Inflammatory Skin Diseases and the Risk of Chronic Kidney Disease – Population-Based Case-control and Cohort analyses

Running head: Inflammatory Skin Diseases and the Risk of CKD

Word count: 3014
Table count: 2
Figure count: 2

Y. Schonmann[1-3], K.E. Mansfield[1], A. Mulick[1], A. Roberts[4], L. Smeeth[1],

*S. M. Langan[1,5,6] *D. Nitsch[1, 7,8]

**Joint senior authors*

[1]Department of Non-communicable Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom

[2]Department of Quality Measurements and Research, Clalit Health Services, Tel Aviv, Israel

[3]Siaal Research Center for Family Medicine and Primary Care, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

[4]Nottingham Support Group for Carers of Children with Eczema, Nottingham, United Kingdom

[5]St John's Institute of Dermatology, Guy's & St Thomas' Hospital NHS Foundation Trust and King's College London, London, United Kingdom

[6]Health Data Research, London, United Kingdom

[7]Renal Department, Royal Free London NHS Foundation Trust, London, United Kingdom

[8]UK Renal Registry, Bristol, United Kingdom

Address for correspondence:

Dr. Yochai Schonmann,

Clalit Health Services, 101 Arlozorov St, Tel Aviv 6209804, Israel

Phone: 972-8-6477432

Fax: 972-8-6477636

E-mail: YochaiS@clalit.org. il, yochais@gmail.com

Type: Original article (Epidemiology)

Funding:

SML was supported by a Wellcome Trust Senior Research Fellowship in Clinical Science (205039/Z/16/Z). The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the funders. SML was also supported by Health Data Research UK (Grant No. LOND1), which is funded by the UK Medical Research Council, Engineering and Physical Sciences Research Council, Economic and Social Research Council, Department of Health and Social Care (England), Chief Scientist Office of the Scottish Government Health and Social Care Directorates, Health and Social Care Research and Development Division (Welsh Government), Public Health Agency (Northern Ireland), British Heart Foundation and Wellcome Trust.

Conflicts of interest: None declared.

Ethical approval: The study was approved by CPRD's Independent Scientific Advisory Committee (#19_011), and the London School of Hygiene and Tropical Medicine Research Ethics Committee (#16353).

What is already known about this topic?

- Emerging evidence supports an association between more common inflammatory skin diseases and chronic kidney disease (CKD), but the size and nature of this association remain unclear.

What does this study add?

- People with CKD were more likely to have atopic eczema (14%), psoriasis (13%) and hidradenitis suppurativa (49%), compared to those without CKD.
- The link between inflammatory skin diseases and CKD did not appear to be mediated through cardiovascular co-morbidity, hypertension or nephrotoxic drugs.
- A stronger association with CKD among those with severe atopic eczema and psoriasis was consistent with a dose-response association (between increasingly severe eczema/psoriasis and increasing CKD).
- There was no evidence of CKD incidence being associated with atopic eczema or psoriasis in the cohort of people with diabetes.

SUMMARY

***Background*:** Emerging evidence suggests an association between common inflammatory skin diseases and chronic kidney disease (CKD).

***Objective*:** To explore the association between CKD stages 3-5 and atopic eczema, psoriasis, rosacea, and hidradenitis suppurativa.

***Methods*:** We undertook two complementary analyses; a prevalent case-control and a cohort study using routinely collected primary care data (UK Clinical Practice Research Datalink [CPRD]).

We matched individuals with CKD3-5 in CPRD on March 2018 with up to five individuals without CKD on GP practice, age and sex. We compared the prevalence of CKD3-5 among individuals with and without each inflammatory skin disease.

We included individuals in CPRD with diabetes mellitus (2004-2018) in a cohort analysis to compare the incidence of CKD3-5 among people with and without atopic eczema and psoriasis.

***Results*:** There were 56,602 cases with CKD3-5 and 268,305 controls without. Cases were more likely than controls to have a history of atopic eczema (odds ratio [OR] 1.14; 99% confidence interval 1.11-1.17), psoriasis (1.13; 1.08-1.19), or hidradenitis suppuritiva (1.49; 1.19-1.85), but were slightly less likely to have been diagnosed with rosacea (0.91; 0.86-0.95), after adjusting for age, sex, practice (matching factors), index of multiple deprivation, diabetes, smoking, harmful alcohol use and obesity. Results remained similar after adjusting for hypertension and cardiovascular disease. In the cohort with diabetes (N=335,827), there was no evidence that CKD3-5 incidence was associated with atopic eczema or psoriasis.

***Conclusions*:** Atopic eczema, psoriasis, and hidradenitis suppurativa are weakly associated with CKD3-5. Future research is needed to elucidate potential mechanisms and clinical significance of our findings.

INTRODUCTION

Chronic kidney disease (CKD) affects up to 13% of the world's population,[1] and is associated with death and progression to end-stage renal disease.[2–5] Established risk factors for CKD include older age, diabetes, and hypertension, but for most cases, the aetiology of CKD remains unknown.[6,7]

Skin diseases are a leading cause of disability worldwide,[8] and inflammatory skin diseases are associated with a range of co-morbidities.[9,10] Emerging evidence supports an association between many inflammatory skin diseases and CKD. Longitudinal studies demonstrate increased CKD incidence in people with psoriasis;[11–14] and cross-sectional evidence supports associations between reduced kidney function or renal abnormalities, and hidradenitis suppurativa, rosacea and atopic eczema.[15–17]. Inflammatory skin diseases may be associated with CKD through increased metabolic syndrome risk and cardiovascular disease in people with skin conditions;[9,18,19] the use of nephrotoxic medications to manage skin diseases (or associated conditions);[20] or chronic low-grade inflammation of skin disease.[21,22]

Exploring the association between inflammatory skin conditions and CKD could help identify at-risk populations who may benefit from regular renal function monitoring. It could also guide prudent systemic nephrotoxic prescribing for people with inflammatory skin conditions, and provide insight into pathologic mechanisms leading to CKD. Elucidating the nature of an association between inflammatory skin diseases and CKD could guide targeted investigations into the possible role of skin conditions as CKD risk factors. We, therefore, aimed to compare the prevalence of specific common skin diseases (i.e. atopic eczema, psoriasis, rosacea, and hidradenitis suppurativa) in adults with and without CKD, and assess whether atopic eczema and

psoriasis are associated with CKD development in a cohort of people with diabetes mellitus.

