A systematic review and meta-analysis suggests obesity predicts onset of chronic kidney disease in the general population

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Obesity and chronic kidney disease (CKD) are public health priorities that share core pathophysiological mechanisms. However, whether high body mass index (BMI) increases risk of CKD *de novo* remains ill-defined. To evaluate the role of BMI in predicting CKD onset in the general adult population, we performed a systematic review and meta-analysis of PubMed and ISI Web of Science databases articles published between January 2000 and August 2016 without language restriction. We selected studies in adult individuals from a general population with normal renal function at baseline that reported the risk of low estimated glomerular filtration (eGFR) (under 60 mL/min/1.73m^2) and/or albuminuria (1+ at dipstick or an albumin creatinine ratio of 3.4 mg/mmol or more) as hazard ratio, odds ratio or relative risk related to obesity, overweight, or BMI as continuous value. A total of 39 cohorts covering 630, 677 participants with a mean follow-up of 6.8 years were selected. Obesity increased the relative risk, 95% confidence interval and heterogeneity (I^2) of developing low eGFR (1.28, 1.07–1.54, [I^2: 95.0%]) and albuminuria (1.51, 1.36–1.67, [I^2: 62.7%]). Increase of BMI unit was also associated with higher risk of low eGFR (1.02, 1.01–1.03, [I^2: 24.3%]) and albuminuria (1.02, 1.00–1.04, [I^2: 0%]). Conversely, overweight did not predict onset of either low eGFR (1.06, 0.94–1.21, [I^2: 50.0%]) or albuminuria (1.24, 0.98–1.58, [I^2: 49.4%]). Thus, a high BMI predicts onset of albuminuria without kidney failure (CKD stages 1–2) as well as CKD stages 3 and higher, the effect being significant only in obese individuals. Hence, our findings may have implications to improve risk stratification and recommendations on body weight control in the general population.

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Obesity is now considered a global public health challenge, with a growing worldwide prevalence.[1] According to the most recent estimates, age-standardized prevalence of obesity will increase from 11% to 18% in men and from 15% to 21% in women by 2025.[2]

Besides the worrisome prevalence, obesity markedly increases the risk of developing hypertension, diabetes, and cardiovascular disease.[3]

Conversely, the association between obesity and chronic kidney disease (CKD) remains controversial. CKD is now recognized as a health priority worldwide due to the negative effects on prognosis and the quality of life of patients, and on the economic resources of countries.[4–6]

Previous analyses detected the association between higher body mass index (BMI) and risk for end-stage renal disease (ESRD) in the general population. However, in most of these studies (with the exception of the study by Hsu *et al.*[7]), the results were flawed by the inclusion of patients with CKD at baseline and lack of adjustment for a baseline estimated glomerular filtration rate (eGFR)[7–11]; these 2 aspects represented a relevant bias because presence of CKD *per se* increases the risk of ESRD. Moreover, the several studies that investigated the role of obesity at the onset of overt CKD provided controversial results, with more recent and larger studies suggesting a predictive role[12–18] that was not confirmed by others.[19–24] No systematic analysis has formally addressed this issue. Only 1 meta-analysis of 19 cohort studies that involved approximately 6.3 million subjects showed a significant association between obesity and kidney disease[25]; however, these authors evaluated a highly heterogeneous renal endpoint, that is, a combination of ESRD, kidney stones, positive proteinuria at dipstick, renal cell carcinoma, and incident CKD (eGFR <60 ml/min/1.73 m^2). Because this latter endpoint was assessed in only 15,000 subjects enrolled in 2 cohort studies, no definitive conclusion could be drawn on the obesity-related risk of CKD. Therefore, whether high body mass index acts as independent predictor of new-onset CKD currently remains undefined.

To fill this relevant gap of knowledge, we performed a systematic review and meta-analysis of longitudinal cohorts derived from an adult general population, to quantify the predictive role of obesity, overweight, and BMI as continuous variables on the risk of new-onset CKD. This issue is critical to improve risk stratification, and consequently, to optimize

preventive strategies aimed at reducing CKD prevalence in the general population.

RESULTS

Characteristics of studies

After screening titles and abstracts, 106 of 5921 studies were considered (Figure 1). The full text of each article was reviewed by 2 authors, and 39 studies were included in the present meta-analysis. Agreement of 2 reviewers was good for study selection and quality assessment ($\kappa = 0.934$ and 0.849, respectively). The reasons for exclusion of 67 studies are shown in Figure 1.

