Body Mass Index and Risk of End-Stage Renal Disease: A Systematic Review and Dose-Response Meta-Analysis

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ABSTRACT

Background: The association of obesity with risk of chronic kidney disease has been accepted, but considering the possible indications of the obesity paradox in patients with early-stage kidney disease, the association between baseline body mass index (BMI) and future risk of end-stage renal disease (ESRD) in the general population has not been established yet.

Methods: We performed a systematic search of PubMed and Scopus for relevant studies published from database inception to June 2018. Longitudinal cohort studies reporting risk estimates of ESRD for three or more categories of BMI in the general population were included. Pooled relative risk (RR) was calculated using a random-effects model.

Results: The analysis included eight prospective cohort studies, one nested case-control study, one nested case-referent study, and two retrospective cohort studies (2,063,895 individuals and 5874 cases of end-stage renal disease). The pooled RR of ESRD for a 5-unit increment in BMI was 1.19 (95%CI: 1.06, 1.35; I2 = 94.1%). The strength of the association might be age-related; in a way that, a significant positive association was found in those with a mean age <50 years, but not those aged ≥50 years. A nonlinear dose-response meta-analysis indicated that the risk of ESRD was similar within BMI of 15-23 kg/m^2, and then increased sharply and linearly at a BMI of approximately 25 kg/m^2.

Conclusion: Obesity and overweight condition are associated with a higher risk of ESRD. Being as lean as possible within the normal weight range may help to prevent ESRD.

Introduction

The increased incidence of chronic kidney diseases (CKDs) during recent years [1] has imposed a financial burden on healthcare systems [2]. CKD is associated with a lower quality of life and higher risk of all-cause and cardiovascular mortality and morbidity [3-5]. Several epidemiological studies indicate that adiposity, a growing pandemic problem, is associated with a higher risk of kidney impairment [6-9]. Adiposity exerts its effects both indirectly, by increasing the risks of hypertension and type 2 diabetes, the two underlying causes of CKD [10-11], and directly, by promoting adverse effects on kidney structure and function [12-15].

Although the association between obesity and future risk of CKD has been well established [16], few studies have addressed the potential effects of adiposity on the risk of end-stage renal disease (ESRD), the later stage of CKD. It is possible that the association between adiposity and kidney failure differs for CKD and ESRD, because ESRD depends on both the incidence and prognosis after development of CKD. A prospective evaluation of approximately half a million US veterans with an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 suggested a relatively consistent U-shaped association between body mass index (BMI) and risk of CKD progression and all-cause mortality in patients with early stages of CKD, with a nadir

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at a BMI of 25–30 kg/m2 [17]. Although the association of obesity with risk of CKD is widely accepted, owing to the prolonged progressive process of ESRD and possible changes in the nutritional status and body weight during the progression of kidney disease, and considering the possible indications of the obesity paradox in patients with early-stage CKD, the association between baseline BMI and future risk of ESRD in the general population has not been well characterized. The existing evidence is relatively inconsistent; some studies suggest a positive association between these parameters [18-19], whereas others suggest a negative association and protective effects of a high BMI [20-21].

A recent meta-analysis of 39 cohort studies of the general population suggested that obesity, but not the overweight condition, is associated with a higher risk of CKD [16]. However, the shape of the dose-response relationship was not determined and the risk of CKD in underweight individuals was not reported. A large prospective cohort study conducted in China revealed a J-shaped association between BMI and the risk of ESRD [22], whereas other studies suggest a linear [18-19] [23], or U-shaped association between these parameters [24]. In addition, the US veterans cohort study suggested that the association between higher BMI and progressive loss of kidney function might strengthen with increasing age [25], but this hypothesis has not been examined in the context of ESRD. Thus, the objective of this review was to examine the relationship between BMI and future risk of ESRD in the general population. To our knowledge, no such meta-analysis has summarized data regarding this relationship previously.

Subjects and methods

We reported this systematic review in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [26].

Search strategy

A systematic literature search for studies published between 1966 and June 25, 2018 was performed using PubMed and Scopus. The searches included combinations of keywords relevant to general and abdominal adiposity, kidney disease, and study design (Supplementary Table 1). The reference lists of all related articles and reviews were also manually searched. The search was restricted to articles published in English.

Eligibility and study selection

Two independent authors (AJ, MSZ) reviewed the titles and abstracts of all studies identified. Prospective and retrospective cohort, nested case-control, and case-cohort studies were included in this review if they met the following criteria: 1) were conducted among adults aged 18 years or older; 2) measured and reported baseline BMI as exposure and in at least three quantitative categories; 3) reported the outcome of interest as ESRD incidence at follow-up (any definition of ESRD was acceptable); 4) reported risk estimates (relative risk (RR), hazard ratio, or odds ratio) and the corresponding 95% confidence intervals (CIs) of ESRD for each category of BMI; and 5) reported number of cases and participants/noncases or personyears in each category of BMI, or reported sufficient information to allow estimation of these numbers. Studies that reported the association between continuous BMI and risk of ESRD were also included. Studies with only two categories of BMI, studies that were conducted in children and adolescents, and studies that were conducted among patients with specific diseases such as type 2 diabetes or CKD were excluded.

Data extraction and assessment of study quality

Two independent authors (AJ, MSZ) reviewed the full texts of eligible studies and extracted the following information: first author's name, publication year, study design, location, follow-up duration, mean age and/or age range, proportion of men, ESRD diagnosis criteria, covariates adjusted in multivariate analysis, exposure levels, number of participants/cases, reported risk estimates, and the 95%CIs of ESRD across different categories of BMI. Effect estimates based on models with the most comprehensive covariate adjustments were included.The Newcastle-Ottawa scale was used to assess the quality of the studies included, and those with more than seven stars were considered high quality [27]. Any discrepancies were resolved through discussion to reach consensus between the two authors.

