TITLE PAGE

Title: Can childhood obesity influence later CKD?

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ABSTRACT

Childhood overweight and obesity affects more and more children. Whilst associations of childhood overweight with later outcomes such as hypertension, diabetes and cardiovascular disease have been well documented, less is known about the association of childhood overweight and obesity with kidney disease. We review the existing evidence for the association of childhood obesity with markers of childhood and adult kidney disease. Whilst there is some evidence for an association, studies have not been able to distinguish between childhood being a sensitive time to develop later kidney problems, or whether observed associations of childhood obesity with poor outcomes are driven by greater lifelong exposure to obesity.

Keywords: Body mass index, Childhood, Obesity, Overweight, Kidney disease, Review

Introduction

Over the last two to three decades the prevalence of childhood overweight and obesity has increased in many parts of the world.[1,2] In developed countries, the prevalence of overweight or obesity has increased from 6.9% in boys and 16.2% in girls in 1980 to 23.8% in boys and 22.6% in girls in 2013. Over a similar time span, in developing countries the prevalence of overweight or obesity increased from 8.1% in boys and 8.4% in girls in 1980, to 12.9% in boys and 13.4% in girls.[3] The majority of overweight or obese children live in developing countries, where the rate of increase has been more than 30% higher than that in developed countries.[4]

Adulthood obesity has been identified as a risk factor for a variety of chronic conditions including hypertension, diabetes, heart disease, high cholesterol, stroke, and certain cancers.[5,6] Tracking of obesity from childhood into adulthood is acknowledged.[7] Correspondingly, research has also focused on the impact of childhood obesity on morbidity and premature mortality in adulthood.[8,9]

A growing number of studies have concluded that adulthood obesity increases the risk for kidney disease.[10] This may be a secondary effect after the development of diabetes and/or hypertension. A recent meta-analysis of 39 cohorts involving 630,677 participants who at baseline had no evidence of CKD and who had had a mean follow-up of 6.8 years [11], found that obesity increased the relative risk (RR, 95% Confidence Interval) of developing low eGFR (eGFR < 60 mL/min/1.73m^2): 1.28, 1.07–1.54 and albuminuria (1+ at dipstick or an albumin creatinine ratio of ≥3.4 mg/mmol): 1.51, 1.36–1.67. There is weak evidence in adults that bariatric surgery may improve renal function[12] but there have been no randomised controlled trials and there is a lack of long term follow up studies[13].

These findings may lead us to believe that childhood overweight or obesity will similarly increase the risk of adulthood kidney disease. However, few studies have directly examined this, and consequently our understanding is limited.

The aim of this review is to see whether there is any evidence for an association between obesity during childhood and adult CKD. This included examining the evidence for an association of obesity with renal function markers in childhood (including a discussion of the study designs involved and measurements used), renal function post paediatric renal transplantation that compare obese to non-obese recipients, the evidence for the effect of bariatric surgery on renal function in the paediatric age, before moving on to studies that examined the association of childhood obesity with adult CKD. Relevant literature was identified in Pubmed, Medline, Embase and Scopus using the following terms as well as MESH terms for: Obesity OR overweight OR weight gain OR body mass index OR metabolic syndrome AND Child OR children OR paediatric OR paediatrics OR adolescence OR teenage OR teenagers OR young AND microalbuminuria OR albuminuria Or proteinuria OR hyperfiltration OR glomerular filtration rate OR kidney OR renal and included only studies that had a full text available in English, leaving out numerous conference abstracts.

Studies in the paediatric age on the association of obesity with early markers of kidney disease

Discussion of study designs used in the paediatric age group

Studies carried out in paediatric populations on the possible association between childhood obesity and early changes in renal filtration and microalbuminuria are listed on Tables 1 and

2 respectively, and consisted of cross sectional studies, "case-control" studies and case series reports. The majority of studies have a cross sectional design where obesity and renal function are measured at the same point in time. A key step in establishing a causal role for obesity is that it should precede the measured effect on renal function. Therefore, cross sectional studies make it hard to attribute a causal effect of obesity on kidney function. Other studies are described as "case-control studies" and typically compared renal function in children who are obese (labelled by authors as "cases") to renal function in children who are not obese (labelled by authors as "controls"). We have used inverted commas, as this design is not a standard case-control design as defined by epidemiologists who would recruit cases (those with renal disease) and controls (those without renal disease) and investigate prevalence of recorded pre-existing obesity before onset of renal disease. In all "case-control" studies on this topic however, the same problem arises as for the cross-sectional studies – renal function is measured at the same time as the obesity status and therefore there cannot be any inference made on the direction of causality. In addition, there are many reasons to doubt whether participants recruited from obesity clinics and their comparator groups are truly representative (i.e. findings generalizable to the general population), and whether the comparisons made are valid, i.e. adjusted for confounding factors related to attending obesity clinics and factors related to recruiting controls. They are joined by a number of case series reports, which provide no comparison group. Well-powered prospective population based cohort studies would provide an opportunity to measure obesity prior to the onset of renal function abnormalities. They are likely to be less biased than case control studies, provided that losses to follow up are kept to a minimum. Unfortunately, to our knowledge, no such cohort studies have been carried out to date.

Problems of measuring obesity and kidney function in the paediatric age

The association has been measured most often either as the difference in mean estimated glomerular filtration rate (eGFR) which involve creatinine and less often on cystatin C concentrations or level of albuminuria or micro-albuminuria in obese children compared to children with normal weight for age and sex. Cystatin C based eGFR are believed to be less influenced than creatinine by changes in muscle mass[14]. In a meta-analysis of studies comparing creatinine to cystatin C based eGFR in adults and children, most of whom had some form of kidney disease, Roos et al[15] concluded that cystatin C was more accurate. The most commonly used measure for obesity is BMI with obesity and overweight classified according to WHO growth data[16]. Other measures such as waist circumference and waist to height ratio have also been used. Associations have been measured using either simple or adjusted correlation coefficients, with the measure of obesity and either eGFR or level of micro-albuminuria as continuous variables. These factors make the interpretation of the findings difficult. Differences in the findings may be explained further by differences in the range of BMI studied, age and sex of participants, age of onset of obesity and its duration, ethnicity, diet and other confounders as well as by differences in the choice of substrate and equations to estimate GFR and by differences in the conditions of measurements of urine albumin (e.g. diurnal effects, exercise, degree of hydration, timed versus spot samples, single or multiple urine sampling). In a large population based study involving 4,305 children aged 6.0 years Miliku et al [17] showed that BMI was not associated with creatinine based eGFR and that BMI was negatively associated with cystatin C based eGFR. The effect was relatively small (–0.61ml/min/1.73m^2, 95% CI –0.96 to –0.26 per unit increase in BMI standard deviation score (SDS), $p < 0.01$). However, they showed that creatinine based eGFR but not cystatin C based GFR was influenced by fat mass (2.68ml/min/1.73m^2, 95% CI 2.14 to 3.21 per 1 SD increase in fat mass percentage, $p<0.001$) and by lean mass percentage (-

2.74 ml/min/1.73m2, 95% CI –3.27 to –2.20 per unit increase in lean mass percentage, p<0.001).

Which statistical association answers the question?

In the search for "independent" effects of obesity, many studies present measures of effect adjusted for risk factors which may be on the causal pathway between obesity and renal function, for example blood pressure, insulin resistance, abdominal obesity, HbA1c. For epidemiologists the question is: Is Obesity a risk factor for CKD? This means that what is of most importance from a public health perspective is the overall effect of obesity, either acting through direct nephrotoxic effects or acting indirectly on the kidneys by its effects in rising blood pressure or causing diabetes with their ensuing effects on the kidneys. From this perspective the overall effect of obesity needs to take into account age, sex, smoking status, socio-economic status and possibly ethnicity, as the key confounders. Therefore, many of these studies are over-adjusted.

Main findings of studies to date

Table 1 summarises the findings of studies on eGFR in relation to obesity. The cross-sectional population based studies found a mix of positive, negative and no associations for eGFR with BMI, whilst for children from obese clinic populations compared to controls there seems to be more of a consistent positive association between eGFR and BMI. The study by Pacifico et al[18] showed that obese children were more likely than children with normal BMI to have a low eGFR as well as being more likely than children with normal BMI to hyperfiltrate. These findings might possibly be explained by a changing effect of obesity on eGFR depending on the duration of obesity. This is an important factor which has not been

measured in this study nor in any of the other listed studies, as most of these only assess overweight or obesity at a single time-point.

Most population-based studies on microalbuminuria have shown either no association with obesity or higher micro-albuminuria in children with normal BMI (Table 2). The reason for this is not clear and some authors have suggested that the finding of micro-albuminuria in non-obese children and adolescents might be confounded by orthostatic proteinuria. However, micro-albuminuria has been found in obese children in studies based on obesity clinics, possibly linked to higher blood pressure.

Paediatric obesity and renal allograft function

The situation in which a recipient receives a new kidney is a unique model in which the influence of recipient-specific factors such as obesity on the transplant kidney function can be prospectively explored. There are a number of retrospective studies on the effect of paediatric obesity on subsequent renal allograft function during childhood. Obesity is common in children receiving a renal transplant and the first 4 months post-transplantation have been found to be a particularly sensitive period for weight gain[19]. This is thought to be at least in part mediated by steroid immunosuppressive therapy [20].