METHODS

Setting

CKD diagnosis relies on blood and urine tests, which are not recommended as routine screening in the general population.[23,24]. It is, therefore, difficult to establish the onset of CKD in routinely-collected data.[24] However, prevalent CKD stages 3-5 (CKD3-5) based on blood tests only can be reliably detected in the general population;[25] and new CKD3-5 cases can be captured among specific at-risk populations (e.g. people with diabetes), who are more likely to undergo guideline-recommended routine renal function testing.[24] We conducted two complementary matched analyses (1. a population-based prevalent matched case-control study in those with and without CKD3-5; and 2. a cohort study restricted to people with diabetes mellitus) using routinely-collected primary care electronic health record data from the United Kingdom Clinical Practice Research Datalink (UK CPRD Gold). We were able to include, through the case-control, a large population-based sample of UK primary care (powered to detect small associations). The complementary cohort analysis offered a view of a smaller specific sub-population (i.e. those with diabetes) where the timing of CKD could be more reliably ascertained. The CPRD includes primary care data, including demographic information, coded diagnoses (Read codes), prescriptions and secondary care referrals.[26,27] Analyses of gaps in data entry and recorded deaths in each practice assure the data quality (i.e. 'up-to-standard' status), and diagnoses recorded in CPRD have been extensively validated.[27–29]. The CPRD is nationally-

representative, covering approximately 7% of the UK population.[27]**Study design and population**

Case-control study

All people aged 25 years or older, alive and registered in an up-to-standard CPRD practice for at least one year on 31/03/2018 were eligible for inclusion. We used a validated algorithm to ascertain current CKD status and restricted to individuals aged 25 years or older, as CKD3-5 below 25 is rare.[25,30] We matched each individual with CKD3-5 (cases) with up to five individuals without CKD3-5 (controls), on age (i.e. same year of birth), sex, and general practice. We compared the proportion of people with an inflammatory skin disease (diagnosed before 31/03/2018) among CKD3-5 cases and controls, repeating the analysis separately for each inflammatory skin condition (i.e. atopic eczema, psoriasis, rosacea and hidradenitis, see "**Outcomes**" and "**Exposures**" sections). See **Figure S1** for a graphic representation of the study designs.

Cohort study

All adults with diabetes mellitus in CPRD, aged 25 years or older (01/04/2004 to 31/03/2018) were eligible for inclusion. Follow up began at the latest of: a) one year after practice registration (to allow time for GPs to record previous medical history, for robust capture of baseline characteristics and so that we could be more confident that we had captured new-onset CKD3-5); b) the date that the general practice reached CPRD quality standards; c) start of the study (01/04/2004); or d) the date of their first record of a diabetes diagnosis. We excluded those with pre-existing CKD3-5 (see **Outcomes** section) and compared new CKD3-5 incidence among people with and without psoriasis or atopic dermatitis (i.e. the more common of the explored skin conditions) at cohort entry. We followed each participant until incident

CKD3-5 (outcome), or the earliest of: a) date of death; b) change of practice; c) last data collection from practice; or d) end of the study (31/03/2018). (**Appendix S2** for diabetes definition)

Outcomes

We defined the primary outcome, CKD3-5, as being on renal replacement therapy, having received a renal transplant, or having two measurements of estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 calculated from serum creatinine test results (using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) recorded in primary care at least three months apart.[31] The CKD-EPI equation accounts for black ethnicity when estimating glomerular filtration rate,[32] as only 3.7% of the CPRD population is black, we classified individuals with no record of ethnicity as white.[25] Various methods are used in the UK to measure serum creatinine, but most laboratories did not report standardised values up to at least 2013.[33] Following the approach taken in previous CPRD studies,[34–36] we multiplied the recorded values of creatinine by 0.95 to correct for lack of isotope-dilution mass spectrometry standardisation.[37]

For the case-control analysis, we identified all serum creatinine test results recorded in primary care over a five-year period (01/04/2013 to 31/03/2018). Using the same approach as a previous validation study, we considered those who did not meet the CKD3-5 criteria during that time-period as not having CKD3-5.[25] In the cohort analysis, we used the latest of the two creatinine measurements (recorded at least three months apart) required to fulfil the diagnostic criteria as the date of incident CKD3-5. Our secondary outcome was CKD stage based on the eGFR recorded on date of incident CKD diagnosis (by eGFR: Stage 3a [45-59 mL/min/1.73m^2]; 3b [30-44 mL/min/1.73m^2]; stage 4/5 [<30 mL/min/1.73m^2]; renal

replacement therapy).[25,38] We excluded from the cohort analysis those with at least one low eGFR<60 ml/min/1.73m^2 or a diagnostic code compatible with RRT before cohort entry.

Exposures

We used definitions of atopic eczema (positive predictive value [PPV] 86%), psoriasis (PPV=90%), hidradenitis suppurativa, and rosacea that have previously been applied in CPRD.[39–42] Diagnoses were based on the presence of recorded diagnostic codes (as well as therapies for atopic eczema). A previous validation study assured the exclusion of non-atopic eczema cases). We chose these specific inflammatory skin diseases as exposures since they are common and predominantly managed in primary care (further details in **Appendix S3**).[41,43,44]

Covariate selection

We used a directed acyclic graph to guide *a-priori* informed selection of covariates and avoid collider bias.[45,46] We, consequently, considered the following covariates: age (categorised into five-year intervals in the cohort study); sex; GP practice; level of deprivation (using quintiles of the 2015 Index of Multiple Deprivation [IMD]); ethnicity (White/South Asian/Black/Other/Mixed); smoking status [current/ex/never]; alcohol use; body mass index (BMI) (<18.5, 20.0-24.0, 25.0-29.0, >30.0 kg/m^2); diabetes; cardiovascular disease (i.e. ischemic heart disease, chronic heart failure and peripheral arterial disease); hypertension; medications used to treat skin conditions with known renal implications (ciclosporin [nephrotoxic requiring monitoring], methotrexate [contraindicated for advanced CKD], mycophenolate mofetil [associated with anaemia and infection risk but not strictly contraindicated]). All morbidity code lists used in this study are available to download

(https://doi.org/10.17037/DATA.00001205), and additional details are available in **Appendix S4**.

