Risk factors for early chronic kidney disease

Date written: July 2012
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EVIDENCE SUMMARY

a. The following risk factors are associated with an appreciable (20%-40%) risk of CKD:
- **Obesity**
- **Hypertension**
- **Diabetes mellitus**
- **Cigarette smoking**
- **Established cardiovascular disease**
- **Age > 60 years**
- **Aboriginal and Torres Strait Islander peoples**
- **Maori and Pacific peoples**
- **Family history of stage 5 CKD or hereditary kidney disease in a first or second degree relative**
- **Severe socioeconomic disadvantage**

b. Metabolic syndrome is associated with an increased risk for CKD but it is still not known whether this constellation improves risk prediction beyond that afforded by its individual components (hypertension, impaired glucose tolerance, dyslipidaemia, etc.).

c. The presence of kidney stones is associated with a modest increased risk of CKD (approximately 6% absolute risk).

d. There is conflicting evidence regarding the roles of alcohol consumption and benign prostatic hypertrophy as risk factors for CKD.

UNGRADED SUGGESTIONS FOR CLINICAL CARE

There are no ungraded statements.

IMPLEMENTATION AND AUDIT

Kidney Check Australia Taskforce (KCAT) education programs for primary health care providers should incorporate the KHA-CARI Early CKD Lifestyle Modification recommendations.

BACKGROUND

Chronic kidney disease (CKD) is a major public health problem in Australia and throughout the world. Based on data from the AusDiab study [1], it is estimated that over 1.7 million Australian adults have at least moderately severe kidney failure, defined as an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2. This pernicious condition is often not associated with significant symptoms or urinary abnormalities and is unrecognized in 80-90% of cases [1-3]. CKD progresses at a rate that requires approximately 2300 individuals each year in Australia to commence either dialysis or kidney transplantation [4]. Furthermore, the presence of CKD is one of the most potent known risk factors for cardiovascular disease, such that individuals with CKD have a 2 to 3-fold greater risk of cardiac death than age- and sex-matched controls without CKD [5-7]. According to death certificate data, CKD directly or indirectly contributes to the deaths of approximately 10% of Australians and is one of the few diseases in which mortality rates are worsening over time [8]. However, timely identification and treatment of CKD can reduce the risks of cardiovascular disease and CKD progression by up to 50% [9].

General practitioners play a crucial role in CKD early detection and management. All people attending their general practitioner should be assessed for CKD risk factors as part of routine primary health encounters.

The objective of the current guideline is to identify what risk factors, present in an appreciable portion (>5%) of the community, are associated with the development of CKD and which are remediable or potentially modifiable, in order to detect early CKD and intervene at the earliest possible stage. The group also considered the recommendations in other guidelines and the evidence underpinning these recommendations.

SEARCH STRATEGY

Databases searched: Text words for chronic kidney disease were combined with MeSH terms and text words for risk factors, detection, predictors and putative risk factors (obesity, metabolic syndrome, diabetes mellitus, smoking, age, indigenous racial status, family history of kidney disease, alcohol, hyperuricaemia, cardiovascular disease, prostatism, benign prostatic hypertrophy, kidney stones, socioeconomic disadvantage, socioeconomic status). The search was carried out in Medline (1966 – 3 August 2009). No language restrictions were placed on the search. The conference proceedings of the American Society of Nephrology from 1994-2009 were also searched for trials. An updated search was carried out in Medline (2009 – Feb 2012). Text words and MeSH terms used for chronic kidney disease and risk factors were the same as for the previous search.

Date of search/es: 25 August 2009 and Feb 2012.

WHAT IS THE EVIDENCE?

Obesity

Obesity, defined as a body mass index [BMI] greater than 30 kg/m^2, has become an important public health challenge in Western countries. According to the recent AusDiab report [10], the prevalence of obesity in the Australian adult population is 20.5%, which is more than double the rate observed in 1980. Similar trends have been observed in other countries, such as the United States of America [11]. The obesity pandemic appears to be driving secondary epidemics of type II diabetes mellitus and hypertension, which in turn have resulted in rising rates of patients with chronic kidney disease (CKD) [12].

In 1974, Weisinger et al. [13] first reported an association between massive obesity and nephrotic-range proteinuria. Since that time, the development of glomerulomegaly and focal segmental glomerulosclerosis has been linked to massive obesity [14-17]. Unfortunately, all of these associations have been limited to case reports or small autopsy series. A recent review of 6818 native renal biopsies received from 1986 to 2000 by the Renal Pathology Laboratory of Columbia [18] Presbyterian Medical Center revealed a progressive increase in biopsy incidence of obesity-related glomerulopathy from 0.2% in 1986-1990 to 2.0% in 1996-2000. This condition appeared to be distinct from idiopathic focal segmental glomerulosclerosis, with a lower incidence of nephrotic syndrome, more indolent course, consistent presence of glomerulomegaly, and milder foot process fusion. Approximately half of these biopsies also revealed focal glomerular basement membrane thickening or focal mesangial sclerosis reminiscent of the changes seen in early diabetic nephropathy (even though the patients were not known to have abnormal glucose tolerance).

In addition to obesity-related glomerulopathy, a high BMI has also been reported to be associated with an increased risk of CKD in general, although results have been somewhat conflicting. In a cohort study of 101,516 Japanese men and women, BMI was inversely related to the risk of end-stage renal disease in women but not men.[19] In contrast, a cross-sectional analysis of the MDRD study observed a positive association between percentage body fat and BMI with glomerular filtration rate in patients with CKD [20]. Chen et al. [11] subsequently reported a cross-sectional study of over 6000 participants over the age of 20 enrolled in the Third National Health and Nutrition Examination Survey (NHANES III). They observed that obesity (defined as a waist circumference ≥ 102 cm in men and ≥ 88 cm in women) was associated with a multivariate-adjusted odds ratio of 2.07 (95% CI: 1.41-3.03) for CKD. The risk of

microalbuminuria in obese subjects did not reach statistical significance (adjusted odds ratio 1.27, 95% CI: 0.92-1.74). The observed association between obesity and the development of CKD is supported by a longitudinal study performed by Fox et al. [21]. A total of 2585 healthy American men and women without kidney disease at baseline were assessed between 1978 and 1982, and again between 1998 and 2001. The mean follow-up period was 18.5 years. 244 people (9.4%) developed CKD, defined as a calculated glomerular filtration rate in the fifth or lower percentile using the Modification of Diet in Renal Disease Study equation. A high BMI at baseline was identified as a significant risk factor for developing kidney disease (OR 1.23 per 1 SD, 95% CI: 1.08-1.41) in a multivariate model. Other risk factors amongst baseline characteristics were increasing age, a low GFR, diabetes and smoking.

In a prospective observational cohort study involving the Framingham Offspring participants (n = 2,676; 52% women; mean age, 43 years) [22], obesity was associated with increased risk of developing stage 3 CKD (OR 1.68, 95% CI: 1.10-2.57, P = 0.02), which was no longer significant after adjustment for known cardiovascular disease risk factors. The authors concluded that the relationship between obesity and stage 3 CKD may be mediated through cardiovascular disease risk factors.

A subsequent systematic review by Wang et al. [23] of 25 observational cohort, 3 cross-sectional and 19 case-control studies published between 1980 and 2007 demonstrated that overweight individuals (BMI 25-30 kg/m^2) had a significantly elevated risk of CKD (RR 1.40, 95% CI: 1.30-1.50) compared with normal-weight individuals (BMI 18.5-24.9 kg/m^2) and that obese were at even higher risk (RR 1.83, 95% CI: 1.57-2.13). This increased risk was independent of other associations of obesity (such as diabetes mellitus and hypertension). Obesity in women (RR 1.92, 95% CI: 1.36-1.63) was associated with a higher risk of CKD than in men (RR 1.49, 95% CI: 1.36-1.63, P < 0.001). Results from cohort studies in patient populations and cross-sectional and case-control studies all indicated a positive association between BMI and risks for CKD. Based on a calculated population attributable risk, the investigators estimated that 24.2% and 33.9% of CKD cases among US men and women, respectively, and in industrialized countries, 13.8% in men and 24.9% in women, could be related to overweight and obesity. The limitations of these studies included a preponderance of Caucasian subjects (such that the results may not have been generalisable to other racial groups) and the crudity of BMI as a measure of fat mass (and specifically of abdominal obesity).

A subsequent prospective observational cohort study of 8792 healthy Korean men who had no known risk factors for CKD and who participated in a comprehensive health evaluation program at a large worksite found that increases in body weight were independently associated with an increased risk for CKD, even when the BMI remained within the normal range [24]. The lowest risk for CKD was observed among those whose weight changed -0.25 to <0.25 kg/yr. (P < 0.001 for quadratic term).

A longitudinal, observational cohort study of 4,295 participants in the community-based Cardiovascular Health Study aged ≥65 years observed that rapid GFR loss was significantly associated with baseline BMI (OR 1.19 per 5 kg/m^2, 95% CI 1.09-1.30), waist circumference (OR 1.25 per 12 cm, 95% CI 1.16-1.36) and fat mass (OR 1.14 per 10 kg, 95% CI 1.05-1.24), after adjustment for age, sex, race, and smoking [25].

In summary, the bulk of evidence suggests that obesity is an important, modifiable, independent risk factor for the development of CKD. Furthermore, in a small proportion of cases, obesity may be associated with a specific form of kidney disease (focal segmental glomerulosclerosis).

Metabolic syndrome

Metabolic syndrome (MS) is a common and often underdiagnosed disease entity, characterised by a clustering of metabolic and cardiovascular atherosclerotic risk factors, including disturbances of glucose and insulin metabolism, hypertension, dyslipidaemia and central obesity [26-30]. It constitutes a major health problem to the Western World and is estimated to affect at least 20% of the adult population and approximately 40% of adults over 60 years [31]. Between 1988-1994 and 1999-2000, the age-adjusted prevalence of MS increased by 23.5% among women and by 2.2% among men, such that an estimated 55 million adults in the United States had MS. Numerous investigations have also demonstrated that MS is a significant risk factor for cardiovascular disease, mortality and chronic kidney disease (CKD) in the general population [28, 32, 33]. In a study of 6980 participants in a hospital-based screening program in Japan, Tanaka et al. [34] observed that MS was a significant determinant of CKD (odds ratio 1.54).

Ryu et al. [35] reported the results of a prospective observational cohort study of 10,685 healthy men without CKD, hypertension, or diabetes who participated in a health check-up program at a large work site (40,617 person-years of follow-up). After adjustment for age, baseline GFR, gamma-glutamyltransferase level, and uric acid level, MS at baseline was significantly associated with an increased risk of CKD (HR 1.99, 95% CI: 1.46-2.73). Considering MS as a time-dependent variable also predicted the development of CKD (HR 1.83, 95% CI: 1.34-2.49). This relationship remained significant, even after further adjustment for the homeostasis model assessment of insulin resistance, high-sensitivity C-reactive protein level, current smoking, alcohol consumption, or regular exercise. The main limitation of this study was generalisability (performed exclusively in Korean men). Nevertheless, similar findings have been reported in elderly Iranian [36], Chinese [37, 38], Korean [39] and Japanese cohorts [40]. It is still not known however, whether the MS constellation improves risk prediction beyond that afforded by its individual components (hypertension, impaired glucose tolerance, dyslipidaemia, etc.).

A recent meta-analysis of 11 observational studies involving 30,146 adult participants with metabolic syndrome reported that the condition was significantly associated with the development of eGFR <60 ml/min per 1.73 m^2 (OR 1.55, 95% CI 1.34-1.80; 10 studies) [41]. There was significant, severe statistical heterogeneity between the included studies (I^2 = 80%, p<0.05) thereby limiting the conclusions that could be drawn from this analysis. There was a graded relationship between the development of eGFR <60 ml/min per 1.73 m^2 and the number of components of metabolic syndrome: 1 component OR 1.42 (95% CI 0.91-2.22, p=0.11), 2 components OR 1.39 (95% CI 1.09-1.78, p<0.01), 3 components OR 1.42 (95% CI 1.22-1.67, p<0.01), 4 components OR 1.66 (95% CI 1.53-1.79, p<0.01), 5 components OR 1.96 (95% CI 1.71-2.24, p<0.01). The studies examining albuminuria as an outcome were unable to be pooled in a meta-analysis, although 3 studies reported an increased risk for development of microalbuminuria or overt proteinuria with metabolic syndrome. The authors concluded that metabolic syndrome and its components are associated with the development of eGFR <60 ml/min per 1.73 m^2 and microalbuminuria or overt proteinuria. However, this meta-analysis was limited by marked trial heterogeneity, and by evidence of possible publication bias on funnel plot. The systematic review was also unable to determine whether the metabolic syndrome constellation improves risk prediction beyond that afforded by its individual components (hypertension, impaired glucose tolerance, dyslipidaemia, etc.).

