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# **Modifiable lifestyle factors for primary prevention of chronic kidney disease: a systematic review and meta-analysis**

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## **Abstract**

### **Background**

Despite the growth of chronic kidney disease (CKD), no evidence-based lifestyle recommendations for primary CKD prevention exist.

### **Objective**

To evaluate the consistency of evidence associating modifiable lifestyle factors and the incidence of CKD.

### **Methods**

MEDLINE, Embase, CINAHL, and references from eligible studies were searched from database inception through June 2019. Cohort studies of adults without CKD at baseline, reporting lifestyle exposures (diet, physical activity, alcohol consumption and tobacco smoking). The primary outcome was incident CKD (estimated glomerular filtration rate [eGFR] <60mL/min/1.73m<sup>2</sup>). Secondary outcomes were other surrogate measures of CKD, including kidney replacement therapy, GFR decline, and albuminuria.

### **Results**

We identified 104 studies of 2,755,719 participants with generally a low risk of bias. Higher potassium (odds ratio 0.78 [95% CI: 0.65-0.94]; I<sup>2</sup>=48%, 7 studies) and vegetable intake (0.79 [0.70-0.90]; I<sup>2</sup>=57%, 5 studies) significantly decreased the odds of CKD, whereas higher salt intake (1.21 [1.06-1.38]; I<sup>2</sup>=59%, 5 studies) significantly increased the odds. Being physically active had lower odds of CKD (0.82 [0.69-0.98]; I<sup>2</sup>=83%, 9 studies) compared with being sedentary. Current and former smokers (risk ratio 1.20 [1.12-1.28]; I<sup>2</sup>=80%, 12 studies) had significantly increased risk of CKD compared with those who never smoked. Compared with no consumption, moderate consumption of alcohol was associated with reduced risk of CKD

(0.86 [0.79-0.93];  $I^2=40\%$ , 14 studies). Results for the secondary outcomes were consistent with the primary finding.

## **Conclusion**

This study identified modifiable lifestyle hazards that consistently predict the incidence of CKD in the community and may inform both public health recommendations and clinical practice.

## Introduction

Chronic kidney disease (CKD) affects 10% of the world's population<sup>1</sup> and ranks in the top 10 non-communicable diseases contributing to disease and disability.<sup>2</sup> Its incidence is increasing worldwide,<sup>1</sup> and mortality owing to CKD rose between 2005 and 2017 from 0.9 million to 1.2 million deaths annually<sup>2</sup>. CKD imposes a significant economic burden on patients and society; many developed countries spend between 2-3% of their annual healthcare expenditure on kidney replacement therapies (KRT, that is, chronic dialysis or kidney transplantation) for 0.2 percent of the total population.<sup>3</sup>

Because prevention is more effective than cure, avoiding exposures to hazards that may cause CKD in the community is a key priority. This is particularly important because the management of patients with established CKD may require dietary adaptations that diametrically differ from those that are needed for primary prevention.<sup>4</sup> However, no evidence-based lifestyle recommendations for the primary prevention of CKD are apparent. Instead, current advice extrapolates from recommendations and inferences drawn from literature concerning cardiovascular disease, hypertension, and diabetes.<sup>5-7</sup> Furthermore, the World Health Organization discusses CKD as a complication of cardiovascular disease and diabetes, which further complicates effective public health messages.<sup>8</sup> To address this critical knowledge gap, we hereby evaluated the consistency of evidence associating modifiable lifestyle factors (specifically diet, physical activity, alcohol consumption and tobacco smoking) and the incidence of CKD.

## Methods

This systematic review and meta-analysis was conducted according to Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist for observational studies<sup>9</sup> and was prospectively registered in PROSPERO (CRD42019137328).

## Data Sources and Searches

We searched MEDLINE, Embase and CINAHL (database inception through June 2019) without date or language restriction (Supplemental Table 1). We used EndNote to de-duplicate and manage citations. For publications in languages other than English, we used translations by native speakers and where not possible, Google Translate. Author pairs completed the title and abstract screening, full-text screening, and manually searched the reference lists of eligible studies and reviews to identify other potentially relevant studies by snowballing. We included a third investigator (J.K. or J.J.C.) and used consensus to resolve disagreements.

## Study Selection

Inclusion criteria were: adult participants without established CKD (i.e., glomerular filtration rate [GFR]  $>60\text{mL}/\text{min}^2$ ) at baseline,<sup>10</sup> including those that reported people without CKD as a subgroup of a larger study; cohort studies, prospective or retrospective; and outcome data (primary or secondary) reported based on levels of exposure to a lifestyle factor, including diet (foods or nutrients), physical activity, alcohol consumption and tobacco smoking. We excluded studies of participants with albuminuria at baseline, whenever this information was available. We did not consider diet pattern exposures in our review, as these have recently been systematically evaluated.<sup>11,12</sup>

The primary outcome was incident CKD, defined as the development of GFR  $<60\text{mL}/\text{min}/1.73\text{m}^2$  during follow-up.<sup>10</sup> Secondary outcomes were other surrogate measures of CKD: KRT, GFR decline, or albuminuria.