Statistical analysis

Case-control study

We initially described the characteristics of those with and without CKD3-5. We then used conditional logistic regression to estimate the odds ratios comparing odds of CKD3-5 in individuals with each skin condition separately (main analysis) compared to those without. All analyses implicitly accounted for matching factors (age, sex, GP practice). We fitted the following sequential regression models: a) a minimally-adjusted model, additionally including IMD; b) a fully-adjusted model, additionally including diabetes mellitus, smoking, harmful alcohol use and obesity; c) a final model also included potential mediators: hypertension and cardiovascular disease. We used complete case analysis.[47] To preserve matching, we excluded entire matched sets if a person with CKD3-5 was excluded (e.g. due to missing data or restrictions in a sensitivity analysis), or if no individuals without CKD3-5 remained in the set.

We conducted sensitivity analyses to explore potential bias introduced by: the algorithm used to define CKD3-5; skin disease definitions; lack of accurate ethnicity data before 2006;[32] information bias due to more frequent renal function testing among those taking medications requiring frequent blood testing; including non-English CPRD practices; and missing BMI data (**Appendix S5)**.

We conducted secondary analyses: a) repeating the analyses after redefining individuals with atopic eczema as having mild, moderate or severe disease; and after redefining people with psoriasis as having mild/moderate or severe disease (based on recorded prescriptions for potent or systemic treatments, phototherapy record and referrals, **Appendix S5**; b) exploring potential effect modification by age and sex; and

c) using multinomial logistic regression to compare the relative risk of various levels of impaired kidney function among individuals with each skin condition to those without skin disease. To account for matching in the multinomial regression, we additionally adjusted for the matching variables (age group categorised as 45-64, 65-69, 70-74, 75-79, 80-84, 85-89, 90+; and sex), and calculated 99% confidence intervals allowing for intra-group correlation within GP practices by using clustered robust standard errors. We estimated the population attributable risk (PAR), the proportion of CKD cases attributable to each skin condition, assuming causality: PAR=P(RR-1)/RR; where P is the proportion of CKD cases with the inflammatory skin condition, (using the calculated matched odds ratio as an estimate for the RR).[48]

Cohort study

For the cohort analysis of individuals with diabetes, we initially presented baseline characteristics of individuals with and without atopic eczema and psoriasis. We then calculated CKD3-5 incidence rates and used Poisson regression to estimate the rate ratio for CKD3-5 among those with and without atopic eczema and psoriasis, using the same framework of covariate selection described above. As in the case-control study, we conducted sensitivity analyses to explore potential bias (**Appendix S6**).

In all analyses, we used likelihood-ratio tests to calculate P-values (unless stated otherwise). We used 99% confidence intervals to reduce the risk of Type 1 error in the context of multiple analyses.[49] Statistical analysis was performed using Stata, version 15.1 IC (StataCorp LP, College Station, Texas). The study was approved by CPRD's Independent Scientific Advisory Committee (#19_011), and the London School of Hygiene and Tropical Medicine Research Ethics Committee (#16353).

RESULTS

Case-control study

We matched 56,602 adults with CKD3-5 in CPRD on 31/03/2018 with a control group of 268,305 people (**Figure 1**). Mean age (standard deviation [SD]) was 78.6 years (10.4), and 42.3% (137,505) were men. Those with CKD3-5 were more likely to be obese than those without (38.8% versus 23.5%), and more likely to be current or ex-smokers (65.0% versus 59.6%). People with CKD3-5 were more likely to have a cardiovascular disease risk factor (i.e. smoking, hypertension, diabetes, obesity) or cardiovascular disease (**Table 1**). Characteristics by CKD3-5 category are provided in **Appendix S5**.

We present the association between all four inflammatory skin disease and CKD3-5 in **Table 2**. Individuals with CKD3-5 were more likely to have a history of atopic eczema (odds ratio [OR] 1.14; 99% confidence interval [99%CI] 1.11 to 1.17), psoriasis (OR 1.13; 99%CI 1.08 to 1.19), or hidradenitis (OR 1.49; 99%CI 1.19 to 1.85) than those without, after adjusting for age, sex, general practice and IMD, as well as diabetes, smoking, harmful alcohol use and obesity. CKD3-5 was associated with lower prevalence of rosacea (OR 0.92; 99%CI 0.87 to 0.97). After additionally adjusting for hypertension and cardiovascular morbidity (i.e. potential mediators), our results were slightly attenuated for all four skin diseases. (**Table 2)**. **Appendix S5** includes absolute numbers and crude proportions of people with inflammatory skin diseases among those with and without CKD3-5.

Participants with atopic eczema and psoriasis were more likely to have CKD3-5 regardless of atopic eczema or psoriasis severity. The association was stronger in people with more severe skin disease (P[trend]<0.0001) (**Figure 2**, **Appendix S5**). In

stratified analyses, there was no evidence of a difference in the association between the inflammatory skin diseases and CKD3-5 between men and women, nor was there evidence for effect modification by age. Our multinomial regression results were consistent with the main regression analysis, but confidence intervals were wide. Our results were similar in sensitivity analyses (**Appendix S5**). Applying the calculated effect estimates, and assuming a causal association, 2.4% of CKD cases may be attributable to atopic eczema, 0.7% to psoriasis and 1.45% to hidradenitis (Supplement S5)

Cohort study

We identified 448,286 eligible individuals in CPRD between 01/04/2004 and 31/3/2018 with a diabetes mellitus diagnosis. 335,827 remained after we excluded those who had at least one eGFR measurement <60 mL/min/1.73m^2 or RRT before cohort entry. Mean age at cohort entry was 58.5 (SD 13.6) years, and 59.7% (200,372) were men. 9.4% (31,585) had atopic eczema, and 4.6% (15,476) had a psoriasis diagnosis (**Appendix S6)**. There was no evidence for an association between pre-existing atopic eczema or psoriasis, and new-onset CKD3-5, a finding that did not differ in sensitivity analyses (**Appendix S6**).

