RESEARCH ARTICLE

Cardiovascular disease risk factors in chronic kidney disease: A systematic review and meta-analysis

Rupert W. Major1,2*, Mark R. I. Cheng3, Robert A. Grant3, Saran Shantikumar1, Gang Xu2,4, Issaam Oozeerally2, Nigel J. Brunskill2,4, Laura J. Gray1

1 Department of Health Sciences, University of Leicester, Leicester, United Kingdom, 2 John Walls Renal Unit, Leicester General Hospital, University Hospitals of Leicester, Leicester, United Kingdom, 3 Department of Medical Education, University of Leicester, Leicester, United Kingdom, 4 Department of Infection, Immunity and Inflammation, University of Leicester, Leicester, United Kingdom

* rwlm2@le.ac.uk

Abstract

Background and objectives

Chronic kidney disease (CKD) is a global health burden and is independently associated with increased cardiovascular disease risk. Assessment of cardiovascular risk in the general population using prognostic models based on routinely collected risk factors is embedded in clinical practice. In CKD, prognostic models may misrepresent risk due to the interplay of traditional atherosclerotic and non-traditional risk factors. This systematic review’s aim was to identify routinely collected risk factors for inclusion in a CKD-specific cardiovascular prognostic model.

Design, setting, participants and measurements

Systematic review and meta-analysis of observational cohort studies and randomized controlled trials. Studies identified from MEDLINE and Embase searches using a pre-defined and registered protocol (PROSPERO ID—2016:CRD 42016036187). The main inclusion criteria were individuals ≥18 years of age with non-endstage CKD. Routinely collected risk factors where multi-variable adjustment for established cardiovascular risk factors had occurred were extracted. The primary outcome was fatal and non-fatal cardiovascular events.

Results

The review of 3,232, abstracts identified 29 routinely collected risk factors of which 20 were presented in more than 1 cohort. 21 cohorts were identified in relation to 27,465 individuals and 100,838 person-years. In addition to established traditional general population cardiovascular risk factors, left ventricular hypertrophy, serum albumin, phosphate, urate and hemoglobin were all found to be statistically significant in their association with future cardiovascular events.
Conclusions
These non-traditional risk factors should be assessed in the development of future cardiovascular prognostic models for use in individuals with CKD.

Introduction
Chronic kidney disease (CKD) is a global health burden estimated to affect up to 15% of adult populations [1–3] and is independently associated with increased cardiovascular (CV) disease risk similar to the risk of diabetes mellitus or coronary heart disease [1–2]. This risk increases as CKD advances and is evidenced by worsening excretory function, usually manifest as declining glomerular filtration rate, and increasing proteinuria [3–4]. The overall cost of CKD accounts for 1.3% of healthcare budgets [5] of which 13% is related to the excess myocardial infarctions and strokes associated with CKD [5].

Assessment of CV risk using prognostic models in the general population, particularly for primary prevention, is embedded in clinical practice [6–9]. Such prognostic models use data from routinely collected risk factors and can be automated using electronic medical records into routine clinical care. CV prognostic models developed specifically for CKD have significant methodological weaknesses, including no external validation and limited model metrics’ assessment, and thus may miscalculate risk in CKD. This contributes to their lack of clinical utility [10].

To our knowledge no systematic review has been performed to identify routinely collected risk factors that may potentially contribute to a composite CV outcome prognostic model in CKD. A new risk factor is only clinically useful if it adds predictive performance to a model beyond currently utilized standard risk factors, i.e. once a model has been adjusted for said factors, therefore additional risk factors must be novel and routinely collected in clinical care. Therefore, assessment of these factors is crucial before prognostic models can be rationally optimised.

Specific validation in CKD is warranted because the relative role of atherosclerosis in CV outcomes diminishes, and is replaced by the confounding—‘non-traditional’ CV risk factors. These uremia-related risk factors may have an increasingly important role with advancing CKD [11]. This may warrant inclusion of risk factors such as calcium and phosphate [12], related to arteriosclerosis and reduced vascular compliance, in CKD-specific CV prognostic models. Equally, consideration of risk factors associated with cardiomypathy, such as echocardiographic evidence of left ventricular dysfunction or systemic inflammation may also be justified [11]. Thus other novel routinely collected risk factors require consideration for validation of CV prognostic models in CKD.

The aim of this systematic review was to identify routinely collected risk factors with potential value in CV risk prediction in CKD beyond those already included in existing CV prognostic models to inform the development of future CKD-specific CV prognostic models.

Methods
Ovid MEDLINE and Embase were searched using a pre-defined and registered systematic review and meta-analysis protocol [13] (PROSPERO ID—2016:CRD42016036187). Search strategies are available in the Supporting Information (Tables A and B in S1 File). Reporting of the current systematic review follows the PRISMA guidance, also available in the Supporting
Information (S2 File). The inclusion criteria were observational cohort studies and secondary analyses of randomized controlled trials in adult (≥18 years of age) with either CKD stage 3a or worse (any eGFR formula <60 ml/min/1.73m²) or proteinuria based on standard definitions [14]. The search was limited to English language manuscripts. General population studies with subgroup analysis presenting results for CKD groups were also included. Studies including individuals with end-stage renal disease, either receiving maintenance dialysis or with a renal transplant, were excluded. Studies of outcomes after acute kidney injury were also excluded. The minimum follow-period was six months. A formal definition of CKD using a standardised eGFR formula was first established in 1999 [15], therefore the search range was restricted from this date until 20th October 2017.

The primary outcome was a composite of CV disease events which includes acute coronary syndrome (including unstable angina), congestive cardiac failure and ischemic stroke. Composite CV outcomes including CV-specific mortality were included unless CV events were grouped with all-cause mortality and/or renal related outcomes.

