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CONCISE REVIEW

Association Between Hepatitis B Virus and Chronic Kidney Disease: a Systematic Review and Meta-analysis

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ABSTRACT

Background. Hepatitis B virus infection and chronic kidney disease are prevalent and remain a major public health problem worldwide. It remains unclear how infection with hepatitis B virus impacts on the development and progression of chronic kidney disease. **Aim.** To evaluate the effect of infection with HBV on the risk of chronic kidney disease in the general population. **Material and methods.** We conducted a systematic review of the published medical literature to determine if hepatitis B infection is associated with increased likelihood of chronic kidney disease. We used the random effects model of DerSimonian and Laird to generate a summary estimate of the relative risk for chronic kidney disease (defined by reduced glomerular filtration rate and/or detectable proteinuria) with hepatitis B virus across the published studies. Meta-regression and stratified analysis were also conducted. **Results.** We identified 16 studies (n = 394,664 patients) and separate meta-analyses were performed according to the outcome. The subset of longitudinal studies addressing ESRD (n = 2; n = 91,656) gave a pooled aHR 3.87 (95% CI, 1.48; 6.25, P < 0.0001) among HBV-infected patients and no heterogeneity was recorded. In meta-regression, we noted the impact of male (P = 0.006) and duration of follow-up (P = 0.007) upon the adjusted hazard ratio of incidence of chronic kidney disease (including end-stage renal disease). No relationship occurred between HBV positive status and prevalent chronic disease (n = 7, n = 109,889 unique patients); adjusted odds ratio, were 1.07 (95% CI, 0.89; 1.25) and 0.93 (95% CI, 0.76; 1.10), respectively. **Conclusions.** HBV infection is possibly associated with a risk of developing reduced glomerular filtration rate in the general population; no link between HBV sero-positive status and frequency of chronic kidney disease or proteinuria was noted in cross-sectional surveys.

Key words. Hepatitis B virus. Chronic kidney disease. Glomerular filtration rate. Proteinuria. Meta-analysis.

INTRODUCTION

Chronic kidney disease is a growing public health issue worldwide. The prevalence of chronic kidney disease, defined by a reduction in glomerular filtration rate and/or increased urinary albumin excretion, exceeds 10% of the adult general population, according to some population-based studies.[1] Conventional risk factors for chronic kidney disease include demographics (aging, gender), lifestyles (smoking, alcohol intake, physical exercise), and co-morbidities (diabetes mellitus, arterial hypertension, anaemia, overweight);[2] also, chronic hepatitis C virus infection has been recently associated to the risk of chronic kidney disease in the general population[3] and among HIV-infected individuals.[4] However, the mechanisms underlying the current frequency of chronic kidney disease in the general population of developed world remain unclear.

Hepatitis B virus (HBV) infection is an important cause of liver disease and cancer and infects about 400 million individuals worldwide. In addition to its effects in the liver, extra-hepatic manifestations may be observed in up to 20% of patients infected with HBV, in both acute and chronic infections. Manifestations related to HBV include mixed cryoglobulinemia vasculitis, polyarteritis nodosa, and renal disease.[5] The association between HBV infection and glomerular disease has been already explored by various authors; the most common type of HBV-related glomerulonephritis is membranous nephropathy, particularly in the Asian

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continent.[6] Also, chronic hepatitis B serum promotes apoptotic damage in human renal tubular cells.[7] Either insulin resistance[8] and oxidative stress[9] have been related to HBV infection; both conditions may contribute to renal injury.

Whether HBV-infected individuals have increased risk for development and progression of chronic kidney disease has not been appropriately investigated. The aim of this study was to review the available evidence on the link between HBV infection and frequency of chronic kidney disease (low estimated glomerular filtration rate and/or detectable proteinuria) at population-based level by performing a systematic review of the literature with a meta-analysis of clinical observational studies.

MATERIAL AND METHODS

This work is in agreement with the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement[10] (Supplementary file 1).

Search strategy and data extraction

Two authors (F.F., and F.M. D.) independently reviewed English-language citations from the national Library of Medicine's Medline database from 1970 through July 1, 2015. Data on HBsAg status were not available before 1970, when the first assay for HBsAg was manufactured. We conducted our search by four Medline databases engines (Embase, Grateful Med, Ovid, and PubMed). Our Medline search was limited to human studies. We applied the following algorithm in medical subject heading and in free text words: ("HEPATITIS B" or "HEPATITIS B VIRUS INFECTION" or "HBsAg POSITIVE STATUS" or "HBc ANTIBODY POSITIVE STATUS") and ("CHRONIC KIDNEY DISEASE" or "CKD" or "END-STAGE RENAL DISEASE" or "ESRD" or "LOW GLOMERULAR FILTRATION RATE" or "RENAL IMPAIRMENT" or "RENAL INSUFFICIENCY" or "RENAL FAILURE" or "PROTEINURIA" or "GLOMERULONEPHRITIS") and ("RELATIVE RISK" or "RISK RATIO" or "RR" or "ODDS RATIO" or "OR" or "HAZARD RATIO" or "HR" or "INCIDENCE"). An additional search was performed with electronic searches of the Cochrane Library; manual searches of selected specialty journals were done to identify all pertinent literature. Reference lists from qualitative topic reviews and published clinical studies were also searched. It was previously demonstrated that a Medline search alone might not be sensitive enough.[11] Data on study design, study period, patient characteristics, HBV prevalence, and kidney disease outcomes were abstracted. Authors of selected papers were contacted to obtain missing data and only data from individuals with known HBV status were included in the meta-analysis. Consensus was achieved for all data. Studies were compared to eliminate duplicate reports for the same patients, which included contact with investigators when necessary. Eligibility and exclusion criteria were pre-specified. Our search was limited to human studies that were published in the English literature.