DISCUSSION

Main findings

In our case-control study, people with CKD3-5 were more likely to have atopic eczema (14%), psoriasis (13%) and hidradenitis suppurativa (49%), compared to those without CKD3-5. There was no evidence to support that the link between inflammatory skin diseases and CKD3-5 was mediated through cardiovascular co-morbidity or hypertension. A stronger association with CKD3-5 among those with severe atopic eczema and psoriasis was consistent with a dose-response association. However, those with rosacea were less likely to have CKS3-5, and we did not find an increased incidence of CKD3-5 among those with atopic eczema or psoriasis within a cohort of people with diabetes.

Strengths and limitations

We studied a large, nationally representative, population-based samples, assuring power and precision in assessing the link between inflammatory skin diseases and CKD3-5. Using real-world, routinely collected data, we were able to account for a wide range of potential confounders and mediators and conducted extensive sensitivity analyses. We explored four different conditions, following a rigorous, pre-approved protocol, and combined complementary approaches with different potential biases to 'triangulate' the association between inflammatory skin diseases and CKD3-5.[50] Integrating diverse data, rather than concentrating on a single disease, supported our attempt to infer on inflammatory skin conditions in general.

However, our study has several limitations. We regarded those without serum creatinine measurements as not having CKD3-5. As people will only have serum creatinine testing when it is indicated (i.e. in acute illness or incentivised monitoring in specific illnesses, e.g. diabetes) and early disease is often asymptomatic. We may

have misclassified people with undiagnosed silent CKD as being CKD-free, potentially diluting our effect estimates towards null. However, a previous validation study has shown that the approach we took reliably captures prevalent CKD3-5 in CPRD.[25] Additionally, due to infrequent urinary testing, we were unable to capture albuminuria, which may have been a more sensitive marker of inflammatory kidney damage. Skin manifestations of late-stage CKD could have been misclassified as inflammatory skin diseases (e.g. xerosis). This limitation of the case-control design was mitigated by our use of validated algorithms (where available) to reduce the likelihood of misclassifying skin disease. Finally, we were unable to capture potentially relevant covariates, including environmental and genetic risk factors, in routinely collected data. Of note, we were not able to capture information on the use of biologic medications, which may have had a mediating role in the development of CKD among people with severe skin conditions.

Comparisons to the existing literature

Longitudinal studies have demonstrated increased CKD incidence in people with psoriasis.[11–14] Cross-sectional or smaller-scale evidence previously suggested an association between CKD and hidradenitis suppurativa,[15] and rosacea.[16] There have been reports of nephrotic syndrome and Henoch-Schonlein purpura in children with atopy;[51–54] and Danish analysis suggests that mortality due to urogenital diseases (ICD10 code groups N00-N99) is more common among those with eczema, although absolute numbers were small.[17] Our findings are consistent with these previous reports, but to the best of our knowledge, the association between atopic eczema and CKD has not been previously explored. Unlike a previous smaller Taiwanese cohort study,[16] we did not demonstrate an association between rosacea and CKD3-5. While GP diagnoses are highly concordant with those made by specialists,[55] a previous

report also suggested substantial misclassification of rosacea by GPs, especially with acne and seborrhoeic dermatitis.[42] Misclassified rosacea diagnoses are likely to be non-differential (i.e. to occur regardless of CKD status), and may have therefore diluted the observed associated between rosacea and CKD3-5 towards null.

Interpretation, implications, future research

We explored a link between inflammatory skin diseases and CKD. We were able to include a large sample of people with atopic eczema and psoriasis, but relatively few with hidradenitis suppuritiva and rosacea, Our case-control analysis supported a positive association between atopic eczema, psoriasis and hidradenitis suppuritiva and CKD, but a negative association between rosacea and CKD. A cohort analysis of people with diabetes failed to demonstrate the associations of atopic eczema and psoriasis with CKD3-5. We discuss below potential explanations for our findings, as well as for the discrepancy between the results of the complementary designs.

We cannot ascertain the temporal direction using our prevalent case-control design (due to its cross-sectional nature), but the consistent results across multiple skin conditions and the apparent association between increasing atopic eczema and psoriasis severity and increasing CKD3-5 highlight the need for further research to explore a causal link. The underlying mechanism for a potential link between inflammatory skin conditions and CKD remains unknown, but one compelling explanation involves chronic inflammation.[56] Autoimmune inflammation is mediated through abnormal activation of the innate immune system, which plays an important role in common skin diseases, such as psoriasis, atopic eczema, hidradenitis suppurativa and rosacea.[57–60] Circulating reactive oxygen species and inflammatory cytokines (resulting from the inflammatory process) could impair endothelial function

leading to accelerated atherosclerosis (with consequent kidney vasculature damage) or independently modulate kidney damage.[61] However, we observed little change in our results after accounting for potential mediators (i.e. ischemic heart disease, chronic heart failure and peripheral arterial disease) and in sensitivity analyses. Our findings, therefore, do not support a mediating role of metabolic syndrome, cardiovascular morbidity, hypertension or nephrotoxic medications in the development of CKD among people with inflammatory skin conditions. We were unable to account for the use of biologic medications, which may have mediated the association among those with moderate to severe skin conditions; further research is needed to elucidate the role of this medication group. While the results of the cohort study did not mirror those of our main case-control design, we believe they highlight methodological issues for future research but do not invalidate its results.

In our cohort study of people with diabetes, there was no evidence for an increased CKD3-5 incidence among people with atopic eczema or psoriasis. However, the mean follow-up for participants in the cohort was 5.3 years, which may have been insufficient to capture differences in CKD3-5 onset between those with and without skin disease. We chose to follow people with diabetes to assure reliable capture of incident CKD, but this approach may have inadvertently precluded us from observing an association. Diabetes, together with hypertension, is associated with most cases of CKD.[62] We, therefore, speculate that the high baseline risk for developing CKD3-5 in a cohort of people with diabetes may obscure a much smaller contributing effect of an inflammatory skin condition.