Data synthesis and statistical analysis

The RR (and 95% CIs) was considered the effect size for all studies. The pooled RRs and 95% CIs were calculated for a 5-unit increment in BMI using a random effects model [28]. The linear dose-response relationship was determined using a generalized least squares trend estimation, according to the methods developed

by Greenland and Longnecker [29-30]. We used the two-stage generalized least squares trend estimation method, which first estimated study-specific slope lines and then combined the data with those from studies in which the slopes were reported directly [30]. Study-specific results were combined using a random effects model. The median point in each category of BMI was assigned to the corresponding RR for each study. If medians were not reported, approximate medians were estimated using the midpoint of the lower and upper bounds. If the highest or lowest categories were open-ended, they were considered to have the same width as the closest category. For studies in which the reference category was not the lowest one, risk estimates were recalculated assuming the lowest category as a reference [31]. Subgroup analyses were performed based on geographical location, follow-up duration, baseline mean age, anthropometric assessment method, and adjustment for main confounders. To assess the possible effect of each study on pooled effect size, an influence analysis was carried out with one study removed at a time. If there were several publications from the same study, the publication with the higher number of participants was included. Publication bias was assessed using funnel plots and Egger's asymmetry and Begg's tests ($P<0.10$) [32]. Between-study heterogeneity was explored using Cochran's Q test of heterogeneity and the I2 statistic ($P<0.05$) [33]. A potential non-linear association was examined by modeling dietary calcium intake levels using restricted cubic splines with three knots at fixed percentiles (10, 50, and 90%) of the distribution [34]. A P-value for non-linearity of the meta-analysis was calculated by testing the null hypothesis that the coefficient of the second spline was equal to zero. All analyses were performed using Stata software, version 13 (Stata Corp, College Station, Texas, USA). $P<0.05$ was considered statistically significant.

Results

Literature search and study characteristics

The initial systematic search identified 17,422 articles, of which 4,523 were duplicates and 12,699 were considered non-relevant and excluded at the initial screening of the title and abstract. Overall, 200 full texts were assessed to examine their eligibility for inclusion in the final analysis, and of these, 188 studies were excluded. Detailed reasons for study exclusion are presented in (Figure 1). Ultimately, 12 studies comprising a total of 2,063,895 participants and 5874 cases of ESRD were included in the final meta-analysis [18-20, 22-24, 35-40]. The general characteristics of the studies are presented in (Table 1) and the numbers of cases and participants/personyears and reported risk estimates of ESRD across different categories of BMI are provided in Supplementary (Table 2).

Table 1.General characteristics of included studies in meta-analyses of body mass index and risk of end-stage renal disease.

Author, year	Country	Study design	Follow-up (years)	Participants/ cases	Men (%)	Mean age/ age range (years)	Diagnosis criteria of ESRD	Adjustments	Quality score (max. 9 point)
Hsu et al. (2006)[18]	US	Retrospective cohort	26.0	320,252/1471	46	38.2	Receipt of renal transplantation or maintenance hemodialysis or peritoneal dialysis	Multiphasic Health Checkup period, age, sex, race, education level, smoking status, history of MI, serum cholesterol, urinalysis proteinuria, urinalysis hematuria, and serum Cr	8
Zitt et al. (2016)[19]	Austria	Prospective cohort	17.5	185,341/403	46	41.6	Chronic renal replacement therapy with dialysis or transplantation	Age, sex, BMI, FBG, BP, total cholesterol, triglycerides , gamma-glutamyl transferase, and smoking status	6
Panwar et al. (2015)[20]	US	Prospective cohort	6.3	21,840/247	45	64.7	US Renal Data System (USRDS)	Age, race, sex, geographic region of residence, education, income, physical activity, cigarette smoking, systolic BP, and a history of CHD and stroke	7
Reynolds et al. (2007)[22]	China	Prospective cohort	8.3	143,802/350	49	55.7	Renal replacement therapy (dialysis or renal transplantation) or death from renal failure	Age, sex, geographic region , urbanization (urban versus rural residence), education, physical activity, cigarette smoking, and alcohol consumption	8
Franceschini et al. (2015)[23]	US	Prospective cohort	11.6	20,117/212	0	63.9	US Renal Data System (USRDS)	Age, race, education, ever smoker, diastolic and systolic BPs, HTN treatment, recruitment center, observational study (versus clinical	7

Table 1.General characteristics of included studies in meta-analyses of body mass index and risk of end-stage renal disease.