Inclusion criteria

Studies were included if they met the following inclusion criteria:

- They presented original data from cohort and cross-sectional studies.
- The outcome of interest was clearly defined as incidence or prevalence of chronic kidney disease, i.e., reduced glomerular filtration rate and/or detectable proteinuria in the adult general population according to HBV serological status; and
- They provided adjusted risk estimates and their confidence intervals.

We considered both case-control studies and cohort studies as eligible for inclusion in the analysis. We included studies where the diagnosis of HBV infection was done by testing for HBsAg in serum and/or HBc antibody. Information on HBV serological status was collected at the time of enrolment. If data on the same population were duplicated in more than one study, the most recent study was included in the analysis.

Ineligible studies

Studies were excluded if they reported inadequate data on the association between chronic kidney disease and HBV sero-positive status (e.g., incomplete information on HBV status or renal outcomes). Unpublished studies, studies that were only published in abstract form or as interim reports were excluded; letters and review articles were not considered for this systematic review.

Quality assessment

The quality of the 13 studies was appraised using a scale adapted from the 'Newcastle/Ottawa Scale (NOS)'.[12] The Newcastle-Ottawa scale is a scoring system that assesses every aspect of an observational epidemiologic study from a methodological point of view. When a study included relevant information that could be associated with the NOS, one point was added. Seven items in cross-sectional studies and eight items in cohort and case-control studies that could be related to the NOS were identified. There-

fore, cross-sectional studies assigned 8-10, 6-7, 4-5, or 0-3 points (stars) were evaluated as very good, good, satisfactory or unsatisfactory studies, respectively. Similarly, cohort/case-control studies with 7-9, 5-6, 4 and 0-3 points (stars) were identified as very good, good, satisfactory or unsatisfactory, respectively. We carried out subgroup analyses based on those studies provided with very good quality. Data extraction and quality scoring were performed independently by two reviewers (F.F. and F.M. D.) and the results were merged by consensus. The complete protocol for quality scoring is available on-line (Supplementary file 2).

Outcomes measures

We performed separate meta-analyses according to the outcome. One meta-analysis included longitudinal studies addressing the incidence of chronic kidney disease or end-stage renal disease; and another regarded cohort studies assessing the prevalence of CKD. An additional meta-analysis was performed for prevalent proteinuria. Staging of chronic kidney disease was categorized according to the Kidney Disease Outcomes Quality Initiative (K/DOQI) definition, and estimated glomerular filtration rate was calculated using the 4-variable MDRD equation.[13] The primary end point was to provide adjusted estimates of the risk (and 95% CIs) of incidence (or prevalence) of chronic kidney disease in the general population according to HBV serological status. Multivariate analysis was made to estimate the independent effect of HBV positive status on the frequency of chronic kidney disease after adjustment for potential confounders (covariates) (e.g., age, gender, race/ethnicity, diabetes mellitus, and others). Longitudinal studies adopted Cox regression analysis to assess the independent predictors of the incidence of chronic kidney disease; multiple logistic regression analyses were done in cross-sectional surveys. An additional end point was the adjusted estimate of the risk (and 95% CIs) of prevalence of proteinuria in the adult general population according to HBV serological status. Cox proportional hazard regression analysis was carried out to assess the effect of HBV sero-positivity per se on the incidence of chronic kidney disease after adjustment for differential follow-up time and distribution of potential confounders.

Data synthesis and analysis

We weighted the study-specific log odds ratios for case control and cross-sectional studies, and log hazard ratios for longitudinal studies by the inverse of their variance to obtain a pooled effect estimate and its 95% confidence intervals. For each study, we used the estimate of the effect measure that was adjusted for the largest number of confounders. We present both fixed-effects and random-effects pooled estimates but use and report the latter when heterogeneity was present. We used the random-effects approach, as described by DerSimonian and Laird.[14] Cochrane Q-test was used for quantifying the heterogeneity.[15] The I^2 statistic, which is the percentage of total variation across studies due to heterogeneity rather than chance, was also calculated.[16] The null hypothesis of this test is the absence of heterogeneity. We explored the origin of heterogeneity by restricting the analysis to subgroups of studies defined by study characteristics such as country of origin, CKD stage, and others. Heterogeneity was also evaluated by meta-regression in order to look at the effect of potential and continuous covariates on the outcome of interest. Subgroup or stratified analyses and meta-regression were pre-specified. We performed random-effects meta-regression using the method of moments or maximum likelihood approaches where appropriate, a single predictor is allowed in each model (simple meta-regression). Publication bias was assessed by the Egger test for funnel-plot asymmetry. All analyses were done with the statistical package Comprehensive Meta-Analysis (CMA), version 2.0 (Biostat Inc., USA, 2005). The 5% significance level was adopted for á risk. Every estimate was given with its 95% CIs.

RESULTS

Literature review

As shown in figure 1, we retrieved 424 articles and 98 full-text papers were assessed for eligibility. The list of the papers is reported in the supplementary file 3. Sixteen studies met our inclusion criteria, they were published in 11 papers[19-30] (Figure 1) and carried out in 3 countries. Two longitudinal papers addressed various outcomes (the risk of chronic kidney disease and end-stage renal disease) in the same population.[20-21] Four papers[23-25,28] gave information on the prevalence of chronic kidney disease and proteinuria in the same population. Thus, some studies contributed data on more than one kidney disease outcome, but each cohort was represented once in any meta-analysis. There was a 100% concordance between reviewers with respect to final inclusion and exclusion of studies reviewed based on the predefined inclusion and exclusion criteria. Diagnosis of HBV infection was made by detecting the presence of HBV surface antigen (HBsAg) in serum; in a few reports[20,21] diagnosis of HBV infection was done by ICD-9 codes. One report addressed the rate of HBV infection by assessing HBcAb serologic status,[22] another survey identified HBV infection by patient medical history.[29]