In a retrospective review of the records of 76 renal allograft recipients from 1994-2000 Mitsnefes et al.[21] found pre-transplant obesity to be associated with decreased allograft function after renal transplantation. Paediatric patients who were obese (BMI $\geq$ 95th percentile) both prior to transplant and 1 year post-transplant had lower mean directly measured GFR than both those who were non-obese prior to transplant but became obese by 1 year post-transplant (46.1 ± 15.0 mL/min/1.73 m^2 v 57.7 ± 24.5 mL/min/1.73 m^2, $p < 0.05$)

and those who were non-obese prior to transplant and 1 year post-transplant (46.1 ± 15.0 mL/min/1.73 m^2 v 60.4 ± 21.5 mL/min/1.73 m^2, $p < 0.01$). The impact of paediatric obesity on long-term outcomes in paediatric patients with renal transplant was studied in an analysis of data from the North American Paediatric Renal Transplant Cooperative on 6658 paediatric age recipients. This showed that there had been an increase in the proportion of obese children from 8.2% in transplant recipients during the years 1987–1995 to 12.4% in children transplanted during the years 1996–2002[22]. This study found no overall difference in patient mortality nor graft survival between obese and non-obese children. However, in a post-hoc subgroup analysis it found a greater risk for death in obese children than non-obese children aged 6 to 12 years, and greater risk of living donor graft loss in obese than non-obese children aged 13-17 years. A study of 197 children from Brazil found decreased graft survival at 36 months post-transplant in children who had had an increase equal to or greater than 1 standard deviation in BMI between 1 month and 6 months post-transplant[20]. In a more recent study of 750 renal transplant recipients in Australia, aged 2 to 18 years and with a median follow-up of 8.4 years, obesity was associated with a 60% greater risk of graft loss (hazard ratio (HR) 1.61, 95% CI 1.05 – 2.47) compared to children with normal BMI. There was no association between BMI and acute allograft rejection[23].

In summary, there are some data from the paediatric transplant population suggesting that obesity of the transplant recipient may be associated with accelerated graft loss.

Effects of bariatric surgery on renal function in paediatric age patients

Another way of looking at this question is to investigate the effect of weight reduction through bariatric surgery performed in children and adolescents on their subsequent kidney function. In a case report published in 2009, Fowler et al[24] described the resolution of

proteinuria resistant to medical treatment after bariatric surgery on a 15 year old girl. This was associated with a reduction in her BMI from 56.8 to 32 kg/m^2 post-surgery. The impact of bariatric surgery on renal function was described in a cohort of 242 severely obese adolescents[25] with a mean age of 17±1.6 years, 29% of whom were aged 13-15 years. Post bariatric surgery there was an average increase in cystatin C based eGFR of 3.9 (95% CI 2.4–5.4) ml/min/1.73m^2 per 10 kg/m^2 decrease in BMI ($p<0.0001$). The majority of improvement in renal function occurred in those with a baseline eGFR of <90 ml/min/1.73 m^2, whose mean (+/-SD) baseline eGFR was 76 +/- 12 ml/min/1.73 m^2. In this group, eGFR improved by 34% to 102 +/- 28 ml/min/1.73 m^2 at the 3-year follow-up evaluation ($P < 0.0001$). Amongst children with albuminuria pre-surgery, there was a fall in the geometric mean from a pre-surgery level of 74 mg/g (95% CI 45–121 mg/g) to 17 mg/g (95% CI 10–28 mg/g) at 3 years ($P < 0.0001$) post bariatric surgery. In 69% of children albuminuria normalized by the 2-year follow-up evaluation, and in 75% albuminuria resolved by 3-years post bariatric surgery. This study did not have a comparator group, there were no standardised selection criteria for surgery, and in addition 24–29% of the 3 year follow up data were missing. It is important to recognise that bariatric surgery is often followed by a change in diet, and if proteinuria was related to high blood pressure in those sensitive to salt, then it may not have been the surgery itself driving those changes in proteinuria over time. The evidence from studies in adults has already been mentioned[13,12]. There have been no randomised controlled trials in adults and many of the studies are underpowered and potential confounding by factors such as those mentioned remains a possibility.

What do epidemiological studies in the paediatric age show?

In summary, there is clear evidence that childhood obesity is associated with cardiovascular risk factors in adulthood, and that obesity in adulthood is associated with markers of incident

CKD. The data are equivocal about whether an association between childhood obesity and renal function markers in childhood exists amongst children of the general population, whilst in clinic-populations of referred obese children there appears to be a subgroup of children with albuminuria and reduced eGFR. It may be that associations are difficult to detect depending on the timing of when the child was overweight and became obese, and how kidney function was measured (bearing in mind the limitations of creatinine based equations). In contrast, the evidence from the paediatric renal transplantation population is very suggestive in that those who are most obese have accelerated graft loss. In addition there are suggestive cross-sectional data on children aged between 5 and 19 years with eGFR of 30-90 mL/min/1.73 m^2 and a diagnosis of CKD participating in the prospective cohort "Chronic Kidney Disease in Children" (CKiD) [26] . Children were divided into non-glomerular (n=513) and glomerular (n = 224) forms of CKD. Using univariate linear regression, in the non-glomerular group BMI was not related to either urinary protein or eGFR but waist circumference (WC) was associated with an increase in urinary protein of 7.51% (95% CI 0.45 – 15.06, $p<0.05$) and no association with eGFR; in the glomerular group, BMI and WC were related to eGFR (BMI: 6.81%, 95% CI 2.67 – 11.12%, $p<0.0$; WC: by 4.34%, 95% CI 0.00 – 8.88%, $p<0.05$) but neither BMI nor WC were related to urinary protein. The main aim of the study was a comparison between BMI and WC as measures of obesity in this group of patients with established CKD and the conclusion was that WC added limited information to BMI in this cohort. However, these cross-sectional data suggest that the association of obesity with renal markers amongst children with CKD may depend on the type of underlying renal damage.

Epidemiological studies of the association of childhood obesity with adulthood kidney function

There have been a number of studies of risk factors with onset in childhood for CKD in adult life, either using ESRD or laboratory measurements to confirm CKD.

Muntner et al[27] reported on 15 cases of ESRD in the Bogalusa cohort. Seven of the cases of ESRD had an unknown aetiology and among other features they had a higher BMI recorded in childhood compared to their counterparts. This study was of limited scope given the weakness in the ascertainment of cases of ESRD and absence of detailed follow up data from childhood to the time when ESRD occurred.

Vivante et al. used a sample of 1.2 million Israelis examined prior to their military conscription at age 17 years in the period 1967-1997, linked to the Israeli ESRD registry for the period 1980-2010[28]. In an adjusted model, overweight (BMI between 85th and 95th centile) and obesity (BMI $\geq$ 95th centile) at age 17 years were both strongly associated with all-cause treated ESRD (HR 3.00, 95% CI: 2.50-3.60 and 6.89, 95% CI: 5.52-8.59, respectively). The authors could not adjust for confounders such as socioeconomic status or smoking.

A third, carefully designed matched case control study[29] examined the incidence of ESRD up to the age of 40 years in relation to risk factors measured in adolescence in males only using data collected at conscription to the Swedish Military service between 1970 and 1975 when most were aged 18 or 19 years of age. The National Patient Register was used to ascertain data on new cases of ESRD from 1985, at least 10 years after the conscription examinations, to reduce confounding by undiagnosed kidney disease in adolescence. There were 534 incident ESRD diagnoses and 5,127 men were selected as controls, representing the most powerful study to date. Elevated BMI at conscription was associated with increased

ESRD risk with an adjusted OR of 3.53 (95% CI 2.04-6.11, p<0.001) for BMI > 30 kg/m^2 compared to those with normal BMI (18.5-25kg/m^2). The odds for ESRD were also increased but to a lesser extent in those who had been overweight (BMI at conscription between 25 and 30 kg/m^2) with an adjusted OR of 2.36 (1.79-3.13, p<0.001) raising the possibility of a dose effect by BMI. The possible confounding effects of social status, and smoking, and the role of the subsequent BMI trajectory post conscription or current BMI were not examined.

In a nationwide population-based case control study using incident cases of CKD as defined by laboratory test results [30], overweight (BMI > 25 kg/m^2) at age 20 was associated with increased odds for CKD in middle-aged men and women, relative to BMI < 25 kg/m^2: OR (adjusted for age, education, smoking, alcohol, and use of paracetamol and salicylates) = 3.1 (95% CI 2.1 to 4.8) in males and 3.0 (95% CI 1.4 to 6.1) in females. The problem of this and other health record database studies using routine creatinine tests to examine this question is that people with BMI have more cardiovascular risk factors and therefore get tested earlier for presence/absence of kidney disease, which introduces information bias in favour of finding an association between BMI and incident CKD. As not everybody was tested the same way, no definitive conclusions can be drawn from this or similar routine health care studies.