								trials), DM, and eGFR	
Akwo et al. (2015) [24]	US	Nested case-control	-	25,28/631	45	53.7	US Renal Data System (USRDS)	Matched for age, gender and race, and adjusted for education and smoking history	8
Bash et al. (2009) [35]	US	Prospective cohort	16.0	8419/124	45	54.6	Initiation of renal replacement therapy (hemodialysis, peritoneal dialysis, or having a kidney transplant), catheter place mentor death from renal failure	Age, race, sex, eGFR, DM, systolic BP, history of CHD, smoking status, serum TG, HDL, and LDL, and center	7
Iseki et al. (2003) [36]	Japan	Prospective cohort	17.0	100,753/404	47	49.6	Chronic dialysis patients residing in Okinawa who survive at least 1 month on scheduled dialysis	Age, systolic blood pressure, and proteinuria	8
Ishani et al. (2006) [37]	US	Prospective cohort	25.0	12,866/213	100	46.1	Initiation of renal replacement therapy (hemodialysis, peritoneal dialysis, or having a kidney transplant), or death from renal failure	Age, race, smoking status, family history of DM, serum TG, HDL, LDL, serum uric acid, FBG, and systolic BP	8
Lew et al.(2017) [38]	Singapore	Prospective cohort	15.5	52,777/827	45	56.0	(i) Serum Cr level ≥ 10 mg/dl, (ii) eGFR of less than 15 ml/min/1.73 m², (iii) undergoing hemodialysis or peritoneal dialysis, or (iv) has undergone kidney transplant.	Age, gender, dialect, educational level and year of interview, physical activity, smoking status, alcohol use, total energy intake, protein intake, red meat intake, baseline history of DM, HTN, stroke, and coronary heart disease	8
Sommar et al.(2013) [39]	Sweden	Nested case-referent	-	496/118	52.4	63	GFR<10-15 (ml/min),starting renal replacement therapy, i.e., dialysis or transplantation	Erythrocyte Cadmium, lead and mercury, DM, HTN, and smoking status	7
Vivante et al. (2012) [40]	Israel	Retrospective cohort	25.5	1,194,704/ 874	58.7	17	Receipt of renal transplantation or maintenance hemodialysis or peritoneal dialysis	Sex, country of origin, period of enrollment in the study, and systolic BP	8

Abbreviations: BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; Cr, creatinine; DM, diabetes mellitus; FBG, fasting blood glucose; GFR, glomerular filtration rate; HDL, high density lipoprotein; HTN, hypertension; LDL, low density lipoprotein; MI, myocardial infarction; TG, triglycerides.

Table 2. Relative risk of end-stage renal disease for a 5-unit increment in body mass index.

Comparison		n	Pooled RR	I2 (%), Pheterogeneity1	Pbetween2
All studies		12	1.19 (1.06-1.32)	94%, <0.001	-
Region					
US		6	1.18 (0.92-1.44)	93%, < 0.001	
Europe		3	1.44 (1.15-1.74)	65%, 0.06	< 0.001
Asia		3	1.05 (0.99-1.11)	63%, 0.07	
Follow-up duration					
< 15 years		3	1.00 (0.96-1.05)	0%, 0.65	< 0.001
> 15 years		7	1.30 (1.09-1.50)	95%, < 0.001	
Mean age					
< 50		7	1.32 (1.05-1.60)	96%, < 0.001	< 0.001
≥ 50		5	1.04 (0.98-1.09)	35%, 0.16	
Anthropometric assessment					
Measured		8	1.28 (1.02-1.54)	96%, < 0.001	
Self-reported		2	1.05 (0.99-1.12)	52%, 0.15	< 0.001
NA		2	1.08 (1.02-1.13)	0%, 0.44	
Adjustments					
Smoking status	Yes	10	1.15 (1.02-1.28)	90%, < 0.001	< 0.001
	No	2	1.31 (0.84-1.78)	99%, < 0.001	
Blood pressure or HTN	Yes	9	1.19 (1.02-1.35)	91%, < 0.001	< 0.001
	No	3	1.03 (0.94-1.46)	98%, < 0.001	
Physical activity	Yes	3	1.03 (0.95-1.11)	59%, 0.09	< 0.001
	No	9	1.27 (1.08-1.46)	95%, < 0.001	
DM or FBG	Yes	4	1.09 (1.03-1.15)	0%, 0.72	0.44
	No	8	1.23 (1.04-1.43)	96%, < 0.001	
Kidney function	Yes	4	1.27 (0.95-1.59)	95%, < 0.001	0.06
	No	8	1.16 (1.00-1.32)	94%, < 0.001	

[1]*P*-heterogeneity within subgroups with the use of a random-effects model.
[2]*P*-heterogeneity between subgroups with the use of a fixed-effects model.
Abbreviations: DM, diabetes mellitus; FBS, fasting blood glucose; HTN, hypertension.

Six of the studies included in the meta-analysis were from the US [18, 20, 23-24, 35, 37], four were from Asia [19, 22, 36, 38], and two were from Europe [39-40]. Two studies were retrospective cohorts [18, 40], one was a nested case-control [24], one was a nested case-referent study [39], and the remainders were prospective cohorts. One study was a prospective evaluation within a multiple risk factor intervention trial [37]. Eight studies measured baseline weight to calculate the BMI [18-20, 22-23, 35, 39-40], two studies used self-reported anthropometry [24] [38], and two studies did not specify the anthropometric assessment method exactly [36-37]. All studies included in the meta-analysis were published after 2003. Six studies measured baseline kidney function [18, 20, 23, 35-37], and 3–11% of the participants in these studies had an eGFR <60 ml/min/1.73 m^2 or displayed proteinuria. One large retrospective cohort study included 1.2 million adolescents aged 17 years [40]; considering the fact that BMI in adulthood is highly correlated with BMI in adolescence [41-42], we decided to include this study in the meta-analysis. Three studies reported an association between continuous BMI and risk of ESRD [35, 37, 39]; hence they were not included in the nonlinear dose-response meta-analysis.