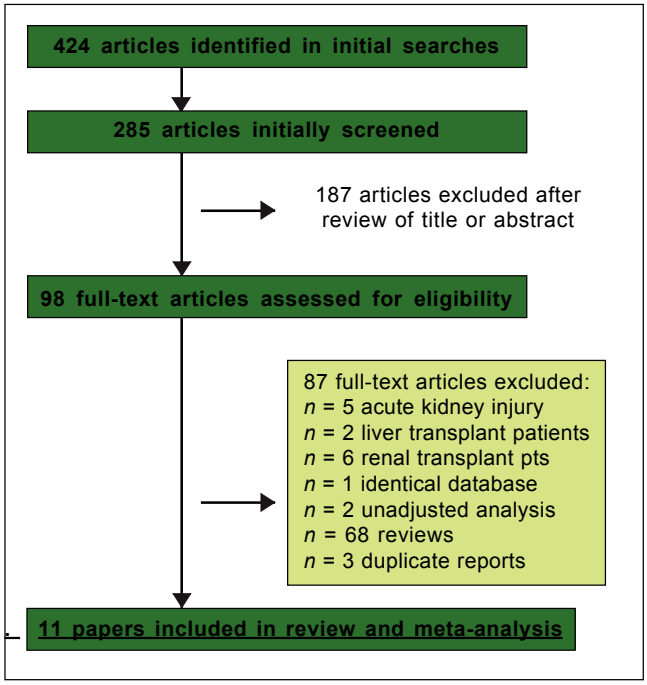

Figure 1. Flow diagram of study selection.

Patient and study characteristics

Tables 1-3 reports some salient demographic, and clinical characteristics of subjects enrolled in the included studies. The mean age of patient cohorts ranged from 18.9 ± 0.5 to 60.8 ± 11.5 years. The gender distribution ranged from 31.2% to 67.6% male. Five reports were Taiwan, four from China, one from Japan and Hong Kong, respectively. The average follow-up ranged between 3.5 and 6.5 years, among longitudinal studies. The quality scores ranged between 7 and 8 points (cohort/case-control studies), and between 8 and 9 (cross-sectional studies) (Supplementary file 2).

- **Summary estimate of outcome: Incidence of CKD *(reduced eGFR or end-stage renal disease)*.** Four longitudinal studies (n = 184,937 patients; 36,192 HBV positive and 148,745 HBV negative patients) gave information on the incidence of CKD (or ESRD) among HBV positive patients[19-22] (Table 1). The relationship between positive HBV serologic status and increased incidence of CKD neared the statistical significance, adjusted HR with HBV across the surveys, 2.22 (95% CI, 0.95; 3.50, NS). There was some heterogeneity (I^2 = 64.7%, P = 0.04) across the four studies (Figure 2). Publication bias was not found (Egger test, P = 0.61) (Figure 3). The subset of longitudinal studies addressing ESRD gave a pooled aHR 3.87 (95%CI, 1.48; 6.25, P < 0.0001) among HBV-infected patients and no heterogeneity was recorded (Table 4).
- **Summary estimate of outcome: Prevalence of CKD (reduced eGFR).** Seven studies (n = 109,889 unique patients; 8,023 HBV positive and 101,866 HBV-negative patients) with cross-sectional (or case-control) design addressed the prevalence of CKD (or reduced GFR) in HBV-infected patients.[23-29] Table 2 shows some demographic, and clinical parameters of subjects enrolled in the included studies. We found no relationship between positive HBV serologic status and increased prevalence of CKD, adjusted OR with HBV across the studies, 1.069 (95% CI, 0.89; 1.248, P = NS). Tests for homogeneity of the aOR across the

Table 1. Longitudinal studies included in the meta-analysis (outcome: frequency of end-stage renal disease or chronic kidney disease).

	Cheng A, *et al.**	Chen Y, *et al.***	Chen Y, *et al.****	Kong X, *et al.*****
Reference year	2006	2014	2015	2016
Country	Hong Kong	Taiwan	Taiwan	China
Study type	Cohort prospective	Nationwide cohort	Nationwide cohort	Cohort prospective
Patients, n	2,838	88,790	88,980	4,329
Mean observation time, yrs	3.5	6.5	6.5	5
HBV rate, n	286 (10.1%)	17,758 (20%)	17,796 (20%)	352 (8.1%)
Anti-HCV rate, n	NA	0	NA	0
Age, yrs	59.7 ±12.9	NA	NA	46.2 ± 13.7
Male, n	1,169 (41%)	51,990 (58.5%)	52,140 (58.5%)	2,907 (67.2%)
Caucasian, n	0	0	NA	0
Diabetes mellitus, n	2,838 (100%)	7,062 (7.9%)	6,841 (7.7%)	352 (8.1%)
Outcome	ESRD	ESRD	CKD	CKD
Adjusted Effect Estimate, 95% CI	HR	HR	HR	HR
Estimate	4.53 (1.1; 18.5)	3.85 (2.36; 6.27)	2.58 (1.95; 3.42)	1.12 (0.65; 1.95)

** ESRD: need for dialysis, doubling of serum creatinine, or serum creatinine ≥ 500 μmol/L. ** ESRD: end-stage renal disease requiring long-term dialysis. *** CKD = decreased eGFR (< 60 mL/min/1.73 m^2) or proteinuria (urine protein > 1+). **** CKD: chronic kidney disease stage 1-5.*

Table 2. Cross-sectional studies included in the meta-analysis (outcome: frequency of chronic kidney disease, or low estimated glomerular filtration rate).