Hypertension

Hypertension has long been recognised as a cause, consequence and accelerant of CKD. A community-based, prospective observational study of 23,534 men and women in Washington County [42] reported that the adjusted hazard ratio (95% confidence interval) of developing CKD among women was 2.5 (0.05 to 12.0) for normal blood pressure (BP), 3.0 (0.6 to 14.4) for high-normal BP, 3.8 (0.8 to 17.2) for stage 1 hypertension, 6.3 (1.3 to 29.0) for stage 2 hypertension, and 8.8 (1.8 to 43.0) for stages 3 or 4 hypertension compared with individuals with optimal BP. In men, the relationship was similar but somewhat weaker than in women, with corresponding hazard ratios of 1.4 (0.2 to 12.1), 3.3 (0.4 to 25.6), 3.0 (0.4 to 22.2), 5.7 (0.8 to 43.0), and 9.7 (1.2 to 75.6), respectively. In the Framingham Offspring Cohort study (n = 2,676; 52% women; mean age, 43 years) [22], systolic blood pressure was a significant independent risk factor for the development of new-onset stage 3 CKD. The development of end-stage renal disease (stage 5 CKD) was evaluated in 332,544 men, aged 35 to 57 years, who were screened between 1973 and 1975 for entry into the Multiple Risk Factor Intervention Trial (MRFIT) and followed until 1990 [43]. During an average of 16 years of follow-up, 814 subjects either died of end-stage renal disease or were treated for that condition (15.6 cases per 100,000 person-years of observation). A strong, graded relation between both systolic and diastolic blood pressure and end-stage renal disease was identified, independent of associations between CKD and age, race, income, use of medication for diabetes mellitus, history of myocardial infarction, serum cholesterol concentration, and cigarette smoking. The adjusted relative risk increased from 1.0 in those with optimal blood pressure (<120/80) to 1.9 with high normal blood pressure, 3.1 with mild hypertension, 6.0 with moderate hypertension, and 11.2 with severe hypertension. Nevertheless, the absolute risk of end-stage renal disease in participants with mild hypertension (140-159/90-99) was low at 0.34% at 16 years. An association between blood pressure and the risk of developing CKD has also been reported in other longitudinal studies [42] and cross-sectional studies in Norway [44], USA [45] and Australia [1].

Numerous randomized controlled trials in non-diabetic [46-50] and diabetic patients [51-59] with early CKD have clearly demonstrated that blood pressure lowering is associated with substantial reductions (1.1-6.2 mL/min/year) in GFR decline. Meta-regression analyses [60-63] have indicated that blood pressure reduction accounts for 50% of the variance in GFR decline and that each 10mmHg reduction

in mean arterial pressure (down to 92 mmHg) confers a benefit in GFR preservation of 3.7-5.0 mL/min/year. The degree of renal protection afforded by blood pressure reduction appears to be proportional to the degree of baseline proteinuria [48, 64, 65] and its reduction following treatment [64].

Diabetes Mellitus

Prior to the contemporary era of intensive monitoring and treatment, it was suggested that approximately one-third (25-45%) of patients with diabetes mellitus developed CKD [66-68]. Approximately 20%-30% developed microalbuminuria by 15 years, of which less than half progressed to overt nephropathy whilst the remainder were either stable or regressed [66, 67]. In the United Kingdom Prospective Diabetes Study (UKPDS) [69-71], the yearly rate of progression from diagnosis to microalbuminuria, from microalbuminuria to macroalbuminuria, and from macroalbuminuria to an elevated plasma creatinine concentration or renal replacement therapy was 2.0, 2.8, and 2.3%, respectively. Observational cohort studies suggest that the risk of developing CKD is comparable in both type 1 and type 2 diabetes mellitus and that the risk is primarily determined by glycaemic control, as determined by HbA1c [69-76]. Several primary prevention RCTs have clearly demonstrated that achieving tighter glycaemic control in patients with diabetes mellitus results in a lower incidence of development of CKD [69-73, 77].

Smoking

Numerous retrospective and prospective studies (some of which have included thousands of patients) have suggested that smoking is associated with renal failure progression in both diabetic and non-diabetic CKD [78-88]. Current smoking confers a greater risk than former smoking. In a retrospective case-control analysis of 4142 non-diabetic participants of the Cardiovascular Health Study Cohort, aged ≥65 years who had two measurements of serum creatinine performed at least three years apart [89], the adjusted odds ratio for serum creatinine rise increased linearly with cigarette consumption to almost 5-fold at ≥20 cigarettes per day. However, it is important to note that only 2.8% of the population experienced an increase in serum creatinine, and only 8.8% of men and 9.8% of women in the study were current smokers, resulting in an increase in serum creatinine of 0.3 mg/dL in only 14 smokers.

Three small cohort studies suggest that cessation of smoking may ameliorate renal failure progression in diabetic and non-diabetic CKD [79, 85, 90].

A meta-analysis of 17 observational or case-control studies found that incident CKD was significantly associated with smoking >20 cigarettes/day (OR 1.51, 95% CI 1.06–2.15) and smoking >40 years (OR 1.45, 95% CI 1.00–2.09) [91]. The systematic review was limited by marked trial heterogeneity and the use of inconsistent methodologies and outcome definitions between the observational studies.

Alcohol

Chronic alcohol consumption has been linked with hypertension [92, 93] and therefore indirectly with CKD. However, there is conflicting epidemiological evidence with some studies demonstrating that moderate-to-heavy alcohol consumption is an independent risk factor for CKD [94-96], some studies suggesting no association between alcohol intake and CKD risk [97, 98], and other studies demonstrating an inverse association between alcohol intake and CKD risk [99, 100]. In the AusDiab study [96], alcohol intake of ≥30 g/day was associated with an increased risk of albuminuria after adjustment for age, sex and baseline kidney function (OR = 1.59, 95% CI: 1.07–2.36), but a reduced risk of eGFR <60 mL/min/1.73 m^2 (OR = 0.59, 95% CI: 0.37-0.95), compared with consumption of <10 g/day. These studies are likely to be limited by selective reporting, under-reporting of heavy alcohol consumption, ascertainment bias, residual confounding and Neyman bias. At this point in time, it is difficult to draw conclusions regarding the impact of alcohol consumption on CKD progression.

Increasing age

After the age of 30 years, GFR progressively declines at an average rate of 8 mL/min/1.73 m^2 per decade [45]. Based on North American data [45], it is estimated that 25% of the Australian population over the age of 70 years will have an eGFR below 60 mL/min/1.73 m^2. A recent analysis of the Australian Diabetes, Obesity and Lifestyle (AusDiab) study [101] suggested that over one-third of patients over the age of 65 years had a GFR between 45 and 60 mL/min/1.73 m^2. Such population studies have been significantly limited by the fact that only single measurements of serum creatinine

and urinary markers of kidney damage were performed, thereby likely overestimating the true prevalence of CKD.

There is ongoing debate as to whether this age-related GFR decline is normal or pathological. Approximately one-third of the population does not experience a decline in GFR with age [102]. Data from the only longitudinal study to address this issue (Boston Longitudinal Study of Ageing) [102] suggest that the decline in GFR with increasing age is largely attributable to hypertension. Other observational cohort studies suggest that age-related decline can be largely attributed to comorbidities, such as heart failure [103] and co-existing cardiovascular disease [104]. Furthermore, an eGFR <45 mL/min/1.73 m^2 predicts significantly increased risks of cardiovascular disease and CKD progression in all age groups and should therefore generally be considered pathological (i.e. CKD) rather than physiological or age-appropriate. An eGFR between 45 and 60 mL/min/1.73 m^2 is predictive of significantly increased risks of adverse clinical outcomes in younger patients (<65-70 years), although the benefits of identifying older people with an eGFR >45 mL/min/1.73 m^2 have yet to be definitively proven [105]. Based on this evidence, the Australasian Creatinine Consensus Working Group [106] concluded that "at this time it was premature to recommend age-related decision points for eGFR but that it was appropriate to advise practitioners that in those patients 70 years and older with an eGFR from 45 to 59 mL/min/1.73m^2, when stable over time and unaccompanied by other evidence of kidney damage, the GFR value may be interpreted as consistent with a typical eGFR for this age and unlikely to be associated with CKD complications." For patients younger than 70 years, an eGFR <60 mL/min/1.73m^2 for at least 3 months is considered diagnostic of CKD.

Family History of Kidney Disease

Genetic predisposition plays a key role in many forms of CKD, including the 2 commonest causes, diabetic nephropathy and chronic glomerulonephritis. In both type 1 and type 2 diabetes mellitus, the likelihood of developing diabetic nephropathy is markedly increased in patients with a diabetic sibling or parent who has diabetic nephropathy [107-111]. Immunoglobulin A (IgA) nephropathy, the commonest form of glomerulonephritis throughout most developed countries of the world, is associated with a history of affected family members in up to 1 in 7 patients [112]. The most common mono-genetic disorder leading to CKD is autosomal dominant polycystic kidney disease, which affects approximately 1 in every 400 to 1000 live births. Offspring of affected individuals have a 50% chance of developing polycystic kidneys.

Freedman et al. [113] reported a family history of end-stage renal disease (ESRD) in first- and second-degree relatives of 20% of all incident dialysis patients treated in Georgia, North Carolina, and South Carolina (ESRD Network 6) in 1994. The prevalence of relatives with ESRD varied by the reported aetiology: 22.2% in diabetes mellitus; 18.9% in hypertension, 22.7% in glomerulonephritis; and 13.0% of other aetiologies (P = 0.001). The study investigators concluded that a large proportion of incident ESRD cases have close relatives with ESRD in whom preventive actions might be directed. A follow-up study by Speckman et al. [114] observed that family history of ESRD was associated with being overweight (OR 1.17, 95% CI: 1.08-1.26), obese (OR 1.25, 95% CI: 1.14-1.37), and morbidly obese (OR 1.40, 95% CI: 1.27-1.55). This finding suggested that management of obesity may be even more important for patients with a family history of ESRD than for the general population. Another observational cohort study of 177,570 individuals from a large integrated health care delivery system in northern California reported that family history of kidney disease was independently associated with de novo end-stage kidney disease (HR, 1.40, 95% CI 1.02-1.90)[115].

There have been few studies examining the prevalence and predictive value of a family history of kidney disease in screening programs. In a cohort of 1742 people participating in targeted, free, community-based CKD screenings (Kidney Education Outreach Program [KEOP]), 23% had been diagnosed with diabetes mellitus and 47% had been diagnosed with hypertension [116]. Twenty-four percent reported a family history of kidney disease and 60% tested positive for microalbuminuria.

Aboriginal and Torres Strait Islander Racial Origin

End-stage renal disease rates among indigenous groups in Australia exceeds non-indigenous rates by up to eightfold [117]. Another Australian study reported that standardised ESRD incidence among Indigenous Australians was up to 30 times the national incidence for all Australians [118]. In urban regions the standardised incidence was much lower, but remained significantly higher than the national incidence and not purely explained by a higher incidence of diabetes mellitus and hypertension. The

benefits of screening Aboriginal and Torres Strait Islanders for CKD were best demonstrated by Hoy et al. [119, 120], who introduced a renal and cardiovascular treatment program into the Tiwi community, which had a three- to fivefold increase in death rates and an annual incidence of treated end-stage renal disease of 2760 per million (c/f Australian average 110 per million). Screened individuals showing any evidence of CKD were treated with perindopril and additional agents as needed to reach defined blood pressure goals, attempts at control of glucose and lipid levels, and health education. Compared with historical controls, the estimated rate of natural deaths, renal deaths and non-renal deaths were 50%, 47% and 54%, respectively, in the screened and treated group. On the basis of screening all indigenous adults for CKD, it was estimated that the number of people needed to treat (NNT) to avoid one terminal event of natural causes was only 11.6.

The increased risk of CKD in Aboriginal and Torres Strait Islander adults may not be manifest in early childhood suggesting that screening strategies should probably commence in adulthood. In a prospective cohort of 2266 Aboriginal and non-Aboriginal children enrolled from primary schools throughout New South Wales from February 2002 to June 2004 and followed for 4 years, the prevalence of baseline CKD risk factors was frequent (2%-7%), but most abnormalities were transient [121, 122]. Persistence of CKD risk factors at final follow-up was low: haematuria (1.9%), albuminuria (2.4%), systolic hypertension (1.5%) and diastolic hypertension (0.2%). There was no difference in the prevalence of persistent CKD risk factors between Aboriginal and non-Aboriginal children over 4 years suggesting that the increased risk for end-stage kidney disease seen in indigenous adults is not yet manifest in schoolchildren and may be potentially preventable.

Maori and Pacific Peoples

As with indigenous Australians, Maori and Pacific peoples have much higher rates of CKD and ESKD than non-indigenous Australians and New Zealanders [117, 123-125]. Compared with Europeans, Maori and Pacific peoples have higher rates of microalbuminuria (up to 5-fold) [126], diabetes mellitus [123, 127], hypertension [123] and kidney disease due to glomerulonephritis [125], diabetes mellitus [127] , hypertension [125] and systemic lupus erythematosus [128]. Obesity, current smoking and lower socio-economic status have also been shown to be independently associated with the risk of developing albuminuria and are all more prevalent in Maori and Pacific populations [129]. Recently, a study of 65 Māori and Pacific peoples (aged 47-75 years) with type 2 diabetes, moderate CKD (>0.5 g proteinuria/day, serum creatinine 130-300 µmol/l) and hypertension randomized to usual care (n = 32) or community/intervention care (n = 33) for 12 months demonstrated that the community-based model of care improved blood pressure control and delayed progression of proteinuria, left ventricular hypertrophy and diastolic dysfunction, suggesting amelioration of heightened renal and cardiac risk in this group [130].