BMI and risk of ESRD

All studies were eligible for inclusion in the linear trend estimation, and the result showed that a 5-unit increment in BMI was associated with a 19% higher risk of ESRD (pooled RR: 1.19; 95%CI: 1.06, 1.32; n=12 studies), with extreme heterogeneity (I2=94.1%; Pheterogeneity < 0.001) (Figure 2).
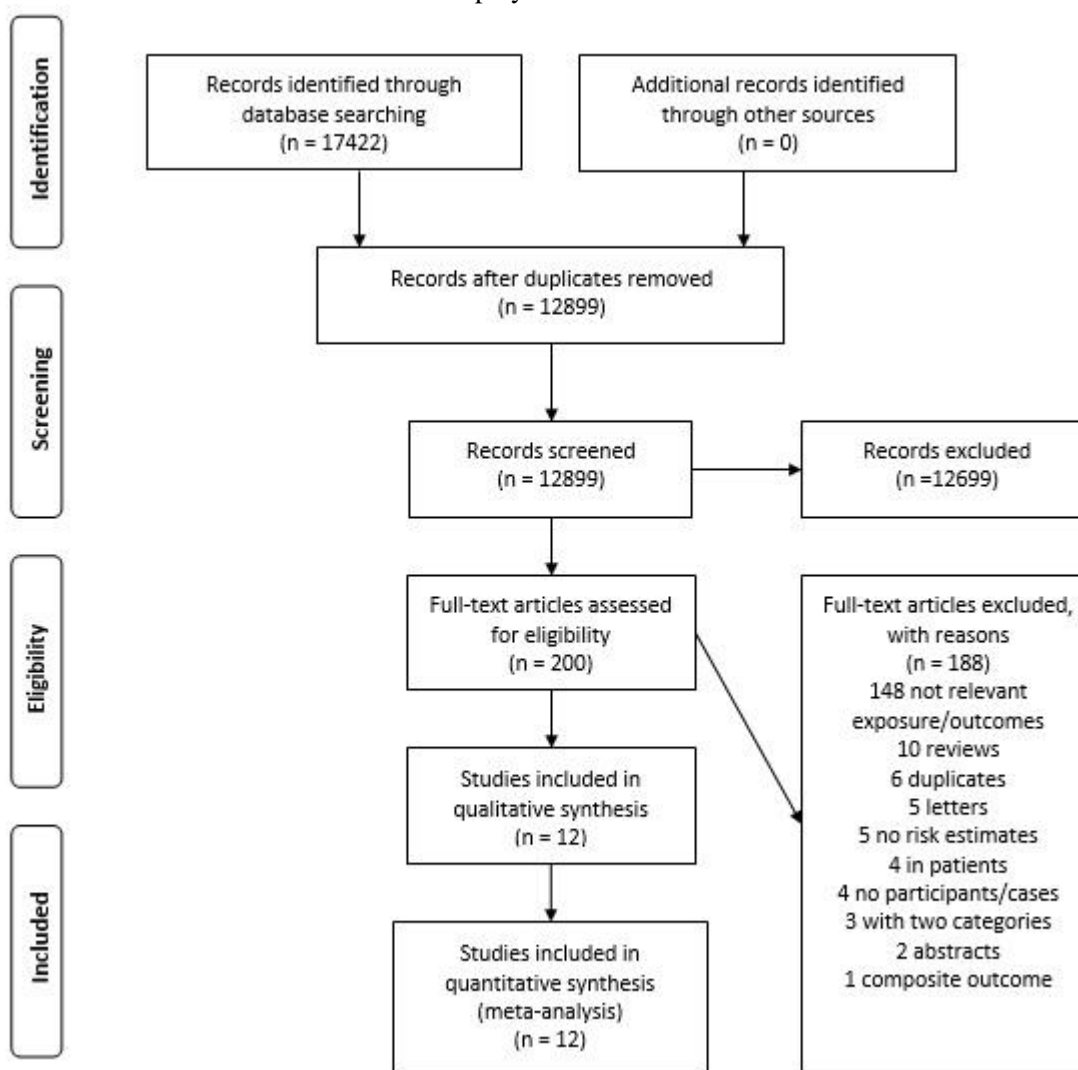

Figure 1. Literature search and study selection process for inclusion in the meta-analysis of body mass index and risk of end-stage renal disease.

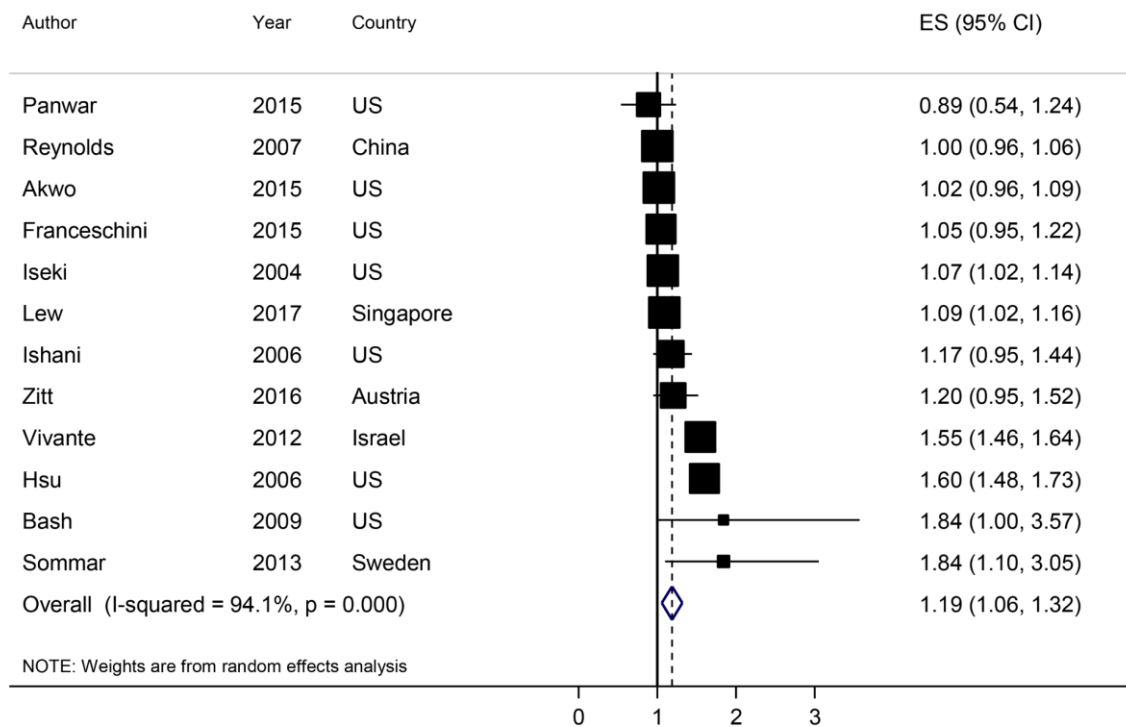| Author	Year	Country		ES (95% CI)
Panwar	2015	US		0.89 (0.54, 1.24)
Reynolds	2007	China		1.00 (0.96, 1.06)
Akwo	2015	US		1.02 (0.96, 1.09)
Franceschini	2015	US		1.05 (0.95, 1.22)
Iseki	2004	US		1.07 (1.02, 1.14)
Lew	2017	Singapore		1.09 (1.02, 1.16)
Ishani	2006	US		1.17 (0.95, 1.44)
Zitt	2016	Austria		1.20 (0.95, 1.52)
Vivante	2012	Israel		1.55 (1.46, 1.64)
Hsu	2006	US		1.60 (1.48, 1.73)
Bash	2009	US		1.84 (1.00, 3.57)
Sommar	2013	Sweden		1.84 (1.10, 3.05)
Overall (I-squared = 94.1%, p = 0.000)				1.19 (1.06, 1.32)