	Ishizaka N, *et al.*	Lee J, *et al.*	Cai J, *et al.*	Lin M, *et al.*	Senghore T, *et al.*	Zeng Q, *et al.*	Su S, *et al.*
Reference year	2008	2010	2012	2013	2013	2014	2015
Country	Japan	Taiwan	China	China	China	China	Taiwan
Study type	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Case-control
Patients, n	12,535	54,966	6,854	3,552	7,745	15,549	8,688
HBV rate, n	130 (1.0%)	5,424 (9.9%)	328 (4.7%)	415 (12.4%)	570	785 (5.0%)	371 (4.2%)
Anti-HCV rate, n	72 (0.6%)	5,189 (9.4%)	NA	188 (5.6%)	NA	94 (0.6%)	169 (1.9%)
Age, yrs	53.1 ± 10.6	60.8 ± 11.5	50.7 ± 10.5	47.5 ± 17	18.9 ± 0.5	49.2 ± 9.3	59.8 ± 15
Male, n	8,054 (64.2%)	17,168 (31.2%)	3,425 (50%)	1,629 (48.6%)	3,265 (42.1%)	10,509 (67.6%)	3,893 (81%)
Caucasian, n	0	0	0	0	0	0	0
Diabetes mellitus, n	2,838 (100%)	5,302 (9.6%)	613 (8.9%)	191 (5.7%)	NA	1,508 (9.7%)	3,182 (36.6%)
Outcome	Low eGFR	Low eGFR	Low eGFR	CKD	CKD	Low eGFR	CKD
Adjusted Effect Estimate, 95% CI	OR	OR	OR	OR	OR	OR	OR
Estimate	0.51 (0.28; 0.92)	1.07 (0.95; 1.15)	1.04 (0.37; 2.93)	1.35 (1.03; 1.77)	1.11 (0.86; 1.43)	0.86 (0.26; 2.89)	1.25 (1.03; 1.52)

Low eGFR: eGFR < 60 mL/min per 1.73 m^2. CKD: CKD stage 1-5 alternatively eGFR < 60 mL/min per 1.73 m^2 with or without proteinuria.

Table 3. Studies included in the meta-analysis (outcome: frequency of proteinuria).

	Huang J, *et al.*	Ishizaka N, *et al.*	Lee J, *et al.*	Cai J, *et al.*	Zeng Q, *et al.*
Reference year	2006	2008	2010	2012	2014
Country	Taiwan	Japan	Taiwan	China	China
Study type	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional
Patients, n	9,934	12,535	54,966	6,854	15,549
Observation time, yrs	0	0	0	0	0
HBV rate, n	1,363 (13.7%)	130 (1%)	5,424 (9.9%)	328 (4.7%)	785 (5.1%)
Anti-HCV rate, n	646 (6.5%)	72 (0.6%)	5,189 (9.4%)	NA	94 (0.6%)
Age, yrs	55.2 ± 6	53.1 ± 10.6	60.8 ± 11.5	50.7 ± 10.5	49.2 ± 9.3
Male, n	4,291 (43.1%)	8,054 (64.2%)	17,168 (31.2%)	3,425 (50%)	10,509 (67.6%)
Caucasian, n	NA	0	0	0	0
Diabetes mellitus, n	1,241 (12.5%)	NA	5,302 (9.6%)	613 (8.9%)	1,508 (9.7%)
Outcome	Proteinuria	Proteinuria	Proteinuria	Proteinuria	Proteinuria
Adjusted Effect Estimate, 95% CI	OR	OR	OR	OR	OR
Estimate	0.94 (0.75; 1.17)	0.50 (0.23; 1.05)	1.04 (0.91; 1.20)	0.79 (0.53; 1.19)	1.27 (0.85; 1.89)

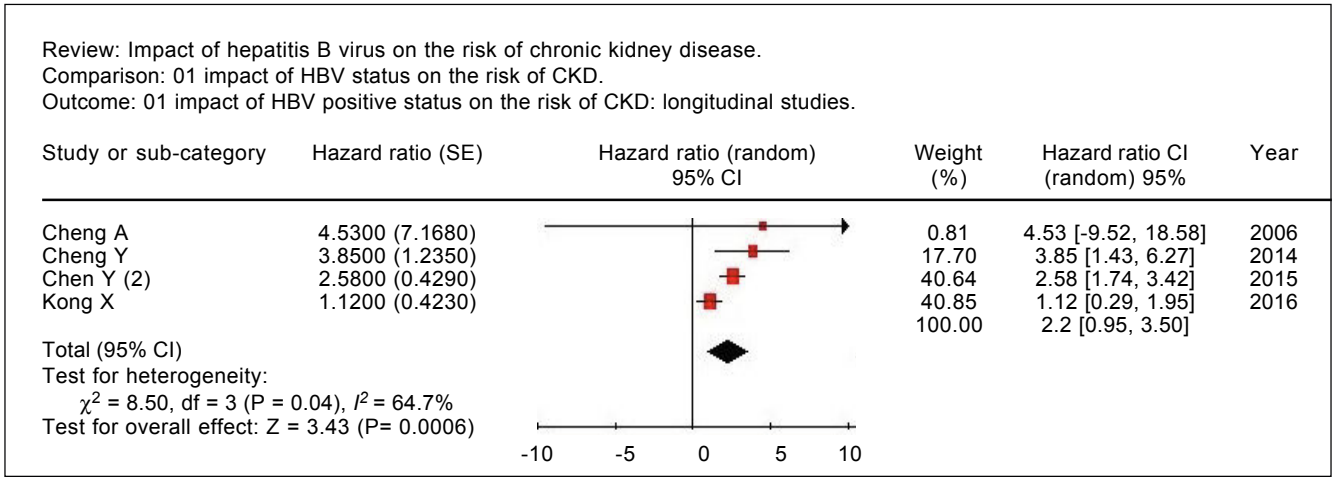

Figure 2. Impact of HBV positive serologic status on the incidence of CKD (longitudinal studies).