Benign Prostatic Hypertrophy

Previous studies have suggested an association between benign prostatic hypertrophy and CKD. A community-based study of men age 50 years or older found a 2.4% prevalence of self-reported renal failure related to a prostate condition (9% reported renal failure from any cause) [131] (116). Most other studies have been of males referred to an urologist. One study found a 7.7% prevalence of renal failure in men presenting for prostate surgery compared to a 3.7% prevalence in age-matched men presenting for non-prostate surgery [132]. Gerber et al. [133] evaluated 246 consecutive men that presented to an urologist for evaluation of lower urinary tract symptoms and found that, 26 (11%) had a serum creatinine concentration ≥133 µmol/L (1.5 mg/dL). CKD was not associated with lower urinary tract symptoms (OR 0.76, 95% CI 0.32–1.80). However, these studies were limited by ascertainment bias (favouring more severe forms of benign prostatic hypertrophy), potential contributions from acute obstruction, and use of serum creatinine (an insensitive test) to screen for the presence of CKD.

Rule et al. [134, 135] randomly selected 2,115 white men (ages 40–79 years) from the Olmsted County, Minnesota, participation rate was 55%. After adjustment for age, hypertension, diabetes, leukocyte esterase positive (indicating possible urinary tract infection), and smoking, CKD, defined as a serum creatinine concentration ≥133 µmol/L, was associated with diminished peak urinary flow rate (<15 mL/sec) (OR 2.96, 95% CI: 1.30–7.01), moderate-severe lower urinary tract symptoms (International Prostate Symptom Score [IPSS] >7; OR 2.91, 95% CI: 1.32–6.62), and chronic urinary retention (postvoid residual >100 mL; OR 2.28, 95% CI: 0.66–6.68). There was no association with a prostate volume >30 mL (OR 0.56, 95% CI: 0.22–1.37) or prostate-specific antigen (PSA) >1.4 ng/mL (OR 1.17, 95% CI: 0.47–2.81).

Similarly, Hallan et al [136] employed the International Prostate Symptom Score (IPSS) to detect the presence and severity of lower urinary tract symptoms (LUTS), a surrogate measure of benign prostate hyperplasia suitable for use in general practice, in 30,466 men from the HUNT II (Second Health Study in Nord-Trondelag; 1995-1997) representing 66.8% of the entire adult male population in Nord-Trondelag County, Norway. Using multivariable Cox proportional hazards model analysis, the authors found no significant association between LUTS and the risk of end-stage kidney failure (stage 5 CKD or commencement of renal replacement therapy). The authors concluded that the use of the IPS to gauge severity of LUTS does not provide a sound basis for kidney failure screening. Another observational study of 2741 consecutive urology clinic patients found that CKD was significantly associated with peak flow rate (p=0.001), but not with prostate-specific antigen level, prostate volume, postvoid residual, or IPSS [137].

In summary, there is no clear evidence of a relationship between prostatic enlargement (benign prostatic hypertrophy) and CKD. Patients with signs and symptoms of bladder neck outlet obstruction do seem to have an increased risk of serum creatinine elevation, although the overall prevalence is low and it is difficult to determine how much of this elevation represents CKD versus acute (and therefore potentially reversible) kidney dysfunction.

Cardiovascular Disease

CKD is associated with a greatly increased risk of cardiovascular disease (CVD) [5-7] and vice versa [138-141]. In a study of 2175 participants in the Enhancing Recovery in Coronary Heart Disease I(ENRICHD) trial and 3640 participants in the Vitamin Intervention in Stroke Prevention (VISP) trial, the prevalence of CKD (27-28%) in both studies was much higher than in the general population (11%) [142]. Moreover, the presence of cardiovascular disease is independently associated with kidney function decline and with the development of kidney disease. Elsayed et al. [143] pooled individual patient data from 2 longitudinal, community-based, limited-access studies, the Atherosclerosis Risk in Communities (ARIC) Study and the Cardiovascular Health Study. Among 13826 participants, 520 (3.8%) individuals experienced kidney function decline, and 314 (2.3%) individuals developed CKD during a mean period of 9.3±0.9 years of follow-up. Baseline CVD, present in 1787 (12.9%) individuals, was associated with an increased risks of serum creatinine elevation (OR 1.75, 95% CI: 1.32-2.32), eGFR decline (OR 1.28, 95% CI: 1.13-1.45), development of CKD (OR 1.54, 95% CI: 1.26-1.89) and all 3 outcomes (OR 1.70; 95% CI: 1.36-2.13).

Based on these studies and others, recently published guidelines from a joint science advisory committee from the American Heart Association Kidney and Cardiovascular Disease Council; the Councils on High Blood Pressure Research, Cardiovascular Disease in the Young, and Epidemiology and Prevention; and the Quality of Care and Outcomes Research Interdisciplinary Working Group recommended that all patients with CVD should be screened for CKD [138, 139].

Socioeconomic disadvantage

Although there is a widely held view that CKD maps concordantly with socioeconomic disadvantage, there has been little study of this in the literature. Drey et al. [144] conducted a retrospective cohort study of all new cases of CKD, defined as a persistently increased serum creatinine level (≥150 µmol/L for 6 months) identified from chemical pathology records, from Southampton and South-West Hampshire Health Authority (population base, 405,000). The directly standardised rates of CKD per million population progressively increased from the least deprived quintile (Townsend score 1, rate 1067 pmp, 95% CI: 913-1221) to the most deprived (Townsend score 5; rate 1552 pmp, 95% CI: 1350-1754). A major limitation of this study was that it relied on patients having had a blood test for serum urea and electrolyte concentrations, such that it likely represented an underestimate of the true population incidence of CKD, particularly in the most disadvantaged groups who likely had less access to medical and pathology services. Moreover, the definition of CKD based on a creatinine measurement was not as sensitive as using an estimate of GFR. There was also no evaluation of albuminuria.

Another study of 61,457 participants enrolled in a national health screening initiative, the National Kidney Foundation's Kidney Early Evaluation Program (KEEP), reported that college graduates had 11% lower odds of decreased kidney function and 37% lower odds of cardiovascular disease compared with individuals not completing high school[145]. This study was limited by a lack of ascertainment of income data to more fully define socio-economic status.

Many of the underlying diseases associated with CKD, such as hypertension [146] and diabetes mellitus [147], have an inverse relationship with socioeconomic status. A cross-sectional study of white participants in the follow-up of the Whitehall II cohort (UK-based European population n=5,533, age 55-79 years, 73% male) demonstrated that participants with a lower occupational grade were at increased odds of having decreased CKD-EPI eGFR (age- and sex-adjusted OR 1.31, 95% CI 1.12-1.53; p=0.001). These odds were attenuated by 23.3% after adjustment for BMI and components of metabolic syndrome (OR, 1.23; 95% CI, 1.06-1.45; P = 0.008) [148]. A case-control study of new patients with ESRD in the United States showed that both education and income were inversely associated with risk [149]. Using data obtained from the Australian and New Zealand Dialysis and Transplant (ANZDATA) Registry, Cass et al. [150] observed a strong correlation between the standardised incident rate ratio of ESRD in Australia and the SEIFA Index of Relative Socio-economic Disadvantage (IRSD), derived from the 1996 Census. They concluded that socioeconomic factors were important determinants of the risk of developing ESRD in Australia.

Kidney stones

End-stage renal disease directly attributed to kidney stones is relatively modest, with an estimated prevalence of 3.2% among patients who start maintenance haemodialysis [151]. A case-control study found that black patients who were on haemodialysis were three times more likely to have been stone formers than black individuals in the general population [152]. Vupputuri et al. [153] conducted a case-control study utilizing 548 hospital cases and 514 age-, race- and gender-matched community controls. The odds ratios (adjusted for confounding variables) for chronic kidney disease (overall), diabetic nephropathy and interstitial nephritis for patients with kidney stones were 1.9 (95% CI: 1.1-3.3), 2.5 (95% CI: 0.87-7.0) and 3.4 (95% CI: 1.5-7.4), respectively. After stratifying by hypertensive status, this increased risk persisted only for study participants reporting no history of hypertension. In a population-based study in Olmsted County, MN, all stone formers (n = 4774) whose condition was diagnosed in 1986 through 2003 were matched 1:3 to control subjects (n = 12,975). During a mean follow-up period of 8.6 years, stone formers were at significantly increased risk for a clinical diagnosis of CKD (6.9 versus 3.1%, OR 2.32, 95% CI: 2.00-2.70), but not for ESRD or death with CKD.

Liver disease

Although the development of acute kidney injury secondary to advanced liver disease (hepatorenal syndrome) is well-described [154], there is emerging evidence that milder forms of liver disease, particularly non-alcoholic fatty liver disease (NAFLD), are associated with an increased risk of CKD[155]. In a prospective observational study of 1760 outpatients with type 2 diabetes, normal or near-normal kidney function and absence of overt proteinuria followed for a mean period of 6.5 years (Valpolicella Heart Diabetes Study cohort), Targher et al [156] reported that NAFLD was associated with an increased risk for CKD (HR 1.69, 95% CI 1.3-2.6). This risk persisted after multivariable adjustment for gender, age, body mass index, waist circumference, BP, smoking, diabetes duration, glycosylated hemoglobin, lipids, baseline estimated GFR, microalbuminuria, and medications (hypoglycemic, lipid-lowering, antihypertensive, or anti-platelet drugs). Similarly, Chang et al [157] observed that NAFLD was a significant independent predictor of CKD development (RR 1.55, 95% CI 1.23-1.95) in 8329 healthy (non-diabetic and non-hypertensive) Korean men with normal baseline kidney function and no proteinuria, even after adjustment for age, GFR, serum triglyceride, and serum high-density lipoprotein cholesterol. In a sub-analysis of the CARDIA study (a longitudinal, multicenter epidemiologic study of the impact of lifestyle and other factors on evolution of coronary heart disease risk factors during young adulthood), Lee et al [158] found that serum gamma-glutamyl transpeptidase levels (a surrogate marker of liver disease) within the physiologic range showed a statistically significant, positive dose–response association with incident microalbuminuria at 10 years. These studies suggest that liver disease (NAFLD) is associated with an increased risk of development of CKD, possibly through shared metabolic risk factors (e.g. diabetes, obesity, hypertension, etc.). However, the available studies are limited and it remains uncertain whether the heightened risk of CKD in patients with NAFLD is independent of these metabolic risk factors.

Rheumatoid arthritis

Even though rheumatoid arthritis is reported to be associated with a variety of renal disorders (such as several forms of glomerulonephritis, AA amyloidosis and drug-related nephrotoxicity), studies of the prevalence of CKD in patients with this condition are scant. In a cross-sectional study of 604 patients

with rheumatoid arthritis, Karstila et al [159] reported that 9% had isolated haematuria, 5% had isolated proteinuria, 1% had combined haematuria and proteinuria and 3% had elevated serum creatinine levels (≥100 µmol/l in women and ≥115 µmol/l in men). A subsequent cross-sectional study of 129 patients with rheumatoid arthritis observed that the prevalence of stages, 1, 2, 3, 4 and 5 CKD were 11%, 20%, 15%, 0% and 0%, respectively [160]. These estimates may be inaccurate because the presence or absence of proteinuria was based on a single urine sample.

Cancer

Patients with malignancy can develop CKD via a variety of mechanisms, including chemotherapy-induced nephrotoxicity, paraneoplastic glomerulonephritis, systemic amyloidosis, pre-renal azotaemia and/or urinary tract obstruction (due to extrinsic compression, crystal-induced nephropathy, myeloma cast nephropathy)[161] . In a retrospective, observational cohort study of 8,223 adult patients with any type of cancer and one or more serum creatinine measurements performed between 1 January 2000 and 31 December 2004 at a single centre, Na et al [162] observed that the prevalence of CKD, defined as a GFR < 60 mL/min/1.73 m^2, was 12.8%. This prevalence is not too dissimilar from that which has been reported in general population studies. The highest prevalence of CKD occurred in patients with kidney and urinary tract cancers (21.4%) followed by hematologic malignancies (17.7%) and liver cancers (17.6%). The lowest prevalence rates of CKD were observed in patients with breast cancer (3.6%) and thyroid cancer (6.0%). Patients with other cancers exhibited CKD prevalence rates between 11.5% and 13.7%. This study was limited by the performance of a single measurement of renal function (leading to possible over-estimation of CKD prevalence) and a failure to adjust for comorbidities (e.g. hypertension, smoking), which may have separately increased the risk of CKD. Another study of 231 cancer patients (142 males, 89 females) receiving chemotherapy reported a CKD prevalence of 25%[163]. Other studies have also reported an increased prevalence of proteinuria in patients with CKD [164-167]. These studies have similarly been limited by often single measurements and limited adjustment for comorbidities (with an attendant risk of residual confounding). It has also been argued that proteinuria in the setting of cancer may reflect a non-specific microvascular response to tumour cytokine products rather than CKD per se [162].