## Data Extraction and Quality Assessment

One author from each team extracted the data from the included studies using standardized data extraction forms created in Microsoft Excel, which was checked by a second author before analysis. Supplemental Table 2 shows the data extracted for analysis. Where we identified more

than one publication for a single cohort study reporting on the same lifestyle factor, we used the data set from the published study contributing the highest number of participants. Within each meta-analysis, we conducted a sensitivity analysis examining the effects of substituting these alternative sources of data on the same cohort. Where questions arose concerning a study's eligibility, missing data, or further information on results, we contacted corresponding authors to request this information. We used author responses to make decision on a study's eligibility and analysis approach.

We assessed risk of bias for each included study, using the Newcastle-Ottawa Quality Assessment Scale,<sup>13</sup> which assesses the methodological quality of the studies across three domains: selection (or representativeness) of cohorts, comparability (of cohorts due to design or analysis) and outcomes (assessment and follow up) (Supplemental Table 2). We applied The Grading of Recommendations Assessment, Development and Evaluation methodology (GRADE) criteria to rate the quality of evidence (low, moderate or high) for each outcome. In analyses that included five or more studies, when the primary outcome showed low or moderate heterogeneity, we constructed funnel plots to examine for effects that may represent publication, selection or reporting bias.

### **Data Synthesis and Analysis**

We used RevMan 5.3 and Stata version 16.0 (StataCorp, College Station, TX) to meta-analyze data when a particular lifestyle factor was reported for the same outcome from 3 separate cohorts; otherwise associations were tabulated and reported using frequencies. Given the observational design and highly varied sample sizes of the primary studies, we used the random-effects model (DerSimonian & Laird) for all meta-analyses. Robustness of the association estimate was evaluated by comparing if any statistically significant association identified through random-effect models became non-significant under a fixed-effects model.

The overall association estimates for all binary outcomes are expressed as odds ratios (OR) or



relative risks (RR), depending on which ratio was predominantly used in the original data, together with 95% confidence intervals (CI). For studies reporting changes in mean values at the end of their observation follow-up periods, we extracted and tabulated the end of the study values with their associated variance. If the association compared a lifestyle factor with a reference exposure that was not homogenous with the other included lifestyle exposures (e.g., high adherence vs low adherence) then the ratio methods were inverted and then combined into the meta-analysis. We used Chi-square testing at an alpha of 0.05, and with the  $I^2$  statistic, rated low (<25%), moderate (25-75%) or high (>75%) to assess for heterogeneity. Supplemental Table 2 gives details of planned subgroup and sensitivity analyses to explore reasons for heterogeneity. In addition to these linear analyses for alcohol consumption, we also conducted a dose-response random-effects meta-regression analysis to account for potential changes in the risk estimate at different dosages of alcohol consumption (methods reported in Supplemental Table 2).

## **Results**

The electronic search retrieved 45,111 citations of which, a total of 104 studies encompassing 2,755,719 participants met the inclusion criteria (Supplemental Figure 1). The characteristics of included studies are reported in Supplemental Table 3. Lifestyle exposures and associations to kidney outcomes varied across the studies, with n=56 reporting diet exposures, n=18 reporting physical activity, n=27 reporting alcohol consumption and n=30 reporting tobacco smoking. The outcomes evaluated included incident CKD in (n=51 studies, KRT in 17 studies, GFR decline in 32 studies, and albuminuria in 20 studies).

## **Lifestyle hazards and incident chronic kidney disease**

The association between lifestyle factors and incident CKD was reported in 51 studies of 1,221,018<sup>14-72</sup>. The main results of the meta-analysis are summarized in Supplemental Figure 2.

**Diet.** The association between 57 different dietary factors with incident CKD was described in 31 studies of 176,625 participants.<sup>14,20,24,26,27,30,38,39,41,46,47,49,51,57,60,61,66,69,70</sup> Meta-analysis was possible for 9 dietary factors (Table 1), of which higher vegetable intake (OR 0.79 [95% CI: 0.70, 0.90];  $I^2=57\%$ ; Evidence quality: Low) and higher potassium intake (OR 0.78 [95% CI: 0.65, 0.94];  $I^2=48\%$ ; Evidence quality: Low) were consistently associated with lower odds of CKD. Higher sodium intake was associated with higher odds of CKD (OR 1.21 [95% CI: 1.06, 1.38];  $I^2=59\%$ ; Evidence quality: Moderate) (Table 1, Figure 1). Meta-analysis of studies evaluating carbohydrate intake, fish, fruit, phosphorus, protein and sugar-sweetened beverages consumption showed no clear association (Table 1).