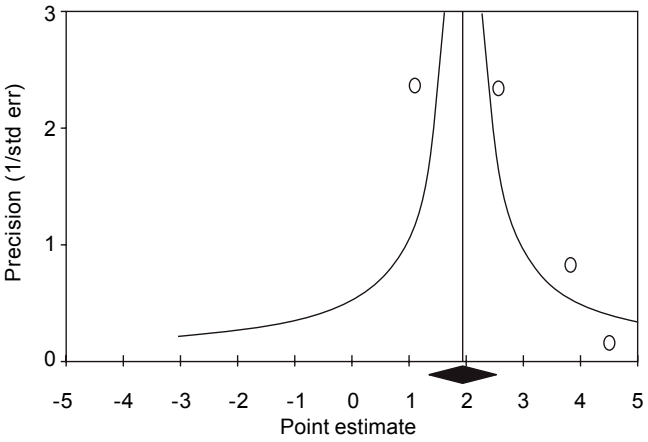

Figure 3. Funnel plot of precision: Impact of HBV seropositive status on the risk of chronic kidney disease (longitudinal studies).

seven studies gave a Q-value (by χ^2 test) of 11.3 (P = 0.007) (I^2 = 47.13), that is, the homogeneity assumption was rejected (Table 4). No publication bias was found, according to the Egger test (P = 0.89).

- **Summary estimate of outcome: prevalence of proteinuria.** Five studies (n = 99,838 unique patients, 8,030 being HBV seropositive and 91,808 HBV negative)[23-25,28,30] evaluated the prevalence of proteinuria according to HBV positive serologic status. Two studies defined proteinuria by semiquantitative urine protein dispstick test[24,30] and three measured albuminuria by spot urine albumin/creatinine ratio.[23,25,28] The summary estimate for adjusted OR of proteinuria with HBV was 0.93 (95% CI, 0.76;1.10, P = NS) across the identified studies (Table 4). The homogeneity assumption was not rejected (Q = 6.02, P = 0.19). Publication bias did not occur (Egger test, P = 0.42).
- **Stratified analysis and meta-regression.** As shown in table 4, there was substantial difference in pooled effect estimates across designs (i.e., cross-sectional *vs.* longitudinal studies) and the homogeneity assumption was rejected in many subsets. As listed in table 5, meta-regression demonstrated an inverse relationship between the frequency of males (P = 0.006) and the outcome of interest (adjusted HR of incidence of CKD among HBV positive patients). In addition, a direct relationship between follow-up duration (P = 0.007) and the outcome of interest (adjusted HR of incidence of CKD among HBV positive patients) was noted.

  There was no significant difference in outcomes according to the diagnosis of HBV infection (data not shown).

DISCUSSION

The association between HBV infection and chronic kidney disease in the general population is controversial even if the renal involvement of hepatitis B virus infection was first reported four decades ago.[31] The relationship between hepatitis B virus infection and CKD occurs in several ways- some forms of renal disease are induced by HBV infection and patients with chronic kidney disease are at increased risk for acquiring HBV. In the current review, we have summarized the scientific evidence and carried out a meta-analysis on the exposure to HBV infection and the risk of chronic kidney disease and proteinuria in the adult general population. This meta-analysis (16 studies, n = 394,664 patients) should suggest an association between positive serologic status for HBV and an increased risk of chronic kidney disease, aHR being 2.22 (95% Confidence Interval, 0.95; 3.50) in HBV infected individuals

Table 4. Summary measure for adjusted effect estimate according to HBV serologic status among various subgroups of interest.

	N	Adjusted Effect Estimate (Random-Effects Model)	Q Value (by χ^2 test)	I^2
Outcome: chronic kidney disease (incidence), aHR				
Longitudinal studies (All)	4	2.22 (0.95; 3.50)	8.57	64.7
Longitudinal studies (outcome: CKD)	2	1.85 (0.41; 3.27)	5.87	82.9
Longitudinal studies (outcome: ESRD)	2	3.87 (1.48; 6.25)	0.00	0.0
Quality score ≥ 8	2	2.71 (1.95; 3.47)	0.83	0.0
Outcome: chronic kidney disease (prevalence), aOR				
All studies	7	1.07 (0.89; 1.24)	11.3	47.1
Studies based on low eGFR (outcome)	5	0.84 (0.41; 1.28)	7.63	60.6
Studies based on CKD (outcome)	3	1.22 (1.03; 1.40)	0.85	0.0
Cross-sectional studies based on CKD (outcome)	2	1.19 (0.93; 1.45)	0.77	0.0
Quality score ≥ 9	3	1.07 (1.0; 1.15)	1.57	0.00
Outcome: proteinuria (prevalence), aOR				
All studies	5	0.93 (0.76; 1.10)	6.02	33.5
Studies from China	2	0.96 (0.51; 1.42)	1.62	38.5
Quality score ≥ 9	2	0.98 (0.78; 1.18)	1.29	22.7
Studies based on spot urine albumin/creatinine ratio	3	0.82 (0.44; 1.21)	3.34	40.1
Studies based on standard dispstick analysis	2	1.00 (0.87; 1.13)	0.48	0.0