NOTE: Weights are from random effects analysis

Figure 2. Relative risk of end-stage renal disease for a 5-unit increment in body mass index. Results were combined using a random effects model.

Sensitivity analysis, subgroup analysis, and publication bias

The pooled RR ranged from 1.14 (95%CI: 1.03, 1.24), with the exclusion of an Israeli military adolescents cohort study [40], to 1.21 (95%CI: 1.06, 1.37), with the exclusion of the China National Hypertension Survey [22]. None of the excluded studies explained the large degree of heterogeneity in the data. A subgroup analysis by age revealed a significant positive association between BMI and risk of ESRD in those with a mean age <50 years (pooled RR: 1.32; 95%CI: 1.05, 1.60; n=7 studies), but not those aged ≥50 years (pooled RR: 1.04; 95%CI: 0.98, 1.09; n=5 studies). In addition, there was a non-significant association between BMI and risk of ESRD in studies that controlled for baseline kidney function (pooled RR: 1.27; 95%CI: 0.95, 1.59; n=4 studies). Further subgroup analyses identified geographical location, follow-up duration, mean age, anthropometric assessment method, and adjustment for physical activity and baseline diabetes as potential sources of the observed heterogeneity (Table 2). Some evidence of publication bias was identified using Begg's test (P=0.06), but not Egger's test (P=0.68) (Supplementary Figure 1).

Nine studies reported sufficient information for inclusion in the nonlinear dose-response meta-analysis[18-20, 22-24, 36, 38, 40], and the result suggested a significant dose-dependent association between BMI and the risk of ESRD (Pnonlinearity<0.001; Figure 3). This nonlinear analysis revealed that, although it was relatively similar in the underweight and normal weight ranges, the risk of ESRD increased sharply and linearly at a BMI>25 kg/m^2; with risk increasing significantly at a BMI of about 23 kg/m^2. In the sensitivity analysis, none of the excluded studies changed the results.
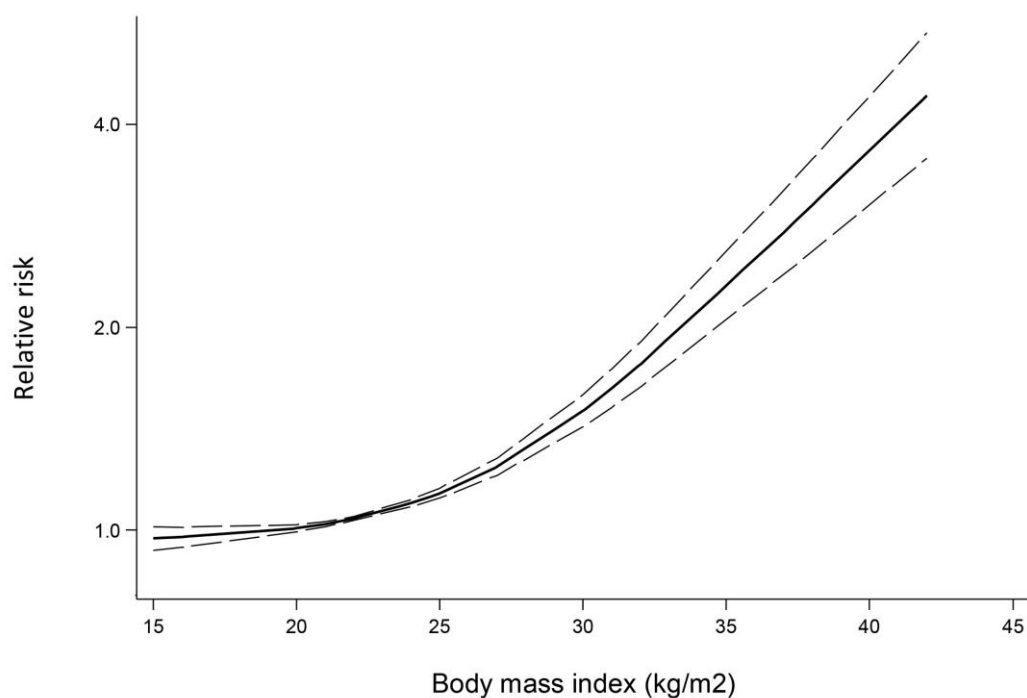
Figure 3. Dose-response association between body mass index and risk of end-stage renal disease, (Pnonlinearity< 0.001, n = 9).The solid line and the long dashed line represent the estimated relative risk and its 95% confidence interval.