For the purposes of this paper ‘risk factor’ will be used throughout to mean a measurable variable at the start of a study that is associated with a future CV disease event during the study’s follow-up. Any variable was considered as a candidate risk factor if it was collected at or prior to the start point of the observational period for the study. In addition, factors were only included if they were likely to be routinely collected as part of standard primary care clinical practice. Whether a variable was routinely collected was assessed independently by three clinicians (RM, IO, GX). Where there was disagreement regarding a variable’s inclusion, it was discussed between the three assessors until a consensus was reached. For all other stages of the methods, assessment was performed independently by at least two of the authors. Where discrepancies occurred, results were compared until a consensus was reached. If no consensus was achievable, a further author was consulted to make a final decision.

The title and abstracts of all studies identified by the literature search were assessed. The full text of any abstract meeting the inclusion criteria was then reviewed. Data were extracted using a standardised extraction form which included a risk of bias assessments based on the ‘Quality in Prognostic Studies’ tool [16]. Confounders adjusted for in each model were also extracted. The data extraction form was modified and optimised after data collection from three manuscripts had been performed. High risk of bias was not used as a reason for excluding a study. Where missing data in relation to a cohort’s characteristics or model were not published, the corresponding author for the cohort was contacted via email.

Data for the risk factors were extracted in the form of hazard ratios (HR) and 95% confidence intervals (CI) for the primary outcome. Categorical risk factors were standardised to the same reference category and continuous variables to the same units (Table C in S1 File). For example, the gender risk factor was presented as the risk for being male. Where different units were reported for the same variable, those units reported in the majority of studies were used, and the minority studies’ results were converted to the same units. A random effects model using the Mantel-Haenszel method was used as heterogeneity was expected to be present [17]. Data were meta-analysed where more than one study reported results for the same risk factor. Heterogeneity was assessed using the I² statistics. Subgroup analysis was considered by CKD stage including both eGFR and proteinuria. Due to the limited clinical applicability and bias of univariate analysis of risk factors, only results from studies where multi-variate adjustment for traditional CV risk factors were considered further. Models were then assessed for the number of ‘core’ risk factors they adjusted for. Core risk factors included age, gender, ethnicity, body mass index, smoking, diabetes mellitus, hypertension, CV disease and dyslipidemia. These risk
Factors are all included in general population prognostic tools or have a firmly established association with CV disease risk [2,6,7,18]. In addition, because of their additive benefit to CV prognostic tools [4], eGFR and proteinuria measurements were also included as core adjustment co-variates. Where the same study had published results for a risk factor in more than one manuscript the paper with the most complete data was used. If the data were the same, the results from the most recent publication were used. Where more than one model was presented in the same publication, the model with the greatest number of core risk factors included was used. All statistical analysis was performed using Stata version 14.1.

Results

Three thousand two hundred and thirty-two abstracts were reviewed. Fig 1 shows the screening process, including the number of cohorts and risk factors identified, and reasons for any
exclusion. Twenty-one cohorts were included in the systematic review [19–39]. Fourteen (66.7%) studies were observational cohort studies with recruitment from nephrology outpatient settings and the others were randomized controlled trials. Six cohorts provided additional data [19–24].

Overall a total of 27,465 individuals were included in these studies representing a cumulative total of 100,838 person-years. Table 1 summarises the characteristics of the cohorts contributing to the systematic review. The risk of bias for all studies was medium to high (see Table D in S1 File). In addition to the observational nature of the studies as a source of bias, other factors relating to study participant inclusion and exclusion, assessment of outcomes, reporting of missing data and statistical methods were considered. Six cohorts (28.6%) were recruited from a single-center. CV outcomes were broadly similar but 15 studies (71.4%) did not blind their outcome assessors. Seven cohorts (33.3%) reported no information in relation to missing data. No study pre-specified or registered their published analysis plan.

Sixty-six potential risk factors for CV events were identified (Table E in S1 File). Twenty-nine of these were deemed to be routinely collected and were therefore included in the systematic review. Nine risk factors were only reported in one study and therefore the data on 20 risk factors reported in multiple studies were pooled to produce a single estimate. The confounders which were adjusted for in all the included models are shown in Table 2. Age was corrected for in 20 out of 21 models (95.2%) and was the most frequently adjusted for variable. Diabetes mellitus was corrected for in 17 out of 19 models (89.5%) making it the comorbidity most frequently corrected for. Ethnicity was included in four models, five models had no published ethnicity data and eleven cohorts had a population with a single ethnicity making up more than 90% of the population. Seventeen (81.0%) studies corrected for eGFR and eleven (52.4%) for proteinuria. Three studies (14.3%) adjusted for all established core CV risk factors.

Data for the extracted risk factors are shown in Table 3. The forest plots for the non-traditional risk factors of albumin, haemoglobin, phosphate and urate are shown in Figs 2 to 6 and forest plots for all other risk factors are shown in Figures A to N in S1 File. Within the traditional risk factors, male gender, increasing age, smoking, established CV disease, diabetes mellitus and increasing total cholesterol were all associated with statistically significant increased risk of a CV event. Systolic and diastolic blood pressures were not associated with increased CV event risk.

In the meta-analysis, non-traditional risk factors associated with increased risk of CV events were albumin (pooled HR 0.62 per g/dL increase, 95% CI 0.52–0.75, p<0.001), haemoglobin (pooled HR 0.90 per g/dL increase, 95% CI 0.86–0.95, p<0.001), phosphate (pooled HR 1.20 per mg/dL increase, 95% CI 1.08–1.33, p = 0.005) and urate (pooled HR 1.07 per mg/dL increase, 95% CI 1.02–1.12, p = 0.004). Left ventricular hypertrophy on echocardiogram (pooled HR 1.78, 95% CI 1.35–2.35, p<0.001) was also found to be associated with an increased risk of a CV event. Serum urea nitrogen, sodium and pulmonary hypertension on echocardiogram were all statistically significant but only present in one study each. Calcium, bicarbonate and parathyroid hormone were not associated with altered risk in the single studies in which they were included.