We were unable to pool data on 32 additional dietary factors reported across 21 studies (Supplemental Table 4).<sup>15,16,18,19,23,25,27,30-32,37,45-47,57,59-62,71,73</sup> We identified 19 dietary factors for which one or both available studies showed an association with in the direction indicating decreased risk: cereal fiber, coffee, dairy, fiber, folate, legumes, magnesium, nitrate, nuts, nuts & legumes, plant protein, omega-3, DHA, EPA, vitamin B12, vitamin C, vitamin D, vitamin E, and zinc. We identified 2 dietary factors for which one or both available studies indicating a harmful relationship: a higher sodium-potassium ratio and red & processed meat consumption (Supplemental Table 4).

**Physical activity.** The association of different levels of physical activity with incident CKD was described in 10 studies of 78,301 participants (Table 1; Figure 2).<sup>28,34,42,44,53,54,58,59,63,72</sup> Meta-analysis of 9 studies showed lower odds of CKD in people who were more physically active compared with those who were less physically active (OR 0.82 [95% CI: 0.69, 0.98];  $I^2=83\%$ ; Evidence quality: Very low).

**Alcohol intake.** The association between alcohol intake and incident CKD was described in 14 studies of 211,072 participants.<sup>22,23,28,40,43,50,52,55,63-65,67,68,72</sup> Compared with lower intakes, meta-analysis showed that higher consumption of alcohol (RR 0.87 [95% CI: 0.79, 0.95];  $I^2=43\%$ ; Evidence quality: Low) and moderate alcohol consumption (RR 0.86 [95% CI:0.79, 0.93];  $I^2=50\%$ ; Evidence quality: Moderate) were associated with lower risk of CKD (Table 1, Figure 3). In a dose–response meta-regression analysis, we modelled the relationship between incident CKD and alcohol intake using restricted cubic splines (Supplemental Table 5 and Supplemental Figure 3) and found that higher alcohol intake was associated with lower risk of incident CKD. This association was generally observed throughout the whole range of alcohol consumption considered with a significant effect size (p values for nonlinearity = 0.03). There was no apparent association when people who had never consumed alcohol were compared with those who had consumed it in the past (former intake) (Table 1).

**Smoking.** The association between smoking and incident CKD was described in 12 studies of 985,086 participants.<sup>28,29,35,43,50,52,53,59,63,65,68,74</sup> Compared with people who never smoked, current and former smokers (ever smokers) showed higher odds of CKD (OR 1.18 [95% CI: 1.10, 1.27];  $I^2=81\%$ ; Evidence quality: Very low) (Table 1, Figure 3). Compared with people who had never smoked, former smokers had increased odds of CKD (OR 1.09 [95% CI: 1.01, 1.17];  $I^2=90\%$ ; Evidence quality: Very low) in 6 studies of 944,931 participants (Table 1). There was no consistent association with CKD in 2 studies comparing current with former smokers (Supplemental Table 4).

### **Lifestyle risk factors and secondary outcomes (KRT, GFR decline, and albuminuria):**

The consistency of associations between the lifestyle factors identified in our primary analysis and other markers of kidney damage is shown in Figure 4.

The association between lifestyle factors and KRT was described in 17 studies of 990,723 participants;<sup>33,35,37,75-88</sup> lifestyle factors and GFR decline in 32 studies of 108,936

participants,<sup>14,20,23,34,46,49,73,86,89-105</sup> and lifestyle factors and albuminuria in 20 studies of 512,403 participants.<sup>23,39,41,88,95,100,101,105-116</sup> Table 2 and the ‘Supplementary Material. Data synthesis for secondary outcomes’ show the details. The risk of KRT was higher among current and former smokers (RR 1.59 [95% CI: 1.30, 1.94]; I<sup>2</sup>=68%; Evidence quality: Moderate) compared with never-smokers (Supplemental Figure 4). The risk of GFR decline was lower in persons with higher potassium intake (RR 0.49 [95% CI: 0.31, 0.79]; I<sup>2</sup>=90%; Evidence quality: Very low) and physically active (OR 0.76 [95% CI: 0.59, 0.97]; 75%; Evidence quality: Very low) (Supplemental Figure 5). The risk of albuminuria was lower among physically active persons (OR 0.88 [95% CI: 0.81, 0.96]; I<sup>2</sup>=0%; Evidence quality: Low) and higher among tobacco smokers (OR 1.67 [95% CI: 1.23, 2.26]; I<sup>2</sup>=88%; Evidence quality: Very low) (Supplemental Figure 6).