To our knowledge the Medical Research Council National Survey of Health and Development (NSHD), a socially stratified sample of 5362 singleton children born in one week in March 1946 in England, Scotland and Wales was the first study to systematically examine the effect of overweight throughout childhood and adulthood on later kidney function in a general population cohort [31,32]. Repeated measurements of BMI between ages 2 and 20 years were used to derive childhood overweight latent classes (‘never’, ‘pre-

pubertal only', 'pubertal onset' or 'always'), which were then related to measures of CKD at age 60-64 years: creatinine- or cystatin C-based eGFR < 60 ml/min/1.73 m^2 or urine albumin-creatinine ratio (uACR) ≥ 3.5 mg/mmol. Relative to being in the never overweight latent class, being in the pubertal onset or always childhood overweight latent classes was associated with CKD at age 60-64 years when considering cystatin C-based eGFR (odds ratio (OR) 2.04, 95% CI 1.09, 3.82). The associations with CKD at age 60-64 years defined by creatinine-based eGFR (OR 1.27, 95% CI 0.71, 2.29) and uACR (OR 1.33, 95% CI 0.70, 2.54) were less marked but in the same direction. Adjustment for social class, lifestyle and health factors (e.g. smoking) had little impact on the effect estimates. The low prevalence of CKD (resulting in low statistical power) and the lack of repeated measurements of creatinine and cystatin C meaning that the CKD chronicity criterion was not met were limitations of the study[33].

Overall, there is some suggestive evidence from the NSHD cohort study, but otherwise studies may be affected by the co-occurrence of social deprivation and smoking.

Mechanisms

The mechanisms relating childhood obesity to later CKD are not well researched[34], which is perhaps unsurprising considering that a follow-up over several decades may be needed to detect associations.

From studies conducted in animals and adults, there is evidence that obesity can lead to inflammation, oxidative stress, abnormal lipid metabolism, activation of the renin-angiotensin-aldosterone system, and increased production of insulin and insulin resistance. These abnormalities could lead to haemodynamic abnormalities, lipotoxicity and inflammation in the kidneys constituting the main mechanisms for obesity related renal

damage[35]. It is thought that the most important mechanism might be haemodynamic abnormalities affecting the renal microvasculature leading to hyperfiltration, development of proteinuria and ultimately to glomerulosclerosis and a reduction in GFR [36-38] Studies in young people include a study in young men (mean age 18.4 years), where hyperfiltration was associated with overweight, elevated blood pressure, and low high-density lipoprotein cholesterol with multivariate-adjusted OR of glomerular hyperfiltration of 6.6 (95% CI 3.8-11.6), 1.8 (95% CI 1.0-3.0), and 2.5 (95% CI 1.5-4.3), respectively[39]. Franchini et al[40] found that the prevalence of microalbuminuria and hyperfiltration was similar between obese and youths with Type 1 diabetes and higher than their control peers (6.0 vs. 8.0 vs. 0%, p=0.02; 15.9 vs. 15.9 vs. 4.3%, p=0.03, respectively). Possible mechanisms mediating paediatric kidney injury and are thought to include inappropriate activation of the renal angiotensin aldosterone system, the inflammatory role of adipokines secreted by fat tissue such as leptin and adiponectin, renal effects of dyslipidaemia and insulin resistance.[41-43] Children who are overweight are at a higher risk of developing high blood pressure and diabetes, though there is a lack of evidence for effects independent of adulthood overweight.[8] A further study using NHSD data investigated the mediatory roles of diabetes, hypertension and obesity in the relationship between low birth weight and later renal function[44], and found that the observed association between low birth weight and low eGFR was not confounded by socioeconomic position and was not explained by diabetes or hypertension. There was some evidence that it was stronger in study members who were overweight in adulthood. These findings thus again suggested that overweight/obesity may accelerate kidney function loss in the presence of other kidney problems.

Challenges and future research directions

Although there is a plethora of studies looking at childhood obesity and renal function, they do not provide enough evidence for a direct causal pathway between childhood obesity and adult CKD. The evidence that obesity is associated negatively with renal function in the paediatric age is not conclusive, and it may be instead that obesity may accelerate renal function loss in the context of other (subclinical) renal damage.

One deficiency in research to date, has been an inability to distinguish whether the effects of childhood obesity on CKD are due to childhood obesity in and of itself (i.e. that childhood is a 'critical period' or a 'sensitive period'[45]), or whether the observed effect is merely due to childhood obesity been indicative of greater lifelong exposure to obesity pressure (i.e. an 'accumulation of risk'[45]). In addition, to date authors have not fully explored the role of other factors that co-occur with obesity such as a bad diet with high calories and salt leading to both obesity and high blood pressure. The challenge of research investigating the question whether childhood obesity causes kidney damage independently of adulthood obesity ('sensitive period') is the statistical necessity to have sufficient subjects who become normal weight in adulthood after being obese in childhood to make analysis tenable, and the fact that reasons for weight loss and the way weight loss occurs may itself impact on kidney health. There were very few subjects in the NSHD data who lost weight which meant that data were not available to address this important question.[32]

The number of years lived with adulthood obesity are known to be directly associated with the risk of all-cause and cause-specific mortality[46]. Since the obesity-related metabolic, oxidative and inflammatory damage to many tissues and organs may accumulate over time,[47] kidney dysfunction resulting from lifelong obesity beginning in childhood would not be unexpected. To date we have not seen evidence that CKD prevalence or ESRD

incidence increase as a result of increasing prevalence of childhood obesity. However, based on the data from the NHSD, the lag time between childhood overweight and adult CKD may well be several decades.[32,31]

It is unclear whether childhood obesity causes pre-adulthood kidney damage. A further investigation of this question would require repeated follow up of very sensitive kidney function markers in a prospective birth cohort study. In general population cohorts this necessitates large sample sizes. Such a study should carefully characterise nutrition and physical activity to better understand which of the pathways that lead to obesity may have most impact on kidney health.

The finding that obesity strengthens the association of low birth weight with later poorer kidney function is particularly worrying in the setting of low middle income countries which are undergoing a rapid rate of urbanization with an associated rise in obesity.[48] Indeed, in the Indian Migrant study, the years lived in urban settings were associated with decreased eGFR amongst rural-urban migrants in age-adjusted analyses[49].

Conclusions

The association between adulthood obesity and kidney disease is well-documented, but the evidence for a similar effect of childhood obesity is patchy. Although there remains much research to be done in this area, in view of the overall impact of childhood obesity on health it is becoming apparent that efforts to prevent and treat obesity early in life could potentially have an impact on the progression, costs and comorbidities of kidney disease[43]. It is thought that reducing the amount of time that individuals live with obesity ("obesity-years")

by preventing early onset may be critical in minimising a variety of long-term hazards of obesity on health[47].

REFERENCES

1. de Onis M, Blossner M, Borghi E (2010) Global prevalence and trends of overweight and obesity among preschool children. The American journal of clinical nutrition 92 (5):1257-1264. doi:10.3945/ajcn.2010.29786
2. Wang Y, Lobstein T (2006) Worldwide trends in childhood overweight and obesity. International journal of pediatric obesity : IJPO : an official journal of the International Association for the Study of Obesity 1 (1):11-25
3. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, Mullany EC, Biryukov S, Abbafati C, Abera SF, Abraham JP, Abu-Rmeileh NME, Achoki T, AlBuhairan FS, Alemu ZA, Alfonso R, Ali MK, Ali R, Guzman NA, Ammar W, Anwari P, Banerjee A, Barquera S, Basu S, Bennett DA, Bhutta Z, Blore J, Cabral N, Nonato IC, Chang J-C, Chowdhury R, Courville KJ, Criqui MH, Cundiff DK, Dabhadkar KC, Dandona L, Davis A, Dayama A, Dharmaratne SD, Ding EL, Durrani AM, Esteghamati A, Farzadfar F, Fay DFJ, Feigin VL, Flaxman A, Forouzanfar MH, Goto A, Green MA, Gupta R, Hafezi-Nejad N, Hankey GJ, Harewood HC, Havmoeller R, Hay S, Hernandez L, Husseini A, Idrisov BT, Ikeda N, Islami F, Jahangir E, Jassal SK, Jee SH, Jeffreys M, Jonas JB, Kabagambe EK, Khalifa SEAH, Kengne AP, Khader YS, Khang Y-H, Kim D, Kimokoti RW, Kinge JM, Kokubo Y, Kosen S, Kwan G, Lai T, Leinsalu M, Li Y, Liang X, Liu S, Logroscino G, Lotufo PA, Lu Y, Ma J, Mainoo NK, Mensah GA, Merriman TR, Mokdad AH, Moschandreas J, Naghavi M, Naheed A, Nand D, Narayan KMV, Nelson EL, Neuhouser ML, Nisar MI, Ohkubo T, Oti SO, Pedroza A, Prabhakaran D, Roy N, Sampson U, Seo H, Sepanlou SG, Shibuya K, Shiri R, Shiue I, Singh GM, Singh JA, Skirbekk V, Stapelberg NJC, Sturua L, Sykes BL, Tobias M, Tran BX, Trasande L, Toyoshima H, van de Vijver S, Vasankari TJ, Veerman JL, Velasquez-Melendez G, Vlassov VV, Vollset SE, Vos T, Wang C, Wang X, Weiderpass E, Werdecker A, Wright JL, Yang YC, Yatsuya H, Yoon J, Yoon S-J, Zhao Y, Zhou M, Zhu S, Lopez AD, Murray CJL, Gakidou E (2014) Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet 384 (9945):766-781. doi:10.1016/S0140-6736(14)60460-8
4. World Health Organization (2018) Facts and figures on childhood obesity. http://www.who.int/end-childhood-obesity/facts/en/. Accessed 4th February 2018 2018
5. Prospective Studies C Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. The Lancet 373 (9669):1083-1096. doi:10.1016/S0140-6736(09)60318-4
6. Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, Qizilbash N, Peto R, Collins R (2007) Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet (London, England) 370 (9602):1829-1839. doi:S0140-6736(07)61778-4 [pii] 10.1016/S0140-6736(07)61778-4
7. Singh AS, Mulder C, Twisk JW, van Mechelen W, Chinapaw MJ (2008) Tracking of childhood overweight into adulthood: a systematic review of the literature. Obesity reviews : an official journal of the International Association for the Study of Obesity 9 (5):474-488. doi:OBR475 [pii] 10.1111/j.1467-789X.2008.00475.x
8. Park MH, Falconer C, Viner RM, Kinra S (2012) The impact of childhood obesity on morbidity and mortality in adulthood: a systematic review. Obes Rev 13 (11):985-1000. doi:10.1111/j.1467-789X.2012.01015.x