Heterogeneity varied substantially between variables (Table 3). Of the potential novel risk factors for incorporation in to prognostic models albumin ($I^2=66.4$%), urate ($I^2=78.3$%) and left ventricular hypertrophy ($I^2=72.1$%) showed substantial levels of heterogeneity. Based on our pre-specified protocol, subgroup analyses to explore heterogeneity were considered for eGFR and proteinuria stages. These sub-analyses, and other post hoc analyses based on core cohort characteristics in Table 1, did not explain the heterogeneity for albumin. For urate and
| Study Name     | Publication Year | Journal                | Study Type | Cohort Size | Mean/median follow-up (months) | Mean/median age, years | Male% | White% | Black% | Other ethnicity% | GFR Measurement | eGFR measurement | urine | CVD% | DM% | HTN% |
|---------------|------------------|------------------------|------------|-------------|--------------------------------|------------------------|-------|--------|--------|------------------|----------------|------------------|-------|------|-----|------|
| AASK[25]      | 2006             | AJKD                   | RCT        | 1094        | 49 55                                      | 61.2                   | 0     | 100    | 0      | 125-ithalamate   | 46             | proteinuria 0.31mg/mg | 51.6  | 0    | 100 |      |
| Ankara[26]    | 2014             | CJASN                  | Cohort     | 403         | 38 53.2                                   | 56.5                   | -     | -      | -      | MDRD             | -20% in each CKD category | 1.61 g/day | 13.4 | 22.6 | 15.9 |
| CanPREDICT[27]| 2016             | Kidney International   | Cohort     | 2529        | 36 68.2                                    | 62.5                   | 88.7  | -      | -      | MDRD             | 28.0           | ACR 16.3 mg/mmol | 33.5  | 48.2 | 26.5 |
| CARE FOR HOME[19] | 2014   | CJASN                  | Cohort     | 444         | 31 65                                    | 60                     | 99.8  | -      | 0.2    | MDRD             | 45-16          | proteinuria 37 mg/g | 30.0  | 38   | 37.2 |
| CREATE[28]    | 2010             | Current Medical Research & Opinion | RCT       | 291         | 24 59.9                                    | 48.8                   | -     | -      | -      | CG               | -              | -                | 93.5  | -    | 90.4 |
| CRIC[29]      | 2013             | AJKD                   | Cohort     | 3904        | 47 58.2                                    | 54.8                   | 45.5  | 41.8   | 12.7   | CRIC-GFR         | 44.8           | 1.07 g/day      | 33.4  | 48.5 | 86.1 |
| CRISIS[30]    | 2015             | Nephrology             | Cohort     | 463         | 46 63.8                                    | 61.8                   | 96    | -      | -      | MDRD             | 29.4           | 0.49 g/L protein | 29.4  | 31.3 | 13.0 |
| Digitalis[31] | 2010             | Circulation: Heart Failure | RCT       | 1974        | 57 68                                      | 65.6                   | 89.2  | -      | -      | MDRD             | 47             | -                | 100   | 50   | 60.2 |
| Fujita[32]    | 2013             | Heart and Vessels      | Cohort     | 404         | 33 67                                      | 63.6                   | -     | -      | -      | MDRD             | 24.1           | 351 mg/g Cr    | 33.2  | 37.6 | 73.5 |
| Genoa[33]     | 2016             | CJASN                  | Cohort     | 445         | 71 64.1                                    | 62.0                   | 100   | 0      | 0      | MDRD             | 39.9           | 0.4 g/d        | 22.0  | 19.1 | 100  |
| ICKD[20]      | 2013             | CJASN                  | Cohort     | 3303        | 36 63.5                                    | 57.8                   | -     | -      | -      | MDRD and EPI-CKD | 23.4 (EPI-CKD) | PCR 1118.3 mg/g | 26.4  | 44.6 | 67.1 |
| Kaohsiung[34] | 2013             | Nephron Clinical Practice | Cohort    | 356         | 25 66.3                                    | 73                     | -     | -      | -      | EPI-CKD           | % stage given | dipstick         | 11.8  | 58.4 | 83.7 |
| Kyushu[21]    | 2014             | Hypertension Research  | RCT        | 320         | 30 72                                      | 68.1                   | 0     | 0      | 100%   | Japanse equation | 18.4           | 1.5 g/day       | 19.0  | 51   | 94   |
| Leuven[22]    | 2015             | Kidney International   | Cohort     | 476         | 57 64                                      | 54.6                   | 98.0  | -      | 20% "non-Caucasian" | EPI-CKD         | 34             | 0.27 g/day     | 27.7  | 18.1 | 70.7 |
| Madrid[23]    | 2010             | CJASN                  | RCT        | 113         | 23 71.6                                    | 64.6                   | 100   | 0      | 0      | MDRD             | 40.1           | 35.5 mg/d albuminuria | 23.0  | 21   | 80  |
| MAURO[24]     | 2015             | CJASN                  | Cohort     | 755         | 31 62                                      | 60                     | 100   | 0      | 0      | MDRD             | 36             | 0.6 milligram/24 hours | 29.0  | 35   | 92   |
| Naples[35]    | 2013             | JACC                   | Cohort     | 436         | 57 65                                      | 58.3                   | 100   | 0      | 0      | MDRD             | 42.9           | 0.31 g/day      | 30.5  | 36.5 | 72.9 |
| OSERCE-2[36]  | 2015             | CJASN                  | Cohort     | 742         | 35 66                                      | 65                     | 99    | 0      | 1      | MDRD             | 27.3           | proteinuria 106 mg/g | 11.0  | 66   | 94   |
| Pravastatin[37]| 2005             | JASN                   | RCT        | 4670        | 64 62.3                                    | 21.3                   | >90   | -      | -      | MDRD             | 56.7           | dipstick         | 75.3  | 12.2 | 48.2 |
| RII[38]       | 2012             | NDT                    | Cohort     | 305         | 32 59.5                                    | 50.5                   | 78.4  | 17.7   | 39     | MDRD,CG          | 28.2           | ACR 192.0 (2–9299) | 36.7  | 30.8 | 88.9 |      |

