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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our [Editorial Policies](#) and the [Editorial Policy Checklist](#).

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a Confirmed

- | | | |
|-------------------------------------|-------------------------------------|--|
| ☐ | ☒ | The exact sample size (n) for each experimental group/condition, given as a discrete number and unit of measurement |
| ☐ | ☒ | A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly |
| ☐ | ☒ | The statistical test(s) used AND whether they are one- or two-sided
<i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i> |
| ☐ | ☒ | A description of all covariates tested |
| ☐ | ☒ | A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons |
| ☐ | ☒ | A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals) |
| ☐ | ☒ | For null hypothesis testing, the test statistic (e.g. F , t , r) with confidence intervals, effect sizes, degrees of freedom and P value noted
<i>Give P values as exact values whenever suitable.</i> |
| ☒ | ☐ | For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings |
| ☒ | ☐ | For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes |
| ☐ | ☒ | Estimates of effect sizes (e.g. Cohen's d , Pearson's r), indicating how they were calculated |

Our web collection on [statistics for biologists](#) contains articles on many of the points above.

Software and code

Policy information about [availability of computer code](#)

Data collection

SAS v9.4 (Cary, NC); Q-View Imager LS (Quansys Biosciences, Logan, UT); Illumina Novaseq 6000; Samui Browser; proteomic measurements outsourced to the academic core: Proteomics Core, Beth Israel Deaconess (Boston, MA)

Data analysis

SAS v9.4; Q-View Software v3.13; GraphPad Prism v8.3.1; JMP 16.0.0; R packages (ggplot2, vcd, circlize, caret); Space Ranger v1.0.0; Visium Human Transcriptome Probe Set v1.0 GRCh38; Seurat v4.0.3

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [guidelines for submitting code & software](#) for further information.

Data

Policy information about [availability of data](#)

All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

The data generated in this study supporting our findings are presented in either the main body of the manuscript, in the Supplementary Data, as the Source data or in the Harvard dataverse repository. The proteomics data for Complement and a prospective binary kidney outcome has been deposited at the Harvard dataverse at

<https://doi.org/10.7910/DVN/ZBVIMF>. Access to subject-level data is restricted in order to protect sensitive human subject data and to adhere to the terms of the informed consent. Kidney tissue proteomics data of the primary dataset are available at the Mendeley Data Repository <https://data.mendeley.com/datasets/83k89shdx5/>. Single cell and spatial transcriptomics kidney tissue data are available at <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE211785>. Publicly available software for pathway analyses can be consulted at <https://davidbioinformatics.nih.gov/> for DAVID, <https://www.genome.jp/kegg/> for KEGG, <https://reactome.org/> for Reactome and <https://www.uniprot.org/> for UniProt. Source data are provided with this paper.

Research involving human participants, their data, or biological material

Policy information about studies with [human participants or human data](#). See also policy information about [sex, gender \(identity/presentation\), and sexual orientation](#) and [race, ethnicity and racism](#).

Reporting on sex and gender	This study invited participants of all genders/sexes, as detailed in Supplementary Table 1. Our multivariable analyses were adjusted for sex, revealing minimal or no confounding effects.
Reporting on race, ethnicity, or other socially relevant groupings	Race is reported in Supplementary Table 1 and is included in our multivariable analyses. Please refer to Supplementary Table 12 on the representativeness of our study population.
Population characteristics	Our study included 5 cohorts of subjects with type 1 and type 2 diabetes and early to advanced kidney stages at baseline. All baseline characteristics are described in Supplementary Tables 1 and 2.
Recruitment	The Joslin Kidney Study enrolled about 3,500 patients with type 1 or type 2 diabetes at the Joslin Clinic from 1991-2009. The PERL trial enrolled 530 participants across 16 recruitment sites in 3 countries from 2004-09. The African American cohort included 123 participants from the Diabetes Heart Studies.
Ethics oversight	The Joslin Diabetes Center Committee on Human Studies approved all the protocols for the current study including the Joslin Kidney Studies. The institutional review board at each site, including the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)-appointed data and safety monitoring board for the PERL study, the Wake Forest University School of Medicine Institutional Review Board for the Diabetes Heart Studies and the University of Pennsylvania Institutional Review Board for the kidney tissue study, approved the protocols for the respective parent studies.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Sample size calculation was not performed in the current study. We determined our sample size based on the number of subjects with available urine specimens for high-throughput or targeted Complement proteome determinations.
Data exclusions	There were no data exclusions.
Replication	Our prospective study design included 5 independent cohorts of subjects with two diabetes types and early to advanced kidney stages. We investigated the urinary Complement proteome in a two-cohort study of advanced DKD and then assessed whether associations with key proteins extended to early/moderate DKD stages in a three-cohort study.
Randomization	Randomization was not applicable to our study. We controlled for confounding by restricting study subjects to specific stages of chronic kidney disease or levels of albuminuria and evaluated potential confounders in our multivariable models.
Blinding	The Somalogic research team performing the outsourced proteomic measurements was blinded to the sample status. Samples were balanced by caseness before being sent, and no additional blinding was used.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about [clinical studies](#)

All manuscripts should comply with the ICMJE [guidelines for publication of clinical research](#) and a completed [CONSORT checklist](#) must be included with all submissions.

Clinical trial registration	The current study was not a clinical trial. It did, however, include 207 participants of the Preventing Early Renal Loss in Diabetes (PERL) trial. Parent study registration: NCT02017171.
Study protocol	Eligibility criteria and study protocol to the parent study of PERL have been published. (Doria et al., NEJM 2020).
Data collection	SAS v9.4
Outcomes	Development of kidney failure in 10 years; continuous GFR slope and GFR-based binary outcomes

Plants

Seed stocks	<i>Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.</i>
Novel plant genotypes	<i>Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.</i>
Authentication	<i>Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosaicism, off-target gene editing) were examined.</i>