9. Reilly JJ, Kelly J (2011) Long-term impact of overweight and obesity in childhood and adolescence on morbidity and premature mortality in adulthood: systematic review. International journal of obesity (2005) 35 (7):891-898. doi:10.1038/ijo.2010.222
10. Wang Y, Chen X, Song Y, Caballero B, Cheskin LJ (2008) Association between obesity and kidney disease: a systematic review and meta-analysis. Kidney Int 73 (1):19-33. doi:5002586 [pii]
10.1038/sj.ki.5002586
11. Garofalo C, Borrelli S, Minutolo R, Chiodini P, De Nicola L, Conte G (2017) A systematic review and meta-analysis suggests obesity predicts onset of chronic kidney disease in the general population. Kidney international 91 (5):1224-1235
12. Neff KJ, Frankel AH, Tam FW, Sadlier DM, Godson C, le Roux CW (2013) The effect of bariatric surgery on renal function and disease: a focus on outcomes and inflammation. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 28 Suppl 4:iv73-82. doi:10.1093/ndt/gft262
13. Li K, Zou J, Ye Z, Di J, Han X, Zhang H, Liu W, Ren Q, Zhang P (2016) Effects of Bariatric Surgery on Renal Function in Obese Patients: A Systematic Review and Meta Analysis. PloS one 11 (10):e0163907. doi:10.1371/journal.pone.0163907
14. Levey AS, Becker C, Inker LA (2015) Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: a systematic review. Jama 313 (8):837-846
15. Roos JF, Doust J, Tett SE, Kirkpatrick CM (2007) Diagnostic accuracy of cystatin C compared to serum creatinine for the estimation of renal dysfunction in adults and children--a meta-analysis. Clinical Biochemistry 40 (5-6):383-391
16. World Health Organization Growth Standards. http://www.who.int/childgrowth/en/. 2017
17. Miliku K, Bakker H, Dorresteijn EM, Cransberg K, Franco OH, Felix JF, Jaddoe VW (2017) Childhood Estimates of Glomerular Filtration Rate Based on Creatinine and Cystatin C: Importance of Body Composition. American journal of nephrology 45 (4):320-326
18. Pacifico L, Bonci E, Andreoli GM, Di Martino M, Gallozzi A, De Luca E, Chiesa C (2016) The impact of nonalcoholic fatty liver disease on renal function in children with overweight/obesity. International journal of molecular sciences 17 (8) (no pagination) (1218)
19. Plumb LA, Pitcher D, Tse Y, Shield JP, Inward C, Sinha MD (2014) Longitudinal changes in body mass index following renal transplantation in UK children. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 29 (1):196-203. doi:10.1093/ndt/gft395
20. Boschetti SB, Nogueira PC, Pereira AM, Fisberg M, Pestana JO (2013) Prevalence, risk factors, and consequences of overweight in children and adolescents who underwent renal transplantation--short- and medium-term analysis. Pediatr Transplant 17 (1):41-47. doi:10.1111/petr.12020
21. Mitsnefes MM, Khoury P, McEnery PT (2002) Body mass index and allograft function in pediatric renal transplantation. Pediatric nephrology (Berlin, Germany) 17 (7):535-539. doi:10.1007/s00467-002-0863-9
22. Hanevold CD, Ho PL, Talley L, Mitsnefes MM (2005) Obesity and renal transplant outcome: a report of the North American Pediatric Renal Transplant Cooperative Study. Pediatrics 115 (2):352-356. doi:10.1542/peds.2004-0289
23. Ladhani M, Lade S, Alexander SI, Baur LA, Clayton PA, McDonald S, Craig JC, Wong G (2017) Obesity in pediatric kidney transplant recipients and the risks of acute rejection, graft loss and death. Pediatric Nephrology 32 (8):1443-1450
24. Fowler SM, Kon V, Ma L, Richards WO, Fogo AB, Hunley TE (2009) Obesity-related focal and segmental glomerulosclerosis: normalization of proteinuria in an adolescent after

bariatric surgery. Pediatric nephrology (Berlin, Germany) 24 (4):851-855. doi:10.1007/s00467-008-1024-6
25. Nehus EJ, Khoury JC, Inge TH, Xiao N, Jenkins TM, Moxey-Mims MM, Mitsnefes MM (2017) Kidney outcomes three years after bariatric surgery in severely obese adolescents. Kidney international 91 (2):451-458. doi:10.1016/j.kint.2016.09.031
26. Patel HP, Saland JM, Ng DK, Jiang S, Warady BA, Furth SL, Flynn JT (2017) Waist Circumference and Body Mass Index in Children with Chronic Kidney Disease and Metabolic, Cardiovascular, and Renal Outcomes. Journal of Pediatrics 191:133-139
27. Muntner P, Arshad A, Morse SA, Patel DA, Manapatra PD, Reisin E, Aguilar EA, Chen W, Srinivasan S, Berenson GS (2009) End-stage renal disease in young black males in a black-white population: longitudinal analysis of the Bogalusa Heart Study. BMC nephrology 10:40. doi:10.1186/1471-2369-10-40
28. Vivante A, Golan E, Tzur D, Leiba A, Tirosh A, Skorecki K, Calderon-Margalit R (2012) Body mass index in 1.2 million adolescents and risk for end-stage renal disease. Arch Intern Med 172 (21):1644-1650. doi:1387591 [pii]
10.1001/2013.jamainternmed.85
29. Sundin PO, Udumyan R, Sjostrom P, Montgomery S (2014) Predictors in adolescence of ESRD in middle-aged men. American journal of kidney diseases : the official journal of the National Kidney Foundation 64 (5):723-729. doi:10.1053/j.ajkd.2014.06.019
30. Ejerblad E, Fored CM, Lindblad P, Fryzek J, McLaughlin JK, Nyren O (2006) Obesity and risk for chronic renal failure. Journal of the American Society of Nephrology : JASN 17 (6):1695-1702. doi:10.1681/asn.2005060638
31. Silverwood RJ, Pierce M, Thomas C, Hardy R, Ferro C, Sattar N, Whincup P, Savage C, Kuh D, Nitsch D (2013) Association between younger age when first overweight and increased risk for CKD. J Am Soc Nephrol 24 (5):813-821. doi:ASN.2012070675 [pii]
10.1681/ASN.2012070675
32. Silverwood RJ, Pierce M, Hardy R, Thomas C, Ferro C, Savage C, Sattar N, Kuh D, Nitsch D (2013) Early-life overweight trajectory and CKD in the 1946 British birth cohort study. American journal of kidney diseases : the official journal of the National Kidney Foundation 62 (2):276-284. doi:10.1053/j.ajkd.2013.03.032
33. Stevens PE, Levin A (2013) Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Annals of internal medicine 158 (11):825-830. doi:1691737 [pii]
10.7326/0003-4819-158-11-201306040-00007
34. Yim HE, Yoo KH (2015) Early life obesity and chronic kidney disease in later life. Pediatric Nephrology 30 (8):1255-1263
35. Wahba IM, Mak RH (2007) Obesity and obesity-initiated metabolic syndrome: mechanistic links to chronic kidney disease. Clinical journal of the American Society of Nephrology : CJASN 2 (3):550-562. doi:10.2215/cjn.04071206
36. Helal I, Fick-Brosnahan GM, Reed-Gitomer B, Schrier RW (2012) Glomerular hyperfiltration: definitions, mechanisms and clinical implications. Nature reviews Nephrology 8 (5):293-300. doi:10.1038/nrneph.2012.19
37. Henegar JR, Bigler SA, Henegar LK, Tyagi SC, Hall JE (2001) Functional and structural changes in the kidney in the early stages of obesity. Journal of the American Society of Nephrology : JASN 12 (6):1211-1217
38. Wolf G, Chen S, Han DC, Ziyadeh FN (2002) Leptin and renal disease. American journal of kidney diseases : the official journal of the National Kidney Foundation 39 (1):1-11. doi:S0272-6386(02)86423-X [pii]
10.1053/ajkd.2002.29865