(Continued)
Table 1. (Continued)

| Study Name | Publication Year | Journal | Study Type | Cohort Size | Mean/median follow-up (months) | Mean/median age, years | Male% | White% | Black% | Other ethnicity% | GFR Measurement | eGFR urine | CVD% | DM% | HTN% |
|------------|------------------|---------|------------|-------------|-------------------------------|------------------------|-------|--------|--------|----------------|----------------|------------|------|-----|-----|
| TREAT[39]  | 2016             | Journal of Human Hypertension | RCT     | 4038        | 29                            | 68                     | 42.7  | 63.6   | 20.2   | 16.1           | MDRD           | 33         | PCR 0.39 g/g | 36.5 | 100 | 92.4 |

'-' refers to data not presented.

*figure based on proportion on RAAS blocker, for the Madrid cohort also 29.2% on CCB and 63.7% on diuretics.

*refers to percentage with hypertensive nephropathy as cause of CKD.

*refers to number with coronary heart disease, 17.6% had cerebrovascular disease.

*refers to proportion with ischaemic heart disease.

Journals: AJKD—American Journal of Kidney Disease, CJASN—Clinical Journal of the American Society of Nephrology, JACC—Journal of the American College of Cardiology, JASN—Journal of the American Society of Nephrology.

GFR measurement: CG—Cockroft-Gault, CKD-EPI—Chronic Kidney Disease Epidemiology Collaboration, MDRD—The Modification of Diet in Renal Disease.

https://doi.org/10.1371/journal.pone.0192895.t001
left ventricular hypertrophy, exploration of heterogeneity was limited by the inclusion of only two studies in the systematic review.

**Discussion**

Whilst CV prognostic models are well established for the general population [6,7] it is unclear how well these models perform in patients with CKD [10]. CV prognostic models developed specifically for those with CKD exist but have poor methodology and limited clinical applicability [10]. The current systematic review, using a pre-defined and registered protocol [13], presents the association between routinely collected risk factors and CV disease events in individuals with CKD. The results confirm that most traditional atherosclerotic related risk factors confer risk in CKD populations. These include age, gender, smoking, established CV disease and diabetes mellitus, all of which were statistically significant risk factors that are incorporated in general population prognostic models and/or are established risk factors.

Studies of non-traditional risk factors associated with uremia-related arteriosclerosis and cardiomyopathy were also identified by the systematic review. Of these risk factors, albumin, haemoglobin and phosphate were included in at least four studies and had a statistically
| Variable                        | Units (continuous)/Comparator (categorical) | Number of Studies | Pooled HR | 95% Confidence Interval | p-value for HR | I² (%)
|-------------------------------|--------------------------------------------|-------------------|-----------|-------------------------|----------------|---------|
| Male                          | female                                      | 9                 | 1.451     | 1.220–1.726             | <0.001         | 0.0     |
| Age                           | per year                                    | 12                | 1.031     | 1.025–1.038             | <0.001         | 58.6    |
| Smoker                        | non-smoker                                  | 5                 | 1.433     | 1.149–1.787             | 0.001          | 3.3     |
| Body mass index               | per kg/m²                                    | 3                 | 0.994     | 0.964–1.025             | 0.7            | 23.0    |
| Cardiovascular disease        | no previous cardiovascular disease event     | 11                | 2.391     | 2.061–2.773             | <0.001         | 68.1    |
| Ischemic heart disease        | no previous ischemic heart disease event     | 5                 | 2.406     | 1.870–3.096             | <0.001         | 43.2    |
| Congestive heart failure      | no diagnosis of congestive heart failure     | 3                 | 1.325     | 0.989–1.774             | 0.06           | 0.0     |
| Peripheral vascular disease   | no diagnosis of peripheral vascular disease  | 1                 | 2.49      | 1.10–5.63               | 0.03           | -       |
| Diabetes mellitus             | no diabetes mellitus                         | 14                | 1.454     | 1.338–1.579             | <0.001         | 73.5    |
| Systolic blood pressure       | per mmHg                                     | 8                 | 1.002     | 0.999–1.004             | 0.17           | 77.8    |
| Diastolic blood pressure      | per mmHg                                     | 3                 | 0.999     | 0.993–1.005             | 0.67           | 0.0     |
| Mean arterial pressure        | per 10 mmHg                                  | 1                 | 1.14      | 1.03–1.27               | 0.01           | -       |
| Pulse pressure                | per mmHg                                     | 3                 | 1.002     | 0.998–1.005             | 0.38           | 58.7    |
| Left ventricular hypertrophy  | no left ventricular hypertrophy on echocardiogram | 2              | 1.78      | 1.354–2.351             | <0.001         | 72.1    |
| Pulmonary hypertension        | no pulmonary hypertension on echocardiogram  | 1                 | 1.23      | 1.00–1.52               | 0.04           | -       |
| Albumin                       | per g/dL                                     | 7                 | 0.624     | 0.519–0.749             | <0.001         | 66.4    |
| Bicarbonate                   | per mEq/L                                    | 1                 | 0.99      | 0.95–1.03               | 0.6            | -       |
| Cholesterol to HDL ratio      | ratio                                       | 1                 | 1.03      | 0.998–1.065             | 0.07           | -       |
| Calcium                       | per mg/dL                                    | 1                 | 0.846     | 0.503–1.422             | 0.5            | -       |
| Hemoglobin                    | per g/dL                                     | 8                 | 0.901     | 0.856–0.948             | <0.001         | 0.0     |
| HDL Cholesterol               | per mg/dL                                    | 1                 | 0.998     | 0.992–1.003             | 0.5            | -       |
| LDL Cholesterol               | per mg/dL                                    | 2                 | 1.001     | 0.999–1.003             | 0.2            | 0.0     |
| Non-HDL Cholesterol           | per mg/dL                                    | 2                 | 1.001     | 1.000–1.003             | 0.04           | 70.4    |
| Parathyroid hormone           | per pg/mL                                    | 1                 | 1.00      | 0.99–1.00               | 1.00           | -       |
| Phosphate                     | per mg/dL                                    | 7                 | 1.198     | 1.084–1.325             | <0.001         | 0.0     |
| Sodium                        | per mmol/L                                   | 1                 | 0.954     | 0.919–0.990             | 0.01           | -       |
| Total cholesterol             | per mg/dL                                    | 3                 | 1.001     | 1.000–1.002             | 0.01           | 65.8    |
| Urate                         | per mg/dL                                    | 2                 | 1.068     | 1.021–1.117             | 0.004          | 78.3    |
| Urea nitrogen                 | per 5mg/dL                                   | 1                 | 1.14      | 1.02–1.29               | 0.03           | -       |