SUMMARY OF EVIDENCE

To summarise, the key modifiable risk factors for CKD in the community are obesity, hypertension, diabetes mellitus, cigarette smoking, established cardiovascular disease (CVD) and socioeconomic disadvantage. The principal non-modifiable risk factors are age >50 years, Aboriginal and Torres Strait Islander racial origin and a family history of CKD. The presence of any one of these risk factors is associated with a risk of developing CKD of up to 40%. There is conflicting evidence regarding the roles of alcohol consumption and benign prostatic hypertrophy as risk factors for CKD. The presence of kidney stones is associated with a modest increased risk of CKD (approximately 6% absolute risk). MS is associated with an increased risk for CKD but it is still not known whether this constellation improves risk prediction beyond that afforded by its individual components (hypertension, impaired glucose tolerance, dyslipidaemia, etc.).

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines: National Institute for Clinical Excellence (NICE): [168]
R25 Offer people testing for CKD if they have any of the following risk factors:

- diabetes
- hypertension
- cardiovascular disease (ischaemic heart disease, chronic heart failure, peripheral vascular disease and cerebral vascular disease)
- structural renal tract disease, renal calculi or prostatic hypertrophy
- multisystem diseases with potential kidney involvement, e.g. systemic lupus erythematosus (SLE)
- family history of stage 5 CKD or hereditary kidney disease

- opportunistic detection of haematuria or proteinuria.

R26 In the absence of the above risk factors, do not use age, gender, or ethnicity as risk markers to test people for CKD. In the absence of metabolic syndrome, diabetes or hypertension, do not use obesity alone as a risk marker to test people for CKD.

Scottish Intercollegiate Guidelines Network [169]

Diabetes mellitus, hypertension, therapy with lipid-lowering agents, smoking, cardiovascular disease, older age and low socioeconomic status should be considered as risk factors for CKD.

Joint science advisory committee from the American Heart Association Kidney and Cardiovascular Disease Council; the Councils on High Blood Pressure Research, Cardiovascular Disease in the Young, and Epidemiology and Prevention; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. [138]

Recommendations

Class I

1. The Modification of Diet in Renal Disease (MDRD) equation should be used to estimate glomerular filtration rate in adult patients with cardiovascular disease. Values <60 mL/min per 1.73 square meters body surface area should be regarded as abnormal. (Level of Evidence: B).

Class IIa

1. The albumin-to-creatinine ratio should be used to screen for the presence of kidney damage in adult patients with cardiovascular disease. Values > 30 mg albumin per 1 g creatinine should be regarded as abnormal. (Level of Evidence: B).
2. All adult patients with cardiovascular disease should be screened for evidence of kidney disease with determinations of estimated glomerular filtration rate using the MDRD equation and albumin-to-creatinine ratio. (Level of Evidence: C).

SUGGESTIONS FOR FUTURE RESEARCH

Further research is required to identify symptoms, complications and outcomes of early CKD. This information would be best obtained from prospective cohort studies involving a large number of patients, representative of the Australian population. In particular subgroups of age, race and socioeconomic status should be included. A particular emphasis should be placed on assessing the significance of early CKD in the elderly population, in whom the significance of a reduced eGFR is unclear. Other outcomes of interest include the prevalence of complications such as anaemia, CKD-MBD, quality of life and less-studied parameters such as impact on relationships and capacity to work.

CONFLICT OF INTEREST

David Johnson has a level II b. conflict of interest for receiving speaker honoraria and advisor's fees from several companies related to anaemia, CKD-MBD, hypertension and cardiovascular disease between 2008 and 2012.

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APPENDICES

Table 1. Characteristics of included studies

Study ID	N	Study design	Participants	Follow up	Comments and results
Obesity					
Kambham et al (2001) [18]	6,818 total biopsies over the period 1986 to 2000. 71 selected for study.	Cross-sectional.	All native renal biopsies received from 1986 to 2000 at the Columbia Presbyterian Medical Centre. Obesity defined as BMI > 30 kg/m^2. Obesity Related Glomerulopathy (ORG) defined as (1) obesity-associated FSGS with glomerulomegaly (O-FSGS) or (2) obesity associated glomerulomegaly alone (O-GM). Excluded obese patients with underlying conditions that could cause FSGS.	NA	A total of 103 cases of ORG were identified for the 15 years from January 1986 to April 2000. There was a progressive increase in biopsy incidence of ORG from 0.2% to 2% over the period 1986-1990 and 1996-2000 respectively. ORG is distinct from idiopathic FSGS, with a lower incidence of nephrotic syndrome, more indolent course and, consistent presence of glomerulomegaly, and milder foot process diffusion.
Iseki et al (1997) [19]	107,192. Serum creatinine data available for 14,609 (14%)	Cohort	All individuals >18 years of age participating in the 1983 Okinawa mass health screening examinations.	10 years	During follow up 60 dialysis patients were identified (0.41%). The adjusted odds ratio (95% confidence interval) was 5.31 (3.39 to 8.32) in men and 3.92 (2.88 to 5.34) in women when compared to baseline serum creatinine levels of less than 1.0 mg/dl in women and 1.2 mg/dl in men. The effect of other confounding variables such as; smoking, obesity, or lifestyle were not examined.
Kopple et al (2000) [20]	1,785 (at baseline prior to randomisation)	Cross-sectional analysis of an RCT (MDRD Study)	Individuals aged from 18 to 70 years with GFR 25 to 55 ml/min/1.73 m^2.	NA	Body fat was weakly correlated with GFR in females and both body fat and BMI was weakly correlated with GFR in males.
Chen et al (2004) [11]	CKD analysis (GFR <60 ml/min/1.73 m^2) – 6,217. Microalbuminuria analysis (ACR 30 to 300 mg/g) – 6,125.	Cross-sectional	Third National Health and Nutrition Examination Survey (representative sample of non-institutionalised US general population). Individuals greater than 20 years of age.	NA	Obesity as defined by a waist circumference ≥102 cm in men and ≥ 80 cm in women significantly associated with CKD but not with microalbuminuria. The multivariate adjusted odds ratio for CKD in obese versus non obese individuals was 2.07 (95% CI 1.41-3.03).

Study ID	N	Study design	Participants	Follow up	Comments and results
Fox et al (2004) [21] and Foster et al (2008) [22]	3867 (baseline) 2,676 (follow-up examination)	Cohort	Participants of the Framingham Offspring Study who attended baseline examination in 1978-1982 and follow up in 1998-2001. Mean age at baseline 43 years.	18.5 years (mean). Range 16-22 years.	Body mass index increased the odds of developing kidney disease by 23% (odds ratio 1.23; 95% CI, 1.08-1.41) SD units. Relative to participants with normal BMI, there was no association between overweight individuals and stage 3 CKD incidence in age- and sex-adjusted models (odds ratio [OR], 1.29; 95% CI, 0.93 to 1.81) or multivariable models (OR, 1.06; 95% CI, 0.75 to 1.50). Obese individuals had a 68% increased odds of developing stage 3 CKD (OR, 1.68; 95% CI, 1.10 to 2.57), which became non significant after adjustment for known cardiovascular risk factors
Wang et al (2008) [23]	25 cohort, 3 cross-sectional and 19 case-control studies.	Systematic review of observational studies	Study inclusion criteria: Measure of RR or OR, adults ≥18 years, sample size ≥ 100, measure of body weight or using BMI or measures that could be converted to BMI, cohort, cross-sectional or case-control study. Meta-analysis constrained to 18 population cohort studies.	NA	Compared with normal-weight individuals (18.5<BMI<25), overweight individuals (25<BMI<30) had elevated risk for KD (RR = 1.40; 95%CI 1.30–1.50); obese individuals were at higher risk (RR = 1.83 (1.57–2.13)). Obesity in women was associated with a higher risk than in men (RR=1.92(1.78–2.07) vs1.49 (1.36–1.63); P<0.001). Estimated that 24.2 % and 33.9 % of KD cases among US men and women, respectively, and in industrialised countries, 13.8% in men and 24.9 % in women, could be related to overweight and obesity.
Ryu et al (2008) [24]	8,792 at baseline from 15,347 participants (3628 excluded and 2927 had inadequate follow up data)	Cohort	Korean male workers ≥ 40 years of age undergoing annual examination and male workers 30 to 39 years undergoing biennial examination. Baseline cohort free of CKD and hypertension and diabetes.	Mean 4.13 (SD 0.72) years	Cox proportional hazards modelling indicate that in both normal weight and overweight groups, a U-shaped association between weight change categories and development of CKD was observed after adjustment for age, baseline GFR, baseline BMI, HDL, fasting blood glucose, uric acid, and exercise habits.
De Boer et al (2009)[25]	4,295	Cohort	Adults from the general community. Four communities took part in the Cardiovascular Health Study, USA.	7 years	Change in eGFR (as defined by the MDRD equation) The mean decrease in eGFR was 0.4 ± 3.6 mL/min/1.73 m^2/year Rapid eGFR loss (>3 mL/min/1.73 m^2/year) occurred in 16% of participants Baseline body mass index, waist circumference and fat mass were associated with an increased risk of rapid eGFR loss; BMI odds ratio 1.19 (95%CI: 1.09-1.30) per 5kg/m^2, (P=0.001); waist circumference OR 1.25 (95%CI: 1.16-1.36) per 12 cm, (P=0.01); and fat mass OR 1.14 (95%CI: 1.05-1.24) per 10kg, (P=0.003) after adjusting for age, gender, race and smoking.

Study ID	N	Study design	Participants	Follow up	Comments and results
Metabolic Syndrome					
Isomaa (2001) [32]	4,483 at baseline with 3,606 assessed at follow up.	Cohort	Participants in a type 2 diabetes family study aged 35 to 70 years. Metabolic syndrome defined as presence of at least 2 of the risk factors: obesity, hypertension, dyslipidaemia or microalbuminuria.	Median 6.9 years	CKD was not an outcome assessed in this study. However, Of the individual components of the metabolic syndrome, microalbuminuria conferred the strongest risk of cardio vascular death (RR 2.80; P 5 0.002)
Tanaka (2006) [34]	6,980 (visiting clinic between May 2003 and March 2004)	Cross-sectional	Adults (30 to 79 years) participating in hospital based screening program in Okinawa. Metabolic syndrome defined following NCEP ATP III guidelines. CKD defined as reduced eGFR or dipstick proteinuria.	NA	Metabolic syndrome was a significant determinant of CKD (adjusted OR1.537 and 95% CI 1.277–1.850, Po0.0001).The adjusted OR (95%CI) was1.770 (1.215–2.579, P=0.0029) for those with four metabolic syndrome risk factors compared to those with no metabolic syndrome risk factors.
Ryu (2009) [35]	10,685 at baseline from 15,347 participants (3,320 excluded and 1,342 had inadequate follow up data)	Cohort	Korean male workers ≥ 40 years of age undergoing annual examination and male workers 30 to 39 years undergoing biennial examination. Baseline cohort free of CKD and hypertension and diabetes.	Mean 3.80 (SD 1.3) years	After adjustment for age, baseline GFR, γ-glutamyltransferase level, and uric acid level, metabolic syndrome at baseline was associated with a significantly increased risk of CKD (HR,1.99;95% CI1.46 to 2.73). Metabolic syndrome over time as a time-dependent variable also predicted the development of CKD (HR,1.75;95% CI1.28 to 2.39)
Fakhrzadeh (2009) [36]	122	Cross-sectional	Participants of a longitudinal survey of elderly (≥60 years) residents of an Iranian charity aged care facility. Metabolic syndrome (MetS) defined as per NCEP ATP III guidelines and CKD as eGFR <60 ml/min/m^2).	NA	Metabolic syndrome was diagnosed in 33.3% of the participants. The multivariate-adjusted odds ratio (OR) for CKD in MetS was 5.81 (95% confidence interval (CI) 1.72-19.58) compared to those without MS.
Luk (2008) [37]	6,350	Cross-sectional	Chinese patients (Hong Kong Diabetes Registry) with type 2 diabetes. Mean age 55.1 ± 13.3 years with mean duration of diabetes 6.6 ± 6.4 years. Metabolic syndrome (MetS) defined as per NCEP ATP III guidelines and CKD as eGFR <60 ml/min/m^2).	NA	The frequency of MetS was 54.2% (n=3,439) In subjects with MetS according to the NCEP-ATPIII definition (n□3204) had an increased risk of association with CKD (OR 1.75, 95% CI 1.37-2.24)