39. Tomaszewski M, Charchar FJ, Maric C, McClure J, Crawford L, Grzeszczak W, Sattar N, Zukowska-Szczechowska E, Dominiczak AF (2007) Glomerular hyperfiltration: a new marker of metabolic risk. Kidney international 71 (8):816-821. doi:10.1038/sj.ki.5002160
40. Franchini S, Savino A, Marcovecchio ML, Tumini S, Chiarelli F, Mohn A (2015) The effect of obesity and type 1 diabetes on renal function in children and adolescents. Pediatric Diabetes 16 (6):427-433
41. Marlais M, Coward RJ (2015) Paediatrics, insulin resistance and the kidney. Pediatric Nephrology 30 (8):1217-1224
42. Gunta SS, Mak RH (2013) Is obesity a risk factor for chronic kidney disease in children? Pediatric nephrology (Berlin, Germany) 28 (10):1949-1956. doi:10.1007/s00467-012-2353-z
43. Savino A, Pelliccia P, Chiarelli F, Mohn A (2010) Obesity-related renal injury in childhood. Hormone research in paediatrics 73 (5):303-311. doi:10.1159/000308161
44. Silverwood RJ, Pierce M, Hardy R, Sattar N, Whincup P, Ferro C, Savage C, Kuh D, Nitsch D (2013) Low birth weight, later renal function, and the roles of adulthood blood pressure, diabetes, and obesity in a British birth cohort. Kidney Int 84 (6):1262-1270. doi:ki2013223 [pii]
10.1038/ki.2013.223
45. Kuh D, Ben-Shlomo Y, Lynch J, Hallqvist J, Power C (2003) Life course epidemiology. Journal of epidemiology and community health 57 (10):778-783
46. Abdullah A, Wolfe R, Stoelwinder JU, de Courten M, Stevenson C, Walls HL, Peeters A (2011) The number of years lived with obesity and the risk of all-cause and cause-specific mortality. International journal of epidemiology 40 (4):985-996. doi:dyr018 [pii]
10.1093/ije/dyr018
47. de Koning L, Hu FB (2011) Commentary: Obesity-years--a new metric to measure health effects of obesity. International journal of epidemiology 40 (4):996-997. doi:dyr053 [pii]
10.1093/ije/dyr053
48. Organization WH (2010) Global status report on noncommunicable disease. World Health Organization, Geneva
49. Bailey PK, Tomson CR, Kinra S, Ebrahim S, Radhakrishna KV, Kuper H, Nitsch D, Ben-Shlomo Y (2013) The effect of rural-to-urban migration on renal function in an Indian population: cross-sectional data from the Hyderabad arm of the Indian Migration Study. BMC nephrology 14:240. doi:10.1186/1471-2369-14-240
50. Lee AM, Charlton JR, Carmody JB, Gurka MJ, Deboer MD (2017) Metabolic risk factors in nondiabetic adolescents with glomerular hyperfiltration. Nephrology Dialysis Transplantation 32 (9):1517-1524
51. Tajbakhsh R, Heshmat R, Safiri S, Vafaeenia M, Motlagh ME, Mansourian M, Beshtar S, Safari O, Asayesh H, Ansari H, Qorbani M, Kelishadi R (2017) Association of glomerular filtration rate with cardiometabolic risk factors in Iranian adolescents CASPIAN III study. Iranian Journal of Kidney Diseases 11 (5):345-351
52. Marmarinos A, Garoufi A, Panagoulia A, Dimou S, Drakatos A, Paraskakis I, Gourgiotis D (2016) Cystatin-C levels in healthy children and adolescents: Influence of age, gender, body mass index and blood pressure. Clinical Biochemistry 49 (1):150-153
53. Correia-Costa L, Afonso AC, Schaefer F, Guimaraes JT, Bustorff M, Guerra A, Barros H, Azevedo A (2015) Decreased renal function in overweight and obese prepubertal children. Pediatric research 78 (4):436-444. doi:10.1038/pr.2015.130
54. Di Bonito P, Sanguigno E, Forziato C, Di Fraia T, Moio N, Cavuto L, Sibilio G, Iardino MR, Di Carluccio C, Capaldo B (2014) Glomerular filtration rate and cardiometabolic risk in an outpatient pediatric population with high prevalence of obesity. Obesity (Silver Spring) 22 (2):585-589. doi:10.1002/oby.20497

55. Ma YT, Xie X, Yang YN, Li XM, Zheng YY (2014) Relationship between serum creatinine and obesity in children in Xinjiang, China. Genetics and Molecular Research 13 (2):2409-2416
56. Soylemezoglu O, Duzova A, Yalcinkaya F, Arinsoy T, Suleymanlar G (2012) Chronic renal disease in children aged 5-18 years: A population-based survey in Turkey, the CREDIT-C study. Nephrology Dialysis Transplantation 27 (SUPPL. 3):iii146-iii151
57. Centers for Disease Control and Prevention. Growth Charts. Available at http://www.cdc.gov/growthcharts. Accessed on 22 January 2016.
58. Koulouridis E, Georgalidis K, Kostimpa I, Koulouridis I, Krokida A, Houliara D (2010) Metabolic syndrome risk factors and estimated glomerular filtration rate among children and adolescents. Pediatr Nephrol 25 (3):491-498. doi:10.1007/s00467-009-1364-x
59. Cindik N, Baskin E, Agras PI, Kinik ST, Turan M, Saatci U (2005) Effect of obesity on inflammatory markers and renal functions. Acta Paediatrica, International Journal of Paediatrics 94 (12):1732-1737
60. Hammer LD, Kraemer HC, Wilson DM, Ritter PL, Dornbusch SM (1991) Standardized percentile curves of body-mass index for children and adolescents. American journal of diseases of children (1960) 145 (3):259-263
61. Bartz SK, Caldas MC, Tomsa A, Krishnamurthy R, Bacha F (2015) Urine albumin-to-creatinine ratio: A marker of early endothelial dysfunction in youth. Journal of Clinical Endocrinology and Metabolism 100 (9):3393-3399
62. Falakaflaki B, Mazloomzadeh S, Moradzade A (2012) Comparison of renal function between normal-weight and overweight children. Indian Journal of Nephrology 22 (3):193-195
63. Savino A, Pelliccia P, Giannini C, de Giorgis T, Cataldo I, Chiarelli F, Mohn A (2011) Implications for kidney disease in obese children and adolescents. Pediatric nephrology (Berlin, Germany) 26 (5):749-758. doi:10.1007/s00467-010-1659-y
64. Xiao N, Jenkins TM, Nehus E, Inge TH, Michalsky MP, Harmon CM, Helmrath MA, Brandt ML, Courcoulas A, Moxey-Mims M, Mitsnefes MM (2014) Kidney function in severely obese adolescents undergoing bariatric surgery. Obesity (Silver Spring, Md) 22 (11):2319-2325. doi:10.1002/oby.20870
65. Larkins N, Teixeira-Pinto A, Craig J (2017) The population-based prevalence of albuminuria in children. Pediatric Nephrology 32 (12):2303-2309. doi:10.1007/s00467-017-3764-7
66. Cho H, Kim JH (2017) Prevalence of microalbuminuria and its associated cardiometabolic risk factors in Korean youth: Data from the Korea National Health and Nutrition Examination Survey. PloS one 12 (6):e0178716. doi:10.1371/journal.pone.0178716
67. Machluf Y, Fink D, Farkash R, Rotkopf R, Pirogovsky A, Tal O, Shohat T, Weisz G, Ringler E, Dagan D, Chaiter Y (2016) Adolescent BMI at Northern Israel: From trends, to associated variables and comorbidities, and to medical signatures. Medicine (United States) 95 (12) (no pagination) (e3022)
68. Gracchi V, Van Den Belt SM, Küpers LK, Corpeleijn E, De Zeeuw D, Heerspink HJL (2016) Prevalence and distribution of (micro)albuminuria in toddlers. Nephrology Dialysis Transplantation 31 (10):1686-1692. doi:10.1093/ndt/gfv407
69. Gurecka R, Koborova I, Sebek J, Sebekova K (2015) Presence of cardiometabolic risk factors is not associated with microalbuminuria in 14-to-20-years old Slovak adolescents: A cross-sectional, population study. PloS one 10 (6) (no pagination) (e0129311)
70. Rutkowski B, Czarniak P, Krol E, Szczeoniak P, Zdrojewski T (2013) Overweight, obesity, hypertension and albuminuria in polish adolescents-results of the sopkard 15 study. Nephrology Dialysis Transplantation 28 (SUPPL.4):iv204-iv211