Other lifestyle hazards did not have sufficient studies to allow meta-analysis, but their associations suggested they may be potentially protective, potentially harmful or having no association to secondary study outcomes based on the direction of the majority (≥50%) of studies. Results are shown in Supplemental Figure 7 and fully detailed in Supplemental Tables 3 & 4. In brief, coffee consumption was associated with lower risk of incident CKD and KRT in 2/2 and 1/2 of studies, respectively. Dairy intake was associated with lower risk of incident CKD and albuminuria in 2/4 and 1/2 of studies, respectively. Red and processed meats was associated with lower risk of incident CKD, KRT and albuminuria in 1/2, 1/1 and 1/1 of studies, respectively.

### **Subgroup and sensitivity analyses**

Subgroup analyses did not show consistent relationships with duration of exposure or geographic region. Replacing individual datasets (substituting alternative reports from the same cohort) did not meaningfully change results (see ‘Supplementary Material. Data synthesis for secondary outcomes’). We also conducted a *post-hoc* sensitivity analysis on the way that

the frequency of alcohol consumption was reported: higher 'daily' consumption of alcohol had no significant association with incident CKD (7 studies; RR 0.98 [95% CI 0.82, 1.18];  $I^2 = 43\%$ ), whereas higher weekly alcohol consumption was associated with a lower risk of incident CKD (6 studies; RR 0.82 [95% CI 0.75, 0.90];  $I^2 = 32\%$ ) (Supplemental Table 6). Subgroup analysis comparing studies with participants baseline GFR  $\geq 89.9$ -70 mL/min/1.73 to GFR  $\geq 90$  mL/min/1.73 showed significant associations between study exposures (except for physical activity) and the risk of incident CKD in studies with participants baseline GFR  $\geq 89.9$ -70 mL/min/1.73. The association of vegetable intake and incident CKD held robust in both baseline GFR subgroups. Whereas in studies reporting participant baseline GFR  $\geq 90$  mL/min/1.73 (which were 37 out of 104; 12 studies able to be meta-analyzed), these associations did not attain statistical significance. However, the direction and magnitude of observed risks in both strata were very similar (Supplemental Table 6).

### **Quality assessment**

The certainty (GRADE) of the evidence for each outcome meta-analyzed is detailed in Supplemental Table 8. The overall risk of bias across the studies was low (Supplemental Figure 8 & 9). Eighty-eight percent of studies had a low risk of bias for sample, whereas 10% were rated high due to being conducted in populations with established diseases (such as type 2 diabetes or hypertension) which are known to increase the risk of incident CKD. With respect to follow-up, 82% of studies had low risk of bias, bias was judged unclear in 13% of studies that reported less than 4 years follow-up; 3 studies (5%) had a high risk of bias due to very short follow-up periods of less than 2 years. The risk of bias in exposure assessment was rated high 92% of studies lifestyle behaviors were assessed by self-report; objective measures were used in 8 studies (8%). Outcomes were captured using appropriate tools in 88% of studies, and high is 6% of studies. Potential analysis bias was low in 73% of studies, where 23% were unclear, because data were not analyzed using ratio statistics to allow statistically data pooling.

## Discussion

This study evaluated the association between modifiable lifestyle factors and incident CKD in the community. In predominately low-to-very-low-certainty evidence, we found higher intake of potassium and vegetables, lower intake of sodium, physical activity, moderate alcohol consumption, and avoidance of tobacco smoking to be consistently associated with lower risk of CKD. We identified consistency with these main results when we examined their association with other surrogates of kidney damage: KRT, GFR decline and albuminuria.

Higher vegetable intake is associated with higher potassium intake: both dietary factors were consistently associated with fewer kidney outcomes. Low vegetable consumption is a strong predictor of mortality in the general population.<sup>117,118</sup> The mechanism is likely, at least in part, through the intermediary diseases that are themselves risks for CKD: cardiovascular disease, hypertension, diabetes, obesity, and metabolic syndrome.<sup>119</sup> Whether there is additionally a more direct relationship between vegetable or potassium intake and kidney health requires further study.