There is no firm evidence to support routine population screening for CKD,[38,63] but some stakeholders advocate targeted testing of individuals at high-risk.[7,64] If non-communicable inflammatory skin conditions are indeed risk-factors or

markers for CKD, future guidelines may consider affected individuals as at-risk populations for regular renal function monitoring.

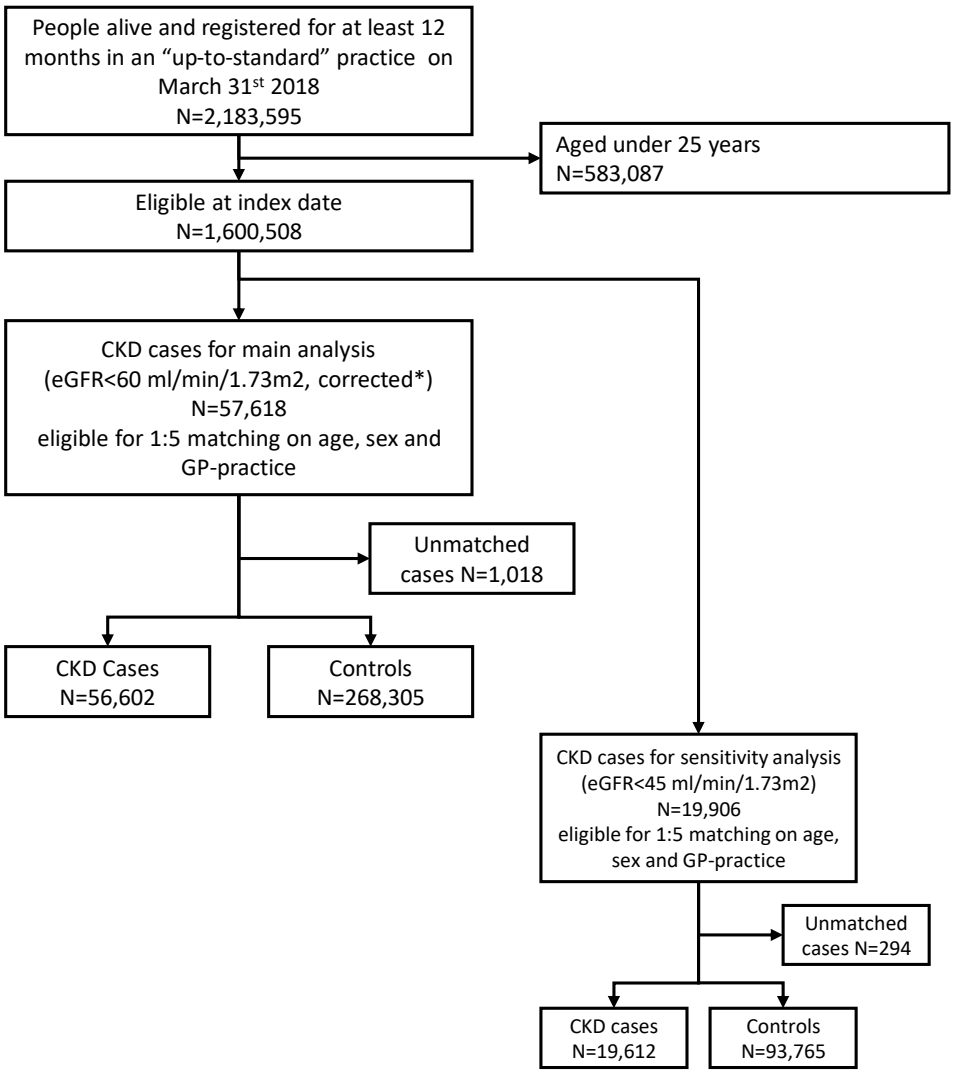
Conclusion

We found that atopic eczema, psoriasis, and hidradenitis suppurativa were weakly associated with CKD, independent of obesity, cardiovascular morbidity, or non-biologic nephrotoxic skin medications. We did not find evidence supporting this association in a cohort of people with diabetes. Further research is needed to elucidate the nature and temporal direction of this link, to account for other potential confounders, and explore whether targeted screening for CKD in people with inflammatory skin diseases is justified.

Acknowledgments: None.

FIGURES

Figure 1 – Case-control study: flowchart illustrating selection of the study population.

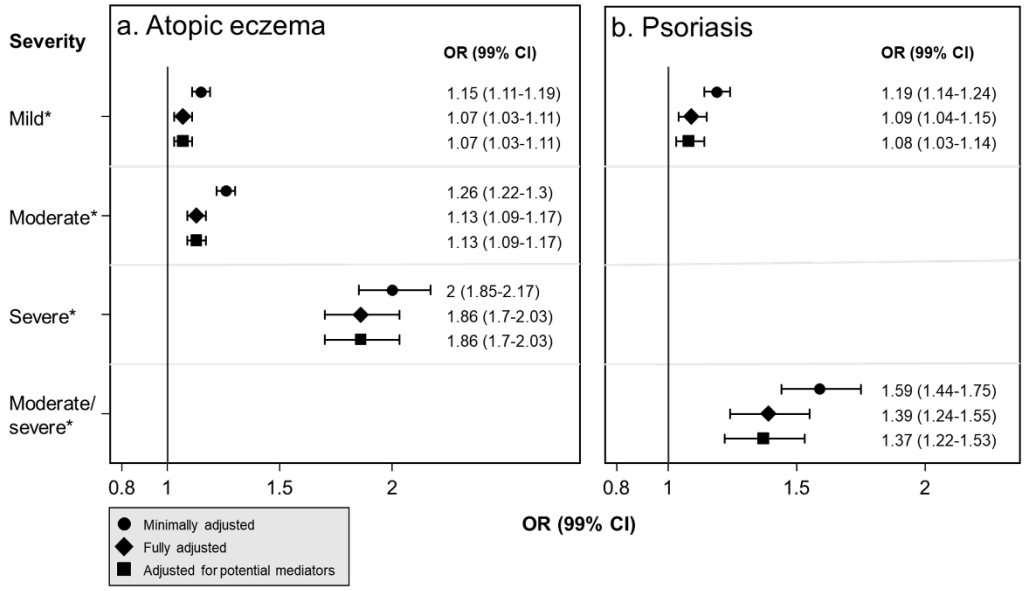


Abbreviations: CKD, chronic kidney disease; CPRD, Clinical Practice Research Datalink; eGFR, estimated glomerular filtration rate;

* Recorded creatinine values were multiplied by 0.95 to give a conservative estimate, corrected for lack of test standardisation. [1,2]

CKD on index date was defined if two consecutive eGFR measurements (including the one closest to the index date) were below 60 ml/min/1.73m^2 and at least 90 days apart; or if there were diagnostic codes indicating renal replacement therapy or a kidney transplant.