71. Okpere AN, Anochie IC, Eke FU (2012) Prevalence of microalbuminuria among secondary school children. African Health Sciences 12 (2):140-147
72. Hirschler V, Molinari C, Maccallini G, Aranda C (2010) Is albuminuria associated with obesity in school children? Pediatric Diabetes 11 (5):322-330. doi:10.1111/j.1399-5448.2009.00599.x
73. Haysom L, Williams RE, Hodson EM, Lopez-Vargas P, Roy LP, Lyle DM, Craig JC (2009) Cardiovascular risk factors in Australian indigenous and non-indigenous children: A population-based study. Journal of Paediatrics and Child Health 45 (1-2):20-27
74. Haysom L, Williams R, Hodson E, Lopez-Vargas P, Roy LP, Lyle D, Craig JC (2009) Risk of CKD in Australian Indigenous and Nonindigenous Children: A Population-Based Cohort Study. American Journal of Kidney Diseases 53 (2):229-237
75. Haysom L, Williams R, Hodson EM, Lopez-Vargas PA, Roy LP, Lyle DM, Craig JC (2009) Natural history of chronic kidney disease in Australian indigenous and non-indigenous children: A 4-year population-based follow-up study. Medical Journal of Australia 190 (6):303-306
76. Nguyen S, McCulloch C, Brakeman P, Portale A, Hsu CY (2008) Being overweight modifies the association between cardiovascular risk factors and microalbuminuria in adolescents. Pediatrics 121 (1):37-45
77. Jafar TH, Chaturvedi N, Hatcher J, Khan I, Rabbani A, Khan AQ, Portman R, Schmid CH, Levey AS (2005) Proteinuria in South Asian children: prevalence and determinants. Pediatric Nephrology 20 (10):1458-1465
78. Csernus K, Lanyi E, Erhardt E, Molnar D (2005) Effect of childhood obesity and obesity-related cardiovascular risk factors on glomerular and tubular protein excretion. European Journal of Pediatrics 164 (1):44-49
79. Radhakishun NNE, Van Vliet M, Von Rosenstiel IA, Beijnen JH, Diamant M (2013) Limited value of routine microalbuminuria assessment in multi-ethnic obese children. Pediatric Nephrology 28 (7):1145-1149
80. Lurbe E, Torro MI, Alvarez J, Aguilar F, Fernandez-Formoso JA, Redon J (2013) Prevalence and factors related to urinary albumin excretion in obese youths. Journal of Hypertension 31 (11):2230-2236
81. Sanad M, Gharib A (2011) Evaluation of microalbuminuria in obese children and its relation to metabolic syndrome. Pediatric Nephrology 26 (12):2193-2199
82. Burgert TS, Dziura J, Yeckel C, Taksali SE, Weiss R, Tamborlane W, Caprio S (2006) Microalbuminuria in pediatric obesity: prevalence and relation to other cardiovascular risk factors. International journal of obesity (2005) 30 (2):273-280. doi:10.1038/sj.ijo.0803136

Table 1: Summary of studies on Childhood Obesity and early changes to GFR detected in childhood

Author, year of publication	n	Age in years	Sampling	Exposure	Outcome*	Findings	Direction of association between obesity and eGFR
Cross-sectional studies							
Lee, 2017[50] Population based	2584	12 – 17y	National Health and Nutrition Examination Survey (NHANES) population survey, USA	Metabolic risk factors including BMI z score, derived from own data	Hyperfiltration defined as eGFR ≥120 mL/min/1.73 m^2. Creatinine based eGFR (ml/min/1.73m2), Schwartz equation: 0.413 × height (cm)/ serum creatinine (mg/dL) Outcome measure: Adjusted Odds Ratio for hyperfiltration	BMI z score OR for hyperfiltration adjusted for sex, age, race and income: 0.96 (0.82–1.12), p = 0.578	=
Tajbakhsh, 2017 [51] Population based	367	10 – 18	Random sampling from national survey of 5625	BMI	Creatinine based e GFR (ml/min/1.73m^2), Schwartz equation: 0.413 × height (cm)/ serum	BMI: r = 0.121, p = 0.02	+

			rural and urban school based children: Childhood and Adolescence Surveillance and Prevention of Adult Noncommunicable Disease III (CASPIAN III), Iran	Waist circumference Waist-height ratio	creatinine (mg/dL) Outcome measure: Correlation coefficient	Waist circumference: r = 0.190, p< .001 Waist-height ratio: r = 0.070, p = 0.18	+ =
Marmarinos, 2016[52] Population based	536	4 – 17	Teaching hospital paediatric clinic, excluding children with chronic conditions or on anti-inflammatory agents, diuretics, anticonvulsants and antibiotics, Greece.	BMI	Cystatin-C (mg/L) Outcome measure: Multivariate regression coefficient	Regression coefficient for BMI (β) adjusted for sex, age (in a variable category that indicates the existence of puberty) and blood pressure: β: +0.03 (0.01, 0.04) p=0.001	-
Correia-Costa, 2015[53] Population based	313	8 – 9y	Birth cohort Generation XXI, Portugal	BMI z-score based on WHO growth data[16]	Creatinine-based and cysteine-C based eGFR: using Schwartz, Filler, Zappitelli-Comb, Schwartz-Comb formulae (ml/min/1.73m^2) and 24 hour creatinine clearance.	Regression coefficient (β) for BMI z score, adjusted for age and sex: eGFR Schwartz-R: -0.51 (-2.17 –1.16), p=0.548	=

					Outcome measure: Multivariate linear regression coefficient	Filler eGFR: −4.26 (−5.77 to −2.74), p < 0.001 Zapitelli-Comb: −2.77 (−4.16 to −1.38), p < 0.001 Schwartz-Comb: −1.10 (−2.01 to −0.18), p = 0.014. 24h Cr Cl: −3.54 (−6.52 to −0.57), p = 0.020	- - - -
Di Bonito, 2014[54] Population based	901	6 – 16y	General paediatric clinic with diagnosis of allergy, gastro-oesophageal reflux, overweight, obesity, excluding chronic liver, renal cardiac,	BMI	Creatinine based eGFR (ml/min/1.73m^2), Schwartz formula: 0.413 x height (cm)/serum creatinine (mg=dl). eGFR: mild-low eGFR (< 20th percentile), high eGFR (>80th percentile), and intermediate eGFR (20-	BMI in: low-mid eGFR = 26+/-6 Intermediate eGFR = 25+/-6 high eGFR 26+/-6, p=0.10	=

			endocrine and infection conditions, Italy		80th percentile and considered as the reference category) Outcome measure: Comparison of mean BMI		
Ma, 2014 [55] Population based	5222	6 – 17	Stratified sampling by ethnic group, China	BMI	Creatinine (μM) Outcome measure: Multivariate linear regression coefficient	Regression coefficient for BMI (β) adjusted for uric acid, glucose, triglycerides, cholesterol, high and low-density cholesterol (but not height): β (6 – 7y) = -0.113(SE 0.265), p=0.479 β (8 – 9y) = -0.37(SE 0.284), p=0.313 β (10 – 11y) = 0.041(SE 0.097), p=0.042; β (12 – 13y) = 0.081(SE 0.074), p<0.001 β (14 – 15y) = 0.18 (SE 0.093), p<0.001, β (16 – 17y) = 0.171(SE 0.22), p<0.01.	= = - - - -
Soylemezoglu, 2012[56]	3079	5 – 18	National population survey, cluster	BMI categories based on CDC	Creatinine based eGFR(ml/min/1.73m2), Schwartz formula:	eGFR in: Underweight:	-

Population based			sampling, Turkey	growth data[57].	k × length (cm)/creatinine (mg/dL) where k = 0.70 in males ≥13 years and 0.55 for the rest Outcome measure: Comparison of mean eGFR	133.30 ± 24.45 Normal: 129.19 ± 22.95 Overweight: 128.18 ± 22.79 Obese: 122.71 ± 21.64 ($p < 0.001$).	
Koulouridis, 2010 [58] Population based	166	3 – 18	Healthy children recruited from sport academies and through local media, Corfu	BMI Waist circumference	Creatinine based eGFR (ml/min/1.73m2), Schwartz formula: k x height(cm)/creatinine (mg/dl) x 88.4 where k = 61.9 in males ≥ 13y and 48.6 for the rest Outcome measure: Correlation coefficient	eGFR correlation coefficient: with BMI: r=0.28, p=0.0004 with Waist circumference: r=0.419, p<0.00001	+ +
Cindik, 2005[59] Population based	85	7 – 16	Obesity screening survey in two primary schools in two cities in two regions Turkey	BMI BMI categories Obese ≥ 95th, controls < 85th, using data from First National Health and	Creatinine based eGFR (mls/min), Leger formula: 56.7 x weight (kg) + 0.142 x height^2 (cm^2)]/serum creatinine (μmol/l) Outcome measure: Comparison of mean eGFR	eGFR in: Obese: 141.8+/-48.2 Controls: 118.6+/-28.4, p=0.092.	=

				Nutrition Examination Study, 1971 to 1974[60]		Correlation between BMI and eGFR: r=0.39 p=0.001	+
"Case[1]" control							
Pacifico 2016[18] "Case" control study	924	3 - 17	Hospital outpatient Clinics and from randomly selected local schools, Italy	BMI categories based on WHO growth data[16]	Creatinine based eGFR (ml/min/1.73m2), Schwartz equation: 0.413 × height (cm)/ serum creatinine (mg/dL) Outcome measure: Comparison of mean BMI	eGFR in: Obese: 115 (104–134) Normal: 108 (100–118), p<0.0001. Numbers with: eGFR < 90: mL/min/1.73 m2, Obese: 22 (6.7%) Normal: 1 (0.77%), p<0.01 eGFR > 139: mL/min/1.73 m2, Obese: 56 (17.0%) Normal: 6 (4.6%), p<0.0001	+ - +
Bartz, 2015[61] "Case" control study[2]	58	14 - 16	Medical centre and through media advertising, USA	BMI category and response to oral glucose tolerance test (OGT)	Creatinine based e GFR (ml/min/1.73m^2): Schwartz equation: 0.413 × height (cm)/ serum creatinine (mg/dL)	eGFR in: Normal BMI: 94.0+/- 4.6 Overweight and Normal OGT:	+