Study ID	N	Study design	Participants	Follow up	Comments and results
Luk (2008)[38]	5,829	Cohort	Chinese patients (Hong Kong Diabetes Registry) with type 2 diabetes. Mean age 54.1 ± 13.0 years. Mean duration of diabetes 6.23 ± 6.17 years. MetS defined as per NCEP ATP III guidelines and CKD as eGFR <60 ml/min/m^2).	Median 4.6 years (1.9-7.3 interquartile range)	The frequency of MetS was 51.2% (n=2,985). The multivariable-adjusted hazard ratio (HR) of CKD was 1.31 (95% CI 1.12–1.54) for subjects with metabolic syndrome compared with those without metabolic syndrome.
Watanabe (2010)[40]	34,986	Cohort	Niigata Preventive Medicine Study a community based cohort study (>20 years old). Metabolic syndrome (MetS) defined as per NCEP ATPIII guidelines and CKD as eGFR <60 ml/min/m^2).		The metabolic syndrome was present in 3679 subjects (11%). During a follow-up of 5.8 years, kidney dysfunction developed in 184 subjects with metabolic syndrome (5.0%) and 746 subjects without MetS (2.4%). The metabolic syndrome was associated with development of kidney dysfunction (hazard ratio [HR], 2.12).
Thomas et al (2011)[41]	11 Studies (n=30,146)	Systematic review, meta-analysis	Prospective cohort studies reporting the development of CKD in adults with metabolic syndrome. Cleveland , USA	NA	Metabolic syndrome (MetS) was associated with the development of eGFR <60 ml/min/1.73m2 (odds ratio 1.55, 95%CI: 1.34-1.80). The strength of the association increased with increasing number of components of MetS (trend P=0.02). One component OR 1.42 (95%CI:0.91-2.22; p=0.11); two components OR 1.39 (95%CI: 1.09-1.78; p<0.01); three components OR 1.42 (95%CI: 1.22-1.67; p<0.01); four components OR 1.66 (95%CI: 1.53-1.79; p<0.01); five components OR 1.96 (95%CI: 1.71-2.24; p<0.01) Individual components of MetS were also individually associated with eGFR <60 ml/min/1.73m2: high blood pressure OR 1.61 (95%CI: 1.29-2.01; p<0.01); impaired fasting glucose OR 1.14 (95%CI:1.03-1.26; p<0.01); elevated triglycerides OR1.27 (95%CI:1.11-1.46; p<0.01); low HDL-cholesterol OR 1.23 (95%CI: 1.12-1.36; p<0.01); obesity OR 1.19 (95%CI: 1.05-1.34; p<0.01)
Hypertension					
Haroun et al (2003) [42]	23,534	Cohort	US population based study of adult volunteers for a cancer study (CLUE). CKD defined by dialysis or transplantation or kidney disease recorded on death certificate.	20 years	The adjusted hazard ratio of developing CKD among women was 2.5 (95% CI 0.05 to 12.0) for normal BP, 3.0 (0.6 to 14.4) for high normal BP, 3.8 (0.8 to 17.2) for stage 1 hypertension, 6.3 (1.3 to 29.0) for stage 2 hypertension, and 8.8 (1.8 to 43.0) for stages 3 or 4 hypertension compared with individuals with optimal BP. In men, the relationship was similar but somewhat weaker than in women, with corresponding hazard ratios of 1.4 (0.2 to 12.1), 3.3 (0.4 to 25.6), 3.0 (0.4 to 22.2), 5.7 (0.8 to 43.0), and 9.7 (1.2 to 75.6), respectively.

Study ID	N	Study design	Participants	Follow up	Comments and results
Klag et al (1996) [43]	332,544	Cohort	Men enrolled in the MRFIT US population based study with mean age of 46±6 years.	16 years	As compared with men with an optimal level of blood pressure (systolic pressure <120 mm Hg and diastolic pressure <80 mm Hg), the relative risk of end-stage renal disease for those with stage 4 hypertension (systolic pressure ≥210 mm Hg or diastolic pressure ≥120 mm Hg) was 22.1 (P <0.001).
Hallan et al (2006) (HUNT II) [44]	3,270 randomly selected from total participants of 65,186	Cross-sectional	Norwegian population based general health survey.	NA	Does not provide association between blood pressure and CKD.
Coresh et al (2003) [45]	15,625	Cross-sectional	Non institutionalised US population based study (NHAMES III) of adults 20 years or older.	NA	Increasing prevalence of CKD (eGFR <60 ml/min/1.73m^2) in groups with hypertension.
Chadban et al (2003) [1]	11,247	Cross-sectional	Non-institutionalised Australian adult (25 year of older) population study.	NA	Age, gender, and hypertension were independently associated with reduced GFR. The odds ratio by univariate analysis for hypertension and eGFR <60 ml/min/1.73m2 was 7.5 (95% CI 6.5 – 8.8).
Klahr (1995) [50] and Klahr (1994) [64]	200	RCT	MDRD study participants with ADPKD.	Mean 2.2 years	Baseline characteristics that predicted a faster rate of decline in GFR in persons with ADPKD were greater serum creatinine (independent of GFR), greater urinary protein excretion, higher mean arterial pressure (MAP), and younger age.
Gansevoort (1995) [46]	41 studies, 1124 patients (558 non diabetic)	Meta-analysis	RCTs with direct comparison between an ACEi and another antihypertensive.	Not stated	Primary focus is on antiproteinuric effect of ACEi rather than relationship between GFR decline and hypertension. ACEIs confer an antiproteinuric effect beyond that attributable to their blood-pressure-lowering effect.
Giatras (1997) [47]	10 studies, 1594 patients.	Meta-analysis	RCTs with direct comparison between an ACEi and another hypertensive excluding studies of diabetic renal disease.	≥year	Primary focus is on progression to ESRD rather than relationship between GFR decline and hypertension. Concluded that ACEi are more effective than other antihypertensive agents in reducing the development of ESRD. It could not be determined whether this beneficial effect is due to the greater decline in blood pressure or to other effects of ACE inhibition.
Hebert (1997) [49]	53 black Americans, 495 white Americans	RCT	MDRD study randomly assigned to usual or MAP goal (<107 and <92 mmHg).	3 years	The mean (±SE) GFR decline over 3 years in the low blood pressure group was 11.8±7.3 mL/min slower than in the usual blood pressure group among blacks (P=.11) compared with 0.3±1.3 mL/min slower among whites (P=.81) (P=.12 between blacks and whites).

Study ID	N	Study design	Participants	Follow up	Comments and results
GISEN Group (1997) [48]	352	RCT	Ramipril versus placebo trial in non-diabetic nephropathy.	42 months	The decline in GFR per month was significantly lower in the ramipril group than the placebo group (0·53 [0·08] vs. 0·88 [0·13] mL/min, p=0·03). However, the rate of GFR decline was independent of baseline and follow up arterial blood pressure.
Lewis (2001) [55]	1715	RCT	Irbesartan versus amlodipine versus placebo in hypertensive patients with nephropathy due to type 2 diabetes.	2.6 years (mean)	The serum creatinine concentration increased 24 percent more slowly in the irbesartan group than in the placebo group (P=0.008) and 21 percent more slowly than in the amlodipine group (P=0.02). These differences were not explained by differences in the blood pressures that were achieved.
Brenner (2001) [51]	1513	RCT	Losartan plus conventional versus placebo plus conventional in patients with type 2 diabetes.	3.4 years (mean)	Losartan reduced the incidence of a doubling of the serum creatinine concentration (risk reduction, 25 percent; P=0.006) and end-stage renal disease (risk reduction, 28 percent; P=0.002) but had no effect on the rate of death. The benefit exceeded that attributable to changes in blood pressure.
Parving (2001) [57]	590	RCT	Irbesartan versus placebo in hypertensive patients with type 2 diabetes.	2 years	The HRs for the primary outcome (time to diabetic nephropathy) compared to placebo was 0.30 (95% CI 0.14 to 0.61) and 0.61 (95% CI 0.34 to 1.08) for the two irbesartan groups. It was concluded that Irbesartan is renoprotective in patients with type 2 diabetes and microalbuminuria, independently of its blood-pressure-lowering effect
Lewis (1993) [54]	409	RCT	Captopril versus placebo in patients with type 1 diabetes and elevated protein excretion.	3 years	The mean (±SD) rate of decline in creatinine clearance was 11 ±21 percent per year in the captopril group and 17 ±20 percent per year in the placebo group (P = 0.03). The difference was independent of the small difference in blood pressure.
Weidmann (1993)[58] and Weidmann (1995) [59]	126 studies, 2,149 patients	Systematic review	Trials of conventional hypertension therapy versus ACEi, nifedipine, or calcium antagonists in diabetes populations with microalbuminuria.		ACEi induced changes in albuminuria correlated significantly with decreases in blood pressure (r=0.58, P<0.001), with a slope indicating a 1.67% proteinuria variation for each % BP change.

Study ID	N	Study design	Participants	Follow up	Comments and results
Lewis (1999) [56]	129	RCT	Patients with type 1 diabetes and elevated urinary protein excretion. Randomised into two treatment groups based on MAP goals.	2 years	The median iothalamate clearance in group I was 62 mL/min/1.73 m2 at baseline and 54 mL/min/1.73 m2 at the end of the study compared with a baseline of 64 mL/min/1.73 m2 and final 58 mL/min/1.73 m2 in group II. There were no statistically significant differences in the rate of decline in renal function between groups. However, There was a significant difference in follow-up total urinary protein excretion between group I (535 mg/24 h) and group II (1,723 mg/24 h; P =0.02).
Estacio (2000) ABCD trial [53]	470	RCT	Intensive versus moderate blood pressure control. Patients with hypertension and type II diabetes.	5.3 years	The mean blood pressure achieved was 132/78 mmHg in the intensive group and 138/86 mmHg in the moderate control group. The mean blood pressure achieved was 132/78 mmHg in the intensive group and 138/86 mmHg in the moderate control group. During the 5-year follow-up period, no difference was observed between intensive versus moderate blood pressure control and those randomized to nisoldipine versus enalapril with regard to the change in creatinine clearance.
Crepaldi (1998) IDDM Study [52]	92	RCT	Lisinopril versus nifedipine versus placebo. Normotensive patients with type 1 diabetes and microalbuminuria.	3 years	Both SBP and DBP levels were related to progression rate of microalbuminuria to macroalbuminuria, to regression of microalbuminuria to normoalbuminuria, and to the absolute change of AER during the follow-up period.
Jafar (2001) [61]	11 studies, 1860 non diabetic patients	Meta-analysis	RCTs comparing ACEi to regimens without ACEi in non-diabetic kidney disease.	2.2 years (mean)	The primary focus is on comparison of ACEi with other antihypertensives, however a greater decrease in blood pressure and urinary protein excretion are associated with lower risk for progression to ESKD, but the beneficial effect of ACE inhibitors is mediated by factors in addition to their effects on blood pressure and urinary protein.
Bakris (2000) [60]	12 studies, 1102 patients	Meta-analysis	RCTs including an ACEi treatment regimen. Hypertensive participants with majority having 25% loss of renal function at baseline (any cause).	$\geq$2 years (average 3 years)	Focus of the review is on the association between acute increases in serum creatinine with ACEi treatment and progression of kidney function.

Study ID	N	Study design	Participants	Follow up	Comments and results
Maki (1995) [63]	14 studies	Meta-analysis	RCTs including any antihypertensive agent.	≥6 months	Focus was on the assessment of whether effects of antihypertensive agents are independent of blood pressure reductions. Each 10-mm Hg reduction in blood pressure caused a relative improvement in glomerular filtration rate (0.18 mL/min per month [0.04 to 0.31 mL/min per month]), but among diabetic patients there was a tendency for dihydropyridine calcium antagonists to cause a relative reduction in glomerular filtration rate (-0.68 mL/min per month [-1.31 to -0.04 mL/min per month]).
Kasiske (1993) [62]	101 studies, 2494 patients	Meta-analysis of controlled and uncontrolled trials	Clinical trials that examined the effects of antihypertensives on blood pressure and renal function.		Blood pressure reduction was associated with a relative increase in glomerular filtration rate (regression coefficient [±SE], 3.70 ± .92 mL/min for each reduction of 10 mm Hg in mean arterial pressure; P = 0.0002).
Ruggenenti (1998) [65]	97	RCT follow up.	Follow up of the REIN study. All patients with proteinuria of 3 g or more per 24 h either continued on ramipril or were shifted to it.	36 months	The mean rate of GFR decline per month decreased from 0·44 (SD 0·54) mL/min per 1·73 m^2 in the core study to 0·10 (0·50) mL/min per 1·73 m^2 in patients originally randomised to ramipril (p=0·017), and from 0·81 (1·12) to 0·14 (0·87) mL/min per 1·73 m^2 in those originally randomised to placebo plus conventional antihypertensive therapy (p=0·017). In both groups, GFR decline and risk of ESRF were independent of baseline and follow-up arterial blood pressure.
Diabetes Mellitus					
Parving (1988) [68]	957	Cross-sectional	Outpatients with type 1 diabetes attending a single clinic (Denmark). Aged ≥ 18 years where diabetes commenced before 41 years if age and of ≥ 5 years duration.	NA	CKD defined on the basis of micro and macroalbuminuria. The prevalence of microalbuminuria and macroalbuminuria was 22% and 19%, respectively. Patients with raised urinary albumin excretion were characterised by an earlier onset and longer duration of diabetes and tended to be men when compared with patients with normoalbuminuria.
Orchard (1990) [67]	657	Cross-sectional	Medical records of Type 1 diabetes patients from a single clinic (US). Aged 8 to 48 years.	NA	The prevalence of overt nephropathy, defined as AER > 200 μg/min and/or renal failure reached 48% in men and 16% in females after 25 years duration of diabetes. The combined prevalence of microalbuminuria and overt nephropathy at 30 years duration of disease was 84% in males and 59% in females.
Newman (2005) [66]		Systematic review	Cohort studies or placebo arms of randomised trials and included subjects with Type 1 or Type 2 diabetes.		In adults with type 1 or type2 diabetes and microalbuminuria at baseline, 19% and 24% progressed to clinical proteinuria. In patients with type 1 diabetes and microalbuminuria there is an RR of developing end-stage renal disease (ESRD) of 4.8 (95% CI 3.0 to 7.5) and in patients with type 2 diabetes the RR was 3.6 (95% CI 1.6 to 8.4).