Abbreviations: HDL—high density lipoprotein, HR—hazard ratio, LDL—low density lipoprotein.

Results are given to 3 decimal places, unless data were only available from a single study that published results to 2 decimal places.

https://doi.org/10.1371/journal.pone.0192895.t003
significant pooled hazard ratio for CV events. Other non-traditional risk factors that could be candidate risk factors for inclusion in a CV prognostic model include those associated with cardiomyopathy, such as left ventricular hypertrophy, urate, and those associated with both cardiomyopathy and arteriosclerosis including calcium, parathyroid hormone and urea nitrogen. Some of these risk factors have been considered in prognostic models identified by the previous systematic review of Tangri et al [10]. McMurray et al demonstrated an association of CV outcomes with serum albumin but not urea nitrogen [40].

The results of some risk factors were more difficult to interpret. Systolic and diastolic blood pressures were not statistically significant in their association with CV events. However, mean arterial pressure was in the single study in which it was considered. Previous studies, including individual participant meta-analysis, have suggested that the relationship of blood pressure with mortality and CV events in CKD is non-linear and may be due to uremic related myocardial and vascular remodelling [41–43]. The limited availability of study-level data, and therefore the opportunity to study non-linear relationships of blood pressure to CV events in CKD, makes it difficult to draw a firm conclusion. The ‘Blood Pressure Lowering Treatment Trialists’ Collaboration’ identified that blood pressure lowering in CKD is probably beneficial but was
unable to identify a clear target [44]. Recent analysis of the SPRINT trial in CKD suggested a possible reduction of CV events with more intensive systolic blood pressure control of <120mmHg versus <140mmHg (HR 0.81, 95% CI 0.63 to 1.05) [45]. Similarly, lipid measurements, including total cholesterol and low density lipoprotein cholesterol, did not have a clear relationship. A previous study of myocardial infarction events has suggested a weaker association with low density lipoprotein cholesterol as CKD advances [46]. Similarly, the association of body mass index with CV events was unclear. We were unable to assess the risk associated with ethnicity as most studies did not present data that could be utilised in models, often because ethnicity was completely, or nearly, homogenous.

Heterogeneity between studies limits the interpretation of the results of meta-analyses, particularly in observational studies [47–49]. Further, poor reporting of individual studies makes comparison of results difficult [50–51]. The ideal method for selecting and combining studies is uncertain, but by limiting our analysis to studies with at least some adjustment for traditional CV risk factors and CKD severity, we aimed to reduce heterogeneity but at the cost of reduced power, via exclusion of some cohort’s results, of the meta-analysis. This approach also ensures that the results of the reported risk factors reflect the additional prognostic
information above already established risk factors. Whilst individual patient data meta-analysis is the ‘gold standard’, the additional data from six studies used in the current study may have reduced bias.

Despite this conservative approach, heterogeneity was substantial [17] for nine risk factors. Two characteristics of the cohorts and their analysis may explain this. Firstly, the difference in variable standardisation between studies’ models may contribute to heterogeneity. Secondly, cohorts varied in the typical stage of CKD, measured through both eGFR and proteinuria, represented and this may have further increased heterogeneity.

Further limitations include, the conversion of many prognostic factors from continuous to categorical variables, leading to a loss of statistical power and comparison difficulties between studies due to differing thresholds [52–55]. Thirdly, models often presented results to a limited number, typically two, decimal places. This was particularly an issue when a continuous variable such as age or blood pressure was presented. The results published would often be the same for both HR and 95% CI e.g. HR 1.01 (95% CI 1.00 to 1.01), thus when meta-analysed the calculation of the standard error was likely to be inaccurate. We avoided changing reported HR units where possible to reduce any further inaccuracies introduced through rounding. Finally, data for eleven risk factors were only included in one study each, of which four had statistically significant association with CV disease events.
Therefore, replication of these findings for peripheral vascular disease, pulmonary hypertension, mean arterial pressure and serum urea nitrogen in other CKD populations is required.

The relatively small number of studies identified by the systematic review reflects its specific pre-specified inclusion criteria. This specificity relates to the outcome inclusion criteria of composite cardiovascular events including CV specific mortality but excluding all-cause mortality and renal related events. Prominent CKD related studies were identified by the literature review but excluded based on the inclusion criteria and/or the nature of the risk factors presented (Table D in S1 File).