					Outcome measure: Comparison of mean eGFR	106.0+/-3.9 Overweight and pre-DM: 108.3+/-4.0. Normal vs Overweight-PreD, p=0.049 Linear regression model: percentage body fat β = 0.40, p = 0.03	 +
Franchini 2015[40] "Case" control study	318	6 – 18y	Obesity Clinic, Diabetic clinic and from admissions to paediatric ward for minor trauma, fractures, Italy	BMI z score (based on Italian reference values)	Creatinine and cysteine-C based eGFR: Bouvet formula: $63.2(1.2/\text{cysteine})^{0.56}$ $(1.09/\text{creatinine})^{0.35}$ $(\text{weight}/45)^{0.3}$ $(\text{age}/14)^{0.4}$ Outcome measures: Comparison of adjusted mean eGFR Multivariate linear regression coefficient	eGFR adjusted for age, sex, and pubertal stage: Obese = 116.15±1.67 Controls: 105.06±1.82 p <0.001 Type 1 DM with normal weight and Obese group had similar degree of hyperfiltration Linear regression coefficient (β) between BMI z-score and eGFR adjusted for age, sex and pubertal stage: r=0.328, p<0.001	+ +

Falakaflaki, 2012[62] "Case" control study	92	7-12y	School children, matched on age and sex, Iran	BMI categories based on 2000 CDC growth data[57]	Creatinine based e GFR (ml/min/1.73m2), Schwartz equation: k × height (cm)/ serum creatinine (mg/dL) Outcome measure: Comparison of mean eGFR	Overweight: 98.90 +/- 4.59 Normal: 96.37+/-3.73, p=0.49	=
Savino, 2011[63] "Case" control study	157	5 - 17	Obesity clinic, and from admissions to paediatric ward with minor illnesses, once recovered, Italy.	BMI categories: Obese= >97th percentile for age and sex. Normal: within 2 SD of the 50th centile	Creatinine based eGFR (ml/min/1.73m^2), Schwartz formula: k × length (cm)/creatinine (mg/dL) where k = 0.70 in males ≥13 years and 0.55 for the rest Outcome measure: Comparison of mean eGFR	Obese: 144.3 ± 26.7 Normal: 136.8 ± 12.7, p = >0.05.	=
"Case[3]" series:							
Xiao, 2014[64] "Case" series	242	≤19	Consecutive cases pre-bariatric surgery at each of five Teen-LABS centres, USA	BMI	Cystatin C-based eGFR (ml/min/1.73m^2): Larsson formula eGFR = 77.24 × (Cystatin-C)$^{-1.2623}$ Outcome measure: Multivariate linear regression coefficient	Regression coefficient (β) for BMI adjusted for sex, age, race, DM, hypertension, HOMA-IR, HbA1c, ferritin, serum albumin, transferrin, dyslipidaemia, kidney stones: β (per 10-unit increase in BMI): −7.90	-

						(−11.60,−4.20), p = < 0.01 .	

Abbreviations:
BMI = Body Mass Index, CDC = Centers for Disease Control and Prevention, DM = diabetes mellitus, eGFR = estimated Glomerular Filtration Rate, HOMA-IR = Homeostatic Model Assessment of Insulin Resistance, SD = standard deviation

Notes:
* = Some studies may have been designed to assess another primary outcome, however in this table we have listed the renal outcome of interest for this systematic review

[1] = cases defined by exposure = obesity

[2] = cases defined by exposure, group 1 = overweight and normal oral glucose test (OGT), group 2 = overweight and pre-diabetes (impaired fasting glucose or impaired glucose tolerance)

[3] = cases defined by exposure = obesity

Table 2: Summary of studies on Childhood Obesity and proteinuria detected in childhood

Author, year of publication, type of study	n	Age in years	Sampling	Exposure	Outcome*	Findings	Direction of association
Cross sectional studies:							
Larkins[65], 2017 population based	975	5 - 18	Australian Health Survey stratified, multistage area design population survey	Overweight or Obesity, based on WHO growth data[16]	Microalbuminuria defined as UACR ≥30 mg/g or ≥3.4 mg/mmol Outcome measure: Adjusted Odds Ratio for microalbuminuria	Overweight/Obese OR, adjusted for age and sex: 0.34 (0.15–0.75), p = 0.009	-
Cho[66], 2017 population based	1,976	10 - 19	Korean National Health and Nutrition Examination Survey (KNHANES)	Obesity, based on Korean National Growth Data Obesity = BMI ≥ 95th percentile or ≥ 25 kg/m^2	Microalbuminuria defined as UACR ≥ 30 mg/g and < 300 mg/g. Outcome measures: Comparison of prevalence Comparison of geometric means	Prevalence in: Obese: 1.7% Normal: 3.2% p=0.238 UACR (geometric mean +/- SE): Obese: 2.1 ± 0.2 Non-obese: 3.2 ± 0.1 p=0.001	= -

					Correlation coefficient	Univariate coefficient (r) (UACR log transformed v BMI-SDS): r = -0.19, p < 0.001)	-
Machluf[67], 2016 population based	113,694	17	Conscripts National Military Service, Israel	Obesity, based on national growth data on BMI: Obesity: > 95th percentile Normal 5th to <85th	Proteinuria: > 200 mg/24 h Outcome measure: Adjusted Odds Ratio for proteinuria	Obesity OR, adjusted for country of birth, country of origin, year of birth, religion, education, intelligence score, residential environment, family size, and blood pressure: 1.07 (0.59-1.94), p>0.05	=
Gracchi[68] 2016 population based	1288	2 -<3	Prospective birth cohort study, Netherlands	BMI	Log UACR Outcome measure: Univariate linear regression coefficient	β = 0.04 (−0.00–0.01), p = 0.063	=
Gurecka 2016[69], population based	2666	14 – 20	State schools, Slovakia	BMI Waist/Height ratio	Microalbuminuria defined as UACR 2.5–25.0 mg/mmol in boys, 3.5–35.0 mg/mmol in girls Outcome measures: Comparison of mean BMI Comparison of	Boys: BMI in: Normo-albuminuria group: 23.2 ± 3.8 Micro-albuminuria group: 21.8 ± 3.0, p<0.05 Waist/Height ratio in: Normo-albuminuria group: 0.45 ± 0.05	- -

					mean Waist/Height ratio	Micro-albuminuria group: 0.42 ± 0.04, p<0.01 Girls: BMI in: Normo-albuminuria group: 22.0±3.4 Micro-albuminuria group: 21.0±3.5, p>0.05 Waist/Height ratio in: Normo-albuminuria group: 0.43±0.05 Micro-albuminuria group: 0.43±0.05 p>0.05	= = =
					Multivariate regression	Neither BMI, nor Weight/Height ratio nor other cardiovascular factors found to be associated with microalbuminuria in multivariate model in either gender	
Rutkowski, 2013[70]	889	14 – 15	Independent schools, Poland	BMI	Albuminuria defined as UACR ≥30 mg	Correlation coefficient r	

population based				Waist to Height ratio (WHtR)	Outcome measure: Correlation coefficient	BMI= −0.198, p>0.05 WHtR= −0.151, p<0.01	= -
Okpere, 2012[71] population based	864	10 - 19	Secondary schools selected by multistage sampling, Nigeria	BMI categories based on CDC growth data[57]	Microalbuminuria defined by urine dipstick strip reading of 20mg/L or more Outcome measure: Adjusted Odds Ratio for microalbuminuria	Obesity OR adjusted for DM, hypertension, FH of DM, FH of hypertension: 0.859 (0.474 - 1.555) p>0.05	=
Hirschler, 2010[72] population based	1564	5 - 14	Random selection of schools, Argentina	BMI categories based on CDC growth data[57] BMI	UACR Natural log UACR (Log n UACR) Outcome measure: Multivariate linear regression coefficient Adjusted Odds Ratio for microalbuminuria	Log n UACR model, BMI β = –0.03; p < 0.001) adjusted by gender, waist circumference, age and systolic and diastolic blood pressure. Adjusted OR for UACR ≥ 3rd quartile by gender, waist circumference, age and systolic and diastolic blood pressure OR in Overweight/Obese: 0.77 (0.64–0.92)	- -

Haysom 2009[73] population based	2266	4 - 14	Government-run primary schools with high Aboriginal population, Australia	BMI SD quartiles based on international normative data SD (z) score	Albuminuria defined as UACR (mg/mmol) ≥ 3.4mg/mmol (on urine dipstick) Outcome measure: Adjusted Odds Ratio for albuminuria	OR for albuminuria by BMI quartile adjusted for ethnicity, age, gender, birthweight, blood pressure and categories of isolation, disadvantage and region. BMI SD -4.8 to -0.8: OR = 1 BMI SD -0.7 to 0.1: OR = 0.67 (0.44 – 1.04) BMI SD 0.2 – 0.7: OR = 0.65 (0.42 – 1.02) BMI SD 0.8 – 6.9: OR = 0.51 (0.32 – 0.82) (p<0.001)), p for trend <0.05	-
Haysom[1] 2009[74] population based	1,432	4 – 14 2-year follow up	Government-run primary schools with high Aboriginal population, Australia	BMI SD (z score)	Albuminuria defined as albumin-creatinine ratio of 3.4 mg/mmol or greater. Outcome measure: Adjusted Odds Ratio for microalbuminuria	Prevalence of Albuminuria: Baseline: 7.3% (Obesity Baseline: 7.1%) At 2 years: 1.5% (Obesity at 2 years 5.3%) OR for microalbuminuria adjusted for ethnicity, age, sex, birth weight, systolic blood pressure, diastolic blood pressure**,** isolation category,	= =

						disadvantage category and school, at 2-year follow up: BMI SD -4.8 to -0.8: OR 1 BMI SD -0.7 to 0.1: OR 0.83 (0.24 – 2.96) BMI SD 0.2 – 0.7: OR 1.31 (0.31 – 5.57) BMI SD 0.8 – 6.9: 0.15 (0.01 – 2.05, p>0.05	
Haysom[1] 2009[75] population based	1506	4 - 14 4-year follow up	Government-run primary schools with high Aboriginal population, Australia	Body mass index (BMI) SD (z Score)	Albuminuria defined as albumin-creatinine ratio of 3.4 mg/mmol or greater. Outcome measure: Adjusted Odds Ratio for microalbuminuria	Prevalence of Albuminuria: Baseline: 7.3% (Obesity Baseline: 7.1%) At 4 years: 2.4% (Obesity at 4 years 5.0%) BMI z score OR for microalbuminuria adjusted for ethnicity, age, sex, birth weight, systolic blood pressure, diastolic blood pressure, isolation category, disadvantage category and school, at 4-year follow up:	=