Figure 2. Case-control study: Odds ratios (99% CI) for prevalent CKD3-5 among individuals with atopic eczema (a) and psoriasis (b), by the severity of the skin condition.



Abbreviations: CKD3-5, chronic kidney disease stages 3-5

Odds ratios are derived from conditional logistic regression models, stratified on the matching variables (i.e. age, sex and GP-practice), and presented with 99% confidence intervals. All P-values for trend <0.0001

The minimally adjusted model is adjusted for age, sex, general practice and index of multiple deprivation (IMD); the fully adjusted model additionally accounts for diabetes status, smoking, harmful alcohol use and obesity; a final model, additionally adjusted for hypertension and cardiovascular disease (ischemic heart disease, chronic heart failure and peripheral arterial disease) as potential mediators.

* Compared to those without the skin condition.

TABLES

Table 1. Case-control study: Characteristics of the study population.

	CKD3-5 N=56,602	**No CKD3-5** N=268,305
Age, years, mean (SD)	79.1 (10.6)	78.4 (10.4)
25-64	4,782 (8.4%)	23,910 (8.9%)
65-74	10,484 (18.5%)	52,401 (19.5%)
75-84	22,549 (39.8%)	111,696 (41.6%)
85+	18,787 (33.2%)	80,298 (29.9%)
Sex, male	24,039 (42.5%)	113,466 (42.3%)
IMD		
1 lowest quintile	13,288 (23.5%)	65,167 (24.3%)
2	9,151 (16.2%)	44,189 (16.5%)
3	12,071 (21.3%)	57,086 (21.3%)
4	12,581 (22.2%)	58,031 (21.6%)
5 highest quintile	9,511 (16.8%)	43,832 (16.3%)
Ethnicity*		
White	26,237 (94.9%)	117,606 (94.9%)
South Asian	742 (2.7%)	2,941 (2.4%)
Black	354 (1.3%)	1,869 (1.5%)
Other/Mixed	310 (1.1%)	1,564 (1.3%)
Body Mass Index (BMI)*, kg/m^2 , mean (SD)	28.4 (5.8)	26.9 (5.2)
Underweight (<18.5)	748 (1.7%)	5,429 (2.8%)
Normal (20.0-24.0)	11,443 (26.6%)	67,144 (35.1%)
Overweight (25.0-29.0)	16,260 (37.8%)	73,763 (38.6%)
Obese (>30.0)	14,555 (33.8%)	44,923 (23.5%)
Current/former smoker *	36,741 (65.0%)	153,407 (59.6%)
Hypertension	44,777 (79.1%)	147,648 (55.0%)
Ischemic heart disease	13,209 (23.3%)	37,399 (13.9%)
Peripheral arterial disease	3,495 (6.2%)	7,971 (3.0%)
Heart failure	7,820 (13.8%)	12,173 (4.5%)
Diabetes	16,612 (29.3%)	36,819 (13.7%)
Harmful alcohol use	2,789 (4.9%)	14,577 (5.4%)
Methotrexate**	1,184 (2.1%)	4,332 (1.6%)
Ciclosporin**	428 (0.8%)	206 (0.1%)
Mycophenolate mofetil**	906 (1.6%)	206 (0.1%)
Renal function, $mL/min/1.73m^2$		
eGFR 45-59 (3a)	32,895 (58.1%)	N/A
eGFR 30-44 (3b)	17,418 (30.8%)	N/A
eGFR <30 (4/5)	5,601 (9.9%)	N/A
RRT/renal transplant	688 (1.2%)	N/A

Abbreviations: CKD3-5, chronic kidney disease stages 3-5; eGFR, estimated glomerular filtration rate; IMD, index of multiple deprivation; IQR, interquartile range RRT, renal replacement therapy; SD, standard deviation;

* Missing values: ethnicity, N=173,284; BMI, N=90,672; smoking status, N=11,281

** Record of at least one previous prescription

Table 2. Case-control study: Odds ratios (99% CI) for prevalent CKD3-5 among individuals with inflammatory skin diseases.

	Model 1 - minimally adjusted	**Model 2 - fully adjusted**	**Model 3 - additionally adjusted for potential mediators**
	N=324,907	N=228,812	N=228,812
Atopic eczema	1.24 (1.21-1.27)	1.14 (1.11-1.17)	1.1 (1.07-1.13)
Psoriasis	1.24 (1.19-1.29)	1.13 (1.08-1.19)	1.12 (1.07-1.17)
Hidradenitis suppuritiva	1.62 (1.34-1.97)	1.49 (1.19-1.85)	1.45 (1.16-1.82)
Rosacea	0.96 (0.91-1)	0.92 (0.87-0.97)	0.91 (0.86-0.96)

Odds ratios are derived from conditional logistic regression models, stratified on the matching variables (i.e. age, sex and GP-practice), and presented with 99% confidence intervals
The minimally adjusted model is adjusted for age, sex, general practice and index of multiple deprivation (IMD); the fully adjusted model additionally accounts for diabetes status, smoking, harmful alcohol use and obesity; a final model, additionally adjusted for hypertension and cardiovascular disease (ischemic heart disease, chronic heart failure and peripheral arterial disease) as potential mediators.

REFERENCES

1 Hill NR, Fatoba ST, Oke JL, *et al.* Global Prevalence of Chronic Kidney Disease – A Systematic Review and Meta-Analysis. *PLoS One* 2016; **11**:e0158765.

2 Van Der Velde M, Matsushita K, Coresh J, *et al.* Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. *Kidney Int* 2011; **79**:1341–52.