Discussion

The results of this meta-analysis indicate that a 5-unit increment in BMI is associated with a 19% higher risk of ESRD. The association stayed significant after adjustment for smoking, blood pressure, and history of diabetes; whereas a non-significant association was found among studies that controlled for physical activity and baseline kidney function. A dose-response meta-analysis suggested that the association might be influenced by age; in a way that, a significant inverse association was found only among those with a mean age <50 years, but not among those aged ≥50 years.

The association between adiposity and risk of kidney failure has been well established. Two previous meta-analyses examined this relationship [16, 43], and the most recent suggested that obesity, but not the overweight condition, is significantly associated with a 28% higher risk of low eGFR (n=13 studies) and a 51% higher risk of albuminuria (n = 7 studies) [16]. The earlier meta-analysis [43] addressed all types of kidney diseases, including CKD, kidney stones, kidney cancers, and ESRD (n=2 studies), and suggested that both obesity and the overweight condition are associated with a higher risk of kidney disease. In comparison with previous reviews, the current meta-analysis included a larger number of studies, more participants (more than 2 million), and a longer follow-up duration, which enabled us to appropriately test the relationship between BMI and ESRD.

A subgroup analysis revealed a significant association between BMI and ESRD in the younger subgroup (mean age<50 years old) but not the older subgroup (mean age ≥50 years). This difference may be due in part to the higher likelihood of survival in younger participants. Younger people live longer, and as a result are more likely to develop ESRD before death. It has also been proposed that the shorter lifespan of patients aged ≥50 years may not allow the complete appearance of the long-term adverse metabolic effects of obesity [25]. In the current analysis, the numbers of participants and mean follow-up durations differed substantially across the age subgroups (1,813,916 participants with a mean follow-up duration of approximately 21 years in the younger subgroup, versus 249,979 participants with a mean follow-up duration of approximately 11 years in the older subgroup); therefore, it is difficult to accurately compare the size of the effect of adiposity on ESRD across age subgroups. In contrast to the results presented here, a prospective evaluation of approximately 3.3 million US veterans with a baseline eGFR >60 ml/min/1.73 m2 suggested that the association between BMI and risk of eGFR decline might strengthen with increasing age. In the US veteran study, higher BMIs were associated with a poorer prognosis in

participants aged ≥40 years, but there was no association between BMI and progressive loss of kidney function in younger individuals [25]. However, the interpretation of the results of this cohort study may have been limited by the relatively short follow-up period (7 years). Furthermore, as above mentioned, the association between BMI and kidney failure differs for CKD and ESRD, as ESRD depends on the incidence and prognosis after CKD development, and it has been suggested that overweight patients might have a lower risk of progression of CKD [17].

The nonlinear dose-response meta-analysis suggested that both obesity and the overweight condition are associated with a higher risk of ESRD. This finding for the overweight category is inconsistent with that of a previous meta-analysis by Garofalo et al. [16], which suggested that obesity, but not the overweight condition, is associated with a greater risk of new-onset low eGFR and albuminuria. However, Garofalo et al. did report a marginally significant association for these parameters in the overweight category (eGFR: pooled RR, 1.06; 95%CI: 0.94, 1.21; n=8 studies; albuminuria: pooled RR, 1.24; 95%CI: 0.98, 1.58; n=2 studies). In the analysis by Garofalo et al., only one study examining albuminuria and three studies examining eGFR had follow-up durations ≥10 years, and two studies had short follow-up durations(<5 years). By comparison, of the nine studies included in the current dose-response meta-analysis, six had follow-up durations ≥10 years, of which five had follow-up durations ≥15 years. It is possible that the relatively short follow-up durations of the studies examined by Garofalo et al. did not allow the complete appearance of adverse metabolic effects associated with the overweight condition. Thus, the inconsistency between the findings of the current analysis and that performed by Garofalo et al. may be attributable to the different follow-up durations of the studies examined.

Mechanisms

There are several reasonable explanations for the observed association between BMI and risk of ESRD. Heavier weight is generally accompanied by a higher risk of type 2 diabetes and hypertension, which are the two main risk factors for CKD development [10-11]. Adiposity is also associated with proteinuria and glomerulosclerosis [14, 44-46], the underlying processes of CKD, and hyperlipidemia, another consequence of obesity, might play a role in the

development of CKD [19].

Strengths and limitations

The current study has several strengths. First, our analysis allowed us to summarize existing evidence regarding the association between greater body mass and risk of ESRD, and show the shape of the dose-response relationship. To our knowledge, this is the first meta-analysis examining the relationship between BMI and ESRD risk. Second, we examined this relationship in both younger and older populations, and found that it is likely to be influenced by age. Third, we included large-scale and high quality cohort studies, with a total of more than 2 million participants, which conferred an acceptable statistical power to the analysis. Finally, of the nine studies included in the nonlinear dose-response meta-analysis, six had follow-up durations longer than 10 years, of which five had prolonged follow-ups of >15 years; consequently, we were able to identify the long-term dose-response relationship between BMI and risk of incident ESRD.