Full guidance on presenting risk factor models has been published by the PROGRESS consortium [56]. We would therefore recommend for future studies of CV risk factors in CKD, models should aim to provide a rationale for the variables used for model adjustment and avoid categorisation of continuous variables.

Based on the findings of this systematic review, at a minimum, the development of CKD CV prognostic models should assess traditional and non-traditional CV risk factors including left ventricular hypertrophy, serum albumin, hemoglobin, phosphate, and urate.
Supporting information

S1 File. Table A—Medline Search Strategy
Table B—EMBASE Search Strategy
Table C—Standardization of Variables
Table D—Summary of bias assessment for included studies
Table E—List of all 66 Risk Factors identified
Figures A to N—Forest Plots for all Risk Factors Meta-analysed
(DOC)

S2 File. PRISMA checklist.
(DOC)

Acknowledgments

The authors would like to thank Sarah Sutton (clinical librarian, University Hospitals of Leicester) for her help in reviewing and refining the literature search.

The authors would also like to thank the following studies and authors for providing additional data:

- CARE FOR HOMe—Professor Dr. Gunnar Heine and Dr. Sarah Seiler-Mueller
Author Contributions

Conceptualization: Rupert W. Major, Nigel J. Brunskill, Laura J. Gray.

Data curation: Rupert W. Major, Mark R. I. Cheng, Robert A. Grant, Saran Shantikumar, Gang Xu, Issaam Oozeerally, Laura J. Gray.

Formal analysis: Rupert W. Major, Mark R. I. Cheng, Robert A. Grant, Saran Shantikumar, Gang Xu, Issaam Oozeerally, Laura J. Gray.

Funding acquisition: Rupert W. Major, Nigel J. Brunskill, Laura J. Gray.

Investigation: Rupert W. Major.

Methodology: Rupert W. Major, Laura J. Gray.

Project administration: Rupert W. Major, Nigel J. Brunskill, Laura J. Gray.

Resources: Rupert W. Major.

Software: Rupert W. Major.

Supervision: Rupert W. Major, Nigel J. Brunskill, Laura J. Gray.

Validation: Rupert W. Major, Mark R. I. Cheng, Robert A. Grant, Saran Shantikumar, Gang Xu, Issaam Oozeerally, Laura J. Gray.

Visualization: Rupert W. Major.

Writing – original draft: Rupert W. Major, Nigel J. Brunskill, Laura J. Gray.

Writing – review & editing: Rupert W. Major, Mark R. I. Cheng, Robert A. Grant, Saran Shantikumar, Gang Xu, Issaam Oozeerally, Nigel J. Brunskill, Laura J. Gray.

References

1. Go A, Chertow G, Fan D, McCulloch C, Hsu C. Chronic renal disease and cardiovascular risk. N Engl J Med 2005; 2005(352):199–200.

2. Tonelli M, Muntner P, Lloyd A, Manns BJ, Klarenbach S, Pannu N, et al. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. The Lancet 2012; 380(9844):807–814.

3. The Chronic Kidney Disease Prognosis Consortium. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality: a collaborative meta-analysis of general population cohorts. The Lancet 2010; 375(9731):2073.

4. Matsushita K, Coresh J, Sang Y, Chalmers J, Fox C, Guallar E, et al. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. The Lancet Diabetes & Endocrinology 2015; 3(7):514–525.

5. Kerr M, Bray B, Medcalf J, O'Donoghue DJ, Matthews B. Estimating the financial cost of chronic kidney disease to the NHS in England. Nephrol Dial Transplant 2012 Oct; 27 Suppl 3:iii73–80.

6. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Minhas R, Sheikh A, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. BMJ 2008 Jun 28; 336(7659):1475–1482. https://doi.org/10.1136/bmj.39609.449676.25 PMID: 18573856
7. Goff DC, Lloyd-Jones DM, Bennett G, Coady S, D’Agostino RB, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014; 63(25, PA).

8. Rabar S, Harker M, O’Flynn N, Wierzbicki AS. Lipid modification and cardiovascular risk assessment for the primary and secondary prevention of cardiovascular disease: summary of updated NICE guidance. BMJ: British Medical Journal (Online) 2014; 349.

9. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). European Heart Journal 2016 August 1; 37(29):2315–2381. https://doi.org/10.1093/eurheartj/ehw106 PMID: 27222591

10. Tangri N, Kitsios GD, Inker LA, Griffith J, Naimark DM, Walker S, et al. Risk prediction models for patients with chronic kidney disease: a systematic review. Ann Intern Med 2013; 158(8):596–603. https://doi.org/10.7326/0003-4819-158-8-201304160-00004 PMID: 23588748

11. Menon V, Gul A, Samak MJ. Cardiovascular risk factors in chronic kidney disease. Kidney Int 2005; 68(4):1413–1418. https://doi.org/10.1111/j.1523-1755.2005.00551.x PMID: 16164165

12. Covic A, Koithawala P, Bernal M, Robbins S, Chalian A, Goldsmith D. Systematic review of the evidence underlying the association between mineral metabolism disturbances and risk of all-cause mortality, cardiovascular mortality and cardiovascular events in chronic kidney disease. Nephrol Dial Transplant 2009 May; 24(5):1506–1523. https://doi.org/10.1093/ndt/gfn165 PMID: 19001560

13. PROSPERO. Cardiovascular risk factors in chronic kidney disease: a systematic review and meta-analysis. http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016036187. Accessed September, 2016.

14. Eknoyan G, Laneire N, Eckardt K, Kasiske B, Wheeler D, Levin A, et al. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int 2013; 83(5):5–14.

15. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med 1999; 130(6):461–470. PMID: 10075613

16. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med 2013; 158(4):280–286. https://doi.org/10.7326/0003-4819-158-4-201302190-00009 PMID: 23420236

17. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions.: Wiley Online Library; 2008.