3 Matsushita K, van der Velde M, Astor BC, *et al.* Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010; **375**:2073–81.

4 Nitsch D, Grams M, Sang Y, *et al.* Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis. *BMJ* 2013; **346**:f324–f324.

5 Webster AC, Nagler E V., Morton RL, Masson P. Chronic Kidney Disease. *Lancet* 2017; **389**:1238–52.

6 Romagnani P, Remuzzi G, Glassock R, *et al.* Chronic kidney disease. *Nat Rev Dis Prim* 2017; **3**:17088.

7 Levin A, Tonelli M, Bonventre J, *et al.* Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy. *Lancet* 2017; **390**:1888–917.

8 Hay RJ, Johns NE, Williams HC, *et al.* The Global Burden of Skin Disease in 2010: An Analysis of the Prevalence and Impact of Skin Conditions. *J Invest Dermatol* 2014; **134**:1527–34.

9 Kwa MC, Silverberg JI. Association Between Inflammatory Skin Disease and Cardiovascular and Cerebrovascular Co-Morbidities in US Adults: Analysis of Nationwide Inpatient Sample Data. *Am J Clin Dermatol* 2017; **18**:813–23.

10 Narla S, Silverberg JI. Multimorbidity and mortality risk in hospitalized adults with chronic inflammatory skin disease in the United States. *Arch Dermatol Res* 2020. doi:10.1007/s00403-020-02043-8.

11 Wan J, Wang S, Haynes K, *et al.* Risk of moderate to advanced kidney disease in patients with psoriasis: population based cohort study. *BMJ* 2013; **347**:f5961–f5961.

12 Chiu H-Y, Huang H-L, Li C-H, *et al.* Increased risk of glomerulonephritis and chronic kidney disease in relation to the severity of psoriasis, concomitant medication, and comorbidity: a nationwide population-based cohort study. *Br J Dermatol* 2015; **173**:146–54.

13 Chi C-C, Wang J, Chen Y-F, *et al.* Risk of incident chronic kidney disease and end-stage renal disease in patients with psoriasis: A nationwide population-based cohort study. *J Dermatol Sci* 2015; **78**:232–8.

14 Parisi R, Rutter MK, Lunt M, *et al.* Psoriasis and the Risk of Major Cardiovascular Events: Cohort Study Using the Clinical Practice Research Datalink. *J Invest Dermatol* 2015; **135**:2189–97.

15 Miller I, Carlson N, Mogensen U, *et al.* A Population- and Hospital-based Cross-sectional Study of Renal Function in Hidradenitis Suppurativa. *Acta Derm Venereol* 2016; **96**:68–71.

16 Chiu H-Y, Huang W-Y, Ho C-H, *et al.* Increased risk of chronic kidney disease in patients with rosacea: A nationwide population-based matched cohort study. *PLoS One* 2017; **12**:e0180446.

17 Thyssen JP, Skov L, Egeberg A. Cause-specific mortality in adults with atopic dermatitis. *J Am Acad Dermatol* 2018; **78**:506–10.

18 Stefanadi EC, Dimitrakakis G, Antoniou C-K, *et al.* Metabolic syndrome and the skin: a more than superficial association. Reviewing the association between skin diseases and metabolic syndrome and a clinical decision algorithm for high risk patients. *Diabetol Metab Syndr* 2018; **10**:9.

19 Silverwood RJ, Forbes HJ, Abuabara K, *et al.* Severe and predominantly active atopic eczema in adulthood and long term risk of cardiovascular disease: population based cohort study. *bmj BMJ* 2018; **361**. doi:10.1136/bmj.k1786.

20 Gisondi P, Pezzolo E, Girolomoni G. Glomerular filtration rate in patients with moderate-to-severe psoriasis. *J Eur Acad Dermatology Venereol* 2019; :1–2.

21 Fox ER, Benjamin EJ, Sarpong DF, *et al.* The relation of C - reactive protein to chronic kidney disease in African Americans: the Jackson Heart Study. *BMC Nephrol* 2010; **11**:1.

22 Amdur RL, Feldman HI, Gupta J, *et al.* Inflammation and Progression of CKD: The CRIC Study. *Clin J Am Soc Nephrol* 2016; **11**:1546–56.

23 National Institute for Health and Care Excellence (NICE). Chronic kidney disease in adults: assessment and management. Clinical guideline 182. , 2014URL http://nice.org.uk/guidance/cg182.

24 McDonald HI, Shaw C, Thomas SL, *et al.* Methodological challenges when carrying out research on CKD and AKI using routine electronic health records. *Kidney Int* 2016; **90**:943–9.

25 Iwagami M, Tomlinson LA, Mansfield KE, *et al.* Validity of estimated prevalence of decreased kidney function and renal replacement therapy from primary care electronic health records compared with national survey and

registry data in the United Kingdom. *Nephrol Dial Transplant* 2017; **32**:ii142–50.

26 Chisholm J. The Read clinical classification. *BMJ* 1990; **300**:1092–1092.

27 Herrett E, Gallagher AM, Bhaskaran K, *et al.* Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015; **44**:827–36.

28 Herrett E, Thomas SL, Schoonen WM, *et al.* Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol* 2010; **69**:4–14.

29 Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. *Br J Gen Pract* 2010; **60**:128–36.

30 Nitsch D, Caplin B, Hull S, *et al.* First National Chronic Kidney Disease Audit (Part 1). , 2017URL https://www.hqip.org.uk/wp-content/uploads/2018/02/HtoEm0.pdf [accessed on 16 November 2018].

31 Levey AS, Stevens LA, Schmid CH, *et al.* A New Equation to Estimate Glomerular Filtration Rate. *Ann Intern Med* 2009; **150**:604.

32 Mathur R, Bhaskaran K, Chaturvedi N, *et al.* Completeness and usability of ethnicity data in UK-based primary care and hospital databases. *J Public Health (Bangkok)* 2014; **36**:684–92.