Cheng, et al.:[19] *HR adjusted for age, age of onset of diabetes mellitus, gender, smoking use, systolic and diastolic blood pressure, body mass index, fasting plasma glucose, total cholesterol, triglyceride, white cell count, estimated glomerular filtration rate, and albumin:creatinine ratio. Chen,* et al.:[20] *HR adjusted for age, gender, diabetes, hypertension, coronary artery disease, hyperlipidaemia, cirrhosis, use of herbs containing aristolochic acid, geographic region, urbanization level, enrollee category, number of medical visits, propensity score, and Charlson comorbidity index score. Chen,* et al.:[21] *HR adjusted for gender, age, diabetes mellitus, hypertension, coronary artery disease, hyperlipidaemia, glomerulonephritis, chronic pyelonephritis, nephrolithiasis, renal and urinary tract tumor, cirrhosis, use of herbs containing aristolochic acid, geographic region, urbanization level, enrollee category, number of medical visits in one year before study entry, Charlson comorbidity index score, propensity score, and interactions terms. Kong,* et al.:[22] *HR adjusted for age, gender, hypertension, diabetes, body mass index, uric acid, total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol. Ishizaka,* et al.:[23] *OR adjusted for age, gender, fasting plasma glucose, systolic blood pressure, and anti-HCV seropositive status. Lee,* et al.:[24] *OR adjusted for age, gender, educational status, body mass index, haemoglobin level, albumin level, cholesterol level, uric acid level, hypertension, and diabetes mellitus. Cai,* et al.:[25] *OR adjusted for age, gender, hypertension, diabetes, waist circumference, HDL cholesterol levels, total cholesterol levels, and nephrolithiasis. Lin, et al.:*[26] *OR adjusted for age, gender, annual income, hypertension, diabetes mellitus, cardiovascular disease, stroke, gout, liver disease, urinary tract disease, cancer, Chinese herbs use, oral analgesic use, analgesic injection, health supplements, cigarette smoking, betel-nut chewing, alcohol drinking, metabolic syndrome, hyperuricemia, haemoglobin, and positivity for anti-HCV. Senghore,* et al.:[27] *OR adjusted for age, gender, body mass index, blood pressure, urine occult blood, blood urea nitrogen, uric acid, total cholesterol. Zeng,* et al.:[28] *OR adjusted for age, gender, anti-HCV seropositive status, arterial hypertension, diabetes mellitus, body mass index, albumin, HDL cholesterol levels, LDL cholesterol levels, triglycerides, total cholesterol, and uric acid. Su,* et al.:[29] *OR adjusted for gender, age, obsesity, income, HCV, hyperuricaemia, anaemia, hyperlipidaemia, smoking status, alcohol abuse, betel nut, exercise habits, groundwater using. Huang,* et al.:[30] *OR adjusted for diabetes, hypertension, HCV serologic status, age, triglycerides, body mass index, ALT level, total cholesterol.*

Table 5. Meta-regression: impact of continuous covariates on the outcome of interest (incidence of CKD).

	Point estimate (std error)	95% CI	P-value
Diabetes	1.35 (7.88)	-14.1; 16.8	0.86
Year	-1.07 (0.41)	-1.88;-0.27	0.008
Follow-up, time	1.03 (0.38)	0.27; 1.79	0.007
Males	-17.5 (6.39)	-30.0; -5.00	0.006
Size	0.0003 (0.0001)	0.000; 0.000	0.007

compared with HBV negative. The subset of longitudinal studies addressing ESRD gave a pooled aHR 3.87 (95%CI, 1.48; 6.25, P < 0.0001) among HBV-infected patients, without heterogeneity.

Several pieces of evidence are in keeping with a detrimental role of HBV on the development of chronic kidney disease.[32-39] In the 2-year cross-sectional HARPE study,[32] renal abnormalities were highly prevalent in chronic HBV infection and occurred before the initiation of any antiviral therapy towards HBV. Around 64% of the patients enrolled in the HARPE study (n = 260) were found to have kidney disease according to the KDOQI/KDIGO classification. In their observational and longitudinal study, Mallet, *et al.*[33] observed 214 patients with chronic HBV infection who were treated with various nucleos(t)ide analogues, the eGFR remained stable or increased over time in patients with chronic HBV mono-infection with a baseline eGFR of 90 mL/min/1.73 m^2 or higher and treated with tenofovir disoproxil fumarate or entecavir. In the GLOBE study,[34] a significant improvement in mean GFR was noted in patients treated with telbivudine for 2 years, but not in those on lamivudine. GLOBE extension studies

demonstrated that the improvement was maintained throughout 4-6 years of continuous telbivudine therapy. The mean increase in eGFR was ± 14.9 mL/min/1.73 m^2 at week 208 ($P < 0.0001$). In 74% (165 of 223) of the telbivudine-treated patients with baseline eGFR of 60-89 mL/min/1.73 m^2 (CKD stage 2), renal function improved to ≥ 90 mL/min/1.73 m^2 after 4 years of treatment. A prospective survey from Germany reported recently that GFR (calculated with the CKD-EPI equation), declined by approximately -2 mL/min/year in HBsAg-positive (n = 60) untreated patients over a median follow-up of 24 months.[35]

Chronic kidney disease is an important public-health problem which significantly increases the likelihood of adverse outcomes and high health-care costs; in addition to the conventional risk factors for chronic kidney disease in the general population, HBV may be an additional agent. Various mechanisms have been implicated in the adverse impact of HBV sero-positive status on chronic kidney disease, including an accelerated endothelial dysfunction at renal level. An atherogenic activity of HBV has been suggested to explain a five-fold increased risk of cardiovascular events in a selected cohort of HBsAg positive patients with type 2 diabetes and overt nephropathy over a median follow-up of 24 months.[17] Steatosis is a typical feature of chronic HBV infection and could induce lipid peroxidation and increase plasma inflammatory biomarkers.[39] The pathogenesis of HBV-associated nephropathy is still under investigation; however, the small number of patients who develop glomerulonephritis suggests that concomitant factors are needed for development of nephropathy (i.e., genetic susceptibility, abnormalities in cell-mediated immunity, and/or environmental conditions).[5] These pieces of evidence are in apparent conflict with other findings from the general population- chronic HCV is an important factor for developing insulin resistance, type 2 diabetes mellitus and atherosclerosis.[41] Such relationships in patients with chronic hepatitis B are not so straightforward.[40, 42-43]

