

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 (<i>n</i>) 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. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> 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 <i>d</i> , Pearson's <i>r</i>), 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	All statistical analyses were implemented using R software (version 4.1.2) with the R package TwosampleMR (version 0.5.6), Radial-MR (version 1.1), and MR-PRESSO (version 1.0) or Python (version 3.9) with the packages listed in the methods. Summary GWAS data for Mendelian randomization analyses is publicly available and was obtained from the MRC-IEU OpenGWAS database or their respective studies. Additional specific details about the data, including, where applicable, links for downloading them, are available in the relevant publications referenced in this study. Additional data and code available at: https://data.mendeley.com/datasets/67f2sxfwxn/draft?a=6d0eaf2c-385b-498d-a599-7a40211a850e
Data analysis	All statistical analyses were implemented using R software (version 4.1.2) with the R package TwosampleMR (version 0.5.6), Radial-MR (version 1.1), and MR-PRESSO (version 1.0) or Python (version 3.9) with the packages listed in the methods. Summary GWAS data for Mendelian randomization analyses is publicly available and was obtained from the MRC-IEU OpenGWAS database or their respective studies. Additional specific details about the data, including, where applicable, links for downloading them, are available in the relevant publications referenced in this study. Additional data and code available at: https://data.mendeley.com/datasets/67f2sxfwxn/draft?a=6d0eaf2c-385b-498d-a599-7a40211a850e

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](#)

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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	Yes, gender breakdown specified in methods for UK Biobank data used.
Reporting on race, ethnicity, or other socially relevant groupings	Yes, ethnicity specified in methods for UK Biobank data used.
Population characteristics	<i>Describe the covariate-relevant population characteristics of the human research participants (e.g. age, genotypic information, past and current diagnosis and treatment categories). If you filled out the behavioural & social sciences study design questions and have nothing to add here, write "See above."</i>
Recruitment	<i>Describe how participants were recruited. Outline any potential self-selection bias or other biases that may be present and how these are likely to impact results.</i>
Ethics oversight	<i>Identify the organization(s) that approved the study protocol.</i>

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	200 flies per group for validation experiments. 1960 individuals from UK Biobank used for MR.
Data exclusions	Removed some data, as described in the text.
Replication	Repeated most experiments at least once, specifics are listed in each figure legend.
Randomization	For each fly genotype, isogenic offspring of each sex were separated into the different conditions, including the vehicle control and test conditions. Random allocation was not necessary since we used isogenic flies and controlled for the vehicle for both sexes and each genotype. Sample splitting and randomization prior to Random Forest modeling and Mendelian randomization was performed using packages described in the methods section. Statistics including multiple covariates (e.g. genotype, sex, diet, and metabolite concentration) included data from all possible combinations.
Blinding	Investigators were not blinded to group allocation. Blinding was not relevant since there would be no placebo effect and outcomes were objective (Number of flies dead). Randomization prior to Random Forest and Mendelian randomization also prevented bias from influencing the outcome of those methods.

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

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	Drosophila melanogaster strains w1118 and Canton S. Flies of all ages throughout the lifespan were used.
Wild animals	Study did not involve wild animals.
Reporting on sex	The GWAS of 1960 individuals used for the MR analysis is 96.6% female and resulted in a female dominant GWAS, yet we also found male-specific effects in flies. Our systems biology approach highlights divergent and opposing effects of how different species react to diet and that the same sex specific responses may not be conserved across species, which is an important point to consider when translating findings from model organisms to humans. When analyzing effects of sex in flies, we included 200 flies of each sex per condition and included sex as a covariate in the cox proportional hazards analysis when appropriate.
Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	No ethical approval or guidance was required since only Drosophila melanogaster and published human data were used.

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

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A