						BMI SD -4.8 to -0.8: OR 1 BMI SD -0.7 to 0.1: OR 1.07 (0.45–2.54) BMI SD 0.2 – 0.7: OR 0.73 (0.28–1.87) BMI SD 0.8 – 6.9: OR 0.66 (0.25–1.75), p>0.05	
Nguyen 2008[76] population based	2515	12 - 19	National Health and Nutrition Examination Survey	Overweight = (BMI of ≥95th percentile) Waist circumference	Microalbuminuria defined as UACR ≥30 mg/g and < 300 mg/g Outcome measure: Comparison of prevalence of microalbuminuria	Prevalence of microalbuminuria: non-Overweight = 8.7% Overweight = 0.3%, p = 0 .005 Prevalence of microalbuminuria: No abdominal obesity: 7.9% Abdominal Obesity: 1.0%, p = 0.03	- - -
Jafar 2005[77] population based	3621	5 - 14	National Health Survey of Pakistan (NHSP) over 4 years (1990–1994) by the	BMI	Proteinuria defined as ≥ 30 mg/dl (on urine dipstick)	BMI OR for proteinuria adjusted by height, socio-economic status,	=

			Pakistan Medical Research Council,		Outcome measure: Adjusted Odds Ratio for proteinuria	ethnicity, urban dwelling, systolic blood pressure: 0.96 (0.90–1.02), p>0.05	
Cindik, 2005 population based	85	7 – 16	Obesity screening survey in two primary schools in two cities in two regions Turkey	BMI categories Obese ≥ 95th, controls < 85th, using data from First National Health and Nutrition Examination Study, 1971 to 1974[60]	Urine microalbumin excretion (mg/24h) Outcome measure: Comparison of means of microalbuminuria	Urine microalbumin excretion in: Obese: 7.3+/-10.9 mg/24h Controls: 5.9+/-5.7 mg/24h, p=0.105	=
"Case^{2}" control studies:							
Pacifico, 2016[18] "Case" control	924	3 - 17	Hospital outpatient Clinics and from randomly selected local schools, Italy	Obesity, using WHO growth data[16]	Microalbuminuria defined as ≥30 mg/24h and < 300 mg/24h Outcome measure: Comparison of prevalence of microalbuminuria	Prevalence of Microalbuminuria: Obese: 13 (4.0%) Normal: 0 (0%), p<0.0001	+
Franchini, 2015[40] "Case" control	318	6 – 18y	Obesity Clinic, Diabetic clinic and from admissions to paediatric ward for minor trauma, fractures, Italy	BMI z-score	Log Albumin Excretion Rate (log AER) Microalbuminuria defined as AER = 20 – 200 μg/min	Log AER adjusted for age, sex, and pubertal stage: Obese = 0.978±0.022 Controls = 0.852±0.024,	+

					Outcome measures: Comparison of adjusted mean log AER Multivariate linear regression coefficient	p<0.001 Regression coefficient for BMI z-score adjusted for age, sex and pubertal stage: β = 0.135, p=0.017	+ +
Bartz, 2015[61] "Case" control study[3]	58	14 - 16	Medical centre and through media advertising, USA	BMI category and response to oral glucose tolerance test (OGT) Percentage body fat	Urine microalbumin excretion (UACR) (mg/g) Outcome measures: Comparison of mean UACR Correlation coefficient	Urine Microalbumin excretion in: Normal BMI group: 4.15+/- 0.53 Overweight and normal OGT: 6.03+/- 0.75 Overweight and pre_DM: 5.74+/- 0.98, p>0.05 Non-significant correlation between lnUACR and percentage body fat in multivariate model	= = = =

Falakaflaki, 2012[62] "Case" control study	92	7-12y	School children, matched on age and sex, Iran	BMI categories based on CDC growth data[57]	Albumin/creatinine ratio (ACR) Outcome measure: Comparison of mean ACR	Albumin/creatinine ratio in: Overweight: 0.049+/-0.04 Normal: 0.043+/-0.03, p=0.74	=
Savino, 2011[63] "Case" control study	157	5 - 17	Hospital Obesity clinic, and from admissions to paediatric ward with minor illnesses, once recovered, Italy.	BMI SD categories: Obese= >2SD for age and sex. Normal: within 2 SD of the 50th centile	Urine albumin excretion rate (AER) (μg/min) Outcome measure: Comparison of mean AER Correlation coefficient	Urine AER in: Obese: 10.2 ± 9.5 Non-Obese: 7.5 ± 1.9, p=0.010 Correlation coefficient BMI and AER: r=0.301, p=0.0001	+ +
Csernus, 2005[78] "Case" control study	165	8 - 17	Obesity clinic, Hungary	BMI Obesity defined as a ratio between actual body weight and the ideal body weight for age, gender and height > 1.2	UACR (mg/g) Outcome measures: Comparison of median UACR Correlation coefficient	Median UACR in: Obese = 11.7 mg/g, interquartile range 12.9 mg/g Normal = 9.0 mg/g, interquartile range 5.1 mg/g,	+

				(corresponding to overweight or obesity by WHO definition[16])		p = 0.003 Correlation between BMI v UACR: r =0.22, p <0.05	 +
"Case[4]" series							
Xiao, 2014[64] "Case" series	242	≤19	Consecutive cases pre- bariatric surgery at each of five Teen-LABS centres, USA	BMI	Microalbuminuria defined as UACR ≥30 mg/g < 300 mg/g Outcome measure: Multivariate linear regression coefficient	No association between BMI and UACR in model adjusted for sex, age, race, DM, hypertension, HOMA-IR, HbA1c**,** ferritin, serum albumin, transferrin, dislipaedaemia, kidney stones	=
Radhakishun, 2013[79] "Case" series	408	3 - 19	Paediatric Obesity clinic	BMI z score	Micro-albuminuria defined as UACR 2.5–25.0 mg/mmol in boys, 3.5–25.0 mg/mmol in girls Outcome measure: Comparison of mean BMIz score Adjusted Odds ratio for microalbuminuria	BMI z score: Microalbuminuria group 3.6±0.7 Normo-albuminuria group: 3.2±0.6, p = 0.047 BMI z score OR for microalbuminuria adjusted by sex, pubertal stage and ethnicity not given, p=0.054	+ =

Lurbe, 2013[80] "Case" series	134	9 - 18	Paediatric Obesity clinic	BMI z score based on WHO growth data[16] Overweight: 1 to <2.0 SDS Moderately Obese: 2.0 – 2.5 SDS Severely Obese: >2.5 SDS of 2.0 or more, namely, moderate obesity as a z score	Microalbuminuria defined as UACR ≥30 mg/g or in the "high-normal range" (UACR: 15–29 mg/g) Outcome measure: Correlation coefficient	Correlation coefficient BMI z score and log UACR: r=0.24, p<0.05	+
Sanad, 2011[81] "Case" series	150	2 - 11	Paediatric Obesity clinic, Egypt	BMI	Microalbuminuria defined as UACR ≥30 mg/g and <300 mg/g Outcome measure: Adjusted Odds Ratio for microalbuminuria	BMI OR for microalbuminuria adjusted for age, gender, abdominal obesity, hypertension, triglycerides, LDL, HDL insulin resistance and metabolic syndrome: 1.15 (1.02–4.55) p<0.01	+
Burgert, 2006[82] "Case" series	277	12 - 15	Obesity clinic USA	BMI z score	Microalbuminuria defined as UACR between 2mg/mmol and 20 mg/mmol	BMI z score in: Normal UACR group: 2.46 (2.41, 2.49) Microalbuminuria group: 2.39 (2.27, 2.51), p = 0.42	=

					Outcome measure: Comparison on mean BMI z score		

Abbreviations:
BMI = Body Mass Index, CDC = Centers for Disease Control and Prevention, DM = diabetes mellitus, HDL = high density lipoprotein, HOMA-IR = homeostatic model assessment of insulin resistance, LDL = low density lipoprotein, OR = odds ratio, SD = standard deviation, UACR = urine albumin-to-creatine ratio

Notes:
* = Some studies may have been designed to assess another primary outcome, however in this table we have listed the renal outcome of interest for this systematic review

[1] = this study was a prospective cohort but the data on BMI and albuminuria was analysed cross-sectionally

[2] = cases defined by exposure = obesity

[3] = cases defined by exposure, group 1 = overweight and normal oral glucose test (OGT), group 2 = overweight and pre-diabetes (impaired fasting glucose or impaired glucose tolerance)

[4] = cases defined by exposure = obesity