This analysis has several potential limitations that should be noted when interpreting the results. First, the data displayed extreme heterogeneity that persisted in most of the subgroups. The subgroup analyses suggested that region, follow-up duration, mean age, anthropometric assessment method, and adjustments for some of the confounders were potential sources of the heterogeneity. In addition, 10 of the 12 studies included in the analysis reported risk estimates greater than 1. Thus, the observed heterogeneity may be largely attributable to differences in the effect sizes of the studies examined, rather than inconsistencies in the direction of the association. Second, the numbers of participants and follow-up durations differed substantially across the age subgroups; hence the observed age-related differences in the association between BMI and ESRD should be interpreted with caution. Third, only 6 of the 12 studies included in the analysis examined baseline kidney function and only 4 studies took this parameter into account in the multivariate analyses. In addition, only one study excluded participants with proteinuria and low eGFR, on the basis of the baseline urine dipstick test [40]. Therefore, we cannot ignore the confounding effects of pre-existing kidney failure on the results, especially considering the fact that there was no significant association between BMI and ESRD in the subgroup of studies that adjusted the results for baseline kidney function (n=4

studies). Fourth, the current meta-analysis included a wide spectrum of individuals, ranging from adolescents to elderly patients. Indeed, the BMI may overestimate the degree of adiposity in younger subjects, who may be overweight but muscular, and may underestimate adiposity in older individuals because of the loss of muscle mass associated with aging. On the basis of these considerations, measurement of waist circumference in conjunction with BMI would provide additional information on the role of aging in ESRD risk. Waist circumference, a measurement of abdominal obesity, provides information that is not accounted for by the BMI. However, due to the lack of available information, we were unable to examine the association between abdominal adiposity and risk of ESRD in the current analysis. Fifth, because the studies included in this meta-analysis did not report sex-specific data, we were unable to determine the association between BMI and ESRD across sex subgroups. Sixth, one prospective cohort study included in the analysis had a very high percentage (72%) of hypertensive individuals[37], and a further six cohort studies also had relatively high proportions (24–53%) of hypertensive participants[19-20, 22-23, 35, 38]. Thus, the confounding effect of pre-existing hypertension should be considered and our results may not reflect the true association between BMI and ESRD in the general population. Finally, all of the studies included in this analysis were published after 2003, and the results of Begg's test and a funnel plot indicated publication bias, possibly leading to overestimation of ESRD risk.

Conclusion

The current analysis summarizes the evidence of an association between BMI and risk of ESRD. The results indicate that both obesity and the overweight condition are associated with a higher risk of ESRD. Being as lean as possible within the normal weight range may help to prevent ESRD. Owing to the long-standing progressive process of ESRD, it may be helpful to consider changes in BMI when assessing the association between BMI and ESRD over follow-up periods.

Abbreviations

CKD   chronic kidney disease
ESRD   end-stage renal disease
BMI   body mass index

References

1. Collins AJ, Foley RN, Chavers B, Gilbertson D, Herzog C, Johansen K, et al. 'United States Renal Data System 2011 Annual Data Report: Atlas of chronic kidney disease & end-stage renal disease in the United States. Am J Kidney Dis. 2012; 59:(1):A7-e1-420.
2. Hunsicker LG. The consequences and costs of chronic kidney disease before ESRD. J Am Soc Nephrol. 2004;15(5):1363-4.
3. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296-305.
4. Shidler NR, Peterson RA, Kimmel PL. Quality of life and psychosocial relationships in patients with chronic renal insufficiency. Am J Kidney Dis. 1998;32(4):557-66.
5. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, et al. Chronic kidney disease and mortality risk: a systematic review. J Am Soc Nephrol. 2006;17(7):2034-47.
6. Domrongkitchaiporn S, Sritara P, Kitiyakara C, Stitchantrakul W, Krittaphol V, Lolekha P, et al. Risk factors for development of decreased kidney function in a southeast Asian population: a 12-year cohort study. J Am Soc Nephrol. 2005;16(3):791-9.
7. Gelber RP, Kurth T, Kausz AT, Manson JE, Buring JE, Levey AS, et al. Association between body mass index and CKD in apparently healthy men. Am J Kidney Dis. 2005;46(5):871-80.
8. Song YM, Sung J, Lee K. Longitudinal relationships of metabolic syndrome and obesity with kidney function: Healthy Twin Study. Clin Exp Nephrol. 2015;19(5):887-94.
9. Yamagata K, Ishida K, Sairenchi T, Takahashi H, Ohba S, Shiigai T, et al. Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. Kidney Int. 2007;71(2):159-66.
10. Hsu CY, McCulloch CE, Darbinian J, Go AS, Iribarren C. Elevated blood pressure and risk of end-stage renal disease in subjects without baseline kidney disease. Arch Intern Med.

2005;165(8):923-8.

11. Williams ME. Diabetic CKD/ESRD 2010: a progress report? Semin Dial. 2010;23(2):129-33.

12. Chagnac A, Weinstein T, Korzets A, Ramadan E, Hirsch J, Gafter U. Glomerular hemodynamics in severe obesity. Am J Physiol Renal Physiol. 2000;278(5):F817-22.

13. Goossens GH, Blaak EE, van Baak MA. Possible involvement of the adipose tissue renin-angiotensin system in the pathophysiology of obesity and obesity-related disorders. Obes Rev. 2003;4(1):43-55.

14. Henegar JR, Bigler SA, Henegar LK, Tyagi SC, Hall JE. Functional and structural changes in the kidney in the early stages of obesity. J Am Soc Nephrol. 2001;12(6):1211-7.

15. Wahba IM, Mak RH. Obesity and obesity-initiated metabolic syndrome: mechanistic links to chronic kidney disease. Clin J Am Soc Nephrol. 2007;2(3):550-62.

16. Garofalo C, Borrelli S, Minutolo R, Chiodini P, De Nicola L, Conte G. A systematic review and meta-analysis suggests obesity predicts onset of chronic kidney disease in the general population. Kidney Int. 2017;91(5):1224-1235.

