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Reporting Summary

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Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. 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
☐	☒	An indication of 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 *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	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 statistics 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 *Give P values as exact values whenever suitable.*
☒	☐	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
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	Zen 2012 and Zeiss Axiocam (Thornwood, NY) for PC for image analysis; Graphpad Prism Version 7 (La Jolla, CA) and SAS version 9.4 (Cary, NC) for statistical analysis; TraceFinder (v 3.0, Thermo Scientific, Waltham, MA) for metabolite peak analysis
Data analysis	Data were analyzed and results were prepared using GraphPad Prism 7 or SAS version 9.4 as indicated in the Methods document.

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/reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research 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 list of figures that have associated raw data
- A description of any restrictions on data availability

Provide your data availability statement here.

Field-specific reporting

Please select 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/authors/policies/ReportingSummary-flat.pdf

Life sciences study design

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

Sample size	MOUSE STUDIES Sample size for metabolomics experiments was based on previous experience. 17 For IRI experiments focused on renal function (i.e., serum creatinine) outcome, sample size was based on previous experience and consideration of the following estimation: serum creatinine of 1.4 ± 0.5 mg/dl among controls vs. 2.1 ± 0.5 mg/dl among IRI mice requires n = 6 mice per group for 80% power and 5% alpha-error. HUMAN STUDIES (1) Sample size was calculated for the uQ:T nested case control study based on uQ:T of 1.1 ± 0.6 in controls vs. 2.8 ± 0.2 in mice with AKI (Fig 1d) and assuming a comparable difference in humans, examining 6 controls vs. 6 AKI-affected subjects was estimated to provide 85% power to detect a between-group difference with α-error 0.05. (2) A post hoc sample size calculation for the ICU cohort study demonstrated that 215 patients with an incident AKI event rate of 24% (n = 51) provided > 80% power to detect an odds ratio of 1.7 per standard deviation of uQ:T. (3) Based upon a comparably-sized previous study of oral Nam pharmacokinetics in healthy volunteers (Ref 6) nine participants were consented for the healthy subject Nam PK study. (4) For the Phase 1 pilot study of oral Nam in cardiac surgery patients, We estimated that 5 subjects per group would provide >95% power to detect differences in serum Nam concentration between the 3 gm/d Nam and placebo groups with α-error 1%. However, based on recent literature describing an AKI event rate of ~40%,8 we estimated a sample size of 10-15 patients per group for this Phase 1 study (each yielding approximately 5 patients with AKI) would be sufficient to assess pharmacokinetic effects of oral Nam in on-pump cardiac surgery patients with and without AKI. To account for screen failures and loss to follow-up, we set the target enrollment for 20 patients per group.
Data exclusions	None
Replication	Serum creatinine measurements in mice were measured in duplicate by an independent core facility. Metabolite measurements were performed in duplicate by investigators blinded to experimental setting. All attempts at replication were successful.
Randomization	MOUSE: All studies involving mice were approved by the Beth Israel Deaconess Medical Center Institutional Animal Care and Use Committee (IACUC). Experiments were performed using littermate controls by an operator blinded to genotype and randomized within each cage to sham vs. AKI model. Creatinine from mouse serum was measured using LC/MS-MS at the University of Alabama Birmingham O'Brien Core Center for Acute Kidney Injury Research in a blinded fashion (NIH P30 DK079337). HUMAN: The Phase 1 pilot study of oral Nam in cardiac surgery patients included blocked randomization schedules that were electronically generated with a block size of 6, and maintained independently by the Beth Israel Deaconess Medical Center research pharmacy, which was not involved in patient care or data analysis. Patients were randomly assigned on a 1:1:1 basis into the three study arms (1 gm/d Nam, 2 gm/d Nam, or placebo).
Blinding	For mouse studies, measurements of serum creatinine were performed by an independent core facility at University of Alabama, Birmingham, that was blinded to experimental setting. For the clinical studies, metabolite measurements were performed by an investigator (AHB) blinded to experimental setting. Furthermore, patients participating in the Phase 1 pilot study of oral Nam in cardiac surgery patients were blinded to study group assignment. For investigators participating in this interventional trial, participants were designated as Groups A, B, and C by the Beth Israel Deaconess research pharmacy.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☒	☐ Unique biological materials
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology
☐	☒ Animals and other organisms
☐	☒ Human research participants