33 Lamb EJ. United Kingdom guidelines for chronic kidney disease. *Scand J Clin Lab Invest* 2008; **68**:16–22.

34 Iwagami M, Caplin B, Smeeth L, *et al.* Chronic kidney disease and cause-specific hospitalisation: a matched cohort study using primary and secondary care patient data. *Br J Gen Pract* 2018; **68**:e512–23.

35 No Title. doi:Pereg D, Tirosh A, Elis A, et al. Mortality and Coronary Heart

Disease in Euthyroid Patients. The American journal of medicine. 2012;125(8):826.e7-826.12. doi:10.1016/j.amjmed.2011.11.023.

36 McDonald HI, Thomas SL, Millett ERC, Nitsch D. CKD and the Risk of Acute, Community-Acquired Infections Among Older People With Diabetes Mellitus: A Retrospective Cohort Study Using Electronic Health Records. *Am J Kidney Dis* 2015; **66**:60–8.

37 Levey AS, Coresh J, Greene T, *et al.* Expressing the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular Filtration Rate with Standardized Serum Creatinine Values. *Clin Chem* 2007; **53**:766–72.

38 Levin A, Stevens PE, Bilous RW, *et al.* KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl* 2013; **3**:1.

39 Abuabara K, Magyari AM, Hoffstad O, *et al.* Development and Validation of an Algorithm to Accurately Identify Atopic Eczema Patients in Primary Care Electronic Health Records from the UK. J. Invest. Dermatol. 2017; **137**:1655–62.

40 Huerta C, Rivero E, Rodríguez LAG. Incidence and Risk Factors for Psoriasis in the General Population. *Arch Dermatol* 2007; **143**. doi:10.1001/archderm.143.12.1559.

41 Ingram JR, Jenkins-Jones S, Knipe DW, *et al.* Population-based Clinical Practice Research Datalink study using algorithm modelling to identify the true burden of hidradenitis suppurativa. *Br J Dermatol* 2018; **178**:917–24.

42 Spoendlin J, Voegel JJ, Jick SS, Meier CR. A study on the epidemiology of rosacea in the U.K. *Br J Dermatol* 2012; **167**:598–605.

43 Augustin M, Herberger K, Hintzen S, *et al.* Prevalence of skin lesions and need

for treatment in a cohort of 90 880 workers. *Br J Dermatol* 2011; **165**:865–73.

44 Sinikumpu S-P, Huilaja L, Jokelainen J, *et al.* High Prevalence of Skin Diseases and Need for Treatment in a Middle-Aged Population. A Northern Finland Birth Cohort 1966 Study. *PLoS One* 2014; **9**:e99533.

45 Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology* 1999; **10**:37–48.

46 Lederer DJ, Bell SC, Branson RD, *et al.* Control of Confounding and Reporting of Results in Causal Inference Studies: Guidance for Authors from Editors of Respiratory, Sleep, and Critical Care Journals. *Ann Am Thorac Soc* 2018; **19**:AnnalsATS.201808-564PS.

47 Hughes RA, Heron J, Sterne JAC, Tilling K. Accounting for missing data in statistical analyses: multiple imputation is not always the answer. *Int J Epidemiol* 2019; **48**:1294–304.

48 Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *Am J Public Health* 1998; **88**:15–9.

49 Ioannidis JPAA. The Proposal to Lower P Value Thresholds to .005. *JAMA* 2018; **319**:1429.

50 Lawlor DA, Tilling K, Smith GD. Triangulation in aetiological epidemiology. *Int J Epidemiol* 2016; **45**:1866–86.

51 Abdel-Hafez M, Shimada M, Lee PY, *et al.* Idiopathic Nephrotic Syndrome and Atopy: Is There a Common Link? *Am J Kidney Dis* 2009; **54**:945–53.

52 Wei C-C, Tsai J-D, Lin C-L, *et al.* Increased risk of idiopathic nephrotic syndrome in children with atopic dermatitis. *Pediatr Nephrol* 2014; **29**:2157–63.

53 Berghea EC, Balgradean M, Popa I-L. Correlation Between Idiopathic

Nephrotic Syndrome and Atopy in Children - Short Review. *Maedica (Buchar)* 2017; **12**:55–8.

54 Wei C-C, Lin C-L, Shen T-C, *et al.* Atopic Dermatitis and Association of Risk for Henoch–Schönlein Purpura (IgA Vasculitis) and Renal Involvement Among Children. *Medicine (Baltimore)* 2016; **95**:e2586.

55 Holme SA, Scott-Lang VE, Ooi ET, *et al.* The south-east Scotland dermatology workload study: 30 years' analysis. *Br J Dermatol* 2012; **167**:123–30.

56 Eyerich K, Eyerich S. Immune response patterns in non-communicable inflammatory skin diseases. *J Eur Acad Dermatology Venereol* 2018; **32**:692–703.

57 Nguyen T V., Cowen EW, Leslie KS. Autoinflammation: From monogenic syndromes to common skin diseases. *J Am Acad Dermatol* 2013; **68**:834–53.

58 Murthy AS, Leslie K. Autoinflammatory Skin Disease: A Review of Concepts and Applications to General Dermatology. *Dermatology* 2016; **232**:534–40.

59 Sá DC de, Festa Neto C. Inflammasomes and dermatology. *An Bras Dermatol* 2016; **91**:566–78.

60 Sinikumpu S, Huilaja L, Auvinen J, *et al.* The Association Between Low Grade Systemic Inflammation and Skin Diseases: A Cross-sectional Survey in the Northern Finland Birth Cohort 1966. *Acta Derm Venereol* 2018; **98**:65–9.

61 Impellizzeri D, Esposito E, Attley J, Cuzzocrea S. Targeting inflammation: New therapeutic approaches in chronic kidney disease (CKD). *Pharmacol Res* 2014; **81**:91–102.

62 Chen TK, Knicely DH, Grams ME. Chronic Kidney Disease Diagnosis and Management: A Review. *JAMA* 2019; **322**:1294–304.

63 Moyer VA, U.S. Preventive Services Task Force. Screening for chronic kidney

disease: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2012; **157**:567–70.

64 Komenda P, Ferguson TW, Macdonald K, *et al.* Cost-effectiveness of Primary Screening for CKD: A Systematic Review. *Am J Kidney Dis* 2014; **63**:789–97.