Study ID	N	Study design	Participants	Follow up	Comments and results
UKPDS 33 (1998) [69] ; UKPDS 34 (1998) [71] ; UKPDS 38 (1998) [70]	5102	RCT	Newly diagnosed type 2 diabetes patients median age 54 years initially randomised to glycaemic control therapies. A subset was subsequently randomised to blood pressure control therapies.	10 years	From diagnosis of diabetes, progression to micro albuminuria occurred at 2.0% per year, from microalbuminuria to macroalbuminuria at 2.8% per year, from macroalbuminuria to elevated plasma creatinine (≥175 μmol/L) or renal replacement therapy was 2.3% per year.
Holman (2008) [74]	3277	Cohort (post trial monitoring of UKPDS)	Newly diagnosed type 2 diabetes patients median age 54 years initially randomised to glycaemic control therapies. A subset was subsequently randomised to blood pressure control therapies.	5 years	Between-group differences in HbA1c levels were lost after the first year. Levels of blood pressure and plasma creatinine and the ratio of albumin to creatinine did not differ significantly between the two groups at any time, except that plasma creatinine levels in the metformin group were 15% higher on average than those in the conventional-therapy group (P<0.04).
DCCT (1995) [72] ; DCCT (2000) [77]	1441	RCT	Type 1 diabetes patients aged from 13 to 39 years, with normal GFR and normotensive at recruitment. Multicentre trial in the US and Canada. Randomised to conventional or intensive blood glucose control under primary prevention or secondary intervention regimen.	Mean 6.5 years (range 3 to 9)	The beneficial effect of intensive therapy on the development of microalbuminuria was consistent in subgroups defined by baseline variables including age, diabetes duration, baseline $HbA1_C$, level of retinopathy, neuropathy, and the presence or absence of hyperfiltration. The risk of new albuminuria was reduced by 86% in the intensive-therapy group, with similar reductions for patients with normal albumin excretion at the end of the DCCT.
EDIC (2003) [73]	1349	Cohort – follow up of DCCT trial.	DCCT participants who had kidney evaluation at years 7 or 8.	8 years after DCCT close out	There was a 50.2% (95% CI, 42.2%-57.1%) reduction in the risk (incidence, hazard) of microalbuminuria per 10% reduction in the current combined meanHbA1c level that explained 7.25% of the variation in risk. There was a 56.4% (95% CI, 43.4%-66.4%) reduction in the risk of clinical albuminuria per 10% reduction in the current combined mean HbA1c level that explains 3.31% of the variation in risk.
Sasaki (1989) [76]	1196	Cohort	Type II diabetes adult patients from a single medical centre (Japan).	Mean 10 years	The mean annual incidence rate of persistent albuminuria per 1000 person-years in the patients was higher in males than in females (18.42 and 12.57, respectively). Development of persistent albuminuria was associated with age at entry, duration of known diabetes, systolic blood pressure, fasting glucose level, presence of diabetic retinopathy and type of treatment.
Smoking					

Study ID	N	Study design	Participants	Follow up	Comments and results
Ward et al (1992) [87]	160	Cohort	Adult outpatients with lupus nephritis at a single centre (US). Older than 17 years at the onset of nephritis.	Median 6.4 year	ESRD developed in 41 (26%) of the 160 patients. Hypertension and smoking status at the onset of nephritis were strongly associated with differences in the time to development of ESRD. The median time to ESRD among smokers was 145 months and among non-smokers it was greater than 273 months. These effects persisted in multivariable analyses adjusting for differences among patients in age, gender, socioeconomic status, renal histology, and immunosuppressive treatment.
Muhlhauser et al (1986) [82]	1254 total, 90 female and 102 male smokers pair matched with non-smokers.	Case control	Adult (age 30±13 years) patients with type 1 diabetes.		Macroproteinuria was found in 19.3% of the smoking and in 8.3% of the non-smoking patients ($p < 0.001$). HbA1c values and the prevalence of hypertension were similar between smoking and non-smoking patients.
Sawicki et al (1994) [85]	93	Cohort	Consecutive sample of outpatients with type 1 diabetes, hypertension and diabetic nephropathy from a single centre (Germany)	12 months	Progression of nephropathy over 1 year was less common in non-smokers (11%) than in smokers (53%), $P<0.001$. In a stepwise logistic regression analysis, cigarette pack years, 24-h sodium excretion, and HbA1c were independent predictive factors for the progression of diabetic nephropathy. The ORs for progression of nephropathy were 2.74 if cigarette pack years increased by 10.
Couper et al (1994) [80]	690 healthy and 169 with type 1 diabetes.	Cohort	Healthy school aged children (11.5 ± 3.38 years) and school aged children (12.4 ± 3.1 years) with type 1 diabetes. (Australia)	24 months	Smoking correlated with albumin excretion rate, independent of age and other variables, in cross-sectional and longitudinal analysis ($p < 0.003$). Smoking was more prevalent in the borderline albuminuria and microalbuminuria groups ($p < 0.004$, $p < 0.001$)
Almdal et al (1994) [78]	230	Cohort	Normoalbuminuric and microalbuminuric patients with type 1 diabetes.	5 years	Smoking was significantly more prevalent in patients with persistent albuminuria compared to those with normoalbuminuria at baseline and follow up (68% versus 40%). However, no difference was found between progressors and non progressors.
Chase et al (1991) [79]	359	Cross-sectional	Young subjects with type 1 diabetes.		It is concluded that cigarette smoking is an independent risk factor and is associated with the development and progression of early diabetic renal damage (albuminuria) and with the worsening of retinal disease in young subjects with diabetes.
Stegmayr and Lithner (1987) [86]	22/22	Case control	Case: patients with type 1 diabetes and ESRD. Control: patients with type 1 diabetes	NA	A significant inverse correlation was found between the amount of tobacco used daily and the number of years preceding the onset of proteinuria in the uraemic patients (n=18; r=047; $p<0.05$) and controls (n=7; r=082; $p<0.01$).

Study ID	N	Study design	Participants	Follow up	Comments and results
Rossing et al (2002) [84]	537	Cohort	Adult (≥ 18 years) patients with type 1(≥5 years duration) diabetes from a single outpatient clinic (Denmark)	Median 9 years	Significant predictors of progression from normoalbuminuria to microalbuminuria or macroalbuminuria were: baseline log urinary albumin excretion rate 2.63 (relative risk; 95% CI 1.65–4.19), HbA1c 1.13% (1.04 –1.23), presence of any retinopathy 1.90 (1.26 –2.88), and smoking 1.61 (1.11–2.33).
Gambaro et al (2001) [81]	273	Cohort	Patients with type 2 diabetes (age at diagnosis <65 years and outpatient follow up minimum of 3 years) attending a single diabetes clinic (Italy). Patients with familial renal diseases; renal disease other than diabetic nephropathy were excluded.	3 years	From logistic regression analysis, smoking (p=0.0012) was the most important factor associated with progression of nephropathy, followed by pack years (p=0.011), HbA1c mean value at follow-up (p=0.024), and total cholesterol (p=0.038). Smoking was the most important factor.
Orth et al (1998) [83]	582 (180 with ESRD, 402 without ESRD)	Case control	Patients with IgA-GN or ADPKD from multiple centres (Germany, Italy, Austria).	NA	In men (matched pairs: IgA-GN N 5 44, ADPKD N 5 28), a significant dose-dependent increase of the risk to progress to ESRF was found with smoking (non-adjusted). After adjustment, the risk for ESRF in men with.> 5 pack years was highly increased for patients without ACE inhibitor treatment [10.1 (2.3 to 45), P <0.002] but not with ACE inhibitor treatment [1.4 (0.3 to 7.1), P < 0.65].
Bleyer et al (2000) [89]	4142	Case control	Non diabetic patients of the Cardiovascular Health Study Cohort. Cases were those who develop serum creatinine 0.3 /dL.		There was an increase in the serum creatinine of at least 0.3 mg/dL in 2.8% of the population. The number of cigarettes smoked per day was associated with increased risk of elevated serum creatinine (OR for greater than 5 per day 1.25 95% CI 1.09-1.44.
Schiffl et al (2002) [90]	90	Cohort	Adult patients with either glomerulonephritis or tubulointerstitial nephritis, and early stage renal failure (creatinine clearance 60 to 90 mL/min/1.73m^2). Smokers were encouraged to stop smoking.	24 months	Twenty six patients refused to change habits and 16 successfully stopped. Compared to ex-smokers or matched non-smoking renal patients, permanent smokers had a significantly faster decline in creatinine clearance during the two-year study period (1.0 ±0.3 mL/min/month compared to 0.5±0.3 mL/min/month). Renal replacement therapy had to be started in 6 smokers, but only in 1 ex-smoker and none of the non-smokers during the study period.
Jones-Burton et al (2007)[91]	17 studies	Systematic review	Observational studies reporting cigarette smoking and renal function in adults. (1966 – 2005)	NA	An increased risk of developing CKD among smokers was associated with male gender RR 2.4, (95%CI: 1.2-4.5); >20 cigarettes smoked /day OR 1.51 (95%CI: 1.06-2.15); and smoking >40 years OR 1.45 (95%CI: 1.00-2.09)
Alcohol					

Study ID	N	Study design	Participants	Follow up	Comments and results
White et al (2009) AusDiab [96]	6537	Cohort	National population based sample (Australian). Adults ≥25 years excluding those self-identified as having been treated for alcohol dependence.	5 years	Participants were self-classified to a scale of alcohol consumption. Moderate or heavy, versus light, drinking was associated with elevated risk of albuminuria in males and females <65 years of age (OR males 1.87, 95% CI 0.99–3.52; females 2.38, 95% CI 1.37–4.14). Odds of de novo eGFR <60 mL/min/1.73 m2 were 0.34 (95% CI 0.22–0.59) and 0.68 (95% CI 0.36–1.27) in males and females, respectively, who were moderate–heavy drinkers.
Shankar et al (2006) [95]	Cross sectional – 4898. Longitudinal – 3392	Cross sectional; cohort	Population based sample aged from 43 to 84 years (US township).	5 years	Classified as current, former or non-drinker and according to a consumption frequency scale to identify heavy drinkers. Heavy drinking was associated with CKD (defined on basis of eGFR), with an OR of 1.99 (95% CI: 0.99, 4.01). Joint exposure to both current smoking and heavy drinking was associated with an almost fivefold odds of developing CKD compared with their absence (OR = 4.93, 95% CI: 2.45, 9.94). Smoking and consumption of four or more servings of alcohol per day are associated with CKD.
Perneger et al (1999) [94]	761 ESRD patients, 361 controls.	Case control	Adults (≥ 20 years) being treated for treated for ESRD (US).		Utilised self-reported consumption of alcoholic drinks. The odds ratio for ESRD remained significantly increased (OR 4.0; 95% CI: 1.2 - 13.0) among persons who consumed an average of >2 alcoholic drinks per day. The corresponding population attributable risk was 9 percent. A lower intake of alcohol did not appear to be harmful.
Reynolds et al (2008) [99]	65,601	Cohort	Male adults (.≥40 years) from the China National Hypertension Survey Epidemiology Follow-up Study).	Average 8 years.	The age standardized rate of ESRD was lowest among men consuming ≥21 drinks per week. After adjustment for risk factors the relative risk (RR) of ESRD was 0.67 (95% CI 0.44-1.01) for men consuming <21 drinks per week and 0.52 (95% CI 0.31–0.89) for men consuming ≥21 drinks per week compared to non-drinkers.
Schaeffner et al (2005) [100]	11,023	Cohort	Participants of the completed Physicians Health Study an RCT on the use of aspirin and β carotene. Apparently healthy male physicians including no known history of renal dysfunction at baseline.	14 years	Self-reported drinking frequency. Compared with men who consumed no more than 1 drink per week, men who consumed 2 to 4 drinks weekly had a multivariable adjusted OR of having an elevated serum creatinine level at follow up of 1.04 (95% CI, 0.81-1.32), men who consumed 5 to 6 drinks per week had an OR of 0.92 (95% CI, 0.68-1.25), and men who consumed at least 7 drinks weekly had an OR of 0.71 (95% CI, 0.55-0.92) (P=.01 for trend across categories).
Increasing Age					