Methods

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

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	Mus musculus C57BL6/J male mice of 8-12 week age for both general AKI experiments and for QPRT+/- experiments. Note that this mouse model was developed in the C57BL6J background by CRISPR gene editing as described in the Methods.
Wild animals	N/A
Field-collected samples	N/A

Human research participants

Policy information about studies involving human research participants

Population characteristics	Covariates and clinical characteristics of the human research participants are described in the Methods and sumamrized as below: 1. uQ:T Discovery Nested Case-Control Study Study Population: We examined the uQ:T ratio as an indicator of risk for AKI in a prospective cohort of patients undergoing nonurgent, on-pump cardiac surgery through a nested case-control analysis. The prospective cohort for this nested case-control study was enrolled over a period of six months. The primary inclusion criterion was planned, on-pump cardiac surgery. Subjects were excluded for any of the following reasons: unresolved AKI 1 week prior to operation, history of kidney transplant, end stage renal disease, pregnancy, younger than 18 years of age, unable to consent, off-pump cardiac surgery, and individuals held in an institution by legal or official order. 2. uQ:T ICU Validation Cohort Study Population: The ICU validation cohort included subjects admitted to the medical or surgical intensive care unit (ICU) at Brigham and Women's Hospital (BWH; Boston, MA) between September 2008 and January 2013. Further details of this cohort have been published (Ref 4 of methods). 3. Healthy Subject PK Study Study Population: Based upon a comparably-sized previous study of oral Nam pharmacokinetics in healthy volunteers,6 nine participants were consented. One subject withdrew from the study following a new diagnosis of a chronic medical condition. The remaining eight, who were free of chronic illness, were given oral Nam 3 gm once daily supplied by the Massachusetts General Hospital research pharmacy (Rugby Laboratories) at 0, 24 and 48 hours between January 2016 to June 2016. 4. Phase 1 Pilot study of Oral Nam in Cardiac Surgery Patients Study Population: In this phase 1 pilot randomized, single blind, placebo-controlled clinical trial, patients were identified and screened through surgical appointment logs and electronic medical records. Patients were approached at their outpatient preadmission evaluation or on inpatient hospital wards, at which time the study explained and written and signed informed consent was obtained prior to enrollment. The trial was approved by the Institutional Review Board of Beth Israel Deaconess Medical Center (IRB 2016P000028) and registered at clinicaltrials.gov (NCT02701127). The study was conducted according to the principles of the Declaration of Helsinki. The inclusion criterion for this study was planned on-pump cardiopulmonary bypass surgery. An additional inclusion criterion of Cleveland Clinic Score ≥ 6 (Extended Data Table 9) was removed through IRB-protocol amendment due to lack of sufficient patients meeting this criterion. Subjects were excluded for any of the following reasons: any new AKI within 1 week prior to operation, kidney transplant status, end stage renal disease, pregnancy, younger than 18 years of age, inability to consent, off-pump cardiac surgery, and individuals held in an institution.
Recruitment	Patients were approached at their outpatient preadmission evaluation or on inpatient hospital wards, at which time the study explained and written and signed informed consent was obtained prior to enrollment. For the healthy subject oral Nam PK study, eligible subjects were identified through flyers posted throughout the Massachusetts General Hospital campus, and online on the Partners Healthcare Clinical Trials in need of Volunteers Website (https://clinicaltrials.partners.org/). Subjects who completed the study were remunerated with a check for $120.