18. Lu Y, Hajifathalian K, Ezzati M, Woodward M, Rimm EB, Danaei G, et al. The primary and secondary prevention of cardiovascular disease: summary of updated NICE guidance. BMJ: British Medical Journal (Online) 2014; 349.

19. Meijers B, Poesen R, Claes K, Dietrich R, Bammens B, Sprangers B, et al. Soluble urokinase receptor as a biomarker of cardiovascular disease in chronic kidney disease. Kidney Int 2010 May; 78(5):1388–1393. https://doi.org/10.1038/ki.2010.197 PMID: 20415839

20. Yoshitomi R, Nakayama M, Ura Y, Kuma K, Fukui A, et al. Ankle-brachial blood pressure index predicts cardiovascular events and mortality in Japanese patients with chronic kidney disease not on dialysis. Hypertension Research 2014; 37(12):1050–1055. https://doi.org/10.1038/hr.2014.120 PMID: 25056682

21. Spoto B, Mattace-Raso F, Sibbruds E, Leonardis D, Testa A, Pisano A, et al. Association of IL-6 and a functional polymorphism in the IL-6 gene with cardiovascular events in patients with CKD. Clin J Am Soc Nephrol 2015 Nov; 8(11):1915–1926. https://doi.org/10.2215/CJN.02302113 PMID: 23929929

22. McMullan CJ, Bakris GL, Phillips RA, Forman JP. Association of BP variability with mortality among African Americans with CKD. Clin J Am Soc Nephrol 2013 May; 8(5):731–738. https://doi.org/10.2215/CJN.10131012 PMID: 23493382
26. Yilmaz MI, Solak Y, Saglam M, Cayci T, Acikel C, Unal HU, et al. The relationship between IL-10 levels and cardiovascular events in patients with CKD. Clin J Am Soc Nephrol 2014 Jul; 9(7):1207–1216. https://doi.org/10.2215/CJN.08660813 PMID: 24789549

27. Kim RB, Morse BL, Djurdjev O, Tang M, Muirhead N, Barrett B, et al. Advanced chronic kidney disease populations have elevated trimethylamine N-oxide levels associated with increased cardiovascular events. Kidney Int 2016; 89(5):1144–1152. https://doi.org/10.1016/j.kint.2016.01.014 PMID: 27083288

28. Locatelli F, Eckardt K, Macdougall IC, Tsakiris D, Clyne N, Burger H, et al. Value of N-terminal brain natriuretic peptide as a prognostic marker in patients with CKD: results from the CREATE study. Curr Med Res Opin 2010; 26(11):2543–2552. https://doi.org/10.1185/03007995.2010.516237 PMID: 20849244

29. Dobre M, Yang W, Chen J, Drawz P, Hamm LL, Horwitz E, et al. Association of serum bicarbonate with risk of renal and cardiovascular outcomes in CKD: a report from the Chronic Renal Insufficiency Cohort (CRIC) study. American Journal of Kidney Diseases 2013; 62(4):670–678. https://doi.org/10.1053/j.ajkd.2013.01.017 PMID: 23496777

30. Alderson HV, Ritchie JP, Middleton R, Larsson A, Larsson TE, Kaira PA. FGF-23 and Osteoprotegerin but not Fetuin-A are associated with death and enhance risk prediction in non-dialysis chronic kidney disease stages 3–5. Nephrology 2016; 21(7):566–573. https://doi.org/10.1111/nep.12664 PMID: 27334535

31. Bowling CB, Pitt B, Ahmed MI, Aban IB, Sanders PW, Mujib M, et al. Hypokalemia and outcomes in patients with chronic heart failure and chronic kidney disease: findings from propensity-matched studies. Circ Heart Fail 2010 Mar; 3(2):253–260. https://doi.org/10.1161/CIRCHEARTFAILURE.109.899526 PMID: 20103777

32. Hasegawa M, Ishii J, Kitagawa F, Takahashi K, Hayashi H, Koide S, et al. Urinary neutrophil gelatinase-associated lipocalin as a predictor of cardiovascular events in patients with chronic kidney disease. Heart Vessels 2016; 30(1):81–88. https://doi.org/10.1007/s00380-013-0454-7 PMID: 24378882

33. Paoloett E, De Nicola L, Gabbai FB, Chiodini P, Ravera M, Pieracci L, et al. Associations of Left Ventricular Hypertrophy and Geometry with Adverse Outcomes in Patients with CKD and Hypertension. Clin J Am Soc Nephrol 2016 Feb 5; 11(2):271–279. https://doi.org/10.2215/CJN.06980615 PMID: 26669021

34. Chen SC, Chang JM, Tsai YC, Huang JC, Chen LI, Su HM, et al. Ratio of transmitral E-wave velocity to early diastole mitral annulus velocity with cardiovascular and renal outcomes in chronic kidney disease. Nephron Clin Pract 2013; 123(1–2):52–60. https://doi.org/10.1159/000351513 PMID: 23774331

35. De Nicola L, Gabbai FB, Agarwal R, Chiodini P, Borrelli S, Bellizzi V, et al. Prevalence and prognostic role of resistant hypertension in chronic kidney disease patients. J Am Coll Cardiol 2013; 61(24):2461–2467. https://doi.org/10.1016/j.jacc.2012.12.061 PMID: 23923908

36. Gorriz JL, Molina P, Cerveron MJ, Vila R, Bover J, Nieto J, et al. Vascular calcification in patients with nondialysis CKD over 3 years. Clin J Am Soc Nephrol 2015 Apr 7; 10(4):654–666. https://doi.org/10.2215/CJN.05170415 PMID: 25770175

37. Tonelli M, Keech A, Shepherd J, Sacks F, Tonkin A, Packard C, et al. Effect of pravastatin in people with diabetes and chronic kidney disease. J Am Soc Nephrol 2005 Dec; 16(12):3748–3754. https://doi.org/10.1681/ASN.2005070779 PMID: 16251235

