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Corresponding author(s): Xiangfeng Lu

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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 *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 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 *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

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	See Methods Section for details. Readfq (version 8, https://github.com/cjfields.readfq), Bowtie2 (version 2.2.4, https://bowtie-bio.sourceforge.net/bowtie2/index.shtml), SOAPdenovo (version 2.04, http://soap:genomics.org.cn/soapdenova.html), MetaGeneMark (version 2.10, http://topaz.gatech.edu/GeneMarK/), CD-HIT (version 4.5.8, http://www.bioinformatics.org/cd-hit), DIAMOND (version 0.9.9, https://github.com/bbuchfink.diamond/) were each used to process microbiome data. TMBQ (version 1.0) was used for processing raw data generated from UPLC-MS/MS.
Data analysis	All statistical analyses were conducted using R software (R version 4.3.1). All data analysis code available on GitHub (https://github.com/Shinarlin/SSBP-and-multiomics).

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

Data Availability

The raw data of metagenomic sequencing in this study have been deposited in the Genome Sequence Archive (https://ngdc.cncb.ac.cn/gsa-human) under accession number HRA014875. The plasma metabolomics data have been deposited in the OMIX (https://ngdc.cncb.ac.cn/omix/) under accession number OMIX013281. Due to the human genetic resources and privacy regulation, these data are available under controlled access for academic research purposes. Data access requests must be submitted through the GSA-Human and OMIX platforms and will undergo review by the Data Access Committee and database administrator within one month. Detailed instructions for submitting requests are provided on the respective platforms. Once approval is granted, users will have one month to download the data. The animal data supporting this study have been deposited in GitHub (https://github.com/Shinarlin/SSBP-and-multiomics). The complete human metadata is available under restricted access due to ethical and legal restrictions. Any individual affiliated with an academic institution may request access from Xiangfeng Lu, PhD (luxf@pumc.edu.cn), and requests will be reviewed and responded to within one months. Source data are provided with this paper.

Code Availability

The core codes used in this study have been made publicly available on GitHub (https://github.com/Shinarlin/SSBP-and-multiomics).

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	Participants were recruited regardless of sex and/or gender. The sex and/or gender of participants was determined by self-report. Given that salt sensitivity of blood pressure is a common trait in both male and female, and the aims of this study is to investigate the etiology of salt-sensitivity hypertension rather than to explore the differences between sexes, thus we did not perform sex- and gender-based analyses.
Reporting on race, ethnicity, or other socially relevant groupings	The race of all participants in this study was Han Chinese, which was determined by self-reporting.
Population characteristics	Population characteristics are summarized in Table 1, Supplementary Tables 1, 12, and 16.
Recruitment	Participants of the MetaSalt study were recruited from four Chinese communities. Participants of the GenSalt study were recruited from six Chinese communities. Participants of the prospective cohort were selected from the InterASIA and China MUCA 1998 cohorts that recruited participants from 15 provinces of China. Informed consent was obtained from all participants.
Ethics oversight	The protocol was approved by the Institutional Review Board and the Ethics Committee of Fuwai Hospital.

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	MetaSalt: 456 participants would be appropriate to achieve 90% power for the detection of a 2.0 mmHg difference in systolic blood pressure between intervention stages at a significance level of 1e-5. To account for a potential dropout rate of 10%, at least 500 participants were recruited. GenSalt: a 1:1 matching method was applied to select participants. All 1,879 participants were taken into account, and selected eligible pairs as many as possible. Eventually, 113 extreme SS individuals and 113 SR individuals were kept. Cohort: no sample size calculation was performed. The study leveraged an existing large-scale prospective cohort, and the full set of eligible participants with available data was included to maximize statistical power Animal experiments: no sample size calculation was performed. Sample sizes were determined based on practices commonly adopted in similar published studies, and a minimum of three biological replicates per group was used.
Data exclusions	Participants were excluded if they did not meet eligibility criteria. See Supplementary Methods for details.

Replication	The GenSalt study was used to replicate the salt-related metabolites identified from the MetaSalt study, and ~78% metabolites was successfully replicated. Animal experiments in Wistar and Dahl-SS rats were conducted to validate the effects of high-sat diet on isovalerylcarnitine, and the effects of isovalerylcarnitine on SS hypertension, which were successfully validated.
Randomization	The MetaSalt study is a multicenter, non-randomized, self-controlled, dietary salt intervention trial.
Blinding	There was no blinding given that this study.

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

Antibodies

Antibodies used	Mouse anti-eNOS (Supplier: Santa Cruz; Cat: sc-376751; mouse mAb; RRID: AB_2832203)
Validation	NOS3 (A-9) is recommended for detection of NOS3 of mouse, rat and human origin by Western Blotting (starting dilution 1:100, dilution range 1:100 1:1000), immunoprecipitation [1-2 µg per 100-500 µg of total protein (1 ml of cell lysate)], immunofluorescence (starting dilution 1:50, dilution range 1:50-1:500), immunohistochemistry (including paraffin-embedded sections) (starting dilution 1:50, dilution range 1:50-1:500) and solid phase ELISA (starting dilution 1:30, dilution range 1:30-1:3000).

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals	Four-week-aged Wistar rat, seven-week-aged Dahl salt-sensitivity rat, and six-week-aged Sprague-Dawley rat
Wild animals	The study did not involved wild animal.
Reporting on sex	All rats in used in this study were male.
Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	All animal experiments were conducted following the recommendations of the Ministry of Science and Technology of China and the protocol was approved by the Experimental Animal Ethics Committee of Fuwai Hospital (License no.: FW-2022-0016).

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

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	ChiCTR1900025171
Study protocol	The DOI of the study protocol was 10.1016/j.cdtm.2021.06.002, and was included in the submission.
Data collection	Participants of the MetaSalt study were recruited from four Chinese communities during August 2019 to November 2019.
Outcomes	The primary outcome was salt sensitivity of blood pressure.

Plants

Seed stocks	*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.*
Novel plant genotypes	*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.*
Authentication	*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, mosiacism, off-target gene editing) were examined.*