In our analysis, higher potassium intake was associated with reduced incident CKD and GFR decline, adding to the growing evidence-base for the protective association of potassium intake in other chronic conditions. In the Prospective Urban Rural Epidemiology (PURE) study, higher potassium excretion was associated with a lower risk of death and cardiovascular events across more than 18 countries worldwide.<sup>120</sup> Higher intakes of potassium have also been demonstrated to lower the risk of stroke<sup>121</sup> and lower blood pressure in adults with and without hypertension.<sup>122,123</sup> In patients in ONTARGET, a high vascular risk cohort, most of whom did not have CKD at baseline, potassium intake was associated with a less rapid GFR decline or need for KRT.<sup>124</sup> In ONTARGET, the relationship between potassium intake and the outcome did not appear to differ by baseline level of albuminuria, but there was a statistically significant interaction suggesting that the protective association with potassium might not be observed in

patients with GFR <45 mL/min (advanced CKD). In these patients, potassium, and with it, fruits and vegetables are often restricted. When discussing dietary advice, it is critical to distinguish whether we are concerned with prevention of incident CKD, prevention of progression (and at what level of GFR), or management of hyperkalemia and management of the risk of hyperkalemia.<sup>125</sup>

Similarly, higher sodium intake showed a consistent association with increased risk of incident CKD, KRT and GFR decline. This supports the growing evidence from clinical trials, demonstrating the effect of sodium intake on blood pressure, proteinuria and extra-cellular volume in CKD.<sup>126</sup> Despite existing controversy surrounding reverse causality at extremely low sodium intakes,<sup>127</sup> our review supports the message that higher sodium intakes are detrimental and public health efforts should be prioritized to reduce population-wide sodium consumption. More work is needed on the optimal level of sodium restriction; our analysis focused on high vs low intake, which in the original studies, the highest exposures of salt defining high intake varied, ranging from  $\geq 9.88$  to 16.27g/day (sodium  $\geq 172$  to 283mmol/day).

A healthy diet pattern, characterized by higher intakes of fruit, vegetables, low-fat dairy, fiber and wholegrain and lower in sodium, red meat and sugar has been associated with a 30% reduced odds of kidney damage.<sup>11,12</sup> Many of the individual diet factors we identified are characteristic of a higher diet quality and overall healthier diet pattern. For example, taking all the data into account, diet factors possibly protective against incident CKD in our current study included fruit, dairy, vegetables, fiber, legumes, nuts, potassium, and unsaturated fatty acids. In contrast, diet factors possibly harmful to incident CKD in our study included excessive carbohydrate intake, high energy intake, red and processed meats, saturated fat, sodium, sodium-potassium ratio and sugar-sweetened beverages. The protective factors, characteristics of a healthy diet, are also strongly associated with reduced risk of overweight and obesity,<sup>128</sup> which is linked with increased risk of incident CKD.<sup>129</sup> These associations fundamentally align



with guidelines for general healthy eating and cardiovascular disease prevention, which is helpful and convenient in guiding public health policy for CKD prevention that aligns with prevention of other chronic diseases.<sup>130</sup>

We found that higher levels of physical activity were consistently associated with a lower risk of all study outcomes evaluated. This aligns with the majority of existing studies, which suggest that physical activity is associated with reduced risk of kidney damage, through attenuating cardiovascular disease risk,<sup>131,132</sup> mortality<sup>133</sup> and rapid declines in kidney function.<sup>134</sup> Whether a relationship independent of cardiovascular and vascular damage truly exists is not known based on current data. Possible mechanisms include reduced blood pressure, improved glycemic control, angiogenesis and vascular regeneration by the up-regulation of endothelial nitric oxide production and other antioxidant enzymes.<sup>135</sup> While the measurement of physical activity was heterogeneous across the included studies, the most common categorization of higher levels of activity was defined as at least 30 minutes a day.<sup>44,59</sup> These findings suggest that public health messages should emulate those of primary prevention of cardiovascular disease, to achieve and maintain a moderate level of physical activity of at least 30 minutes a day and avoiding extended periods of being sedentary.<sup>136,137</sup>

We found an inverse association between alcohol consumption and incident CKD, KRT and GFR decline. While the relationship between alcohol consumption and kidney function decline has not been consistent in the current body of literature, many clinical studies have indeed shown that moderate alcohol consumption is associated with lower occurrence of CKD.<sup>40,55,64,68</sup> In contrast, existing literature has shown that chronic alcoholism is associated with CKD,<sup>56,65</sup> leading to the hypothesis that excessive alcohol consumption directly damages the kidney, independent of liver damage.<sup>138,139</sup> Similarly, some reports included in our review found that heavy drinking, in contrast with moderate drinking, was associated with increased risk of albuminuria and CKD.<sup>56,105,140</sup> This distinction, that moderate, but not high, alcohol



consumption is associated with lower prevalence of albuminuria and CKD compared with abstinence or with lower intakes, is consistent with a number of other studies.<sup>139,141,142</sup> There is also the possibility that unadjusted confounders may be at play, for example, social integration as a product of moderate alcohol consumption and overall well-being, which are good for health.<sup>143</sup> It would appear that despite minor international variations,<sup>144</sup> and the heterogeneous categorization for the higher alcohol consumption (ranging in grams per day (range 20 to 48g/day), grams per week (210g/week), total drinks per day (range >1 to 4 drinks/day), drinks per week (range 5 to >15 drinks/ week), that moderate alcohol consumption in-line with public health guidelines seems safe and unlikely to cause kidney damage in the general population.