Study ID	N	Study design	Participants	Follow up	Comments and results
Coresh et al (2003) [45]	15,625	Cross-sectional	Non institutionalised US population based study (NHAMES III) of adults 20 years or older.	NA	Decreased kidney function (GFR < 60 mL/min/1.73 m2) was uncommon in younger individuals without diabetes or hypertension (0.1% in the age group 20 to 39 years, 1.2% in the age group 40 to 59 years), however it was quite common (16%) among individuals older than 70 years.
White et al (2010) [101]	11,579	Cross sectional	Baseline data from a national population based sample (Australian). Adults ≥25.	NA	The mean age of participants with no CKD was 49.3 ± 13 years (overall prevalence of 85%), while the mean age of participants with eGFR <60 and ≥45 ml/min/1.73 m^2 was 72.2 ±8.6 years (overall prevalence of 5%).
Lindeman et al (1985) [102]	446	Cohort	"Normal" volunteers in Baltimore Longitudinal Study of Aging.	30 years	Excluding participants with possible renal or urinary tract disease on diuretics and antihypertensives the mean decrease in creatinine clearance in the remaining 254 participants was 0.75 ml/min/year. One third of all participants followed had no absolute decrease in renal function.
Fliser et al (1997) [103]	24 – young healthy 29 – elderly healthy 25 – elderly hypertensive 14 elderly with heart failure	Case control	Excluded participants with primary renal disease were excluded. Health controls from University of Heidelberg, hypertensive cases from outpatient clinic. Ages were: (i) young healthy 26±years; (ii) elderly healthy 68±7 years; (iii) elderly hypertensive 70±6 years; (iv) elderly heart failure 69±6 years.	NA	Authors concluded that GFR (measured as inulin clearance) was only modestly lower in healthy elderly than in young healthy individuals, and cardiovascular diseases such as hypertension and heart failure have a major adverse effect on renal hemodynamics and other aspects of renal function.
Baggio et al (2005) [104]	2981	Cohort	Elderly (65-84 years) Italian population longitudinal study.	3.6 years	Multiple logistic regression analysis showed that risk factors for pathological loss of renal function (rise of SCr >26.5 mmol/l) were: current smokers >20 cigarettes/day (OR = 2.3; 95% CI 1.0–5.3), fibrinogen values >3.5 g/l (OR=2.2; 95% CI 1.6–3.3), diabetes (OR=1.8; 95% CI 1.1–2.8), age >75 years (OR=1.7; 95% CI 1.2–2.4) and isolated systolic hypertension (OR=1.6; 95% CI 1.0–2.6).
Roderick et al (2009) [105]	15,336	Cohort	Elderly (≥75 years) patients registered with selected UK general practices.	Median 7.25 years.	The adjusted hazard ratio for all-cause mortality in the eGFR band 45 to 59 ml/min/1.73m^2 was not significantly different to eGFR ≥60 ml/min/1.73m^2 (1.13 95% CI 0.93 to 1.37).
Family History of Kidney Disease					

Study ID	N	Study design	Participants	Follow up	Comments and results
Pettitt et al (1990) [108]	316 families; 349 parents; 499 offspring.	Cross sectional	Pima Indian families with type 2 diabetes identified in 2 successive generations.	NA	After adjustment for sex and other risk factors, proteinuria occurred among 14.3% of the diabetic offspring if neither parent had proteinuria, 22.9% if at least one diabetic parent had proteinuria, and 45.9% if both parents had diabetes and proteinuria. Among male offspring, an elevated serum creatinine concentration (> 177 gmol/1) was present in 11.7% if the parent had an elevated creatinine and in 1.5% if the parent did not.
Satko et al (2002) [109]	66 families; 211 siblings	Cross sectional	African American families containing an index case with type 2 diabetes or ESRD and at least one additional diabetic sibling.	NA	More than 60% of index cases had at least one diabetic sibling with a UAC ratio of 30 or greater and 300 mg/g or less. Nearly 35% of index cases had at least one sibling with a UAC ratio greater than 300 mg/g. Nearly 24% of index cases had at least one sibling with an elevated SCr level (≥1.4 mg/dL in women, ≥1.6 mg/dL in men).
Borch-Johnsen et al (1992) [107]	49 families (probands); 51 siblings	Cross sectional	Outpatients of diabetes care units (Denmark) with diabetes onset prior to 40 years of age, diabetes duration ≥10 years with and without diabetic nephropathy who have diabetic siblings.	NA	Diabetic nephropathy (defined as urinary albumin excretion > 300 mg/24 hr.) was found in 7 out of 21 siblings to patients with nephropathy and 3 out of 30 siblings to normoalbuminuric patients (P < 0.04). A significant correlation within sibling pairs of HbA1c was found, thus clustering of nephropathy may indicate genetic link or shared environment effects.
Seaquist et al (1989) [110]	27 probands and siblings	Cross sectional	Probands and siblings with diabetes of minimum duration of 10 years in probands and 7 years in siblings (11 probands with diabetic nephropathy and 26 without) (US).	NA	Of the 29 diabetic siblings of probands with diabetic nephropathy, 24 (83 percent) had evidence of nephropathy (P <0.001), including 12 with ESRD. Nephropathy in the proband was the only factor significantly predictive of the renal status of the diabetic sibling.
Scolari et al (1999) [112]	185	Cross sectional	Outpatients (Italy) with IgA nephropathy.	NA	Twenty six of the 185 patients were related to at least one other patient with IgA nephropathy belonging to 10 families. No common nephrotoxic factor was identified in the families.
Freedman et al (1997) [113]	4365	Cross sectional	Registered ESRD Medicare patients during 1994 (North Carolina, US).	NA	Among race-sex groups. 14. 1% of Caucasian men, I4.6% of Caucasian women, 22.9% of African-American men, and 23.9% of African-American women reported a first- or second-degree relative with ESRD (P = 0.001).

Study ID	N	Study design	Participants	Follow up	Comments and results
Speckman et al (2006) [114]	25,883	Cross sectional	Incident ESRD patients between 1995 and 2003 in US ESRD Network 6 (Georgia, North Carolina and South Carolina).	NA	Twenty-three percent of patients reported a family history of ESRD. After controlling for age, race, sex, primary cause of ESRD, history of diabetes, history of hypertension, and estimated glomerular filtration rate at dialysis therapy initiation, reported family history of ESRD was associated with being overweight (OR, 1.17; 95% CI, 1.08 to 1.26), obese (OR, 1.25; 95% CI, 1.14 to 1.37), and morbidly obese (OR, 1.40; 95% CI, 1.27 to 1.55).
Harward et al (2009) [116]	1742 particpants, 1694 medical histories	Cross sectional	Participants (any person ≥18 years who could provide a urine sample and complete a questionnaire) in the Kidney Education Outreach Program (KEOP) screening program (US).	NA	The mean age of screening participants was 54 years old; 70% were female, 50% were African American, and 13% were Latino. More than 40% of subjects were obese. Twenty three % had been diagnosed with diabetes mellitus and 47% had been diagnosed with hypertension. Twenty-four percent reported a family history of kidney disease. While 60% of the participants tested positive for microalbuminuria.
Hsu et al (2009)[115]	177,570	Cohort	Members of Kaiser Permanente of Northern California who took part in the Multiphasic Health Testing Services Program in Oakland and San Francisco, USA	5,275,957 person-years	Family history of kidney disease was identified as an independent risk factor for end-stage kidney disease HR 1.40 (95%CI: 1.02-1.90) Other novel risk factors for ESKD included lower haemoglobin level HR 1.33 (95%CI: 1.08-1.63); higher serum uric acid HR 2.14 (95%CI: 1.65-2.77); and self-reported history of nocturia HR 1.36 (95%CI: 1.17-1.58)
Aboriginal and Torres Strait Islander Racial Origin					
McDonald et al (2003) [117]	16,607	Cross sectional	ANZDATA Registry – all patients who began RRT between October 1991 and September 2000.	NA	ESRD rates among indigenous groups in Australia and New Zealand exceeded non-indigenous rates up to eightfold. The median age of indigenous ESRD patients was younger (51 vs. 60 years, P<0.0001), and there was an excess of comorbidities, particularly diabetes.
Cass et al (2001) [118]	719	Cross sectional	ANZDATA Registry - Indigenous patients starting ESRD between 1 January 1993 and 31 December 1998	NA	Standardised ESRD incidence among Indigenous Australians is highest in remote regions, where it is up to 30 times the national incidence for all Australians. In urban regions the standardised incidence is much lower, but remains significantly higher than the national incidence. Forty-eight per cent of Indigenous ESRD patients come from regions without dialysis or transplant facilities and 16.3% from regions with only satellite dialysis facilities.
Hoy et al (2003a,b) [119, 120]	267 treated and 327 historical controls	Cohort with historical controls.	Members of the Tiwi community with hypertension and albuminuria regardless of blood pressure or diabetes. Primary treatment was with perindopril with calcium channel blockers and diuretics as required.	Mean 3.36 years	Albuminuria and GFR stabilized or improved. Rates of natural deaths were reduced by an estimated 50% (P< 0.012); renal deaths were reduced by 57% (P = 0.038); and non-renal deaths by 46% (P = 0.085). Benefit was absent among the low death rates of people without albuminuria and questionable among people with GFR <60ml/min.

Study ID	N	Study design	Participants	Follow up	Comments and results
Haysom et al (2009a,b) [121, 122]	2266	Cohort	Aboriginal and non-Aboriginal children enrolled in primary schools throughout NSW.	4 years	Prevalence of baseline CKD risk factors was frequent (2%–7%), but most abnormalities were transient. Besides persistent obesity (5.0%), persistence of CKD risk factors at final follow-up was low: haematuria (1.9%), albuminuria (2.4%), systolic hypertension (1.5%) and diastolic hypertension (0.2%). There was no difference in prevalence of persistent CKD risk factors between Aboriginal and non-Aboriginal children.
Maori and Pacific Peoples					
Collins et al (2010) [123]	N/A	Review	Maori and Pacific people in New Zealand	NA	The incidence of commencing renal replacement therapy is 3.5 fold higher in Maori and Pacific patients compared to non-Maori/non-Pacific people. Microalbuminuria was found to be five times more common in Maori and Pacific people compared with Europeans. Approximately 1 in 3 of Maori and Pacific people had hypertension (BP>140/90) compared with 1 in 5 others The age of diagnosis for diabetes in Maori and Pacific people is 50 years compared to 60 for those of European origin. Glomerulonephritis has also been shown to be more common amongst Maori and Pacific people compared with Europeans.
Stewart et al (2004) [125]	Maori = 554,517 Pacific Island people = 204,076 Other New Zealander = 2,949,905	Registry analysis	Australia and New Zealand Dialysis and Transplant Registry (ANZDATA). Maori, Pacific Island people and all 'other' New Zealanders and Indigenous and non-Indigenous Australians.	1992-2001	Maori and Pacific Island people have similar incidence rates of end stage renal disease (ESRD), a little more than half those of Indigenous Australians but two to ten times higher than in 'other' New Zealanders and non-Indigenous Australians. The main causes of ESRD in Maori and Pacific Island people were: type II diabetic nephropathy (740 and 799 per million in Maori and Pacific Islander people respectively compared to 18.5 per million in 'other' New Zealanders); hypertensive renal disease (81.4 and 88.1 per million in Maori and Pacific Islander people respectively compared to 13.4 per million in 'other' New Zealander); and glomerulonephritis (114 and 127 per million in Maori and Pacific Islander people compared to 30 per million in 'other'.

Study ID	N	Study design	Participants	Follow up	Comments and results
Metcalf et al (1997) [126]	3,960	Cross-sectional	Non-diabetic, non-hypertensive, non-lipidaemic, non-proteinuric, European, Maori and Pacific Island men and women, aged 40 years and over.	N/A	The relative risks of microalbuminuria were 4.87-fold (95%CI: 3.10-7.64) higher in Maori, and 4.96-fold (95%CI: 3.40-7.24) higher in Pacific Islanders compared to European New Zealanders. Adjusted relative risks for high albumin: creatinine ratios were 6.38 (95%CI: 4.27-9.53) in Maori and 5.14 (95%CI: 3.54-7.48) in Pacific Islanders compared to European workers. Workers with microalbuminuria had higher urinary creatinine concentrations than those with urinary albumin in the normal range. Maori and Pacific Islanders had significantly higher urinary albumin concentrations than Europeans even after adjusting for age, gender, waist, height, 2hr glucose, urinary creatinine, systolic blood pressure and body mass index.
Sundborn et al (2008) [127]	1,011= Pacific 1,745 = European New Zealanders	Cross-sectional population based survey	Pacific ethnic groups (Samoan, Tongan, Niuean, Cook Islanders, other Pacific [mainly Fijian]) and European New Zealanders.	N/A	Cardiovascular risk among the Pacific groups was significantly higher than Europeans. The five-year risk score of CVD for women was: 4.3% Niuean, 5.2% Samoan, 5.6% Tongan, and 6.2% Cook Islands compared with 3.0% European. The five-year risk score of CVD for men was: 7.1% Niuean, 9.1% Cook Islands, 9.4% Samoan, 10.8% Tongan compared with 6.8% European. Diabetes prevalence was highest in Samoan men (26.2% vs. 6.3% European) and Tongan women (35.8% vs. 5.5% European). Niueans had the lowest diabetes prevalence of both sexes (men 14.9%, women 10.8%).
Benign Prostatic Hypertrophy					
Hunter et al (1996) [131]	2002	Cross sectional	Population survey (Madrid) of men ≥50 years.	NA	Main outcome was the self-reported International Prostate Symptom Score. The prevalence of renal failure related to prostate problems as reported by a physician was 2.4% compared to 9.0% for all causes.
Hill et al (1993) [132]	382 cases, 191 controls	Retrospective cohort	Patients who underwent prostatectomy during 1985 in Central Oxford Hospitals (UK). Age matched controls selected from the same hospital.	NA	The prevalence of renal impairment in the prostatectomy patients was 7.7% compared to 3.7% in the control group.
Gerber et al (1997) [133]	246 (109 with history and 137 with no history of diabetes or hypertension)	Cross sectional	Consecutive patients presenting for evaluation of lower urinary tract symptoms at a single centre (US).	NA	An elevated serum creatinine level was noted in 11% of patients. Only a history of diabetes or hypertension predicted the presence of renal insufficiency. Among men with no history of comorbid disease, increasing age was significantly associated with the finding of an abnormal creatinine. The overall symptom score (IPSS) was not associated with the likelihood of detectable renal dysfunction.