The findings from our meta-analysis are subject to several limitations. First, many studies were cross-sectional, a design that does not allow for causal inference and can overestimate relative risks given its reliance on prevalence ratios. When restricted to cross-sectional studies, no significant relationship was found between hepatitis B serologic status and frequency of CKD and proteinuria. Therefore, there is some evidence that the findings may be impacted by study design. Second, we included in the current review only studies providing adjusted estimates of outcomes (risk of end-stage renal disease or chronic kidney disease, or proteinuria), but residual confounding (confounding remaining after adjustment) likely exists as full information has not been given on various covariates in all studies retrieved. As an example, information on HBV DNA or HBV genotypes, socioeconomic status, compliance with medical visits over follow-up, and substance abuse which are important potential confounders was incomplete. Finally, the occurrence of significant heterogeneity clearly precluded more definitive conclusions; our subgroup analysis with meta-regression was not able to capture all the sources of heterogeneity observed. As an example, all the studies enrolled in our systematic review came from Asia and we need studies from other continents.

In conclusion, this meta-analysis of observational studies should suggest a relationship between HBV infection and higher incidence of low eGFR and/or end-stage renal disease in the adult general population. We need additional studies with appropriate size and design (i.e., prospective longitudinal studies) to increase our knowledge on this issue and to explore potential mechanisms underlying such association. A heightened awareness of an increased chronic kidney disease risk should dictate more careful follow-up of renal defects among patients with hepatitis B virus infection.

SUPPORTING INFORMATION

- **Supplementary file 1.** PRISMA 2009 check list.
  PRISMA's items and their application within the paper.

- **Supplementary file 2.** Quality study.
  Details on the quality study process (cohort and cross-sectional studies).

- **Supplementary file 3.** Excluded papers.
  List of excluded papers sorted by publication year.

ABBREVIATIONS

- **ACR:** albumin to creatinine ratio.
- **APR:** albumin to protein ratio.
- **CC:** case-control.
- **CKD:** chronic kidney disease.
- **CI:** confidence intervals.
- **Co:** cohort.
- **CS:** cross-sectional.
- **eGFR:** estimated glomerular filtration rate.
- **ESRD:** end-stage renal disease.
- **HBV:** hepatitis B virus.
- **HBcAb:** hepatitis B core antibody.
- **HBsAg:** hepatitis B surface antigen.
- **HCV:** hepatitis C virus.
- **HR:** hazard ratio.
- **MDRD:** Modification of Diet in Renal Disease.
- **NOS:** Newcastle/Ottawa Scale.
- **OR:** odds ratio

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DISCLOSURES

None.

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SUPPLEMENTARY FILE 1.

PRISMA 2009 check list.

PRISMA's items and their application within the paper.

Section/topic	No.	Checklist item	Reported on page No.
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1-2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	1-2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not available
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	2
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	2
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	3

Supplemetary file 1.

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	3
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	3-4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	3-4
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	3-6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	3-6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	3-6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	3-6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	3-6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	3-6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	3-6
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	6-8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	6-8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	6-8
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	9

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit: www.prisma-statement.org

SUPPLEMENTARY FILE 2.
Quality study.
Details on the quality study process (cohort and cross-sectional studies).

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

(Cohort studies)

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability (maximum 8 items, 9 stars).

Selection (Maximum 4 stars).

1. Representativeness of the exposed cohort.
   a) Truly representative of the average _____ (describe) in the community.
   b) Somewhat representative of the average _____ in the community.
   c) Selected group of users, e.g. nurses, volunteers.
   d) No description of the derivation of the cohort.

2. Selection of the non-exposed cohort.
   a) Drawn from the same community as the exposed cohort.
   b) Drawn from a different source.
   c) No description of the derivation of the non exposed cohort.

3. Ascertainment of exposure.
   a) Secure record (e.g. surgical records).
   b) Structured interview.
   c) Written self-report.
   d) No description.

4. Demonstration that outcome of interest was not present at start of study.
   a) Yes.
   b) No.

Comparability (Maximum 2 stars).

1. Comparability of cohorts on the basis of the design or analysis.
   a) Study controls for _____ (select the most important factor).
   b) Study controls for any additional factor (this criteria could be modified to indicate specific control for a second important factor).

Outcome (Maximum 3 stars).

1. Assessment of outcome.
   a) Independent blind assessment.
   b) Record linkage.
   c) Self report.
   d) No description.

2. Was follow-up long enough for outcomes to occur.
   a) Yes (select an adequate follow up period for outcome of interest).
   b) No.

3. Adequacy of follow up of cohorts.
   a) Complete follow up - all subjects accounted for.
   b) Subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost).
   c) Follow up rate < ____% (select an adequate %) and no description of those lost.
   d) No statement.

NEWCASTLE-OTTAWA QUALITY ASSESSMENT SCALE

(Cohort studies)

Cheng A, *et al.* (*Diabetologia*, 2006).

- SELECTION.
  1c no star.
  2a one star.
  3a one star.
  4a one star.

- COMPARABILITY.
  1a one star.
  1b one star.

- OUTCOME.
  1b one star.
  2a one star.
  3d no star.

N = 7 stars

Chen Y, *et al.* (*Kidney Int*, 2015).
Chen Y, *et al.* (*BMC Nephrology*, 2015).

- SELECTION.
  1a one star.
  2a one star.
  3a one star.
  4a one star.

- COMPARABILITY.
  1a one star.
  1b one star.

- OUTCOME.
  1b one star.
  2a one star.
  3d no star.

N = 8 stars

Kong X, *et al.* (*Chronic Dis Transl Med*, 2016).

- SELECTION.
  1b one star.
  2a one star.
  3d one star.
  4a one star.

- COMPARABILITY.
  1a one star.

- OUTCOME.
  1b one star.
  2a one star.
  3d no star.

N = 7 stars

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

(Adapted for cross-sectional studies) (Maximum 7 items, 10 stars).