Selected studies were grouped in 9 categories based on 3 predictors (obesity, overweight, BMI) and 3 outcomes (isolated low eGFR, isolated albuminuria, and CKD defined by either eGFR <60 ml/min/1.73 m^2 or albuminuria, whichever was used in a given report). When considering obesity as a predictor, 13 studies reported data on the risk of low eGFR,[12–24] 7 studies reported on isolated albuminuria,[13,14,17,19,23,26,27] and 3 studies reported on CKD.[19,28,29] When considering overweight as a predictor, 8 studies reported data on the risk of low eGFR,[15,18,20,23,24,30–32] and 2 studies reported on the risk of albuminuria.[23,26] BMI, as continuous variable, was analyzed in 13 studies that reported data on the risk of low eGFR,[15,24,33–43] 2 studies reported on the risk of albuminuria,[44,45] and 3 reported on CKD risk[46–47] (Table 1). Data on the measured incident rate of low eGFR related to obesity were available in only 1 study.[16] We also found 6 studies that evaluated the risk of low eGFR or CKD among obese subjects with and without metabolic syndrome.[12,13,48–51]

Selected studies are listed in Table 1. Overall, studies included information on 630,677 individuals. The sample size of these studies ranged from 454 to 123,764 participants. Age range of the selected cohorts was 35 to 76 years. Mean follow-up duration (6.8 years; range: 2.0–18.5), was >5 years in 23 studies and >10 years in 4 studies (Table 1). eGFR was estimated by the Modification of Diet in Renal Disease (MDRD) equation in 32 studies, whereas the remaining used the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Twenty-nine studies included Asian Pacific populations (n = 512,230 participants), that is, Japan (n = 16), Korea (n = 10), China (n = 2), and Thailand (n = 1), whereas 10 studies included Western populations (n = 118,447 participants), that is, United States (n = 7), Austria (n = 1), and Iran (n = 2). As described in Table 1, 32 studies adjusted for the main demographic characteristics, laboratory characteristics, and clinical comorbidities, whereas adjustment was performed only for age and sex in 3 studies and not adjusted in 1 study; however, in these latter 4 studies, the prevalence of previous cardiovascular events and diabetes was low (<10%). The quality score (range: 6–8 points) was high (Supplementary Table S1).

Demographic and main clinical characteristics of the populations examined in the included studies (n = 39) did not differ from those excluded because of lack of predictors (n = 38) (data not shown).

Obesity and development of CKD *de novo*

Overall, during a mean follow-up of 8.5 years, low eGFR occurred in 9.4% of participants (31,164 of 330,139). In

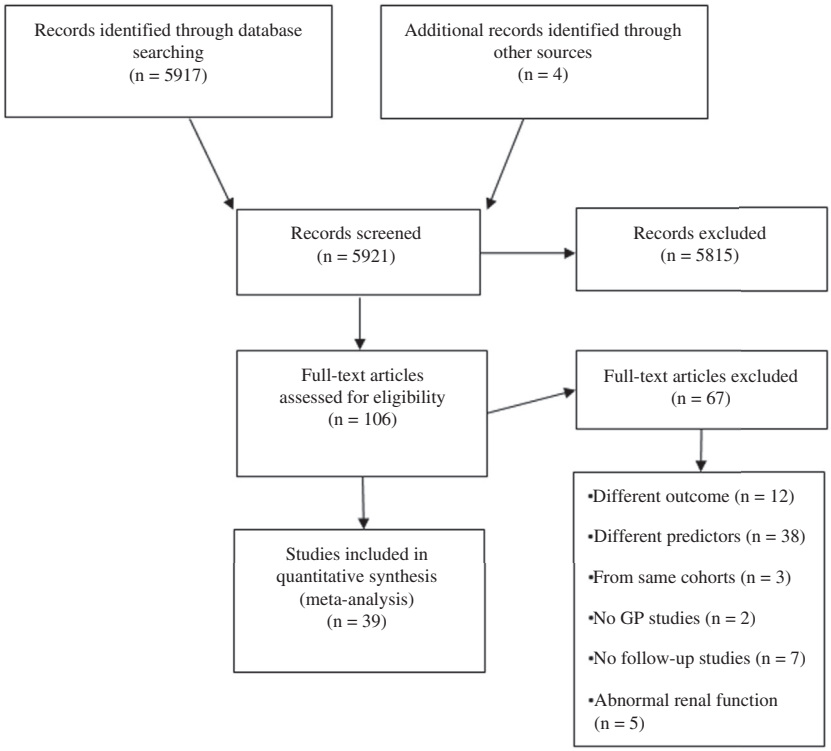

Figure 1 | Flow of selection for studies through review. GP, general population.