Current and former smokers had higher risk of incident CKD compared with those who never smoked. Tobacco smoking has been previously identified as a risk factor for incident CKD and KRT in the general population.<sup>145</sup> While the mechanism is uncertain, smoking may lead to insulin resistance<sup>146</sup> which might explain the large effect size (67% increase in risk) of smoking on risk of albuminuria observed in our study, consistent with previous observations.<sup>147</sup> The harmful effects of smoking may also be mediated by endothelial cell dysfunction, inducing advanced glycation end products due to glycotoxins present in cigarettes, increased vascular permeability and pathological vascular changes of kidney disease, and insulin resistance in diabetic and non-diabetic subjects.<sup>145</sup> Taken together, these risk factors for kidney function decline clearly support a public health message to avoid tobacco smoking to prevent kidney, as well as cardiovascular disease.

This study has strengths as the first evidence synthesis of lifestyle risk and protective factors and primary prevention of CKD: it is broad in scope and we have taken a rigorous approach to meta-analysis. However, this study has limitations. First, there was scarce evidence for some exposures, particularly for diet factors, precluding meta-analysis; for these factors our output

is simply descriptive. Second, there was variation in the definition of the different exposures across the different lifestyle factors, in the degree of adjustment for potential confounders, and in definition and reporting for study outcomes. For example, there were no consistent adjustments for activity, age, education and sex (as reported in Supplemental Table 3) in all studies included in the analyses. Furthermore, 10 different definitions of incident CKD were used in the included studies, with similar heterogeneity in the definitions of the secondary outcomes). This leads to heterogeneity in the analysis; and precludes clear recommendations in terms of possible targets, goals or thresholds. Third, while we were able to perform meta-analysis to account for the known non-linear associations of alcohol consumption and kidney outcomes, we were unaware of any such assumptions for the other lifestyle factors, and the original studies did not commonly report their associations in this way. The original papers usually made a linear assumption and analyzed data with linear models. It is possible that nonlinear effects or threshold effects may be missed in this way. Fourth, because we evaluated cohort studies and not randomized trials, the findings do not imply causality. However, there were no trials of this nature in our search and it is unlikely that studies of sufficient rigor, size, and duration will be conducted, given the resource intensive nature of such trials. We combined RR and OR; for rare events, these are numerically similar though calculated differently. Fifth, we used the NOS to assess bias rather than the more comprehensive ROBINS-I tool<sup>148</sup> because our resources to complete the study were finite. Finally, in order to conduct meta-analysis, each putative risk and protective factor was considered separately and we do not know whether there are quantitatively important interactions between the different factors (e.g., does the effect of carbohydrate intake differ at different levels of physical activity), as no study has evaluated such hypotheses.

Allowing for the limitations of inferences from observational studies, our work suggests the lifestyle factors we have evaluated are probably those that patients have the most control, they

are not the only ones that public health authorities should target. For example, other potentially modifiable hazards known to increase the risk of kidney damage include environmental pollution,<sup>149,150</sup> excessive body weight related to nutrition,<sup>129</sup> inappropriate use of medications (including analgesics, antibiotics, antiretrovirals or proton-pump inhibitors)<sup>151</sup> and heavy metal exposure and intake (in-particular cadmium).<sup>152</sup> Finally, society has a further role to play in facilitating the more personal choices, through food labelling, alcohol and tobacco labelling, health policy around exercise and policy around the ease of walking and cycling in the built environment and walkability.

We recognize that these findings are based on non-randomized data with risk of residual and unknown confounding, particularly in the setting of studies with low-to-very-low certainty of the evidence. However, the generalizability and overall importance of these findings should not be undermined, as they are well in-line with public health recommendations for preventing related chronic conditions and general healthy lifestyle principles. Therefore, the results can represent an important indication for public policy, advocacy, and be hypothesis-generating for future randomized trials. It is not trivial to ask patients to change their lifestyle. Diet, in particular, is a highly social and cultural issue; furthermore, many patients are constrained by external factors, including economic factors, in their decisions. For these reasons, we believe that lifestyle intervention studies to address unanswered questions examining the whole range of clinically important outcomes, including the incidence and progressions of CKD, continue to be justified.

## **Conclusion**

Increased vegetable and potassium intake, physical activity and moderate alcohol consumption were consistently associated with reduced risk of CKD. Increased dietary salt intake, and tobacco smoking were consistently associated with increased risk of CKD. In the absence of

trial evidence, these findings can inform both public health recommendations and patient-centered discussions in clinical practice.