Study ID	N	Study design	Participants	Follow up	Comments and results
Rule et al (2005a) [134]	2115 participants (476 randomly selected for detailed assessment)	Cross sectional	Community based sample of white males aged 40 to 79 years (US). Excluded those with prostate cancer or surgery, bladder cancer, or other disorders that could affect normal urinary function.		After adjustment, CKD (serum creatinine ≥133 μmol/L) was associated with diminished urinary flow (<15ml/sec) OR 2.96 (95% CI 1.3.0-7.01), moderate-severe lower urinary tract symptoms (IPSS>7) OR 2.91 (95% CI 1.32-6.62), and chronic urinary retention (post void residual >100 ml) OR 2.28 (95% CI 0.66-6.68). There was no association with prostate volume or PSA.
Rule et al (2005b) [135]	No details	Descriptive review	Medline search no details provided	NA	Authors' conclusion: "The extent of the association between BPH and CRF is unknown and more community based, observational studies are needed. However, an association exists and it should be considered in men presenting with obstructive BPH or CRF."
Hallan et al (2010)[136]	30,466 men	Prospective cohort	Adult men taking part in the HUNT II Study. Nord-Trondelag County, Norway	10.5 years	There was no significant risk of kidney disease in men with moderate HR 1.16 (95%CI: 0.65-2.07; P=0.5) or severe HR 1.47 (95%CI: 0.61-3.52; P=0.9) lower urinary tract symptoms (LUTS) compared with men with no/mild LUTS, after adjusting for age and educational attainment
Cardiovascular Disease					
Bang et al (2009) [142]	ENRICHD 2481 VISP 3680	Cohort	Participants from the ENRICHD (a study including acute myocardial infarction patients) and VISP (a study of patients with non-disabling stroke) multi centre cardiovascular trials.	ENRICHD mean 29 months VISP 24 months	Prevalence of CKD (eGFR <60ml/min/1.73m^2) in ENRICHD participants was 27% and 28% in the VISP study.
Elsayed et al (2007) [143]	13,826	Cohort	Participants of ARIC and CHS longitudinal community based studies.	Mean 9.3 years	Baseline CVD, present in 1787 individuals (12.9%), was associated with an increased risk of eGFR for kidney function decline and development of kidney disease with ORs of 1.28 (95% CI 1.13-1.45) and 1.54 (95% CI 1.26-1.89) respectively.
Socioeconomic Disadvantage					
Drey et al (2003) [144]	4,228	Retrospective cohort	All new cases of detected CKD (SCr > 1.7 mg/dL for > 6 months) in a UK Health Authority region.	Mean 5.5 years	The directly standardised rates of CKD per million population increased with increasing Townsend deprivation quintile as follows: 1 (least deprived): - 1,067 (95% CI 913-1,221); 2: - 1,274 (95% CI 1,097-1,451); 3: - 1,319 (95% CI 1,138-1,499); 4: - 1,296 (1,128-1,454); 5 (most deprived): 1,552 (95% CI 1,350-1,754). The excess incidence in the most deprived group was 40%.

Study ID	N	Study design	Participants	Follow up	Comments and results
Perneger et al (1995) [149]	716 cases; 361 population controls	Case control	Cases selected from all newly diagnosed ESRD patients from a defined geographical area (US), controls age matched from the same geographical area.	NA	African Americans were more than 7 times more likely than white Americans to have ESRD. The steep and significant gradient risk across annual income categories ranged from 1.0 to 7.0. The proportions of ESRD that could be attributed to each risk factor were 46% for minority race, 53% for income categories, and 33% for missing teeth.
Cass et al (2001) [150]	5013	Cross sectional	Patients from Australian capital cities registered in ANZDATA as commencing ESRD treatment between April 1993 and December 1998.	NA	There was a significant negative relationship between standardised incidence ratios for postcode regions with the Index of Relative Socio-economic Disadvantage for (IRSD) the region (r=-0.41, p=0.003). If the relatively disadvantaged capital city areas (IRSD <1000) had the same adjusted incidence rate of ESRD as the relatively advantaged capital city areas (IRSD> 1000), 22.8% of cases (463 cases) in the six-year period would be avoided.
Choi et al (2011)[145]	61,457	Observational cohort	Adults taking part in the Kidney Early Evaluation Program (KEEP), USA	Median 3.7 years	College graduates had 11% lower odds of decreased kidney disease and 37% lower odds of cardiovascular disease compared to individuals not completing high school
Al-Qaoud et al (2011)[148]	5,533	Cross sectional	Adult participants taking part in the Whitehall II study, UK	NA	Participants with a lower occupational grade were at increased odds of having decreased eGFR (age and sex-adjusted OR 1.31; 95%CI: 1.12-1.53; P=0.001) compared to participants with higher occupational grade. The odds decreased to 1.23 (95%CI: 1.06-1.45; P=0.008) after adjusting for BMI and components of metabolic syndrome
Kidney Stones					
Jungers et al (2004) [151]	1391	Cross sectional	Consecutive patients starting maintenance dialysis at a single centre (France)	NA	The overall proportion of nephrolithiasis related ESRD was 3.2%. Infection (struvite) stones accounted for 42.2%; calcium stones, 26.7%; uric acid nephrolithiasis, 17.8%; and hereditary diseases, 13.3% of cases.
Stankus et al (2007) [152]	300	Cross sectional	Adult (≥ 18 years) African American ESRD patients at a single centre (US). General population comparison taken from the NHANES III study.	NA	Self-report history of kidney stones used as the basis for identifying per ESRD kidney stone formers. The prevalence of pre ESRD kidney stone formers was 8.3% (95% CI 5.2-11.5%). The age and sex adjusted stone prevalence estimated to be 2.8% (95% CI: 2.2–3.3%) among African Americans participating in the NHANES III survey and significantly lower.
Vupputuri et al (2004) [153]	548 cases, 514 controls	Case control	Cases – patients aged ≥ 30 years from one of four centres (US) with newly diagnosed CKD with 2 or more SCr >1.5 mg/dL. Population cases selected randomly and age and sex matched.	NA	The adjusted odds ratios for chronic kidney disease (overall), diabetic nephropathy and interstitial nephritis for patients with kidney stones were 1.9 (95% CI: 1.1, 3.3), 2.5 (95% CI: 0.87, 7.0) and 3.4 (95% CI: 1.5, 7.4), respectively.

Study ID	N	Study design	Participants	Follow up	Comments and results
Liver Disease					
Targeher et al (2008)[156]	1,760	Prospective study	Adult participants with type 2 diabetes, with normal or near-normal kidney function and without overt proteinuria, were recruited from the Valpolicella Heart Diabetes Study, (US)	6.5 years	Incident CKD developed in 547 patients; their mean ± (SD) eGFR was 55± 12 ml/min/1.73m^2. Seven patients developed ESRD requiring dialysis, 112 developed CKD with overt proteinuria, while 428 did not have overt proteinuria. Non-alcoholic fatty liver disease (NAFLD) was associated with increased risk of CKD (hazard ratio 1.69; 95%CI: 1.3 – 2.6, P<0.001). After adjusting for various variables, the association remained significant (adj HR 1.49; 95%CI: 1.1 – 2.2. P<0.01)
Chang et al (2008)[157]	8329	Prospective study	Korean men with normal baseline kidney functions and no proteinuria, working in a manufacturing company in Seoul, Korea	3.21 years	Incident CKD developed in 324 men. Non-alcoholic fatty liver disease (NAFLD) was significantly associated with CKD (RR 2.18; 95%CI: 1.75 – 2.71) and remained significant after adjustment for various variables (adj RR 1.55; 95%CI: 1.23 – 1.95) There was also an association between NAFLD and incident CKD in the group with elevated γ-glutamyltransferase (GGT) (adj RR 2.31; 95%CI: 1.53 – 3.50)
Lee et al (2005)[158]	2478	Prospective study	Black and white men and women between 18 and 35 years of age were recruited and examined at four clinical sites in the US. They were re-examined at 2, 5, 7, 10 and 15 years.	15 years	Adjusted odds ratios across quartiles of serum GGT were 1.0, 0.39 (95%CI: 0.21 – 0.73), 0.54 (0.29 – 0.99) and 0.94 (0.51 – 1.75) (P<0.001 for quadratic term) for serum GGT levels: <12, 12 to <18, 18 to <29 and ≥29 U/L respectively. Among participants who had hypertension or diabetes, year 10 serum GGT showed a positive dose-response association with incident microalbuminuria, odds ratio: 1.0 for <12 and 12 to <18 U/L serum GGT, 2.66 (95%CI: 0.88 – 8.09) and 4.38 (95%Ci: 1.48 – 12.93) for 18 to <29 and for ≥29 U/L serum GGT, respectively (P<0.01 for trend). Participants with neither hypertension nor diabetes showed a U-shaped association with it serum GGT: odds ratios 1.0, 0.40 (95%CI: 0.21 – 0.80), 0.39 (95%CI: 0.18 – 0.83) and0.56 (95%CI: 0.25 – 1.27) for serum GGT levels: <12, 12 to <18, 18 to <29 and ≥29 U/L respectively, (P=0.01 for quadratic term)
Rheumatoid Arthritis					
Karstila et al (2007)[159]	604 = original study 205 = follow-up	Population-based cross-sectional	Adult patients with rheumatoid arthritis were examined for markers of renal disease. Finland.	N/A	Of the 604 patients with rheumatoid arthritis (RA), 103 had clinical renal findings (17%). Results included: 9% (54) patients with isolated haematuria; 5% (27) patients with isolated proteinuria (urine protein excretion of 150mg/24 hours or more); 1% (seven patients) with combined haematuria and proteinuria and 3% (15 patients) with chronic renal failure without haematuria or proteinuria (serum creatinine of ≥100µmol/l in women and ≥115µmol/l in men, in two consecutive samples)

Study ID	N	Study design	Participants	Follow up	Comments and results
Karie et al (2008)[160]	129	Cross-sectional	Patients with rheumatoid arthritis were examined for markers of renal disease. Single-centre, France	N/A	80 patients had serum creatinine and urinary dipstick results available and 37 of these patients (46.3%) were detected to have kidney disease according to the National Kidney Foundation classification.\ 43/80 (53.8%) had eGFR ≥60ml/min/1.73m^2 (normal function) without kidney damage Stage 1: 9/80 (11.3%) had normal function with kidney damage; Stage 2: 16/80 (20%) mild renal insufficiency with kidney damage Stage 3: 12/80 (15%) moderate renal insufficiency Stage 4 & 5: no patients at this level.
Cancer					
Na et al (2011)[162]	8,223	Retrospective observational study	Adults with all types of cancer and older than 18 years of age were included in the study. Single centre, Korea.	Mean 49.2 months (SD 34.6)	A total of 1,051 (12.8%) patients had CKD (baseline eGFR <60ml/min/1.73m^2) Patients with kidney and urinary tract cancers have the highest prevalence of CKD (21.4%). Haematologic malignancy and liver cancer also showed high prevalence of CKD (17.7% and 17.6%) respectively. While breast and thyroid cancer showed relatively lower prevalence of CKD (3.6% and 6.0%) respectively. Patients with other cancers showed prevalence of CKD between 11.5% and 13.7% The 5-year cumulative incidence rates for death were 0.57 for patients without CKD and 0.76 for patients with CKD. The hazard ratio for the risk of death was 1.12 (95%CI: 1.01 – 1.26, P=0.04) for patients with 30≤ eGFR<60ml/min/1.73m^2 and 1.75 (95%CI: 1.32-2.32, P<0.001) for patients with eGFR <30ml/min/1.73m^2