Selection (Maximum 5 stars).

1. Representativeness of the sample:
   a) Truly representative of the average in the target population* (all subjects or random sampling).
   b) Somewhat representative of the average in the target population* (non-random sampling).
   c) Selected group of users.
   d) No description of the sampling strategy.

2. Sample size:
   a) Justified and satisfactory.*
   b) Not justified.

3. Non-respondents:
   a) Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory.*
   b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.
   c) No description of the response rate or the characteristics of the responders and the non-responders.

4. Ascertainment of the exposure (risk factor):
   a) Validated measurement tool.**
   b) Non-validated measurement tool, but the tool is available or described.*
   c) No description of the measurement tool.

Comparability (Maximum 2 stars).

1. The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.
   a) The study controls for the most important factor (select one). *
   b) The study control for any additional factor. *

Outcome: (Maximum 3 stars)

1. Assessment of the outcome:
   a) Independent blind assessment.**
   b) Record linkage.**
   c) Self report.*
   d) No description.

2. Statistical test:
   a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value).*
   b) The statistical test is not appropriate, not described or incomplete.

This scale has been adapted from the Newcastle-Ottawa Quality Assessment Scale for cohort studies to perform a quality assessment of cross-sectional studies for the systematic review.

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

(Cross-sectional studies)

CAI J, *et al.* (*Clin J Am Soc Nephrol*, 2012).

- SELECTION.
  1a one star.
  2a one star.
  3 not applicable (no star).
  4a two stars.
- COMPARABILITY.
  1a one star.
  1b one star.
- OUTCOME.
  1b two stars.
  2a one star.

N = 9 stars

ISHIZAKA N, *et al.* (*Hepat Res*, 2008).

- SELECTION.
  1d no star.
  2a one star.
  3 not applicable (no star).
  4a two stars.
- COMPARABILITY.
  1a one star.
  1b one star.
- OUTCOME.
  1b two stars.
  2a one star.

N = 8 stars

ZENG Q, *et al.* (*J Int Med Res*, 2014).

- SELECTION
  1d no star.
  2a one star.
  3 not applicable (no star).
  4a two stars.
- COMPARABILITY.
  1a one star.
  1b one star.
- OUTCOME.
  1b two stars.
  2a one star.

N = 8 stars

Lin M, *et al.* (*Clin J Am Soc Nephrol*, 2013).

- SELECTION.
  1a one star.
  2a one star.
  3 not applicable (no star).
  4a two stars.
- COMPARABILITY.
  1a one star.
  1b one star.
- OUTCOME.
  1b two stars.
  1a one star.

N = 9 stars

Lee J, *et al.* (*Am J Kidney Dis*, 2010).

- SELECTION.
  1d no star.
  2a one star.
  3 one star.
  4a two stars.
- COMPARABILITY.
  1a one star.
  1b one star.
- OUTCOME.
  1b two stars.
  1a one star.

N = 9 stars

SENGHORE T, *et al.* (*J Exp Clin Med*, 2013).

- SELECTION.
  1c one star.
  2a one star.
  3a one star.
  4a one star.
- COMPARABILITY.
  1a one star.
- OUTCOME.
  1b one star.
  2a one star.

N = 7 stars

HUANG J, *et al.* (*J Intern Med*, 2006).

- SELECTION.
  1b one star.
  2a one star.
  3a one star.
  4c one star.
- COMPARABILITY.
  1a one star.
- OUTCOME.
  1b one star.
  2a one star.

N = 7 stars

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

(Case-control studies)

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection.

1. Is the case definition adequate?
   a) Yes, with independent validation.
   b) Yes, e.g. record linkage or based on self-reports.
   c) No description.
2. Representativeness of the cases.
   a) Consecutive or obviously representative series of cases.
   b) Potential for selection biases or not stated.
3. Selection of controls.
   a) Community controls.
   b) Hospital controls.
   c) No description.
4. Definition of controls.
   a) No history of disease (endpoint)
   b) No description of source

Comparability.

1. Comparability of cases and controls on the basis of the design or analysis.
   a) Study controls for _____ (select the most important factor).
   b) Study controls for any additional factor (this criteria could be modified to indicate specific control for a second important factor.)

Exposure.

1. Ascertainment of exposure.
   a) Secure record (e.g. surgical records).
   b) Structured interview where blind to case/control status.
   c) Interview not blinded to case/control status.
   d) Written self-report or medical record only.
   e) No description.

2. Same method of ascertainment for cases and controls.
   a) Yes.
   b) No.

3. Non-response rate.
   a) Same rate for both groups.
   b) Non respondents described.
   c) Rate different and no designation.

Su S, *et al.* (*BMC Nephrol*, 2015).

- SELECTION.
  1a one star.
  2a one star.
  3a one star.
  4a one star.

- COMPARABILITY.
  1a one star.
  1b one star.

- OUTCOME.
  1a one star.
  2a one star.
  3c none.

N = 8 stars

Supplemetary file 2.

SUPPLEMENTARY FILE 3.

Excluded papers.

List of excluded papers sorted by publication year.

STUDIES BASED ON UNADJUSTED ANALYSIS

1. Lo M, Lee K, Chan N, Leung W, Ko G, Chan W, So W, et al. Effects of gender, Helicobacter pylori and hepatitis B virus serology status on cardiovascular and renal complications in Chinese type 2 diabetics with overt nephropathy. *Diabetes Obesity Metabolism* 2004; 6: 223-30.

STUDIES BASED ON SIMILAR DATABASE

1. Lee J, Lin M, Chang J, Hung C, Chang J, Chen H, Yu M, et al. Hepatitis C virus infection increases risk of developing end-stage renal disease using competing risk analysis. *Plos One* 2014; 9: e100790.

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Supplemetary file 3.