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## **Conflict of interest**

J.K. has received consultancy fees from Amgen for travel and lecture presentations, and consultancy fees from HealthCert for topics unrelated to the submitted work. J.J.C reports grant funding from AstraZeneca, ViforPharma and Astellas, consulting for Baxter and AstraZeneca, and speaker fees for Abbott, Nutricia, AstraZeneca and ViforPharma, all outside the submitted work. C.M.C. has received consultation, advisory board membership or research funding from the Ontario Ministry of Health, Sanofi, Johnson & Johnson, Pfizer, Leo Pharma, Astellas, Janssen, Amgen, Boehringer-Ingelheim and Baxter. K.L.C. has received consultation, advisory board membership for research funding from Queensland Health, Nestle Health Sciences and the Dietitians Association of Australia. The rest of co-authors have no conflict of interest to report.

## **Authors' Contributions**

JK, and JC contributed to the study conception. JK, SM, HX, GS, AG, XQ and LZ conducted the literature search, extracted data and appraised risk of bias. JK conducted the data analysis. JK was responsible for writing the first draft of the manuscript. JC reviewed the first draft of the manuscript. KC and CC critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

## Supplemental Material

Additional Supplemental Material may be found in the online version of this article at the publisher's web-site:

Supplementary Material. Data synthesis for secondary outcomes

Supplemental Table 1. Search terms used across the electronic databases

Supplemental Table 2. Summary of the methods relating to data extraction, risk of bias, meta-regression and planned subgroup and sensitivity analyses

Supplemental Table 3. Characteristics of the included studies

Supplemental Table 4. Lifestyle hazards and kidney disease outcomes from individual studies which could not be statistically pooled into meta-analysis

Supplement Table 5. Summary of the studies between alcohol intake and incident CKD

Supplemental Table 6: Subgroup analysis for Incident CKD

Supplemental Table 7. Results from sensitivity analysis

Supplemental Table 8: GRADE table summarizing the quality of the evidence for each outcome

Supplemental Figure 1. Study flow diagram

Supplemental Figure 2. Summary of the associations between modifiable lifestyle risk and protective factors and risk of incident CKD,

Supplement Figure 3. Dose–response relationship between alcohol intake (gram per day) and incident CKD estimated with a random-effect meta-regression-restricted cubic spline model

Supplemental Figure 4: Association of Tobacco smoking and ESKD

Supplemental Figure 5: Summary of the associations between modifiable lifestyle risk and protective factors and risk of GFR decline

Supplemental Figure 6: Summary of the associations between modifiable lifestyle risk and protective factors and risk of Albuminuria

Supplemental Figure 7. Consistency of associations in lifestyle factors which could not be statistically pooled across the markers of kidney function decline.

Supplemental Figure 8. Risk of bias across the included studies

Supplemental Figure 9: Individual assessment of risk of bias across the included studies

Supplemental Figure 10: Funnel plots for lifestyle hazards and incident CKD

Supplemental Figure 11: Funnel plots for lifestyle hazards and secondary outcomes

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## Figure legends

**Figure 1.** Association of vegetable intake (panel 1A), potassium intake (panel 1B), sodium intake (panel 1C) and incident chronic kidney disease. Note the association estimate for each lifestyle factor is presented on the ratio (OR or RR) which was predominantly used in the included studies.

**Figure 2.** Association of physical activity level and incident chronic kidney disease.

**Figure 3.** Association of alcohol consumption (panel 3A), tobacco smoking (panel 3B) and incident chronic kidney disease. Note the association estimate for each lifestyle factor is presented on the ratio (OR or RR) which was predominantly used in the included studies.

**Figure 4.** Consistency of associations in lifestyle factors across the markers of kidney function decline<sup>a</sup>. The 4 studies of sodium intake and GFR decline were not meta-analyzable because 2 of the studies reported means and variance, but not ratio data.

**Table 1.** Meta-analyses performed in the review showing the association of alcohol consumption, diet, physical activity and smoking exposure to the risk of incident CKD

