Renal Disease (MDRD) Study equation, Cockcroft Gault equation, or 24 hour creatinine clearance), 3) undergoing hemodialysis or peritoneal dialysis, or 4) has undergone kidney transplant.⁵⁴ Criteria 1 to 3 had to be persistent for more than 3 months to qualify as ESRD.^{53,54}

The cohort was followed-up annually via linkage with the Singapore Registry of Births and Deaths for date and cause of death. We also conducted two follow-up interviews among surviving participants from 1999–2004 and 2006–2010 to update selected lifestyle factors and medical history. As of 31 Dec 2012, only 47 subjects (0.07%) from our cohort were known to be lost to follow-up due to migration out of Singapore or for other reasons, suggesting that follow-up via linkage with the nationwide registry was virtually complete.

Statistical analysis

The current analysis included data from 52,777 participants, after excluding 110 subjects who had ESRD at baseline, and 10,054 subjects who had missing height and/or weight information at baseline. Primary outcome was defined as incident ESRD. Person-years for each participant were calculated from date of baseline interview to date of ESRD, lost-to-follow-up, death or 31 December 2012, whichever occurred first. The differences between baseline characteristics by ESRD status were examined using the chi-square test for categorical variables and Student's t-test for continuous variables. The categorization of BMI was based on the World Health Organisation identified "trigger points" for public health action in Asian populations: $< 18.5 \text{ kg/m}^2$ for underweight, $18.5\text{--}<23.0 \text{ kg/m}^2$ for increased but acceptable risk, 23.0 kg/m^2 for increased risk and $\geq 27.5 \text{ kg/m}^2$ for high risk in adults.⁶⁶ Cox proportional hazards regression was used to compute the hazard ratio (HR) and its 95% confidence interval (CI) for developing ESRD by using the lowest category of BMI as the reference group.

The selection of potential confounders was primarily based on prior consideration of their associated risk with ESRD in this population. Three different analytical models were used: a) Model 1 adjusted for age (years), sex, year of baseline interview (1993–1995, 1996–1998), dialect (Hokkien/Cantonese) and educational level (none, primary school, secondary school or higher); b) Model 2 additionally adjusted for lifestyle risk factors including smoking status (never, ever), alcohol consumption (none, occasionally, weekly, daily), physical activity (defined as any weekly moderate, or vigorous activity, or sports lasting at least 30 minutes), total protein intake and red meat intake; and c) Model 3, in addition to variables in Models 1 and 2, additionally adjusted for self-reported histories of physician-diagnosed hypertension, diabetes, coronary heart disease and stroke. As mentioned, we

restricted study subjects in The Singapore Chinese Health Study to the two major dialect groups of Chinese in Singapore - the Hokkiens who originated from the southern part of Fujian Province and the Cantonese who came from the central region of Guangdong Province. For our cohort participants, most of their parents would have come from the same province in China and belonged to the same dialect group. Hence, in all our analyses, we have included dialect group as a covariate to account for any possible genetic heterogeneity between these two dialect groups.

Tests for linear trend were performed by treating BMI categories (1, 2, 3, and 4) as continuous variables in the Cox regression models. We also did Cox regression analysis by dividing participants into 10 groups of increasing BMI using $<18 \text{ kg/m}^2$, the lowest BMI category, as the referent group, and 27 kg/m^2 as the highest BMI group, with approximately 1 kg/m^2 increment in each successive BMI category. We further evaluated the relationship between BMI and ESRD risk by restricted cubic splines to test the non-linearity in multivariate adjusted Cox regression analysis in participants with and without co-morbidity separately. Number of knots was selected based on the best model fit according to lowest value of Akaike information criteria (AIC). Using the first or second knot as reference, the corresponding HRs and CIs for BMI values were computed in each model.

The heterogeneity in the BMI-ESRD risk association between individuals with at least one of the self-reported history of physician diagnosed co-morbidities (ie diabetes, hypertension, coronary heart disease or stroke) and those without was tested by introducing a product term between BMI category and co-morbidity status in the Cox model. Finally, sensitivity analysis was conducted by repeating our analysis on subjects with more than 4 years of follow-up (N=50,638).

Restricted cubic analysis was done by Stata Statistical Software, Release 14.1 (Stata Corporation, College Station, TX). All other analyses were performed using SAS version 9.2 (SAS Institute Inc., Chicago, IL). Statistical significance was based on two-sided probability of 0.05.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ESRD end stage renal disease

CKD	chronic kidney disease
BMI	body mass index
CI	confidence interval
HR	hazard ratio
SD	standard deviation

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Fig 1a.

Restricted cubic spline demonstrating the linear dose-dependent increase in hazard ratios (95% confidence intervals) for risk of ESRD according to BMI in a sub-cohort of subjects without any history of known co-morbid risk factors (ie. Diabetes, hypertension, chronic heart disease or stroke) in a model that adjusted for age, gender, dialect, educational level and year of interview, physical activity, smoking status, alcohol use, total energy intake, protein intake and red meat intake.

Figure 1b.

Restricted cubic spline demonstrating the linear dose-dependent increase in hazard ratios (95% confidence intervals) for risk of ESRD according to BMI in a sub-cohort of subjects with history of at least one of the co-morbid risk factors (diabetes, hypertension, stroke or chronic heart disease) in a model that adjusted for age, gender, dialect, educational level and year of interview, physical activity, smoking status, alcohol use, total energy intake, protein intake and red meat intake.