17. Lu JL, Kalantar-Zadeh K, Ma JZ, Quarles LD, Kovesdy CP. Association of body mass index with outcomes in patients with CKD. J Am Soc Nephrol. 2014;25(9):2088-96.

18. Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS. Body mass index and risk for end-stage renal disease. Ann Intern Med. 2006;144(1):21-8.

19. Zitt E, Pscheidt C, Concin H, Kramar R, Lhotta K, Nagel G. Anthropometric and Metabolic Risk Factors for ESRD Are Disease-Specific: Results from a Large Population-Based Cohort Study in Austria. PLoS One. 2016;11(8):e0161376.

20. Panwar B, Hanks LJ, Tanner RM, Muntner P, Kramer H, McClellan WM, et al. Obesity, metabolic health, and the risk of end-stage renal disease. Kidney Int. 2015;87(6):1216-22.

21. Perry HM Jr, Miller JP, Fornoff JR, Baty JD, Sambhi MP, Rutan G, et al. Early predictors of 15-year end-stage renal disease in hypertensive patients. Hypertension. 1995;25(4 pt 1):587-94.

22. Reynolds K, Gu D, Muntner P, Chen J, Wu X, Yau CL, et al. Body mass index and risk of ESRD in China. Am J Kidney Dis. 2007;50(5):754-64.

23. Franceschini N, Gouskova NA, Reiner AP, Bostom A, Howard BV, Pettinger M, et al. Adiposity patterns and the risk for ESRD in postmenopausal women. Clin J Am Soc Nephrol. 2015;10(2):241-50.

24. Akwo EA, Cavanaugh KL, Ikizler TA, Blot WJ, Lipworth L. Increased body mass index may be associated with greater risk of end-stage renal disease in whites compared to blacks: A nested case-control study. BMC Nutr. 2015; 1:24.

25. Lu JL, Molnar MZ, Naseer A, Mikkelsen MK, Kalantar-Zadeh K, Kovesdy CP. Association of age and BMI with kidney function and mortality: a cohort study. Lancet Diabetes Endocrinol. 2015;399):704-14.

26. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283(15):2008-12.

27. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603-5.

28. DerSimonian R, Laird N. Meta-analysis in clinical trials. Contemp Clin Trials. 2015;45(Pt A):139-45.

29. Berlin JA, Longnecker MP, Greenland S. Meta-analysis of epidemiologic dose-response data. Epidemiology. 1993;4(3):218-28.

30. Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data. Stata Journal. 2006; 6:40.

31. Hamling J, Lee P, Weitkunat R, Ambuhl M. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. Stat Med. 2008;27(7):954-70.

32. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34.

33. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60.

34. Orsini N, Li R, Wolk A, Khudyakov P, Spiegelman D. Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. Am J Epidemiol. 2011;175(1):66-73.

35. Bash LD, Astor BC, Coresh J. Risk of incident ESRD: a comprehensive look at cardiovascular risk factors and 17 years of follow-up in the Atherosclerosis Risk in Communities (ARIC) Study. Am J Kidney Dis. 2010;55(1):31-41.

36. Iseki K, Ikemiya Y, Kinjo K, Inoue T, Iseki C, Takishita S. Body mass index and the risk of development of end-stage renal disease in a screened cohort. Kidney Int. 2004;65(5):1870-6.

37. Ishani A, Grandits GA, Grimm RH, Svendsen KH, Collins AJ, Prineas RJ, et al. Association of single measurements of dipstick proteinuria, estimated glomerular filtration rate, and hematocrit with 25-year incidence of end-stage renal disease in the multiple risk factor intervention trial. J Am Soc Nephrol. 2006;17(5):1444-52.

38. Lew QJ, Jafar TH, Talaei M, Jin A, Chow KY, Yuan JM, et al. Increased body mass index is a risk factor for end-stage renal disease in the Chinese Singapore population. Kidney Int. 2017; 92(4):979-987.

39. Sommar JN, Svensson MK, Bjor BM, Elmstahl SI, Hallmans G, Lundh T, et al. End-stage renal disease and low level exposure to lead, cadmium and mercury; a population-based, prospective nested case-referent study in Sweden. Environ Health. 2013; 12:9.

40. Vivante A, Golan E, Tzur D, Leiba A, Tirosh A, Skorecki K, et al. Body mass index in 1.2 million adolescents and risk for end-stage renal disease.

Arch Intern Med. 2012;172(21):1644-50.

41. The NS, Suchindran C, North KE, Popkin BM, Gordon-Larsen P. Association of adolescent obesity with risk of severe obesity in adulthood. JAMA. 2010;304(18):2042-7.

42. Tirosh A, Shai I, Afek A, Dubnov-Raz G, Ayalon N, Gordon B, et al. Adolescent BMI trajectory and risk of diabetes versus coronary disease. N Engl J Med. 2011;364(14):1315-25.

43. Wang Y, Chen X, Song Y, Caballero B, Cheskin LJ. Association between obesity and kidney disease: a systematic review and meta-analysis.

Kidney Int. 2008;73(1):19-33.

44. Adelman RD. Obesity and renal disease. Current opinion in nephrology and hypertension. 2002; 11:331-5.

45. de Jong PE, Verhave JC, Pinto-Sietsma SJ, Hillege HL; PREVEND study group. Obesity and target organ damage: the kidney. Int J Obes Relat Metab Disord. 2002; 26;4:S21-4.

46. Ribstein J, du Cailar G, Mimran A. Combined renal effects of overweight and hypertension. Hypertension. 1995;26(4):610-5.