Exposure	Studies	Participants	Association ratio [95% CI] <sup>a</sup>	Heterogeneity [ <i>I</i> <sup>2</sup> ]	Evidence Quality <sup>b</sup>
<b>Diet Factors</b>					
Fish	3	21,226	OR 0.94 [0.86, 1.02]	<i>I</i> <sup>2</sup> =5%	Low
Fruit	4	28,779	OR 0.91 [0.79, 1.06]	<i>I</i> <sup>2</sup> =60%	Very low
Vegetables	5	32,054	OR 0.79 [0.70, 0.90]	<i>I</i> <sup>2</sup> =57%	Low
Sugar-sweetened beverages	4	22,760	OR 1.45 [0.97, 2.15]	<i>I</i> <sup>2</sup> =68%	Very low
Carbohydrates	3	20,238	OR 1.08 [0.85, 1.36]	<i>I</i> <sup>2</sup> =63%	Very low
Protein	3	19,835	OR 1.08 [0.91, 1.28]	<i>I</i> <sup>2</sup> =47%	Very low
Phosphorus	3	23,466	OR 1.00 [0.75, 1.32]	<i>I</i> <sup>2</sup> =72%	Very low
Potassium	7	32,647	OR 0.78 [0.65, 0.94]	<i>I</i> <sup>2</sup> =48%	Low
Sodium	6	43,772	RR 1.21 [1.06, 1.38]	<i>I</i> <sup>2</sup> =59%	Moderate
<b>Physical Activity</b>					
Physical activity - High vs Low levels	9	70,828	RR 0.82 [0.69, 0.98]	<i>I</i> <sup>2</sup> =83%	Very low
<b>Alcohol Consumption</b>					
Alcohol - High vs Low intakes	13	216,291	RR 0.87 [0.79, 0.95]	<i>I</i> <sup>2</sup> =43%	Low
Alcohol - Moderate vs Low intakes	7	165,415	RR 0.86 [0.79, 0.93]	<i>I</i> <sup>2</sup> =50%	Moderate
<b>Tobacco Smoking</b>					
Tobacco smoking - Never vs Former	6	944,931	OR 1.09 [1.01, 1.17]	<i>I</i> <sup>2</sup> =90%	Very low
Tobacco smoking – Current or Former vs Never	12	985,086	OR 1.18 [1.10, 1.27]	<i>I</i> <sup>2</sup> =81%	Very low

Abbreviations: CKD: chronic kidney disease; RR: relative risk; OR: odds ratio. <sup>a</sup> Figures in square brackets are 95% confidence intervals; <sup>b</sup> Summary of Findings table which details the reasons for downgrading evidence quality is reported in Supplemental Table 7.

**Table 2.** Meta-analyses performed in the review showing the association of alcohol consumption, diet, physical activity, and smoking exposure to secondary outcomes (kidney replacement therapy, GFR decline, and albuminuria)

<b>Kidney Replacement Therapy<sup>a</sup></b>					
<b>Tobacco Smoking</b>	<b>Studies</b>	<b>Participants</b>	<b>Association ratio [95% CI]<sup>b</sup></b>	<b>Heterogeneity [I<sup>2</sup>]</b>	<b>Evidence Quality<sup>c</sup></b>
Tobacco smoking - Former v current	7	1,126,913	RR 1.25 [1.13, 1.39]	I <sup>2</sup> =39%	Moderate
Tobacco smoking - Current or Former vs Never	8	1,230,390	RR 1.59 [1.30, 1.94]	I <sup>2</sup> =68%	Moderate
<b>GFR decline<sup>d</sup></b>					
<b>Diet factors</b>					
Potassium	4	10,729	RR 0.49 [0.31, 0.79]	I <sup>2</sup> =81%	Very low
Protein	5	18,507	OR 1.07 [0.96, 1.19]	I <sup>2</sup> =42%	Low
<b>Physical Activity</b>					
Physical activity - High vs Low levels	5	15,161	OR 0.77 [0.63, 0.93]	I <sup>2</sup> =75%	Very low
<b>Alcohol Consumption</b>					
Alcohol - High vs Low intakes	5	16,580	OR 0.88 [0.72, 1.07]	I <sup>2</sup> =15%	Very low
<b>Albuminuria</b>					
<b>Diet Factors</b>					
Sodium	3	11,751	OR 1.01 [0.89, 1.14]	I <sup>2</sup> =0%	Very low
<b>Physical Activity</b>					
Physical activity - High vs Low levels	4	110,154	RR 0.88 [0.81, 0.96]	I <sup>2</sup> =0%	Low
<b>Alcohol consumption</b>					
Alcohol - High vs Low intakes	7	220,479	RR 1.03 [0.88, 1.20]	I <sup>2</sup> =59%	Low
<b>Tobacco Smoking</b>					
Tobacco smoking - Current or Former vs Never	7	184,302	OR 1.67 [1.23, 2.26]	I <sup>2</sup> =88%	Very low

Abbreviations: GFR: glomerular filtration rate; RR: relative risk; OR: odds ratio <sup>a</sup> Meta-analysis not possible for diet factors, physical activity or alcohol consumption; <sup>b</sup> Figures in square brackets are 95% confidence intervals; <sup>c</sup> Summary of Findings table which details the reasons for downgrading evidence quality is reported in Supplemental Table 7; <sup>d</sup> Meta-analysis not possible for tobacco smoking.