38. Chandra P, Sands RL, Gillespie BW, Levin NW, Kotanko P, Kiser M, et al. Predictors of heart rate variability and its prognostic significance in chronic kidney disease. Nephrol Dial Transplant 2012 Feb; 27(2):703–709. https://doi.org/10.1093/ndt/gfr724 PMID: 21765187

39. Theilade S, Claggett B, Hansen T, Skali H, Lewis E, Solomon S, et al. Pulse pressure is not an independent predictor of outcome in type 2 diabetes patients with chronic kidney disease and anemia—the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT). J Hum Hypertens 2016; 30(1):46–52. https://doi.org/10.1038/jhh.2015.22 PMID: 25810068

40. McMurray JJ, Uno H, Jarolim P, Desai AS, de Zeeuw D, Eckardt K, et al. Predictors of fatal and nonfatal cardiovascular events in patients with type 2 diabetes mellitus, chronic kidney disease, and anemia: an analysis of the Trial to Reduce Cardiovascular Events with Aranesp (darbepoetin-alfa) Therapy (TREAT). Am Heart J 2011; 162(4):748–755. e3. https://doi.org/10.1016/j.ahj.2011.07.016 PMID: 21982669

41. Mahmoodi BK, Matsushita K, Woodward M, Blankestijn PJ, Cirillo M, Ohkubo T, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without hypertension: a meta-analysis. The Lancet 2012; 380(9854):1649–1661.

42. Weiss JW, Johnson ES, Petrik A, Smith DH, Yang X, Thorp ML. Systolic blood pressure and mortality among older community-dwelling adults with CKD. American Journal of Kidney Diseases 2010; 56(6):1062–1071. https://doi.org/10.1053/j.ajkd.2010.07.018 PMID: 20961677

43. Kovessy CP, Trivedi BK, Kalantar-Zadeh K, Anderson JE. Association of low blood pressure with increased mortality in patients with moderate to severe chronic kidney disease. Nephrol Dial Transplant 2006 May; 21(5):1257–1262. https://doi.org/10.1093/ndt/gfk057 PMID: 16421161
44. Blood Pressure Lowering Treatment Trialists’ Collaboration, Ninomiya T, Perkovic V, Turnbull F, Neal B, Barzi F, Cass A et al. Blood pressure lowering and major cardiovascular events in people with and without chronic kidney disease: meta-analysis of randomised controlled trials. BMJ 2013 Oct 3; 347: f5680. https://doi.org/10.1136/bmj.f5680 PMID: 24092942

45. Cheung AK, Rahman M, Reboussin DM, Craven TE, Greene T, Kimmel PL, et al. Effects of Intensive BP Control in CKD. J Am Soc Nephrol 2017 Sep; 28(9):2812–2823. https://doi.org/10.1681/ASN.2017020148 PMID: 28642330

46. Tonelli M, Muntner P, Lloyd A, Manns B, Klarenbach S, Pannu N, et al. Association between LDL-C and risk of myocardial infarction in CKD. J Am Soc Nephrol 2013 May; 24(5):979–986. https://doi.org/10.1681/ASN.2012080870 PMID: 23687359

47. Sutton AJ, Higgins J. Recent developments in meta-analysis. Stat Med 2008; 27(5):625–650. https://doi.org/10.1002/sim.2934 PMID: 17590884

48. Fleiss JL, Gross AJ. Meta-analysis in epidemiology, with special reference to studies of the association between exposure to environmental tobacco smoke and lung cancer: A critique. Journal of Clinical Epidemiology 1991; 44(2):127–139. PMID: 1995774

49. Shrier I, Boivin JF, Steele RJ, Platt RW, Furlan A, Kakuma R, et al. Should meta-analyses of interventions include observational studies in addition to randomized controlled trials? A critical examination of underlying principles. Am J Epidemiol 2007 Nov 15; 166(10):1203–1209. https://doi.org/10.1093/aje/kwm189 PMID: 17712019

50. Hemingway H, Philipson P, Chen R, Fitzpatrick NK, Damant J, Shipley M, et al. Evaluating the quality of research into a single prognostic biomarker: a systematic review and meta-analysis of 83 studies of C-reactive protein in stable coronary artery disease. PLoS Med 2010; 7(6):e1000286. https://doi.org/10.1371/journal.pmed.1000286 PMID: 20532236

51. Riley R, Abrams K, Sutton A, Lambert P, Jones D, Heney D, et al. Reporting of prognostic markers: current problems and development of guidelines for evidence-based practice in the future. Br J Cancer 2003; 88(6):1191–1198. https://doi.org/10.1038/sj.bjc.6600866 PMID: 12698183

52. Altman DG, Royston P. The cost of dichotomising continuous variables. BMJ 2006 May 6; 332(7549):1080. https://doi.org/10.1136/bmj.332.7549.1080 PMID: 16675816

53. Altman DG, Lausen B, Sauerbrei W, Schumacher M. Dangers of using “optimal” cutpoints in the evaluation of prognostic factors. J Natl Cancer Inst 1994 Jun 1; 86(11):829–835. PMID: 8182763

54. Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. Stat Med 2006; 25(1):127–141. https://doi.org/10.1002/sim.2331 PMID: 16217841

55. Turner EL, Dobson JE, Pocock SJ. Categorisation of continuous risk factors in epidemiological publications: a survey of current practice. Epidemiologic Perspectives & Innovations 2010; 7(1):1.

56. Steyerberg EW, Moons KG, van der Windt, Danielle A, Hayden JA, Perel P, Schrotter S, et al. Prognosis Research Strategy (PROGRESS) 3: prognostic model research. PLoS Med 2013; 10(2):e1001381. https://doi.org/10.1371/journal.pmed.1001381 PMID: 23393430