Table 1

Baseline characteristics of cohort participants who developed ESRD and the rest of the cohort: The Singapore Chinese Health Study (1993–2012) (N=52,777)

Characteristics ^a	BMI Categories (kg/m ²)			
	< 18.5	18.5–<23.0	23.0–<27.5	27.5
Number of participants, n	4062	23365	19899	5451
ESRD cases, n (%)	28 (0.7)	292 (1.3)	357 (1.8)	150 (2.8)
Age (years), mean (SD)	57.3 (8.2)	55.9 (8.0)	55.9 (7.8)	55.9 (7.8)
Male, n (%)	1966 (48.4)	10524 (45.0)	9233 (46.4)	2173 (39.9)
Dialect, n (%)				
Cantonese	1996 (49.1)	11891 (50.9)	10791 (54.2)	3046 (55.9)
Hokkien	2066 (50.9)	11474 (49.1)	9108 (45.8)	2405 (44.1)
Secondary school or higher, n (%)	1202 (29.6)	7797 (33.4)	6218 (31.3)	1366 (25.1)
Ever smoker, n (%)	1706 (42.0)	7233 (31.0)	5588 (28.1)	1441 (26.4)
Hypertension, n (%)	391 (9.6)	4021 (17.2)	5978 (30.0)	2248 (41.2)
Diabetes, n (%)	176 (4.3)	1652 (7.1)	2113 (10.6)	763 (14.0)
Coronary heart disease, n (%)	109 (2.7)	820 (3.5)	922 (4.6)	310 (5.7)
Stroke, n (%)	73 (1.8)	301 (1.3)	295 (1.5)	83 (1.5)
Physically active ^b , n (%)	1212 (29.8)	8332 (35.7)	7388 (37.1)	1693 (31.1)
Alcohol intake, n (%)				
Non-drinkers	3495 (86.0)	20482 (87.7)	17591 (88.4)	4922 (90.3)
Weekly drinkers	330 (8.1)	1995 (8.5)	1760 (8.8)	404 (7.4)
Daily drinkers	237 (5.8)	888 (3.8)	548 (2.8)	125 (2.3)
Total Protein Intake, mean (SD)	57.7 (23.2)	60.0 (23.8)	60.6 (24.6)	60.5 (26.3)
Red meat intake, mean (SD)	29.8 (23.7)	30.4 (23.8)	31.4 (25.0)	32.4 (26.7)

^a p values based on the chi-square test for categorical variables and ANOVA for continuous variables. All p-values < 0.05

^b defined as any weekly moderate activity, vigorous activity or strenuous sports lasting at least 30 minutes

Table 2

Hazard ratios (95% confidence intervals) for risk of ESRD according to BMI (N=52, 777).

	BMI categories (kg/m ²)				p for linear trend
	< 18.5	18.5–<23.0	23.0–<27.5	≥ 27.5	
Cases/person-years	28/59,532	292/362,251	357/310,501	150/83,511	
Multivariate Model 1	0.56 (0.38–0.82)	1.00	1.39 (1.19–1.62)	2.17 (1.78–2.64)	<0.001
Multivariate Model 2	0.54 (0.37–0.79)	1.00	1.40 (1.20–1.64)	2.13 (1.74–2.59)	<0.001
Multivariate Model 3	0.72 (0.49–1.07)	1.00	1.02 (0.87–1.20)	1.27 (1.04–1.56)	0.079

Multivariate model 1: adjusted for age, gender, dialect, educational level and year of interview.

Multivariate model 2: model 1 plus physical activity, smoking status, alcohol use, total energy intake, protein intake and red meat intake.

Multivariate model 3: model 2 plus baseline history of diabetes, baseline history of hypertension, baseline history of stroke, baseline history of coronary heart disease.

Table 3

Hazard ratios (95% confidence intervals) for risk of ESRD according to BMI (N=52, 777), stratified by self-reported history of at least one of the co-morbid risk factors (ie. hypertension, diabetes, chronic heart disease or stroke).

	BMI categories (kg/m ²)				p for linear trend
	< 18.5	18.5–<23.0	23.0–<27.5	≥27.5	
<u>No co-morbidities</u>					
Cases/person-years	10/52,079	86/285,678	72/202,490	27/44,713	
Multivariate Model 1	0.59 (0.31–1.14)	1.00	1.15 (0.84–1.58)	1.91 (1.24–2.95)	0.021
<u>Presence of co-morbidities^a</u>					
Cases/person-years	18/7,452	206/76,574	285/108,011	123/38,798	
Multivariate Model 2	0.94 (0.58–1.52)	1.00	0.93 (0.78–1.12)	1.07 (0.85–1.35)	0.93
<u>No hypertension</u>					
Cases/person-years	16/54,663	150/304,743	151/221,781	44/50,365	
Multivariate Model 2	0.64 (0.38–1.07)	1.00	1.14 (0.90–1.43)	1.22 (0.87–1.72)	0.15
<u>Hypertension</u>					
Cases/person-years	12/4,868	142/57,508	206/88,721	106/33,145	
Multivariate Model 2	1.06 (0.59–1.92)	1.00	0.89 (0.72–1.10)	1.18 (0.91–1.52)	0.66
<u>No diabetes</u>					
Cases/person-years	17/57,559	177/341,604	196/282,407	95/73,426	
Multivariate Model 2	0.66 (0.40–1.10)	1.00	1.02 (0.83–1.25)	1.56 (1.21–2.02)	0.017
<u>Diabetes</u>					
Cases/person-years	11/1,972	115/20,648	161/28,094	55/10,084	
Multivariate Model 2	1.01 (0.54–1.88)	1.00	0.94 (0.74–1.20)	0.84 (0.60–1.17)	0.34

^a Presence of at least one of the following co-morbidities at baseline: hypertension, diabetes, chronic heart disease or stroke

Multivariate model 1: adjusted for age, gender, dialect, educational level and year of interview, physical activity, smoking status, alcohol use, total energy intake, protein intake and red meat intake.

Multivariate model 2: model 1 plus baseline history of diabetes, hypertension, stroke and coronary heart disease.